Evolution in Space and Time

The Second Synthesis between Ecology, Evolutionary Biology, and the Philosophy of Biology

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Experience without theory is blind, but theory without experience is mere intellectual play

Immanuel Kant

This thesis is dedicated to the man who inspired me to be a thinker and a teacher,
my grandfather, Dr. William “Elbo” Linneman (1926-2022).
You live on through me.

Summary

Change is the fundamental idea of evolution. Explaining the extraordinary biological change we see written in the history of genomes and fossil beds is the primary occupation of the evolutionary biologist. Yet it is a surprising fact that for the majority of evolutionary research, we have rarely studied how evolution typically unfolds[1] in nature, in changing ecological environments, *over space and time.*

This has resulted in a biology that has yet to realize its scientific potential. Since its modern origins, an implicit yet stark division between theoretical and empirical efforts has beset biological practice. The first major synthesis of biology—i.e., *the Modern Synthesis* (*circa* 1918-1956)—united the subdisciplines of biology and organized them into a coherent theoretical and mathematical framework of evolution, leading to the legitimization of biology as a scientific discipline and natural selection as a reputable scientific theory. Yet while ecology played a major role in the eventual acceptance (and *dominance*) of the population genetic viewpoint of evolution in the synthetic era, it held a lesser role in the development of evolutionary theory until the 1980s, when we began to systematically study the evolutionary dynamics of natural populations *in space and time*. As a result, evolutionary theory was initially constructed in an abstract vacuum that is unrepresentative of evolution in nature.

Evolutionary biology has since undergone a profound shift in thinking spurred by its recent synthesis with ecology. Ecological insight has described a biological world that is immeasurably complex, with causal relations extending from the smallest macromolecule to the largest ecosphere, interweaving between symbiotic species, and dependent on many interacting causes that vary *in space and time*.

Unifying ecology with evolutionary biology has thus progressed our knowledge of natural selection theory. We are no longer asking *if natural selection is operating in natural populations* but *how natural selection affects natural populations over spatiotemporal contexts*. Such profound advancements have recently revealed how natural selection varies in strength, direction, form, and, more surprisingly, level of biological organization. The causal dynamics of natural selection are no longer reducible to lower levels of biological organization (i.e., individuals, *selfish genes*) over shorter timescales but have been expanded to include adaptation at all levels and timescales.

The novel concept of *evolvability* plays an organizing role throughout this thesis since its recent rise to popularity provides some of the best evidence of how biologists have persistently neglected *evolution in space and time* throughout history. Since Darwin, evolutionary biologists have routinely failed to explain the evolutionary existence of adaptive genetic variation mechanisms (e.g., adaptive mutation, sexual recombination, HGT)—what I elucidate as an active problem for evolutionary biology called *the paradox of adaptive variation*. Mounting evidence in the 20th century exposed an internal anomaly between the available evidence on adaptive genetic

[1] *Evolution* derives from the Latin '*evolutio'*, which translates to *the unrolling* or *the unfolding* (of a book or papyrus).

variation and natural selection theory. Not only were genetic variation mechanisms exposed to selective environments, overturning the modern synthetic assumption of *random variation*, but most species were found to exhibit greater flexibility (i.e., *evolvability*) to cause adaptive genetic changes in response to ecological pressures than was theoretically allowable. Evolvability, as *an emergent adaptation of populations* that is prompted by ecological changes, thus finally became revealed within an evolutionary biology that embraced *evolution in space and time*. How such a central process as evolvability can go relatively unnoticed in theory until recent times thus highlights the areas of biology that warrant urgent progress.

Evolutionary biology is currently suspended at an intermediate stage of scientific progress that calls for the organization and integration of overflowing knowledge stockpiles—produced by its recent synthesis with ecology—into a coherent and unified theoretical framework, just like that seen in the first synthesis. This is where recent advancements in the philosophy of biology can be of great use, acting as a bridge between previously divided subdisciplines of biology and inventing new theoretical strategies to organize and accommodate divided knowledge. Philosophers have recommended transitioning away from outdated philosophies that were originally derived from physics within the philosophical zeitgeist of *logical positivism* (i.e., monism, reductionism, and monocausation) and toward a distinct philosophy of biology that can capture the natural complexity of multifaceted biological systems within diverse ecosystems—one that embraces the emerging philosophies of *pluralism*, *emergence*, and *multicausality.*

I, therefore, see recent advances in ecology, evolutionary biology, and the philosophy of biology[2] as laying the groundwork for another major biological synthesis, what I refer to as the *Second Synthesis* because, in many respects, it is analogous to the aims and outcomes of the first synthesis (but is notably distinct from what some have self-proclaimed as *the extended evolutionary synthesis*). With the general development of a distinctive philosophy of science, biology has rightfully emerged as an autonomous science.

In this thesis, I offer an historical reconstruction of the philosophical, technological, and natural forces that led to the Second Synthesis in hopes of recognizing the significant advancements that have overtaken biology in the past generation. I then offer my normative recommendations, prescribing a pluralistic theory of natural selection that is capable of explaining complex emergent phenomena like evolvability to resolve *the paradox of adaptive variation*. I do so by building a bridge between greater biology and the history/philosophy of biology, bringing into focus the primary achievements made by historians and philosophers over the past generation and how these advancements can modernize biological thought.

The first synthesis *legitimized* biology; the Second Synthesis *autonomized* biology. Now it is once again time to organize and structure our new knowledge into a coherent theoretical

[2] There is a fourth prospective element of the Second Synthesis that I could not grant a central role in this thesis, and that is *development*. Evolutionary developmental biology has recently transformed our concepts of biological innovation and novelty. While these concepts are intertwined within the research on evolvability presented in this thesis, they live, for now, outside of the scope of this thesis, as I cannot reasonably argue for their inclusion until I see further evidence of how development affects evolutionary trajectories in the long-term (and, speaking with humility, gain greater knowledge in this area, since the evidence may lie outside of my causal perspective).

framework, using the theoretical strategies suggested by philosophers to represent a new way of looking at the evolution of life on earth—*and likely beyond*.

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I owe a great and incalculable debt to so many names that it would take a new book to fill. Several people stand out as the structural causes of the ambitious thesis expounded in the following, for without their support, I would have never completed this project.

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Secondly, I would also like to thank Prof. Rosario Gil and everyone in the Biodiversity and Evolutionary Biology department for their help and willingness to answer all of my questions (which there were plenty). I would also like to thank my fellow lab members, Jesus and Emilio, for their help.

Thirdly, I must thank the professor who became more than a teacher or mentor to me but a close friend whom I can always count on, Dr. Lauren Harris. Without your guidance and good spirit, I would have never continued within academia. Moreover, Lauren sparked my interest in HPS perspectives on science, the perfect example of a well-rounded academic to whom I aspire towards.

Lastly, to my parents, who at times thought I was certifiably insane to undertake a career in academia but have stood in support of my dreams since day one. It is hard to imagine a better set of parents, and I am eternally grateful for all you have done for me. I would be nothing without you.

Author's Note on Writing Style

I have attempted to, where applicable, remove all unnecessary jargon and write this thesis in a manner that emphasizes reader comprehension regardless of scientific background. Although there are certain areas that I wish to cover in greater detail, such as the historical narratives pushed throughout this thesis, the assumed role I am taking as a bridge between various disciplines requires me to favor brevity and readability over erudite precision. I attempt to write in as plain of terms as humanly possible without destroying any epistemic content or essential nuances. You will also find specific terminology that could not be simplified as adequately defined in the glossary section of this thesis, such as *reductionism* or *empirical realism*.

Because of the sheer breadth of topics I attempt to cover in this thesis, I always provide a concise summary of background knowledge in boxes. These boxes are thus necessary for the foundations of my argument, but they lie outside of the flow of this thesis.

Lastly, there are specific instances throughout this thesis that I prefer to write more actively and pander to subjectivity in hopes of acknowledging the limits of my knowledge (often expressed in footnotes). In other instances, I write more passively, attempting to describe putative truths or where I believe the edges of knowledge to lie currently. Scientific writing demands good storytelling, and there is a time and place for all forms of writing in science.

Preface

As I look back now, a rather fortunate sequence of events led to the argument expounded in this thesis. Luckily, I always found myself researching at the right place, at the right time, and under the right circumstances.

As a humble undergraduate student at Michigan State University (MSU), I undertook a research assistant position in a pedagogical lab that studied how students can better understand complex and abstract concepts of evolution such as natural selection and fitness, thus familiarizing myself with the theoretical core of evolutionary theory—a skill that would prove useful later. I carried out a modest research project of my own and decided to study the "*naïve concepts of evolution"*, which were ostensibly misguided ways of thinking about evolution. One of these naïve concepts, *group selection*, was so forcefully taught as an anathema that I remember thinking, "this is strange".

Around the same time that I was researching and familiarizing myself with the core of evolutionary theory, I was also being taught the frontiers of biological science, from genetics, ecology, and neurobiology. To my luck, I was never a great student, but I was observant. I noticed stark contrasts between the "gospels" of evolutionary theory and what I was being taught in my other biological courses. Several anomalies presented themselves to me. Firstly, variation was the supposed lifeblood of evolution. However, I discovered that the mechanisms governing the production of variation (i.e., mutation and recombination) were anything but *invariably random*, contrary to what I was so dogmatically taught in my evolutionary course. Finding this anomaly sparked my curiosity.

Additional research introduced me to *the paradox of sexual reproduction*, or biologists' problems explaining the evolution and function of sexual reproduction. *Why?* Because evolutionary biologists did not have the theoretical tools to explain the complex nature of sex. Several authors suggested that *evolvability* could be the reason why sex evolved, leading me down the rabbit hole of the *evolvability* literature.

I was then motivated to carry out a second research project within the renowned BEACON program at MSU, alongside some of the best *evolution in action* experiments like Richard Lenski's famous *Long Term Evolution Experiment*. In this research project, I used computational strategies to experiment (not simulate) how varied life-history traits affect the evolvability of populations in the long term. To my surprise, the digital populations with lower-initial fitness but higher evolvability eventually outcompeted the higher-initial fitness but lower-evolvability populations, *but only after several generations and following environmental changes*. I never published this research, but now I had the supporting evidence to confirm my suspicions that the evolutionary process was profoundly more complex than conventional theory assumed,

especially when considering evolution in varying spatial environments and over longer stretches of time.

After I graduated from MSU, I wanted to approach the evolvability concept from a different angle than my contemporaries. After reading several works by philosophers of science such as Michael Ruse or Elliot Sober, I became convinced that their philosophical treatments of fitness and selection were profoundly more complex and accurate than what I was reading from empirical biologists. This motivated me to pursue the concept of evolvability from a similar historical and philosophical lens. Surprisingly, I knew this would consign me to years of financial hardship and uphill battles since historical and philosophical analyses are not always met with positivity amongst practicing scientists or funding bodies. Nevertheless, I chose the history and philosophy of science (HPS) anyway, hoping that it will bear more fruits in the long run.

Unfortunately, my suspicions were almost immediately realized. During my tenure as an HPS graduate student, I endured rejection after rejection from funding bodies, scientific institutions, and scientific journal editors. I have never received so much as a dime for pursuing my research, putting myself through school by doing odd jobs or taking out student loans[3]. Nearly every institution denied the value of my work. Moreover, every scientific journal editor either found my work to be too philosophical, too historical, or not scientific enough—*yada yada yada*. What I have found—or rather *exposed*—is that by taking such an integrative approach, one places their research outside the limited scope of most scientific journals, irrespective of its value to science. Most editors will not even grant you the courtesy of sending your work out for peer review, to let the scientists decide on its value.

What troubles me about this situation is that I include history and philosophy in my scientific analyses because of their inherent value to science, affording a more holistic and rounded viewpoint of scientific ongoings. Yet the broad scope and *generalizability* of HPS research are why it sometimes falls through the cracks and goes unnoticed or unrecognized in science.

Do not get me wrong; part of the onus falls on me. I could have easily fit the prefabricated molds of what journal editors or scientific institutions seek. But a part of me is stubborn. I do science *how I think science should be done*. And I think there is a profound role for the kind of scientific inquiry that I do, given the overflowing epistemic reservoirs of most sciences today with nobody to sift through such large stockpiles of knowledge and turn it into useful theory.

This is why I do science differently. I do science that transcends disciplinary boundaries and does not fit within the conventional mold of science. I do not cohabit in a laboratory, assess PCR tests, or trifle with the dreaded *R*-program—although I have a profound respect for those who have the patience to do *normal science*. I do science by sitting in whatever makeshift office I can find—commonly, some hipster coffee shop—and I just *read*. I read from the frontiers of greater science, biology, history, philosophy, or whatever material seems to be relevant to my broadly

[3] I am reminded of the time that Nobel laureate Ada Yonath visited our institution in Valencia to give a lecture. I hesitantly approached her and explained my research, to which she replied: “So all you do is read and think? Who pays you for such a thing!”

construed research question on *evolvability*. I read between the lines of extensive and esoteric literatures, looking for the main ideas or where the research may be heading. Nobody really taught me what to do or how to do it. I just started doing it and finding my way as I went along. So, bear with me while I demonstrate the necessity of this kind of work in the following thesis.

However, before I begin my demonstration, I would like to recognize an obvious shortcoming of my thesis. I have chosen an incredibly complex starting topic: *evolvability*. I feel it is within reason to claim evolvability as one of the most metaphysically and epistemically challenging topics in modern biology and philosophy today—precisely because it directly mirrors *the problem of fitness* but at higher levels of biological organization. Perhaps because of its complexity, I do not view this as a completed research project by any means. I am limited in what philosophical issues I can touch on and what I have to leave behind (e.g., biological individuality, levels of selection, the species problem, reductionism vs. emergence). I have to accept some issues at face value and move past them for the time being. The best advice I have received regarding my thesis is that "you have to stop somewhere". I think the contents and flow of this thesis would have been disrupted if I deviated to include each of these issues.

Being metacognitive of these shortcomings, I still believe the following thesis is justified of a Ph.D., merely because of the amount of time and effort I have put into forming my argument. The broad and intertwining scope offered in this thesis results from the constant questioning and prodding for the causal reasons why natural selection theory cannot effectively explain evolvability. *Why is sex a paradox?* Because of reductionism. *Why reductionism?* Because of logical positivism. So on and so forth it went, that once I thought I answered one question, my research revealed a thousand new ones.

The history of biology suggests that there are three necessary elements to achieve theoretical progress: (1) An accurate historiography that identifies the problem, (2) abundant and sufficient evidence in support of the new view, and (3) a pragmatic solution to solve the problem. Failed programmes such as Orthogenesis, Lamarckism, or Wynne-Edwards' *Group Selection* lacked in one or more of these elements. Even today, the Extended Evolutionary Synthesis (Pigliucci & Muller, 2010; Laland *et al.*, 2014) lacks in all three (see my chapter and others in Dickens & Dickens, *forthcoming*). Moreover, most philosophical work done today often achieves (1) and (3), but fails to provide abundant evidence (2) to underly their theoretical prescriptions. This thesis is thus my attempt to achieve all three necessary elements of progress, by being an empirically-sufficient and scientifically-informed philosophical reconstruction of natural selection theory.

This work does not stand alone as an historical thesis, scientific thesis, or philosophical thesis, but as an interdisciplinary thesis, of the kind that is sorely missing in the scientific literature today. The following is thus my attempt to do science *differently* since I find most biological work done today—from evo-devo to genetics to ecology—lacking in the holistic awareness that is afforded from an historical and philosophical perspective of science.

Introduction: The Indispensable Roles of History and Philosophy of Science

> "A knowledge of the historic and philosophical background gives that kind of independence from prejudices of his generation from which most scientists are suffering. This independence created by philosophical insight is—in my opinion—the mark of distinction between a mere artisan or specialist and a real seeker after truth" (Albert Einstein to Thornton, 7 December 1944, EA 61-574).

Scientific knowledge is progressing at an unprecedented rate never seen in history[4]. Technological advances mean new evidence and knowledge are being turned out by the scientific machine at an alarming rate, bearing new methods of research, new ways to look at old problems, or founding entirely new disciplines of inquiry and research. In biology, novel molecular, ecological, and experimental research has generated an explosion of highly detailed information that has yet to be fully integrated into theoretical frameworks (Müller *et al.*, 2019). New knowledge takes time to be structured and organized, translated into theory, and maintained over time. This is where philosophy, and perhaps more surprisingly *history*, become abundantly useful enterprises.

Einstein once famously remarked, *"science discovers, philosophy interprets*" (Hermanns, 1983, 98). Philosophy has never been as helpfull of a tool to science as it is today and *vice versa* (Laplane *et al.*, 2019). Philosophy should always be grounded in the empiricism of science. But science also needs philosophy to question the scientific process, reinterpret and organize knowledge, and examine the methods designed to output such knowledge. I firmly believe that we can build a better science through philosophy. However, we first must resolve the history of ostensible conflict between the two disciplines (Pigliucci, 2019; 2010; e.g., Weinberg, 1993, 166-167; Hawking & Mlodinow, 2010, 5).

For most of its short history, the philosophy of science has operated externally to the sciences, either by design or as a function of scientists' contempt for philosophy. Even today, the majority of philosophy of science papers are published in philosophy of science journals and tiptoe around the whims of scientists, treating them like external objects (Pigliucci, 2019; Mayr, 2004; Godfrey-Smith, 2003). *Well, this is not the best or only way to do the philosophy of science!* The philosophers and scientists whom I revere most—those who have made significant scientific contributions using philosophical knowledge—are the ones that have married the two disciplines. Great minds such as the late Charles Darwin, the founders of the Vienna Circle, Ernst Mayr, Albert Einstein, Stephen Jay Gould, R.A. Fisher, and Sewall Wright or those still practicing today such as E. O. Wilson, Elliot Sober, Sandra Mitchell, Roberta Millstein, John Dupré, Robert

[4] Indeed, given the rate that modern science is now turning out new knowledge and data, we should see more syntheses, revolutions, or advances in the 21st century than in previous centuries. However, we first need to construct a new science, akin to biological organisms, that can evolve rapidly (evolvability) while maintaining its primary causal structures (robustness).

Sapolsky, Sarah Otto, Robert Brandon, Tim Lewens, Laura Nuño de la Rosa, Hasok Chang, Graham Bell, Massimo Pigliucci, and of course, my thesis supervisor Andres Moya—these great minds not only hold a venerable commitment to science and scientific empiricism but are also willing to use philosophical insight to inform *science* and look at scientific problems from new angles. This is what, I believe, differentiates the original scientific thinkers in their pursuit of objective truth from the ordinary (*albeit essential*) bench scientist who toes the line.

The forthcoming chapters are therefore as much an exercise in the history and philosophy of science as they are grounded in hard science and evolutionary biology, although they are meant to be consumed by the common biologist. Philosophy has much to offer the sciences, particularly within the realms of *theoretical construction* (Laplane *et al.*, 2019) and *causation* (Anjum & Mumford, 2018). In this thesis, I use philosophical and historical knowledge to clarify conceptual issues surrounding natural selection; to bridge the explanatory interests of previously divided disciplines (i.e., ecology, evolutionary biology, and the history and philosophy of biology); to clarify how the age-old *levels of selection debate* is a dispute over *reductionism*; to *carve nature at its joints* and 'clean-up' our theoretical structure by providing explicit conceptual parameters, thus improving the internal consistency of evolutionary theory; and most importantly, to take a step back and view scientific discourse from a holistic standpoint and identify the prevailing attitudes or methods that are fettering scientific progress in biology. Biological progress today *necessitates* an intimate knowledge of the history and philosophy of biology.

For example, asking *how and why species adapt to their environment* remains the primary explanatory objective of evolutionary biology. However, in this thesis, I will show how prevailing attitudes and presuppositions of science have caused biologists to neglect key aspects of adaptation and frame natural selection in a limited causal light. Remnants of *physics envy* abound in modern biological practice due to the influences of *logical positivism* on twentieth-century science, which is clearly expressed within the leading theoretical disciplines of population and quantitative genetics. Explanatory reductionism and monism are attractive mindsets that aim to reduce the diversity of explanations to a small number of theories or mathematical laws at a privileged level of discourse (Mitchell, 2003). But the pursuit of monocausal explanatory models of absolute natural phenomena ("laws") is not a working strategy in biology due to the causal complexity and spatiotemporal restrictiveness of biological phenomena—and many have questioned its utility even in physics (Dupré, 2001). Biology is not physics, nor should it try to be so. Biological theories like natural selection should thus reflect the ontological complexity of biological and ecological systems, acting at multiple levels of biological organization and varying in space and time, dependent on myriad ecological factors. This calls for a new philosophy of biology that is grounded in pluralism, multicausality, and emergence.

It is the thankless job of the historian to elucidate such new trends, draw parallels between the past and present, and predict where we may be heading in the future. In this thesis, I use history as a contextual tool to expose the various anachronisms that still pervade modern evolutionary

thought and the intellectual forces that motivated them, so that we may retire from old patterns of thinking[5].

A common criticism that I have received when presenting parts of this thesis is that my work does not add anything new to the existing scientific literature. It is true that many of the ideas expressed in the following do not derive from my pen alone and have a rich history in the literature (i.e., maintenance selection, multilevel selection theory, species selection theory, evolvability)—and perhaps even a majority now supports them[6]. However, scientific fact and theory are based on the net opinion of *the consensus*. Dissenters still abound, and where applicable, I cite their dissenting opinions. To progress biological theory requires consensus. None of the aforementioned ideas have been forcefully argued to the point of creating any consensus within the evolutionary biology community, and they certainly have not been structured in conjunction with each other. A goal of this thesis is thus to convince the remaining skeptics that natural selection causes adaptation at multiple levels of biological organization since ecological insight has finally proved beyond any reasonable doubt the ontological realism of multilevel selection, and the philosophy of biology can help facilitate its smooth integration into modern evolutionary theory.

Thus, this thesis aims to elucidate the profound transitions that have overtaken evolutionary biology—and biology more generally—spurred by its recent synthesis with ecology. I then argue for its culmination using contemporary knowledge from the frontiers of philosophy to arrive at a novel perspective of the evolutionary process. Another implicit aim of this thesis is to make a significant scientific contribution using HPS methods and knowledge, in hopes of demonstrating the value of HPS to a broader scientific audience.

Just as the *Modern Synthesis* culminated in the overwhelming acceptance of natural selection theory and the unification of the biological sciences, my hope for the Second Synthesis is that it will finally put to rest the anachronistic and reductive model of natural selection, culminating in the overwhelming acceptance of a pluralistic theory of natural selection, as well as lead to the final ratification of biology as an autonomous science from the physical sciences.

[5] This sort of integrative approach is sorely missing from the scientific literature today. Perhaps this is because of the painstaking effort that undertaking such a project requires in the *publish-or-perish* mentality of academia, which values short-term success and quantity rather than the quality and comprehensiveness of scientific investigations. As my historical reconstruction will show, the fundamental shift in the 1980s evolutionary biology community stemmed from a greater emphasis on empirical realism, where meticulous longitudinal field studies profoundly transformed evolutionary thought. The best things in science take time—this seems like a cliché, but our academic environment is not conducive for long-term scientific progress (or, at the very least, is not *as conducive* for long-term success *as it could be*).

[6] Science communication has operated under the journal system for 350+ years now. Scientific fact and objectivity are based on the consensus. Yet, we still have no means of surveying the diversity of opinions or consensus, which are both important markers of scientific knowledge, despite living in a 21st-century world where there are no longer any limits to communication. This is a major problem for modern science and needs to change urgently.

History

To understand a science it is necessary to know its history

August Comte

Chapter 1 – A Brief History of the Philosophies of Science

The history of science shows us that scientists have constructed epistemological structures in the form of causal models (*theories* or *laws*) that have abstracted away from the innate causal complexity of the natural world. The sciences have since uncovered a natural world that is as rich and complex in its causality as it is irregular and indeterminate. In the biological sciences, we examine causal phenomena that occur on multicomponent, multilevel, and evolved systems while constructing causal models that are spatiotemporally restricted due to the capriciousness of surrounding ecosystems. Natural selection theory stands as the quintessential example of a modern theory that would benefit from transitioning away from past philosophies of science or concepts of causation that were tailored for an age when classical physics reigned as a paragon for the other sciences to follow, towards a pluralistic philosophy that enforces greater empirical realism and embraces multicausal/multilevel modeling to better suit its explanatory needs (Ch. 4).

History[7], if viewed as a repository for more than mere anecdote or chronology, alongside *philosophy*, if viewed as a method for knowledge construction that is founded on scientific empiricism and not *a priori* justification, can elucidate the anachronisms of modern science and procure a decisive transformation in scientific methodology, particularly in the biological and evolutionary sciences. In this chapter, I briefly examine the general influence that the underlying philosophies of science and concepts of causation have had on biological practice in the past and argue why such philosophies are no longer useful in the context of modern biology.

1.1 The History of the Philosophy of Science in Focus

Past philosophies of science have had a tremendous impact on scientific methodology, often directing the explanatory scope that the various sciences have taken in the past. Such philosophies can be convincingly argued to have motivated the enormous success of science and technology in the twentieth century. The study of which philosophies have inspired success is the primary occupation of the contemporary philosopher of science, deriving from the convention of the *Vienna Circle* (*circa* 1922-1936).

The radical philosophical movement that grew out of the Vienna circle called *logical positivism* accorded philosophy a new role. Constructing the ontological structure of the natural world now belonged to 20th-century science. The positivists thought that philosophy could once again contribute to the advancement of knowledge by being a method for analyzing scientific explanations and the logical structure of theories. Such a new method was argued to be grounded

[7] In this paper, I will focus on the history of ideas from within an academic and intellectual setting, not as if they were uninfluenced by external or sociopolitical factors, but to first elucidate the diachronic transitions in our knowledge that have recently ensued. This historiography may also appear hagiographical or linear due to its succinct nature, but the actual history is actually more complex. I merely use history to inform and contextualize my philosophical arguments, not to build a comprehensive historiography of the subject at hand. I leave that to the professional historians.

in the empirical observation of natural phenomena rather than the *a priori* reasoning of classical metaphysics, which made untestable claims and described phenomena in an ethereal reality. Thus, the philosophy of science was officially born as a separate discipline to that of *philosophy* and *science* because it primarily studied *scientific methodology*:

- What science is,
- How scientific methods differentiate from each other and other branches of knowledge,
- And what are the aims of science, or how scientists construct knowledge into theories.

The prescribed role for the philosophy of science was not to be as doctrine or as having its own subject matter to investigate but to act as an interpreter of scientific activity.

Positivist philosophy influenced future philosophies of science in the twentieth century (e.g., Hempel, 1965; Nagel, 1961). The positivists were particularly impressed with the logic and mathematics of classical physics, setting it as the standard for scientific success that the other sciences should try to imitate. This began a long tradition of *scientific unity* in the sciences, where scientists aimed to reduce the diversity of explanations to a small number of theories or laws at a privileged level of discourse, thereby "unifying science" both between and among disciplines (for more, see Fodor, 1974; Dupré, 1983; 1993; 1996; Sherman, 1988; 1989; Mitchell, 2003*:* 177). The strongest proposal of scientific unity came as an 'over-arching metascientifc hypothesis' called *epistemic reductionism*, which maintains that the unification of all scientific terminology, laws, and theories should be reducible to physics in the long run (e.g., Oppenheim & Putnam, 1958)[8]. In its weaker form known as *explanatory monism/reductionism*, scientific unity came to mean the favoring of one type of explanation or one fundamental level of explanation from which others can be derived or reducible to; what was often the result of emergent phenomena being reducible to lower-level events (Mitchell, 2003). However, the idea of scientific unity is largely untenable in the context of modern science.

1.2 Scientific Causation and The Modern Philosophical Movement Towards *The Disunity of Science*

The sciences have since unraveled a natural world far too complex in its causation to be accurately represented by the simplified, reducible, or idealized causal models built in the zeitgeist of *logical positivism* or earlier. In most, if not all, cases of scientific causation there are multiple causes, causal conditions, and interferers that influence effects at various levels of integration (Anjum & Mumford, 2018). Add onto that the immense irregularity and indeterminacy of fundamental processes found in physics (e.g., the quantum world), biology (e.g., mutational dynamics), or other sciences (e.g., complex social behavior patterns in psychology). Thus, the more we understand our universe, the more causally complex and less deterministic natural phenomena seem to be, which is the primary motivation behind the emerging philosophical notion of *multicausality* (Anjum & Mumford, 2018).

[8] Evolution has always maintained the image of being irreducible to physics and chemistry because of its metaphysical components. This is why Smocovitis (1992; 1996) argued that biology could only claim autonomy from the physical sciences after its integration with evolutionary biology in the synthetic era (1918-1957). However, biology still has remnants of philosophical reductionism riddled throughout its core, hence why it has never been truly autonomized until *The Second Synthesis*.

Yet from its onset, science has abstracted away from the innate complexity of the universe. Scientists have focused on finding monocausal or "absolute" phenomena (i.e., *laws*), screened off interferers, modeled causes in simulations and/or under simplified assumptions, isolated test subjects in constant laboratory conditions, experimented with similar or identical test subjects (e.g., *model species*), constructed causal models that only apply *ceteris paribus—ad infinitum* (Anjum & Mumford, 2018; Mitchell, 2003; 2009). Indeed, such abstraction or idealization is warranted in some instances to meet specific epistemic goals (Van Bouwel *et al.*, 2011). But our representational causal models in the form of scientific theories or laws should attempt to match the complexity of the natural world (i.e., be *externally valid*). This is therefore an issue of epistemology; an issue of how we construct and structure our abstract causal models to match natural processes.

In light of such issues, the philosophy of science has undergone a transformative shift in perspective over the last forty years. The history of science suggests that there has never been *one way to do science*, one underlying philosophy of science that was universally applicable across the diverse stretches of scientific interests. Such acknowledgements run contrary to the arguments and aims of *logical positivism*. Positivism has been replaced by a philosophical movement that calls for *scientific disunity* and *explanatory pluralism* to explain such causal complexity (e.g., Dupré, 1993; Hacking, 1996; Galison & Stump, 1996; Cartwright, 1999; Teller, 2001; Mitchell, 2003; 2009).

Between the sciences, it is useless to search for the lawful coextension of predicates from sciences at different levels, designating the causal phenomena that each science investigates as distinctive from the others, which is particularly true when comparing biological and physical phenomena[9] (Fodor, 1974). Within scientific domains, *explanatory monism* has consistently placed too much weight on one explanation or one type of explanation, leading to

Box 1: Why Causation is Important in the Sciences

If *causality is the cement of the universe*, as Hume famously quipped, then modern scientists are the architects endeavoring to reconstruct the blueprint of the universe through causal modelling. While suspicions of causation have arisen in various forms throughout the history of modern science, particularly within the realm of physics (Russell 1913*:* 193; Heisenberg, 1959, 82; Feynman, 1967, 147; Price & Corry, 2007; Norton, 2007, 14; Ladyman *et al.*, 2007, 3–4; French, 2014, 228; taken from Anjum & Mumford, 2018, 11), it is now generally accepted by most philosophers that science is conducted under the investigation of natural causes (Russel, 1948; Illari & Russo, 2014; Anjum & Mumford, 2018).

Causal interventions remain the basis of scientific experimentation. We would not be able to control, observe or predict using only a control group. Treatment groups warrant causal interventions. In the case of particle physics, huge and expensive colliders causally intervene by smashing atoms apart to view the smallest constituents of matter. And measurements in science also generally require causal affectation. For example, if presumed to be accurate, a voltmeter can determine the amount of stored energy in a battery which causes the movement of the hand across the dial in a causally determinate manner. If the hand were moving randomly all the time, whether connected to the battery or not, we would not think it was measuring the energy of the battery (Anjum & Mumford, 2018). The empirical commitment that scientists naturally accept is thus founded on a realist notion of causation.

Furthermore, if there is a discernible and generalizable trend of scientific progress available in the history of science, it is that we have gotten progressively better at predicting and manipulating natural phenomena, presumably because our causal models in the form of scientific laws or theories have become progressively more accurate and precise in their representation (i.e., external validity) of the complex causal fields underlying natural phenomena (a causal interpretation of Hilary Putnam's [1975] famous *no miracles argument* for scientific realism). Causality thus lies at the heart of scientific investigation because the understanding of natural phenomena in causal terms allows for more accurate scientific inferences, explanations, predictions, retrodictions, and manipulations—all of which are hallmarks of *good science* (Anjum & Mumford, 2018).

[9] With the possible exception of the explanatory overlap between the origins of life question, since it will likely entail a physical explanation.

gross oversimplifications or heavily idealized causal models.

It is this last philosophy that I will direct most of my attention to in this thesis, using the theory of natural selection as an example of an over-idealized and reductive causal theory that could be more externally valid in light of a philosophy of science that is grounded in *pluralism*, *multilevel, and multicausal explanations*. Logical positivism has thus failed because the utility of underlying philosophies varies *between* as well as *within* scientific disciplines.

Like most active problems in the sciences, this issue is deeply rooted in the topic of *causation*. Scientists often fight over the external validity of causal models because a more accurate representational model allows for more accurate scientific inferences, explanations, predictions, retrodictions, and manipulations (Illari & Russo, 2014; Anjum & Mumford, 2018). This is why causality is important to know and study in the sciences (see **Box 1**).

1.3 Historical Concepts of Causation in the Sciences

Following Newton, early concepts of causation were developed in concert with the explanatory aims of the physical sciences, thereby becoming tied to the idea of *causal, classical,* or *strict determinism*—that is, the idea that any given natural phenomenon has a preceding underlying cause that can be determined and precisely predicted given a known set of initial conditions that generally hold regardless of changes in space or time (see for more Dhar & Guiliani, 2010; Hoefer, 2016). This idea is characteristically *monocausal* and reductionistic in its approach, meaning that it focuses on finding *one cause behind an effect* (for more, see Anjum & Mumford, 2018*:* 70). Universal, exceptionless laws of absolute and monocausal phenomena became a paragon for the sciences to pursue.

Causal determinism still lives as an objective within the physical sciences today. Non-quantum physicists continue to search for monocausal absolute phenomena using precise mathematical equations ("laws") that intend to hold without exceptions in space and time. But many philosophers have argued that such pursuits are worthless. Nancy Cartwright (1983, 1999) has argued that simple physical laws like the law of universal gravitation are false. Many, if not most, physical objects are subject to forces other than gravitation and therefore do not behave in accordance with the laws of gravitation altogether (Dupré, 2001, 12). Horgan (1996) thinks that theoretical physics is becoming less "scientific" than it used to be, evolving into an esoteric, mathematical model-building exercise that has little contact with the natural world (found in Godfrey-Smith, 2003)—analogous to the enterprise of population genetics in biology, which I criticize in Chapter 2.

Since the days of Newton, however, the sciences have uncovered a natural world that is as rich and complex in its causality as it is irregular and random. In the 20th century, scientific discoveries such as quantum mechanics prompted new strategies to approach the messy causation inherent to the natural phenomena studied in most sciences (Anjum & Mumford, 2018). These advances yielded a new conceptualization of causation known as *adequate (*or *statistical) determinism*—that is, complex natural phenomena are governed by multiple causal forces and *chancy* processes, making the causal determination and prediction of these causal

events only probabilistic in space and time (which is to say that even the most accurate causal models can probabilistically predict future states). Apart from non-quantum physics, most sciences operate under this assumption since most natural systems are causally complex and partly non-deterministic yet deterministic enough to analyze using probabilistic methods (Joffe, 2013). A modern consensus among philosophers of science has therefore been reached that maintains causal determinism as the *exception* rather than the *norm* for most sciences (Illari *et al.*, 2011; Anjum & Mumford, 2018).

A major reason for this shift in perspective is that most, *if not all*, cause-effect relationships in the sciences are highly context-dependent or *not exceptionless*. Natural phenomena are complex, variable, and contingent on multiple interacting causes at multiple levels of integration (Salmon, 2002, 125[10]; Mitchell, 2003; Joffe, 2013). This rings particularly true within the "special sciences" of biology and the health sciences since most biological phenomena are highly spatiotemporally restricted, and deterministic law-making plays a smaller role in theory construction when compared to the physical sciences (Mayr, 1961; 2004; Fodor 1974, Rosenberg & McShea 2008). As Nobel laureate Max Delbruck once remarked:

> "a mature physicist, acquainting himself for the first time with the problems of biology, is puzzled by the circumstance that there are no 'absolute phenomena' in biology. Everything is time-bound or space-bound. The animal or plant or micro-organism he is working with is but a link in an evolutionary chain of changing forms, none of which has any permanent validity" (Delbruck, 1949: 173).

As noted here by Delbruck, the association between mutable organisms and the characteristic spatiotemporal restrictiveness of biological phenomena is not a coincidence. Instead, it is a defining feature of biology.

1.4 Causal Generalizations in Biology: *Nothing is a Constant but Change* in Biology

> "Today, the word law is used sparingly, if at all in most writings about evolution. Generalizations in modern biology tend to be statistical and probabilistic and often have numerous exceptions. Moreover, biological generalizations tend to apply to geographical or otherwise restricted domains. One can generalize from the study of birds, tropical forests, freshwater plankton, or the central nervous system but most of these generalizations have so limited an application that the use of the word *law*, in the sense of the laws of physics, is questionable" (Ernst Mayr, 1982: 19).

Biology is a lawless science by the nature of the phenomena it explores. Most causal generalizations in biology are contingent on a set of conditions bounded by space and time (Mayr, 1961; 2004; Beatty, 1995; Fodor 1974, Rosenberg & McShea, 2008). For example, in a high-temperature environment, one species of flour beetle (*Tribolium confusum*) nearly always displaces the other (*T. castaneum*). Recessive alleles that cause sickle cell anemia are more likely

[10] Another major reason why most models of cause-effect relationships are assumed to be highly context-dependent is because of selective bias—"Our choice of model decides what phenomena we regard as readily explicable, and which need further investigation" (Maynard Smith, 1987, 120).

in ecosystems with malaria due to the resistance that it confers when expressed in the heterozygote form. Causal generalizations are also made within the spatiotemporal contexts of life histories, as younger social insects tend to perform in-nest tasks while older individuals do outside jobs (for another example, see Price & Grant, 1984). Even Mendel's "law" of segregation is dependent on a causal evolutionary mechanism (i.e., sexual reproduction) and is subject to exceptions that are driven by space and time (e.g., meiotic drive). Thus, rather than view the spatiotemporal restrictiveness of biological generalizations as a defect when compared to the common law-making practices of physics—a mistake that several philosophers have made in the past (e.g., Smart, 1959; 1963)—we should instead see it *as a defining feature of biology.*[11]

In place of law construction, biologists construct causal models of biological phenomena in the form of representational concepts, theories, or causal mechanisms that are *restricted in space and time* (Sober, 1997; 2000; *sensu* "concepts" in Mayr, 2004). Such models are law-like in that they make predictive generalizations about what will happen if a certain set of conditions are satisfied by a system. However, unlike the phenomena studied in non-quantum physics, pinpointing the causal mechanisms behind biological phenomena is often a laborious task, as any one effect—especially at the level of the organismal *phenotype*—entails multiple interacting causes that act at multiple levels of organization. Thus, given the level of uncertainty and indeterminacy, causal models in biology tend to be probabilistic (e.g., the propensity interpretation of fitness), exception-ridden (e.g., the Price equation), and/or asserted *ceteris paribus* (e.g., the Hardy-Weinberg; for more, see Anjum & Mumford, 2018). A list of exhaustive conditions must usually be met for a causal model to be accurate and predictive, yet casual interferers can always intercede biological causation.

One reason our causal models are spatiotemporally restricted is that biological causation ensues at multiple levels of biological organization (Mitchell, 2003). Biological systems are rich in emergent properties at every level of biological organization—genes, cells, organisms, groups (e.g., insect colonies), populations, and entire ecosystems (Mayr, 2004; for more, see Lobo, 2008). Biological systems thus exhibit order in the way a whole is composed at multiple levels of biological organization, with a number and variety of causal processes within and between these levels (e.g., upwards and downwards causation, that are not simply reducible to causal actions at lower levels.

Nonetheless, the main reason why our models are spatiotemporally restricted is because of the connection between organisms and their environment. Biological systems are a product of their ecological environments, and *ecosystems are incredibly variable* (Grant & Grant, 2002; Hendry, 2017). Sudden and dramatic shifts of ecological variables cause consequent shifts in the relationships between key variables in populations or genotypes across different ranges of variation. An immutable biological system would not survive very long within an ever-changing ecology. This is the key insight to be described in the following sections. Genetic processing is only partly rigid because the errors generated create novel genetic variation, allowing for

[11] Here, I am not ruling out the possibility of universal or exceptionless regularities in biology, which is how a "law" is most commonly defined in science. Some may exist in biology, such as the Law of Increasing Complexity (see McShea & Brandon, 2010). The usage of the price equation as a *general schema* may be the closest epistemological tool we have to a "law" in biology (Luque, 2017). However, given what we know about biological causation, I am of the opinion that there is no such thing as a law in biology, and likely in the other sciences as well.

adaptation to changing ecological circumstances. Biologists thus deal with investigating and explaining more irregular cause-effect relationships than physicists, precisely because of the influences of ecology. Causal generalizations in biology are often heavily restricted to the ecological circumstances in which particular causal mechanisms operate.

Our causal models and methods used to study biological systems should thus reflect the causal complexity of biological systems and the natural vicissitudes of ecosystems. Yet for most of its history, biological and evolutionary theory has developed somewhat independently from ecology. The Second Synthesis between ecology and evolutionary biology has thus shed light on the various weaknesses of evolutionary theory developed within the context of positivist philosophy.

1.5 Chapter 1 in Summary

Philosophies of science, often expressed implicitly within prevailing scientific paradigms, have had a tremendous impact on how science was performed within the last few centuries. Philosophers invent new or better ways to match causal models to natural phenomena. Today, the movement to *disunify science* has moved the biological sciences away from causal determinism toward a probabilistic model of causation. Biological causation is exceptionally complex and often *lawless*, entailing causal processes at multiple levels of biological organization and across varying spatiotemporal contexts. Such an important shift in philosophies has been, in part, spurred by recent empirical findings from ecology.

Chapter 2 – *The Second Synthesis* Between Ecology and Evolutionary Biology

Theoretical and empirical efforts have had a tumultuous, and at times contradictory, history in biology. A stark chasm between theory and empiricism has enfeebled biological methodology since its nascence, starting with the fierce division between the *Mendelians* and the *biometricians* around the turn of the twentieth century and continuing through to modern times.

One reason for this divide is that we have not had the technological capacities or the reserve to systematically observe the evolution of species in their natural ecosystems over more extended periods until quite recently, thus hindering our capacity to develop externally valid causal models to match the natural vicissitudes of complex ecosystems. This is why it is commonly claimed that "research initiatives in ecology and evolution have periodically dated but never married (Hendry, 2017*:* IX)", or the stronger historical claim "curiously largely unnoticed is the fact that ecology also missed out of the Modern Synthesis (Pigliucci & Muller, 2010, 8)". To a truthful extent, these two disciplines have developed somewhat independently of one another for most of their history—ecologists and evolutionary biologists have published in different journals, attended different conferences, divided interdepartmentally, or separated along institutional lines (Bell, 2017; Huneman, 2019a).

However, I find the history to be more nuanced than what most authors imply. In the rare occasions where these two disciplines have *dated*, dramatic theoretical progress has resulted. Whereas ecology did not play a major role in the early development of evolutionary theory through the vehicle of population genetics, it did play a more significant role in the overall acceptance of the population genetic viewpoint of evolution, leading to the first major advancement of evolutionary theory since Darwin known collectively as *the Modern Synthesis* (*circa* 1918-1956[12]).

Yet the founding principles of population genetics—motivated by the philosophical movement of *logical positivism*—were already well-established in evolutionary theory when they first met ecology. The causal models deriving from this period were not accurate representations of the natural, causally complex biological phenomena that they were chartered to explain, and remnants of positivist reductionism are still riddled throughout modern evolutionary theory

[12] Historians vary in the dating of the Modern Synthesis. My start date, 1918, is motivated by Fisher's (1918) influential paper that was the first to demonstrate how continuous variation could result from discrete Mendelian characters, thus reconciling the long debate between the biometricians and the Mendelians. My end date, 1956, is more unusual and open to debate. There still exists substantial disagreement among historians over what constitutes the aims of The Modern Synthesis (see for more Huneman, 2019a); the most accepted is that the synthesis culminated in an overwhelming acceptance of a natural selection theory. This is why I hold 1956, the last of Bernard Kettlewell's (1955; 1956) influential papers that outline his field studies of the peppered moth, as the end date since this was the most widely touted empirical corroboration of the synthetic theoretical model, leading to the overwhelming acceptance of natural selection theory.

today. Population genetics has continued to model natural selection as a relatively uniform cause of evolution, acting similarly across ecological contexts, reduced to a privileged unit or level of selection, with individual fitness operationalized as a universal measure of selection *for all biological entities* in *every spatiotemporal context*.

What is truly exciting is that we are now living through another major synthesis (unrelated to what some have self-proclaimed as *the extended evolutionary synthesis*) prompted by the recent marriage between evolutionary biology and ecology (Schoener, 2011; Hendry, 2017). Without ecology, evolutionary theory was initially developed in an abstract vacuum that neglected the causal complexity of nature. Now in light of ecology, we are beginning to understand how evolution and selection unfold in nature, *over space and time*.

These advances are now beginning to reveal how selection varies in its strength, form, direction, and most recently at various levels of biological organization, all dependent on ecological conditions. Such advances have never been fully realized by theory, thus warranting a theoretical shift towards a pluralistic model of natural selection (Ch. 5 & 6). In the following, I historically reconstruct several of the major technological advancements, intellectual forces, and conceptual challenges that led to the Second Synthesis[13]. I wish to be explicit, however, that this is by no means a comprehensive historical account of the multifarious, subtle, and indirect steps that led to this recent synthesis. That undertaking would require a compendium of historical analyses on the scientific, philosophical, and sociopolitical influences that lie outside the scope of this thesis.

2.1 The First Theoretical/Empirical Divide: The Mendelians vs. The Biometricians

Before biology can ever be claimed to be its institutional form as *biology*, and indeed a step prior in biological history that indisputably led to the legitimization of biology as a reputable scientific discipline, was the fierce debate between the *Mendelians* (aka *saltationists*) and the *biometricians* over the basis of inheritance and its relevance in the evolutionary process.

As their name suggests, *The Mendelians*—e.g., William Bateson, Hugo de Vries, and later Thomas Morgan—were fierce supporters of Mendelian inheritance and the idea of *discontinuous variation*, that is, that variations are placed into discrete, individual categories like blue eyes or brown. The Mendelians were early visionaries in the field of experimental evolution, being the first to coin the term *mutation* after their experiments revealed the heritable transmission of large-scale changes (i.e., *saltations*) passed down to progeny.

Their rival faction, *the biometricians*—e.g., Karl Pearson, Sir Francis Galton, and Walter H. Weldon—focused more on the statistical studies of phenotypic variation and therefore argued for the idea of *continuous variation*, which are variations distributed along a continuum like height or weight. The vivacious debate that ensued in the first two decades of the 20th century led *the*

[13] Performing a modern historiography such as this is no easy task and leads the hopeful historian to recognize the diversity of opinions that have likely always existed in every period of history. This is, in part, the crux of recent historical movements away from a hagiographic and presentist methodology toward a more contextualized approach.

biometricians to claim statistical and mathematical rigor, whereas *the Mendelians* claimed to have a greater knowledge of biological processes.

The result of this great and vivacious debate? A peculiar tie, as both parties came out somewhat correct when the population geneticists—R.A. Fisher (1930), Sewall Wright (1931), and J.B.S. Haldane (1932)—combined the two approaches and showed how natural selection could act on both types of variation to cause adaptations at the population level, thus initiating the start of the first synthesis[14].

Why is this historically important? Because it marked the first clear division between theoretical and empirical efforts in biology, with the biometricians wielding theoretical and mathematical rigor over empirical evidence, and the Mendelians seeing experimental evidence as tmore revealing of how biological processes play out in nature. Although the epistemic content of their confrontation was resolved in the first synthesis, their lines of distinct methodologies started two rival traditions within biology.[15]

From this point onwards, there would always be a theoretical wing and an empirical wing in biology, with some crosstalk happening between the two, but never to any unified extent that would allow for the construction of externally valid causal models. This divide thus continued well into the twentieth century, particularly when we look at the history of ecological insight within an evolutionary sphere.

2.2 The Role of Ecology from Darwin to the First Synthesis

Many biologists seem to forget that Darwin was himself the logical antecedent of a modern ecologist, a *naturalist*, who conceived of natural selection theory after performing strenuous fieldwork[16]. His observation of the local adaptation of finches to the natural conditions of the disparate Galapagos islands led him to conclude that different ecological circumstances produce varying evolutionary and selective outcomes. However, he saw the evolutionary process as long and gradual, proclaiming "we see nothing of these slow changes in progress, until the hand of time has marked the long lapse of ages" (Darwin, 1859, 84).

Due to the Darwinian notion of *gradualism*, evolutionary dynamics were thought to be nearly impossible to directly observe until one member of the biometric faction, Walter H. Weldon, established the first observational study of evolution in natural populations using the land snail *Clausilia laminate*[17]. Weldon found no difference in the mean value of the radius of shells between juvenile and adult individuals, but the standard deviation was consistently greater in juveniles, demonstrating that extreme individuals must have been removed by selection (i.e.,

[14] Interesting side note: two of the most important movers of modern genetic theory—Mendel and Fisher—conducted their research outside of the traditional academic sphere. This is one reason why we should normalize independent research in modern science.
[15] This is a grave oversimplification, of course, but it contains an important kernel of truth for the history of biology.
[16] As Michael Ruse notes, Darwin conceived of natural selection as a causal theory in order to conform to the predominant philosophies of science of his time (Ruse, 1979, chap. 7).
[17] This is also around the time that Hugo de Vries established one of the first experimental studies in evolutionary genetics leading to our first understanding of mutational dynamics.

stabilizing selection). In one stroke, Weldon had unambiguously observed natural selection acting in contemporary populations and precisely estimated its force using ingenious quantitative methods that mirror those of modern times (Bell, 2009). He would eventually publish his results (Weldon, 1901; 1904; di Cesnola, 1907), but alas, his work appears to be virtually forgotten after his untimely death in 1906, as ecological studies were pushed into the background with the coming rise of theoretical population genetics in the 1920s and 30s (Bell, 2009). Not one founder of population genetics would cite Weldon's work, or other early ecological analyses for that matter (e.g., Hermon Bumpus).

However, this is where I diverge from most modern historiographies. Historians and biologists alike commonly lump the development of population genetics in with *the Modern Synthesis* (e.g., Huneman, 2019a; 2019b; Provine, 1971). They also commonly claim that ecology played a smaller role in the Modern Synthesis (e.g., Futuyma, 1986; Bell, 2009; Pigliucci & Müller, 2010; Schoener, 2011; Pianka, 2011). For example, Pigliucci (2009*:* 136) remarked, "Less well understood is the equally puzzling fact that the Modern Synthesis basically ignored ecology (despite a strong research program in evolutionary ecology), so much so that ecologists and evolutionary biologists now hardly talk to each other, and we have no organic theory of how community and ecosystems ecology are connected to evolutionary biology." Little mention was also made to ecology in Mayr & Provine's (1980) firsthand account of *the Evolutionary Synthesis*[18], as well as Julian Huxley's (1942) *Evolution: The Modern Synthesis*[19]. Yet while I find it to be historically accurate that ecology *did not* play a major role in the initial development of population genetic theory, it did however play a major role in the Modern Synthesis and the eventual acceptance of a population genetic viewpoint of evolution.

The foundations of population genetics built by R.A. Fisher (1918; 1930), Sewall Wright (1931), and J.B.S. Haldane (1932) were initially obscured by the fact that they were almost exclusively theoretical, with little empirical corroboration (besides a few experimental studies referenced), and omitted major issues such as speciation that were of great import to empirical biologists (Ayala & Fitch, 1997). Thus, the population genetic viewpoint of evolution went largely uncelebrated among the various (at this time *separated*) fields of evolutionary biology outside of theoretical genetics; the most influential population genetic paper ever published, Wright's (1931) paper, had an average citation of 3.6x per year for the first ten years. However, this would change with the publication of *Genetics and the Origin of Species* by the doyen of evolutionary genetics, *Theodosius Dobzhansky* (1937).

Historians and participants of the Modern Synthesis are in agreement that Dobzhansky's *Genetics* was crucial in taking the population genetic viewpoint of evolution mainstream and "triggering" the Modern Synthesis (Mayr, 1982; Mayr & Provine, 1980; Huneman, 2019a). In *Genetics*, Dobzhansky advanced the population genetic viewpoint of evolution by corroborating their (primarily *Wright's*) theoretical arguments with empirical evidence from both the laboratory and the field—marking the first major bridge extended not only between naturalists and experimental geneticists but also between the theoretical and empirical traditions of the time.

[18] It should be noted that E.B. Ford, the founder of ecological genetics, offered some brief reflections near the end of this thesis on the tenuous relationship between the synthesis and ecology.

[19] In *Evolution: The Modern Synthesis*, Huxley did mention several times the need to link evolutionary biology with ecology.

Surprisingly forgotten is that Dobzhanksy's *Genetics* was steeped in ecological traditions, even if it is rarely considered within the ambit of *ecology*.[20] As L.C. Dunn rightly stated in the preface, the book symbolized "something which can only be called the Back-to-Nature Movement." Dobzhansky observed fluctuating gene frequencies in natural populations of the wild vinegar fly (*Drosophila pseudoobscrua*), then combined his fieldwork observations with the latest experimental findings from evolutionary genetics. He centralized his book around the key finding *that natural populations harbor an extensive amount of genetic variation*[21], thus providing ample variation for natural selection to cause adaptive evolutionary change when confronted with ecological pressures[22]. Future editions of *Genetics* (1941; 1951) would also afford a greater role to the study of selection in natural populations by incorporating new results from his observational studies performed in the 1940s[23].

Following the publication of Dobzhansky's first *Genetics*, the virtue of unifying theoretical genetics with ecology became evident to all parties. Population geneticists quantified evolution and distilled evolutionary variables into a measurable and testable framework that allowed for the comparison of early ecological findings (Smocovitis, 1992). Now famous observational studies were performed in this vein that tracked the gene frequency changes of populations in the short-term and used population genetic equations to determine whether mechanisms such as selection or drift were at play (see for an extended list Millstein, 2012). For example, between 1941 and 1948, Dobzhansky and the population geneticist Sewall Wright collaborated on a series of influential papers in the journal *Genetics* under the general heading "The Genetics of Natural Populations (1941-1948; V, VII, X, XII, XV)". In this series, Wright would interpret and calculate the selection coefficients of Dobzhanksy's data that he obtained in the field (e.g., Wright, 1943).

In a similar symbiotic relationship to that of Dobzhansky and Wright, R.A. Fisher collaborated with his student, E.B. Ford, to found the discipline of *ecological genetics*—the "taking of

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[20] Once asked in a letter by Mayr what his crowning scientific achievements were, Dobzhansky replied with three: (1) the transitioning of studying Drosophila from the laboratory to the field (because of the greater empirical realism) afforded by ecological analyses); (2) observation of cyclic changes in the frequencies of certain inversion polymorphisms in natural populations (because of his first achievement); (3) his idea that "a population can cope with diversity of environments either by having genetic variety or by having genotypes with adaptively flexibly manifestations" (Dobzhansky, 15 Dec. 1970; found in Carvalho, 2019).

[21] It is important to note that in the 1940s, evolutionary biologists did not have the molecular techniques to quantify and determine levels of genetic variation in natural populations. Most analyses were done by measuring morphological characters or chromosomal inversions. Dobzhansky preferred using the latter, as he measured five different third chromosome inversions (Standard, Arrowhead, Chiricahua, Tree Line, and Santa Cruz) in three localities over four years. He found considerable seasonal variation in these frequencies, which led him to suggest that these were not random fluctuations but represented combinations of alleles in each inversion which improved fitness in different seasons: "The available data seem to fit best a fourth hypothesis, which assumes that the carriers of different gene arrangements in the third chromosome have different ecological optima" (Dobzhansky, 1943; found in Mueller, 2019). His early recognition of evolvability will be discussed in Ch. 6.

[22] This would become a key finding for the subsequent approval of the integral role of natural selection in evolutionary theory; more on this in the next chapter.

[23] Interestingly, Dobzhanky also noted that natural populations underwent significant and regular changes in gene frequency aligned with seasonal change, therefore challenging the Darwinian notion of gradualism. But this observation was again discarded by the consensus, as most participants would come to endorse gradualism by the end of the synthesis (Jepsen, Mayr, & Simpson, 1949).

(population) genetics into the field" to understand how natural selection performs in real ecological settings, as Ford would later reflect (Mayr & Provine, 1980*:* 338)[24]. Ford performed key ecological analyses using Fisher's statistical methods to measure the changes in gene frequency and the intensity of selection in natural populations, all in hopes of confirming Fisher's theoretical predictions (e.g., Fisher & Ford, 1947). Classical studies, such as Bernard Kettlewell's (1955, 1956) famous peppered moth (*Biston betularia*) study, were performed in this tradition that eventually corroborated population genetic theory and solidified the position of natural selection as a major evolutionary mechanism (see for more Millstein, 2012).

The first synthesis therefore culminated in the overwhelming acceptance of the population genetic viewpoint of evolution and natural selection theory[25], but only because of the empirical corroborations made by early ecological analyses (Huneman, 2019a). Nevertheless, despite these few instances where theoretical modeling intersected with early ecology, regardless of how influential these rare encounters were, *evolutionary ecology* went largely unnoticed and underdeveloped in the synthetic era (see for more reasons why Futuyma, 1986).

The direction of scientific verification in this era went from theoretical to empirical but rarely *vice versa*. Dobzhansky, Ford, and other ecologists performed key observational analyses that confirmed the theoretical predictions of the population geneticists using population genetic equations but rarely used observational findings to develop new theory (Huneman, 2019a). Ecology, and the empirical commitment that comes with viewing populations in their natural habitats, therefore played little to no role in the initial theoretical development of population genetic theory but played a much larger role in the subsequent approval of the population genetic viewpoint of evolution *and* natural selection theory.

Ford would later note this initial disconnect between theory and empiricism in his famous book *Evolutionary Genetics*:

> It is a surprising fact that evolution, the fundamental concept of biology, *has rarely been studied in wild populations by the fundamental techniques of science, those of observation and experiment. Consequently, the process has seldom been detected and analyzed in action*. However, I have for many years attempted to remedy that omission by a method which has in fact proved effective: one which combines fieldwork and laboratory genetics…. The fieldwork needed in these investigations is of several kinds. It involves detailed observation…having strict regard to the ecology of the habitats. Also it

[24] It is important to note that several historians have distinguished between two major schools of thought following the Modern Synthesis (e.g., Depew, 2011), one that was a "stricter and less pluralistic Darwinism" referred to as the hardening of the Modern Synthesis (Jay Gould, 2004*:* 46) that primarily convened in the UK, and an American school that was more open to the possibility of pluralism (Smocovitis, 1996; Depew, 2011).
Depew (2011) forcefully argued that there were two syntheses: one school that operated under the philosophy of adaptationism in the UK such as Fisher and Ford, and another that was intrinsically more pluralistic such as Wright, Dobzhansky, Mayr and Huxley. Here I will not go into greater depth on such considerations, for readability purposes.

[25] Historians disagree about what is meant by the Modern Synthesis, or what exactly differentiates a scientific synthesis from a revolution. The Journal of the History of Biology recently devoted a special issue to this topic, but more work will certainly need to be done to achieve any sort of agreement on this matter. See Huneman (2019b) for more.

> often requires long-continued estimates of the frequency of genes or of characters controlled on a polygenic or a multi-factorial basis. (Ford 1964*:* 1; emphasis added)

Alas, Ford's vision for a new methodological emphasis on *empirical realism*—that is, designing empirical studies that match natural settings—would not immediately manifest. Most of these early observational studies of selection in natural populations were attributable to anthropogenic influences (e.g., industrial melanism, insecticide resistance, heavy metal tolerance), which were believed to enact a much stronger force of selection than natural selection in the wild.

Thus, while early evolutionary ecologists such as Dobzhansky and Ford whittled away at the Darwinian notion of *gradualism*, evolutionary and ecological processes were still considered by most to play out on such different timescales that their dynamics were largely seen as incommensurate for most of the twentieth century (e.g., Slobodkin, 1961; Jepsen, Mayr, & Simpson, 1949)[26]. But the creeping realization that evolutionary processes may unfold on ecological timescales supervened in the latter part of the twentieth century, making the systematic study of selection in natural populations not only a methodological possibility but a top research priority by the 1980s (Bell, 2009). Yet by this time, the central principles of evolutionary theory would already be well-entrenched by population genetics.

2.3 The Development of Population Genetics in the Zeitgeist of *Logical Positivism*

Before the Modern Synthesis (*circa* 1918), evolutionary biology was largely seen as an underdeveloped and immature science[27], support for natural selection theory was marginal[28], biological knowledge was deeply divided along disciplinary lines, and in the larger context of science, a philosophical movement was brewing that would administer a decisive blow to the old ways of doing science (i.e., as natural *history* or *philosophy*) and biology (e.g., *vitalism*). After the Modern Synthesis (*circa* 1956), natural selection was a universally acknowledged mechanism of evolution, biological knowledge was integrated into a coherent and unified theoretical framework, and evolutionary biology was finally seen as a respectable scientific discipline (Smocovitis, 1992; 1996).

Indeed, the development of population genetics played a central role in these transitions, as Beatty (1986*:* 125) noted: "the core of the synthetic theory is pretty much just the theory of population genetics." But sorely omitted from most historiographies are the intellectual forces that motivated population genetics and why its development was viewed as such an important transition in early 20th-century science.

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[26] As rightly noted by Futuyma (1986), the ecological analyses performed by Dobzhansky and Ford convinced several key figures of early evolutionary ecology that ecological and evolutionary processes may play out on the same timescales. However, the Darwinian notion of gradualism had a pervasive following in evolutionary biology for most of the twentieth century, particularly in its theoretical wing of population genetics.

[27] As the Harvard physiologist William John Crozier told his students, "Evolution is a good topic for the Sunday supplements of newspapers, but isn't science: You can't experiment with two million years!" (Taken from Smocovitis, 1992, 16).

[28] What the historian of science Peter J. Bowler referred to as '*The Eclipse of Darwinism*' (Bowler, 1983).

A rare historical analysis by V. B. Smocovitis (1992; 1996) filled this gap in our knowledge by elucidating how the philosophical movement to *unify science* in the early twentieth century—i.e., *logical positivism*—infiltrated the biological sciences and helped spur a movement to unify biological knowledge[29]. As she notes, the adoption of a robust mathematical program that quantified evolution (i.e., population genetics) lent evolutionary biology a new legitimacy within the broader intellectual zeitgeist of positivism. A new biological methodology was to be fashioned after the "acceptable" sciences of Newtonian physics and chemistry while also allowing biology to preserve its supposed autonomy from these sciences.

All three of the founders of population genetics attempted to bring biology on par with the physical sciences and drew explicit exemplars from the exact and rigorous sciences. For example, Fisher clearly stated his intent to model evolution after physics and chemistry in *The Genetical Theory of Natural Selection* (1930)—where he outlined his "fundamental theorem*"* of natural selection as the biological analog of the second law of thermodynamics. J.B.S. Haldane and his father, J.S. Haldane (1931), were also vociferous supporters of the *Unity of Science Movement*, with the father Haldane going so far as to note that biology would eventually become reducible to physics.[30]

Dobzhansky also followed suit, focusing his analyses on genetics since it remained the material basis of evolution. As he later would note in his oral memoirs:

> "Genetics is the first biological science which got in the position in which physics has been in for many years. One can justifiably speak about such a thing as theoretical mathematical genetics, and experimental genetics, just as in physics. There are some mathematical geniuses who work out what to an ordinary person seems a fantastic kind of theory. This fantastic kind of theory nevertheless leads to experimentally verifiable prediction, which an experimental physicist has to test the validity of. Since the time of Wright, Haldane, and Fisher, evolutionary genetics has been in a similar position (Dobzhansky, 1962, 500-1)."

Again noted here by Dobzhansky, the empirical practices of evolution aimed to confirm the theoretical predictions of the "mathematical geniuses," similar to the methodology of the physical sciences that, up until this point, had produced the greatest successes that science has ever seen.

Smocovitis summarized these advancements:

> "Evolutionary change would thus be constructed on models of physical change so that evolution would demonstrate law-like regularities analogous to the law-like regularities in Newtonian physics…The 'evolutionary synthesis,' held by commentators to involve the synthesis between 'genetics and selection theory,' can be reinterpreted as the bringing

[29] For a counter opinion, Joe Cain (2000) gave a surprisingly unfavorable review of Smocovitis' Unifying Biology (1996), which led Smocovitis (2000) to adequately defend her position.

[30] Most biologists and philosophers of biology of this time sought a middle ground between physics and biology, advocating for a more rigorous biological methodology fashioned after the physical sciences, but one that was irreducible to physical phenomena.

> together of the material basis of evolution (the gene) with the mechanical cause of evolutionary change (selection), to make a mechanistic and materialistic science of evolution that rivaled Newtonian physics while still preserving the autonomy of the biological sciences…As natural selection became measurable and testable, and came to seen as a causo-mechanical explanation for organic change, much of the metaphysical and speculative status of the phenomena came to be removed" (Smocovitis, 1992: 21-24).

The result of such intents was the complete quantification of evolutionary theory, or the mathematical formalization of complex evolutionary forces into simplified, quantifiable, and abstract causal models that mimicked the law-building pursuits of physics. This new methodology was so successful that it would eventually become the norm for theoretical research and conceptual construction for the majority of the twentieth century (as rightly recognized by Müller *et al.*, 2019).

Logical positivism and the *Unity of Science Movement* thus motivated the development of population genetics; ecological analyses corroborated the population genetic viewpoint of evolution; and, in turn, population genetics ensured the stature of evolutionary biology in modern science. Yet while population genetics received all the benefits from positivist philosophy, in retrospect, it also suffers from many of the same issues described in **Chapter 1**, such as the neglect of the complex causal dynamics typically found in nature.

2.4 An Historical Critique of Population Genetics

> "Whereas it is mainly ecology that tries to provide source laws for natural selection, the consequence laws concerning natural selection are preeminently part of the province of population genetics. It doesn't matter to the equations in population genetics *why* a given population is characterized by a set of selection coefficients, mutation and migration rates, and so on. These values may just as well have dropped out of the sky" (Sober, 1984*:* 59).

Today, more than 90 years after its inception, the primary causal structure of evolutionary theory built by population genetics remains surprisingly untouched (Okasha, 2016)—of course, with theoretical additions, new emphases, and updates attached to its theoretical core since then (Futuyma, 2017a; *forthcoming*; Millstein, 2012).

This is why recent papers have implicitly referred to the population genetic view of evolution as *standard evolutionary theory* (see Scott-Phillips, 2013 or Dickens & Dickens, *forthcoming*; e.g., Crow & Kimura 1970; Hartl & Clark 1997; Lynch, 2007a; Hamilton, 2009); that is, evolution ensues as a change in allele frequency in a population, from one generation to the next, as the consequence of four major evolutionary causal processes: *natural selection*, *genetic drift*, *mutation*, and *migration* (e.g., Futuyma, 2017b). Population geneticists construct abstract mathematical models that aim to represent the changes in the genetic variation of populations over time via these four major causal processes (or *five*, if we include *assortative mating*). As Scott-Phillips *et al.* (2013: 1232-3) put it, "the latter two (processes) generate variation; the first two sort it. One of these processes, natural selection, sorts this variation in such a way that, over

Box 2: Drift as a Zero-Force State

Philosophers of biology have recently stressed the importance of understanding evolution and natural selection in physical, causal terms, with philosophical research inventing a novel model of causation for drift and natural selection. Sahotra Sarkar (2011) superbly argues that drift is not a cause of evolution, but rather a state in which no causation of adaptive evolution ensues, or a zero-force state of evolution (see for more Sober, 1984; Millstein, 2017). In fact, methodological analysis in molecular evolution is predicated on the assumption that drift *is the zero-force state of evolution*, which is to say that systems left alone drift, or what is known as *neutral theory*. Systems may undergo changes of state without any causes operating, simply due to the background conditions operating within a system.

For example, the conditions that are thought to bring about drift are a lack of selective pressure and a decreased population size (Sarkar, 2011). It is established that (i) the effective population size is generally correlated with genetic variance, that is, smaller populations tend to have lower genetic variance and thus drift (Kliman *et al.*, 2008; c.f., *Lewontin's Paradox*; Roberts, 2015). It is also established that (ii) the causal efficacy of natural selection is dependent on the standing variation of a population (from Fisher's *fundamental theorem*). When viewing drift as a zero-force state, it therefore seems logical to conclude from premises (i) and (ii) that genetic variance is the dependent factor of drift, and not population size, since size is simply a measurement (see for more Millstein *et al.*, 2009), while standing variation appears to be the causal reason why population size matters. Substituting out population size as a dependent factor of drift, the lack of causation from natural selection seen in drift-states should instead be considered as a consequence of: (1) low standing variation whereby the causal efficacy of natural selection is greatly reduced, or (2) a lack of selective pressure acting to cause (Sarkar, 2011). Drift thus becomes an evolutionary state in which there is no causal efficacy or no causal agents of evolution are acting on evolutionary systems (which is not to say that evolution *cannot happen*, but that it does not happen in an adaptive direction).

The first consequence (1.) is precisely the reason why small populations are vulnerable, because their evolvability is relatively low and their probability of fixating deleterious variations is high. Theory predicts that species with more standing variation are at a lowered risk of inbreeding depression, have increased fitness benefits, and hold more evolutionary potential than species with limited variation (Sherwin & Moritz, 2000; Frankham *et al.*, 2002). It follows that high variation and selective pressure are necessary conditions to move evolutionary systems out of drift-states and allow natural selection to cause adaptive evolutionary change, although this is no guarantee that natural selection will cause adaptive evolution if these conditions are met, only that they probabilistically could—i.e., they are not sufficient conditions for natural selection, only necessary conditions. Moreover, small populations are more prone to drift and fixate deleterious mutations *because* there is insufficient variation at any given locus, therefore impeding the causal efficacy of selection to purge deleterious alleles. While this interpretation of drift is, for the time-being, only a forethought, I think it explains more natural phenomena in greater depth and organizes evolution into a formal model of causation.

time and on average, genes that enhance fitness are disproportionately retained at the expense of those that decrease fitness, and the result of this is adaptation." Population geneticists then extrapolate hypothetical conclusions about the likely patterns of genetic variation in actual populations and test their conclusions against empirical data (Okasha, 2016).

In the eyes of many practicing population geneticists, population genetics remains "the cornerstone of modern evolutionary biology" (Michod, 1981, 2; e.g., Lynch, 2007a). Yet while population genetic theory has weathered a maelstrom of criticisms in the twentieth century, I think the proportion of evolutionary biologists who question the undue status of population genetics on evolutionary theory has now reached a breaking point, precisely because of the discontents with its implicit reductionism and abstract modeling. Many evolutionary biologists, particularly in fields rich in empiricism, such as evolutionary ecology, have come to realize that "models of genetic changes in populations do not provide us with much illumination of the way in which populations evolve" (Dupré, 1993*:* 138). These recent points of contention are further

supported by the historical fact that early population genetic models were initially constructed in an abstract vacuum without much empirical input.

To start, early population genetic models made many simplifying assumptions that abstracted away from the natural complexity of evolutionary systems. Early models viewed the evolutionary dynamics of populations as infinitely large, sexually reproducing, and randomly mating with Mendelian heredity (Millstein & Skipper, 2007; Otto, 2009; Nei, 2013). However, natural populations are not infinitely large, they often nonrandomly mate, rates of sex have been observed to vary, and genes clearly do not follow perfect Mendelian patterns (e.g., epistasis, incomplete dominance, etc.). Therefore, such dangerous assumptions made it difficult to model certain evolutionary phenomena that did not fit within the stringent conditional clauses of these early models, such as sex, to be discussed in the next chapter (Otto, 2009; Meirmans & Strand, 2010).

Yet perhaps the greatest overstep of the population genetic model has been the viewing of the causal processes of evolution as acting independently from one another under conditional clauses asserted *ceteris paribus* (i.e., monocausality). Indeed, each causal process does cause allele frequency changes in populations in statistical terms. But they do not fall into ideal, delineated causal processes that cause evolutionary change independently of one another when applied to nature (Caroll & Fox, 2008). For example, as I will evince in the next chapter titled *The Paradox of Adaptive Variation*, *de novo* mutation and standing variation are likely modified and caused by natural selection, thus calling for a reciprocal model of causation rather than the historical monocausal model of causation contemporary to population genetics.

Likewise, it should be obvious that each causal process does not cause evolutionary change similarly to the others. For example, drift is not a cause in the same way that selection is a cause, and it may not be a cause of evolution after all but rather a default state of evolutionary systems (see **Box 2**). Alternatively, take gene migration as another example. When we view gene migration from a higher level of perspective, e.g. the species level, then gene migration does not directly introduce novel variation similar to the mutation process. Instead, the gene migration shifts this variation (Brown & Pavlovic, 1992; **Figure 1.1**). Within this same perspective, sufficient migration between populations often *precludes evolutionary change* by maintaining genetic similarity between populations rather than causing evolutionary change through genetic divergence (Slatikin, 1994). So, processes that we have always assumed as *causes of evolution* may not be causes at all, or at the very least, we need a more

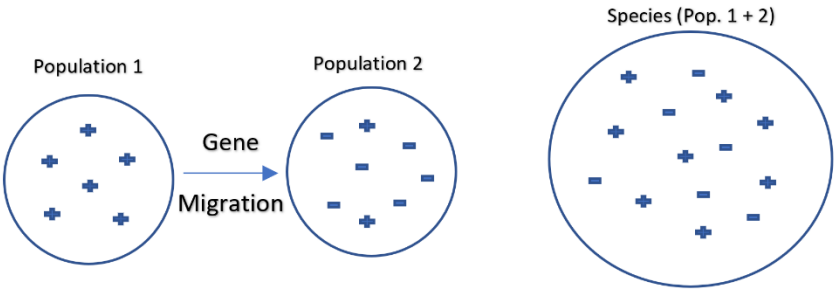

Figure 1.1: Despite sufficient gene migration from population 1 to population 2, thereby providing novel genetic variation for population 2, this does not introduce new variation when we broaden our perspective to the species-level.

nuanced reading of what it means to be a cause of evolution than typically offered through a population genetic lens.

Reducing evolution to fundamentally a process that produces changes in allele frequency over time is thus problematic because we are forced to accept some dangerous assumptions about causation (e.g., monocausality) that limits our causal explanatory scope to *within populations*. Moreover, limiting our evolutionary scope to *within populations* thus sets specific abstract conditions under which to view the causal processes of evolution (Pigliucci, 2008a), which oversimplifies the causal dynamics of each respective process. However, early 20th-century technological limitations also caused population and evolutionary geneticists to be confined to performing within-population analyses. It was nearly impossible to study the extent of genetic variation between populations using Mendelian methods—which only became possible after the advent of proper genome sequencing techniques in the 1980s. Evolutionary research was therefore executed almost exclusively by studying allele frequency changes *within populations* rather than *between populations* (Nei, 2013). This is one reason *relative fitness* is the most common metric of natural selection used in population genetics and mainstream evolutionary biology, compared to the measurement of *absolute fitness* that is often used in ecology (Bell, 2017). These technological limitations and simplifications ultimately restricted our causal models of evolutionary dynamics to *within populations over shorter-time scales*.

Such criticisms also remain true for understanding the primary cause of evolution, *natural selection*. In the twentieth century, the causation of natural selection was primarily modeled using simple organisms: *E. coli*, fruit flies, mice, and other asocial insects and vertebrates in which discrete individuals can be easily identified and counted. The explanatory extrapolations that were drawn from observing these simple organisms, along with the technological limitations described above that led to a focus on within-population analyses, therefore painted a limited, reductionist, and singular causal picture of natural selection in which natural selection was seen to only take place at the level of the individual organism (Gould & Lloyd, 1999). In reality, biological systems are rich in emergent properties because newly isolated properties can emerge at multiple levels of integration (Mayr, 2004). In many instances, it is also nearly impossible to delineate an 'individual' from a group or species, such as bacterial colonies, cellular slime molds, mycelial fungi, clonal plants, and colonial invertebrates such as coral, anemones, bryozoans, and ascidians (Folse III *et al.*, 2010). Explanatorily reducing natural selection to a single unit or level has thus limited our causal models of selection dynamics, excluding how natural selection works at multiple levels of biological organization over longer timescales (Okasha, [2006]2013).

Using individual fitness as a metric for selection has thus concealed other higher-level fitness components that are beginning to be revealed in the literature, such as *evolvability* (Graves & Weinreich, 2017).[31] It is established that environmental changes shift the optimum phenotype

[31] In a blog post published in *Scitable* by Nature Education, Sedeer el-Showk perfectly captures the sentiment I am attempting to express: "In my opinion, the gene-centered population biology view of evolution often fails to appreciate that fitness is just a metric. By treating changes in gene frequencies as the heart of evolution rather than as a readout of the process, this approach risks oversimplifying evolution in the interest of idealism. Fitness isn't a property of a given gene or genotype; it's always contextually dependent on the interaction between the gene of interest and a range of other factors. While I appreciate the oft-quoted importance of genes as fundamental units of replication, I think it's a mistake to confuse the process of evolution with keeping count of replicators. This

away from the mean phenotype thereby reducing mean fitness by causing a phenotype-environment mismatch (Hendry *et al.*, 2018). Natural selection appears to shift its adaptive interests away from the genetic viability or survivability or fecundity of individual organisms to the evolvability of populations when experiencing a fitness valley (more on this in Ch. 5). Natural selection does not invariably reach for higher fitness peaks *only* but also *for the ability to traverse and explore the adaptive landscape* (i.e., evolvability). Conceptualizing fitness in this way marks the recent shift in thinking away from *natural selection as a fitness maximizer*[32] (e.g., Galor & Klemp, 2019; Mittledorf & Martins, 2014; Birch, 2016). Natural selection does not invariably reach to maximize individual fitness irrespective of ecological context, as adaptive interests appear to shift along with environmental change. Individual fitness is therefore inadequate as an adaptive propensity/realized metric of selection because it fails to capture the complex causal dynamics of selection (a) acting at higher levels of biological organizations and, relatedly, (b) following changes in environmental contexts.

When taken together, population geneticists have largely failed to produce any major advancement in our knowledge of evolutionary dynamics because they have abstracted away from the causal complexity of natural evolutionary systems. This becomes doubly true in evolutionary considerations of long-term evolutionary phenomena, such as species extinction or speciation (Millstein & Skipper, 2007), as well as *evolvability*, to be later shown in Chapter 5.[33] The causal workings of evolution are so much more intricate than their mathematical models allow for, resulting in gross oversimplifications and ambiguities of theory that do not match the complex causal relations that are only recently being revealed in the natural biological world.[34]

I want to make clear that I am not arguing that population or quantitative genetics are useless ventures. There is a time and place for simplified, reducible, monocausal modeling, like when we need to standardize empirical findings or simplify the common core of evolutionary theory (which is useful for instruction). However, I reject the monolith of population genetics and its default yet outdated methodological approach to representing biological phenomena with idealized mathematical models, which then treat these models as explicit and accurate representations of the evolutionary process as they are found in nature. Population genetics is not

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approach has certainly generated valuable insights, but such a strict reductionist approach can also generate unnecessary constraints. Realizing that fitness is simply a metric of the underlying process of natural selection does more than just liberate evolutionary biology from false accusations of circular reasoning; it also provides the intellectual space to discuss and consider things like macro-evolution and selection operating at different levels, subjects which seem to be an endless source of controversy and debate, and which touch on aspects of theoretical & experimental biology as well as philosophy" (El-Showk, Nov. 10, 2014).

[32] The notion of natural selection as a fitness maximizer, exemplified in Fisher's *Fundamental Theorem* and Wright's *Adaptive Surface*, has always been questioned. The ecologist Simon Levin (1978, 1983a) noted that, "the conclusion that populations evolve towards maximization of mean fitness is easily vitiated, and the worst culprit is frequency dependence."

[33] This is hardly a new realization, though, as Julian Huxley once made an explicit distinction between what population genetics could explain (i.e., adaptation) and long-term evolutionary trends such as extinction and speciation (Huneman, 2019a).

[34] According to Dykhuizen (2016): "in population genetics, it is assumed that one can estimate an average selection coefficient over all the environments experienced by the population in a set period without needing to specify the environments or their effect on birth and death rates…Because population genetics is interested in the effects or consequences of natural selection, not the *causes*, it is satisfactory to treat natural selection as a constant without understanding the causes of natural selection. Unfortunately, this simplification has led to a caricature of natural selection as a constant, given a genetic difference" (Dykhuizen, 2016*:* 2).

the *end-all be-all* that several high-status proponents suppose it to be (e.g., Lynch, 2007a; read for more Millstein, 2012).

Thus, with population genetics as the main theoretical wing of evolutionary biology (largely influenced by positivist reductionism), evolutionary biologists have persistently failed to theoretically model evolutionary and selective dynamics as they are found in nature. In the latter half of the 20th century, another major synthesis began to emerge between evolutionary biology and ecology that was, in part, a reaction to the discontents with population genetics, leading to a dramatic increase in our understanding of the evolutionary process as it truly unfolds in nature.

2.5 The Lead Up to the Second Synthesis: The Founding of Evolutionary Ecology (and Population Biology)

The period after the first synthesis finally saw the development of ecological methodology within an evolutionary context. Evolutionary ecology—and its distinctive theoretical wing, population biology—blossomed into a legitimate discipline in the late 1950s and 60s with different research interests to that of both mainstream ecology and evolutionary biology, but that greatly integrated specific knowledge from both fields (Futuyma, 1986; e.g., Lewontin, 1974; Levins, 1968). Integrative studies focused on life-history parameters, phenotypic plasticity, mating/breeding systems, sexual selection, foraging strategies, degrees and patterns of genetic variation, population dynamics, and demography, but the most important development was the viewing of evolutionary dynamics concerning *environmental heterogeneity*.

These important developments were, in part, a reaction to the discontents of the first synthesis and population genetics (Futuyma, 1986). Up to this point, population genetics generally treated all individuals in a population as effectively equivalent without consideration of life-history parameters (Ayala & Fitch, 1997). As noted by the famous ecologist Richard Levins (1966), one of the founders of this new movement:

> "For population genetics, a population is specified by the frequencies of genotypes without reference to the age distribution, physiological state as a reflection of past history, or population density. A single population or species is treated at a time, and evolution is usually *assumed to occur in a constant environment*. Population ecology, on the other hand, recognizes multispecies systems, describes populations in terms of their age distributions, physiological states, and densities. The environment is allowed to vary but the species are treated as genetically homogeneous, so that evolution is ignored.
>
> *But there is increasing evidence that demographic time and evolutionary time are commensurate*. Thus, population biology must deal simultaneously with genetic, physiological, and age heterogeneity within species of multispecies systems *changing demographically and evolving under the fluctuating influences of other species in a heterogeneous environment…Thus, a satisfactory model could not cover all of population biology*[35]. (Levins, 1966: 421, 431; emphasis added)"

[35] Levins here was implicitly arguing for a pluralistic model of natural selection, which will be further discussed in chapters 4 & 5.

Population biology was the first concerted effort to unite evolution, ecology, and genetics from a theoretical standpoint (Futuyma, 1986; e.g., Lewontin, 1974; Levins, 1968). It also led to the first compelling arguments made *against* the theoretical traditions of that time. Population biologists saw the idealizing assumptions made by population genetics, such as holding fitness as a constant or limiting studies to only one species, as major failures of external validity (Prout, 1965; Millstein, 2012).

Ambitious attempts were made to fashion a new evolutionary theory that allowed for the natural complexities of ecological phenomena, but they were largely unsuccessful. Joan Roughgarden's (1979) classic textbook *Theory of Population Genetics and Evolutionary Ecology: An Introduction* was one of the first to approach the topic of evolution in spatiotemporally varying environments (for reasons why this was not very successful, see Millstein, 2012). Alas, population biology "never engaged much attention from theorists or experimentalists (in evolutionary biology)" (Ayala & Fitch, 1997, 7695). The "development of the field was not so much abandoned as postponed" (Singh & Uyenoyama, 2009, 3).

Evolutionary theory was certainly expanded during this era by the new insights gleaned from evolutionary ecology (e.g., density- or frequency-dependent selection, limiting similarity, red queen, etc.). But the primary causal structure built by population genetics in the first synthesis was still unmoved by ecological insight.

D.J. Futuyma (1986, 311) summarized the important transitions that had occurred during this time at an evolutionary ecology conference: "Without doubt, a very considerable synthesis of ecology and evolutionary theory has occurred. . . yet asymmetries exist, and some areas of ecology have not incorporated evolutionary theory to any significant extent[36]". The focus of evolutionary biology remained on how evolutionary theory can influence ecology, rarely on the influences that ecology could have within an evolutionary sphere. However, several developments in the 1980s would finally cement ecology's place within evolutionary theorizing and initiate the Second Synthesis.

2.6 Heralding the Second Synthesis: *Natural Selection in the Wild*

Perhaps the greatest advancement in thinking about evolution since the first synthesis came in the late 1980s and 1990s from the realization that ecological and evolutionary processes are intimately linked and *often* proceed on a similar timescale. Evolutionary change is directly influenced by ecological change and *vice versa* (Kirkpatrick & Peischl, 2013). Before this time, (1) most cases of natural selection in the wild were attributable to anthropogenic causes, which were assumed to enact a much stronger force of selection and therefore cause higher rates of

[36] Also found in Futuyma (1986, 307), "As Kimler notes in citing John Harper's definition of the subject, modern evolutionary ecology is in essence the analysis of the evolutionary origin of ecological phenomena with an explicit recognition of the distinction among, and the consequences of, selection at various levels (gene, organism, kin group, population, or higher) … The new evolutionary ecology saw the hand of natural selection everywhere, recognized distinctions in level, and, most important, applied the concepts of individual selection and adaptation to properties of species -- such as life-history patterns -- that had not been addressed before."

evolution than selection in nature (Millstein, 2012); (2) these cases demonstrated adaptive phenotypic change in response to the anthropogenic pressures, yet still, we lacked the technological capacities to clearly discern their genetic origins (Pelletier *et al.*, 2009); and (3) while students of population biology and evolutionary ecology were acutely aware of the commensurability of the two, evolutionary biologists remained either unconvinced or largely unaware of recent transitions in evolutionary ecology[37].

During this time, technological advances in genetics made it possible to corroborate the genetic origins of the adaptive phenotypic changes observed in response to anthropogenic pressures (Endler, 1980; Stearns, 1983; Grant, 1986; Brakefield, 1987). This finally provided an unequivocal link between the phenotype and genotype, drawing a clear causal relationship between the fitness differences expressed by genotypes and the resultant phenotypic evolution driven by natural selection (Brookfield, 2016).

Furthermore, the development of a robust mathematical program to test, quantify, and link natural selection to the evolutionary dynamics of natural populations allowed for the systematic study of *evolution in the wild* to become a realizable and worthy endeavor (Bell, [1997] 2009; Siepielski, 2009)[38]. Early work provided an elegant mathematical framework for measuring selection as the covariance between a trait and relative fitness, with the response to selection as the genetic covariance between breeding values for a trait and fitness (Price, 1970; Robertson, 1966). This framework was quickly expanded in the early 1980s to include measuing the strength of selection on multiple quantitative traits (Lande, 1979; Lande & Arnold, 1983; Arnold & Wade 1984a; 1984b). Evolutionary ecology finally had a standardized framework that allowed for the estimation of selection gradients in a large variety of traits in natural populations.

Such methodological advances precipitated an explosion of field studies of evolution in natural populations that Jerry Endler reviewed in his classic *Natural Selection In the Wild* (1986)[39]. In his assessment of the literature up to 1983, he argued that the coefficients of selection found in natural populations were higher than previously assumed. Rates of evolution could be exponentially faster than we have always anticipated. In support of this finding, the evolutionary ecologists' Rosemary and Peter Grant (Grant, 1986; Grant & Grant, 1989) published a comprehensive account of their observational results obtained from a long-term field study of Galapagos finches (which, until then, was unparalleled among field studies). Their findings provided conclusive observational evidence that selection not only varies significantly in space and time but also that selection can proceed at the same speeds as suggested by Endler. Within only a few years, they observed strong and fast selection on bill depth during a drought period (Mueller, 2019). Such findings motivated a renewed research interest into the direct causal agents of selection (see **Box 3**).

[37] See Bell (2010) for how population genetics reinforced the gradualist interpretation of evolution.
[38] Future developments of a viable measurement for fitness and genetic variance for fitness-related traits also underscored progress in the estimation of these parameters in wild populations (see for more Pelletier *et al.*, 2009)
[39] Endler's assessment, however, reviewed 25 studies that were performed before 1983.

Box 3: The Direct Causation of Natural Selection, Where Ecology and Environmental Biology Meet

The fact that ecology and evolutionary have developed somewhat independently of one another is particularly unsettling for our joint understanding of natural selection, since natural selection performs in "the ecological theater and the evolutionary play (Hutchinson, 1965);" that is, the ecological context provides the setting for the adaptive landscape and determines the fitness consequences of biological traits, therefore driving selection dynamics. To understand and describe natural selection in causal terms *necessitates* an appreciation for ecology (MacColl, 2011).

Population genetics has overshadowed the fact that the analysis of selection is essentially an ecological and not a statistical question. Natural selection traditionally defined as a quantitative measurement of differences in fitness in individual organisms merely captures *how selection operates to change the distribution of traits* (Caruso *et al.*, 2017; e.g., Lewontin, 1970; Lande & Arnold, 1983; Futuyma, 2017b). In contrast, the question of *why selection operates in a certain way* belongs to ecology. The identification of the direct causal agents of natural selection requires a knowledge of population-environment relationships in an ecological context (Ford, 1964; Endler 1986; Wade & Kalisz 1990; MacColl 2011; Hendry, 2017). Wade & Kalisz (1990) clearly summarize this point:

> 'When we ask, *Why does selection change the phenotypic distribution?* we are asking, *What is the agent of selection in nature?* or *For what environmental reason does an association between fitness and phenotype exist?* The fitness of an individual is the result of the interaction of the phenotype with the environment and not an intrinsic feature of either one. For example, melanic forms of the moth, *Phigalia pedaria*, are not intrinsically more or less fit than nonmelanic forms; the fitness of each morph depends upon the local environmental conditions.... In our view, the environment provides the "context" in which there can be a causal relationship between phenotype and fitness. If the environmental context changes, then we expect the relationship between phenotype and fitness to change as well. For this reason, the contribution of a particular trait to overall fitness will often depend jointly upon the value of the phenotype and the value of a local environmental variable. It is this environmental variable that is the selective agent. Thus, identifying those environmental contexts in which there is a relationship between phenotype and fitness is an important first step to identifying the causal basis of fitness' (Wade & Kalisz, 1990*:* 1949).

Most, if not all, of the conceptual confusion surrounding the causality of natural selection and fitness today (and historically) hinders on the understanding of this one quintessential point: *the reference environment determines the causal relationship between phenotype and fitness*. We have a problem characterizing fitness and the causality of natural selection today *because we have a problem generalizing ecological environments and the direct causal agents of natural selection* (Abrams, 2009). Whether a biological trait is deemed advantageous, neutral, or deleterious is determined by the reference environment that surrounds said trait. And when environments change, which they do often, then the trait covariation consequently changes.

The direct causal agent of natural selection therefore lies in the selective pressures of abiotic and biotic factors, which come in many forms such as diverse nutrients, temperature, toxic agents, pathogens, symbioses, predators, competitors, or climate variables (MacColl, 2011). Selective pressures should be considered as the *triggering causes* of natural selection (*sensu* Dretske's model of causation, see for more Ramsey, 2015). *Ecological pressures are how selection causes adaptive evolutionary change, with ecological analyses answering why they cause adaptive evolutionary change.*

Measuring or quantifying selection is indeed important, but this is only the first step. To really understand the causal mechanisms behind natural selection requires the identification of the environmental factors that are actually causing the covariance between trait and fitness. As MacColl (2011) recounts, "an understanding of natural selection cannot be complete without knowing its causes, their relative importance and how they interact to form the eco-evolutionary landscape." This appeal has recently been heard, as Caruso *et al.* (2017) has performed a meta-analysis of the studies that have investigated the environmental determinants of selection, with their most notable finding being that biotic factors should not be assumed to be more important causes of selection than abiotic factors. However, more research attention is certainly warranted in this area.

Following these two major publications, alongside concomitant developments in systematics and phylogenetics, the evolutionary biology community finally retired the Darwinian conception of *gradualism.* Evolution was universally seen as capable of proceeding at faster rates than what was originally observed in the fossil record, and these rates were also assumed to be common and sustainable in nature (Hendry & Kinnison, 1999; Reznick & Ghalambor, 2001). Such a conceptual advance led to a greater emphasis on *empirical realism* in evolutionary biology. Now that evolution was widely known to be readily observable, previous discouragements to laboratory experimentation were also lifted. As a result, the field of experimental evolution began to flourish (Dykhuizen, 2016).

Perhaps more importantly, however, was the new role afforded to evolutionary ecology and the systematic study of evolution in natural populations within evolutionary biology. Evolutionary biologists from all walks, including population geneticists, began taking ecological findings more seriously and using them to inform their theoretical modeling. Joan Roughgarden (1996*:* vii) noted this new trend in her second edition of *Theory of Population Genetics and Ecology: An Introduction:* "Theoretical population biology is not a new field although its current visibility is unprecedented…What is truly recent is the beginnings of a union of population genetic theory with the theory of population ecology".

Thus, the influx of field studies of selection performed between 1980 and 2000 enabled a major advance in our knowledge of the causal dynamics of natural selection (reviewed in Kingsolver *et al.*, 2001; Hoekstra *et al.*, 2001; Kruuk, 2004). Abundant evidence was gathered that showed how selection varies in strength (e.g., strong or weak; Kingsolver *et al.* 2001; Hereford *et al.* 2004), direction (e.g., positive or negative), or form (e.g., linear or non-linear; Brodie *et al.* 1995).[40] But these first-gen causal models were not without their limitations. They specifically focused on the short-term dynamics of selection, asking *whether* natural selection operates in natural populations, not *how* it varies spatiotemporally in changing ecosystems (Siepielski *et al.*, 2009).

2.7 Selection Varying in Space and Time

Students of ecology have always appreciated the need to view how evolution proceeds with changes in space and time (Dobzhansky, 1937; Ford, 1964; Levins, 1968; Roughgarden, [1979]1996; Endler, 1986; Grant, 1986; Bell, 1997). While the first-generational studies coming out of the Second Synthesis greatly increased our understanding of the strength and direction of selection (Endler, 1986; Kingsolver *et al.*, 2001; Hoekstra *et al.*, 2001; Hereford *et al.*, 2004), our general understanding of the temporal and spatial dynamics of selection in nature was still largely lacking until the 2010s (Grant & Grant, 2002; 2014; Siepielski *et al.*, 2009; 2011; 2013;

[40] *Direction* and *form* of natural selection are not mutually exclusive and overlap many of the same phenomena, and thus in many cases quadratic coefficients may be misleading (Schluter & Nychka, 1994). Also, see Hersch & Phillips (2004) for potential issues with the early reviews that estimate the strength of selection.

2016; Bell, 2010; MacColl, 2011). It was not until quite recently that a research and theoretical emphasis has been placed on how populations respond to changing environments within the evolutionary biology community (Kirkpatrick & Pieschl, 2013; Dykhuizen, 2016), largely because of the increasing interest in the *evolutionary rescue* of populations in response to rapid anthropogenic climate change (Chevin *et al.*, 2010; MacColl, 2011; e.g., Siepielski *et al.*, 2017; Bell, 2017; see **Box 4**).

Evolutionary biologists have since become increasingly aware of this profound gap in our basic knowledge and have tried to correct it by devoting more attention to the structure and consequences of ecological variation on selection dynamics, or *how selection varies spatiotemporally* (Otto, 2009; Palmer & Feldman, 2011; Caruso *et al.*, 2017; Siepielski *et al.* 2009, 2011, 2013; MacColl, 2011; Hanski, 2012; Dykhuizen, 2016; Bell, 2010; Canino-Koning *et al.*, 2019). Hanski (2012) even referred to the growing interest in spatial dynamics as the "final frontier for ecological theory".

Such a shift in research attention has clearly shown how different ecological conditions and selective pressures give rise to different evolutionary and selective outcomes, implying that biological populations experience selection differently in strength or direction contingent on ecological conditions (Weis *et al.* 1992; Grant & Grant, 2002; Steele *et al.* 2011; Siepielski *et al.*, 2009; 2011; 2013; Caruso *et al.*, 2017). Focusing on evolutionary dynamics in changing spatiotemporal conditions has also revealed how *fitness determinants vary in space and time* (Siepielski, 2011; Saether & Engen, 2015; Graves & Weinreich, 2017; Caruso *et al.*, 2017; Hendry *et al.*, 2018). What is selectively adaptive in one environmental context may not be adaptive or *as adaptive* in the next.

Box 4: The Development of the Evolutionary Rescue

Conservational biology took off in the late 1980s and 90s due to the seminal work of Soule (1986), Lande (1988), and E.O. Wilson (1992), whose preeminent mission was to understand how natural populations respond to novel stressors, usually imposed by human activities, and how to prevent their extinction. The 1990s thus saw the first flood of theoretical work from population/quantitative genetics devoted entirely to the influences of environmental heterogeneity on evolving populations (Frank & Slatkin, 1990; Charlesworth, 1993; Lynch & Lande, 1993; Burger & Lynch, 1995; Lande & Shannon, 1996). More theoretical attention was also given to all types of evolutionary plasticity, thus birthing the independent research front on *evolvability* that has seen substantial growth over the years (Nuño de la Rosa, 2017).

One of these early influential theoretical pieces published by the population geneticist Richard Gomulkiewicz and the theoretical ecologist and evolutionary biologist Robert Holt drew key equations from population biology and population genetics to develop the first theoretical U-shaped curve representing a populations' change in size over time and following an abrupt shift in the environment (Gomulkiewicz & Holt, 1995)—what is today a staple of evolutionary rescue in natural populations. Their calculations suggested that a population is likely to persist when its size is initially large, with ample genetic variation for natural selection to cause adaptation to the new environmental conditions[1].

Yet quite similarly to the historical steps that led up to the Modern Synthesis, there was a time lag between the early theoretical work and the empirical work that burgeoned the new research front on evolutionary rescue. Expressing this sentiment, Andrew Gonzalez—now a leader in the field—recently remarked that "evolutionary rescue was a mid '90s idea that sat around in the literature without taking off for quite a while" (quote taken from McDermott, 2019). The empirical work began to pick up in the 2010s, with Bell & Gonzalez (2009) being the first to demonstrate evolutionary rescue in an experimental setting using yeast.

Since then, evolutionary rescue has developed into a vibrant and mature research front (Bell, 2017; Thompson & Fronhofer, 2019). However, there is almost no theoretical work that uses a multilevel model of selection, and empirical work is typically limited to experiments performed on unicellular model species such as yeast or bacteria. More observational and experimental data is certainly warranted that better matches natural conditions and community dynamics, that utilizes a multilevel selection framework.

Recognizing this has now paved the way for constructing a novel conceptual interpretation of *what biological fitness is* and *how it varies across ecological conditions* (Saether & Engen, 2015; Graves & Weinreich, 2017).

An accidental consequence of observing selection over longer timescales (e.g., *evolutionary rescue*, see **Box 4**) was the finding that selection *causes adaptation at multiple levels of biological* organization. While most of the studies outlined in the reviews of spatiotemporal variation of selection were limited to within-population analyses (e.g., Siepielski, 2009; 2011; 2013), other long-term studies have inadvertently demonstrated how population-level properties cause differences in the rates of population extirpation and survival (e.g., Lenski, 2017). As will be discussed more heavily in the following chapters, there is now abundant evidence that natural selection does not invariably select to maximize individual fitness (fecundity, survival, or mating success) but can also select for population-level features that increase population fitness (e.g., evolvability) over longer timescales and frequent spatial changes. A balance between short-term and long-term evolutionary goals is thus the evolved result of many lineages.

Thus, the first generation of results to develop out of the Second Synthesis increased our understanding of the strength and direction of selection. Second-gen studies increased our understanding of how selection and fitness vary spatiotemporally. And as a consequence of this second generation, recent work has begun to shed light on how selection causes adaptation at multiple levels of biological organization (to be extended in the following chapter). A future focus of the third-gen studies should therefore be placed on how selection varies between levels of biological organization in the space and time of nature.

2.8 *The Second Synthesis* Today

Evolutionary biology and ecology have undergone a major yet subtle synthesis in the past generation spurred by technological, conceptual, and methodological advances in viewing complex evolutionary dynamics (Futuyma, 1986; Pelletier *et al.*, 2009; Schoener, 2011; Hendry, 2017; 2019; De Meester *et al.*, 2019). When we are constantly reminded that "ecology and evolutionary biology have developed independently of one another" or that the Modern Synthesis did not include ecology in its initial program, what we mean is that *ecology has never played a central role in the development of evolutionary theory*. However, the burgeoning of the systematic study of evolution in natural populations has led to a dramatic increase in our knowledge of evolutionary and selective dynamics. Evolutionary ecologists are now thinking more explicitly about the *nature* of natural selection, rather than identifying its mere presence in populations. This has led to the development of an integrative field of research dedicated to investigating how ecological change influences evolutionary change, how evolutionary change influences ecological change, and how these two pathways can sometimes influence each other in a process called *eco-evolutionary dynamics* (Hendry, 2017; 2019; De Meester *et al.*, 2019)[41].

[41] As of late, more research emphasis has been on the evo-to-eco feedback loop (e.g., niche construction) than eco-to-evo (Schoener, 2011). I am not privy to the literature, but from afar it appears that there are few empirical examples of evo-eco causal interactions. Kevin Laland has forcefully pushed for the salience of this idea, but his arguments appear to be tapering off from their initially bold promises (e.g., Clark *et al.*, 2020).

The Second Synthesis is therefore evinced by the significant expansion of research attention that is now devoted to ecological (or *empirically real*) insight within the past two decades, including but not limited to: the greater attention that major evolutionary textbooks are now devoting to ecological studies performed in the wild (Zimmer & Emlen, 2020; Futuyma, 2017b); the greater attention that population/quantitative geneticists are paying to complex evolutionary dynamics and/or basing their analyses off of results obtained in the field (Dayan *et al.*, 2019; Carja *et al.*, 2014; see for more examples Millstein, 2012); the resurgence of population biology (Roughgarden, 1996; Singh & Uyenoyama, 2009); increasing interest in *evolution in action* studies (Culotta & Pennisi, 2005; Lenski, 2017); or the persistent calls for greater realism in our experimental studies (Hendry, 2019; Dykhuizen, 2016; De Meester *et al.*, 2019). The latter is, effectively, a direct product of the successes of ecological insights on evolutionary thought.

Students of ecology have always appreciated the scientific value of *empirical realism* on evolutionary epistemology, coming in either form of observational or experimental results. However, many studies of eco-evolutionary dynamics are still performed in unnatural laboratory settings (Hendry, 2019). There are valid reasons for choosing unnatural and/or controlled venues for experimentation to meet specific epistemic goals. For example, simplified approaches allow for increased replication, more precise and focused treatments, better controls, and may avoid unwanted variance, thus allowing for the identification of the causal effects of one (or a few) causal factors in a controlled laboratory setting (Skelly & Kiesecker, 2001; Stewart *et al.*, 2013; Zuk & Travisano, 2018). Experimental studies can thus be used to identify key causal relationships that are not readily identifiable in observational studies (Caruso *et al.*, 2017), which is important for the initial discovery of new causal phenomena[42] (Anjum & Mumford, 2018).

The issue addressed in the last two chapters is that natural environments are causally complex, with many covarying and interfering factors that will likely affect whatever causal relationship is under investigation. Researchers should therefore treat laboratory results as 'proof of principle' that specific treatments are efficacious while remaining aware that these treatments are not representative of the effects likely to be found in nature (De Meester *et al.*, 2019; Hendry, 2019; Zuk & Travisano, 2018; Carpenter, 1990; 1996). Future studies can hope to close the inferential gap between laboratory studies and studies in natural environments by emphasizing real-world parameters such as those seen in semi-natural mesocosms and/or common gardens since they often include many of the same interfering or covarying factors that are found in nature (Stewart *et al.*, 2013; for more on this, see Hendry, 2019]. Indeed, one meta-analysis on plant functional traits found that selection estimates did not consistently differ between studies conducted in greenhouses, common gardens, or natural populations (Geber & Griffen, 2003).

Long-term evolutionary experiments performed in semi-natural mesocosms have greatly increased our knowledge of evolutionary dynamics (Dykhuizen, 2016; Lenski, 2017; Ezard *et al.*, 2009). Although these studies typically use simple organisms, they benefit from the realism

[42] A meta-analysis performed by Caruso *et al.* (2017) surprisingly found that selection was more spatiotemporally variable in the experimental studies they analyzed than in the observational studies. This finding does not directly support the primary thesis of this paper, that the shift towards greater empirical realism in evolutionary biology has demonstrated a greater causal complexity in nature, but it does not negate it. The preponderance of evidence still lies in support of this position, and there is a number of issues with meta-analytic methods that could make this finding unlikely (Hendry, 2019).

of viewing evolutionary dynamics in the long-term with frequent spatiotemporal changes and novel selective pressures that can be controlled. However, some evidence suggests that manipulative experiments fashioned after natural environments do not produce results consistent with observational studies (Yuan *et al.*, 2017). A deeper understanding of the complex causal relationships of natural phenomena requires more complex analyses than laboratory experiments can typically offer, using multiple populations of multiple species spanning a wide variety of ecological conditions under a community ecosphere.

Recent advances in evolutionary epistemology instigated by the transition in philosophies towards empirical realism should therefore bring theoretical progress if, as should always be the practice, new scientific discoveries are coupled with theoretical reflection and the development of new causal generalizations; generalizations that can lead to more externally valid and predictive causal-explanatory models. However, profound divisions still exist between the theoretical wing of evolutionary biology (e.g., population genetics) and ecology, principally because their underlying philosophies of evolutionary modeling do not match up. For an example that will be extended upon in the following chapters, ecologists call for a switch in explanatory tactics towards explanatory pluralism to resolve *the paradox of sex*. In contrast, population geneticists still call for a more general, reductive explanation of sex (Meirmans & Strand, 2010). The consequence of such persistent divisions? The findings gathered from the Second Synthesis have never been fully integrated into evolutionary theory. Future efforts should therefore focus on consolidating the findings of the Second Synthesis and integrating them into modern evolutionary theory (Pelletier *et al.*, 2009; Hendry, 2019; Govaert *et al.*, 2019; Fussmann *et al.*, 2007).

Today, we are thus suspended at an epistemic juncture where we have recently experienced a dramatic increase in our knowledge of evolutionary and selective dynamics, but the evolutionary biology community has yet to acknowledge such a profound advancement and its underlying historical forces. Such an intermediate stage calls for a general and coherent conceptual framework to be built from the overflowing evidence and knowledge gathered by the Second Synthesis (Hendry, 2019). This is where a new philosophy of biology grounded in pluralism can be of great use, as will be argued in the following chapters.

2.9 Concluding Remarks and Future Directions

Our underlying philosophies of science and causation were tailored for another age. Trying to build causal models of absolute and monocausal natural phenomena is a vestige of science past when the law-making enterprise of classical mechanics stood as a paragon for the other sciences to follow—modeling the biological sciences after classical physics is also part of a long tradition of *scientific unity* in the sciences, encouraged by *logical positivism*. Scientific verification moving from theory to empiricism may be a suitable methodology in physics (or, at the very least, one that defined the golden age of physical methodology in the 19th and 20th centuries). But biological methodology should never orient itself in this way. Empirical investigation should always drive theoretical development in biology. *Why?* Because biologists investigate more irregular, less absolute, multilevel/multicausal phenomena than physicists. When constructing causal models in biology, we are therefore forced to adopt different methods to match the natural

vicissitudes and complexity of biological and ecological phenomena—what is *a defining feature of biology*.

The causal story of natural selection, and evolution more generally, is therefore incomplete. Reducing natural selection to a privileged unit or level has historically concealed its complex causal dynamics. But the recent recognition of this trend by several biologists within specific lines of research underlies the substantial increase in experimental or observational studies that examine how selection varies in space and time. Their findings recommend that the causal field of natural selection cannot be adequately modeled using simple, reducible, linear, or monocausal models, but rather necessitates a switch in philosophies (Ch. 4 & 5). Selection causes adaptation at multiple levels of biological organization, with different selective pressures causing different selective responses in space and time, and selection thus shifts its adaptive interests in space and time, with individual fitness being *inapplicable* as a universal measure for selection in space and time. A methodological and epistemological shift towards pluralism is therefore not an embarrassment for evolutionary biology. Instead, it is the mark of a science recognizing and overcoming its flaws, developing outside the bounds of other sciences (e.g., physics) and finally maturing into an autonomous science with its own philosophy.

This is, after all, not a new argument in the philosophical literature. Dupré (1993), Mitchell (2003; 2009), and other philosophers from the so-called 'Stanford school' have been calling for a philosophical shift towards pluralism in the biological sciences for over thirty years now, often citing the perceived complexity of ecosystems as evidence for justifying this shift. Perhaps such a shift is even inevitable in the progressive development of sciences since there appears to be a general trend in the history of science *towards pluralism* that is correlated with an increasing complexity of subject matter, with no such trend occurring in the opposite reductive direction, contrary to what positivist philosophy predicts (Mitchell, 2003).

However, philosophical arguments have failed to persuade the common biologist and ignite any major movement in biology because of the relative disconnect between philosophy and science. Firstly, these works were published in largely philosophical books and thus did not attract the attention of biologists. Secondly, the empirical evidence supporting their philosophical and theoretical prescriptions was likely insufficient to attract the attention of biologists and/or validate their prescriptions. Thirdly, no historian or philosopher of biology has historically acknowledged or contextualized the recent transitions that are ensuing within biology today. To understand why population genetics has failed to produce any major epistemological progress in evolutionary biology, one must understand the intellectual zeitgeist (i.e., logical positivism) that championed the population genetic model. Moreover, to understand why our understanding of evolutionary dynamics has exponentiated over the last forty years and the resultant theoretical potential of these advances, one must understand the historical forces that have finally bridged evolutionary biology and ecology. This thesis is thus an attempt to build on the previous work already established in the philosophical literature and connect it to the scientific literature, using extant empirical knowledge to support my theoretical prescriptions argued in Chapters 4 & 5.

In the next chapter, I dive into the scientific empirical literature on the evolutionary dynamics of sex and mutation (and other genetic evolvability mechanisms like horizontal gene transfer) to exemplify how reductionistic positivist philosophy—through the vehicle of population

genetics—has instigated one of the most severe and longest-standing explanatory problems in the history of evolutionary biology, *the paradox of adaptive genetic variation*.

Empricism

There is no shortcut to truth, no way to gain knowledge of the universe except through the gateway of the scientific method.

Karl Pearson

Observation, reason, and experiment make up what we call the scientific method.

Richard Feynman

Chapter 3 - *The Paradox of Adaptive Variation*: An Historical and Scientific Review of Adaptive Genetic Variation

In this chapter, I call attention to perhaps the most storied problem in the history of evolutionary biology—*the paradox of adaptive variation*. Novel findings starting in the late 1950s began to challenge the reductive interpretations of natural selection that (1) variation is generated independently of exposure to selective environments and therefore is *random*, and that (2) natural selection operates strictly at the individual level. A growing empirical literature in the last 60 years has exposed the inaccuracies of both these assumptions, given the increasing evidence that the production, conservation, or domestication of novel genetic variation is adaptive following frequent environmental changes or stressors, but adaptive at levels of selection higher than the individual. In this chapter, I attempt to comprehensively review the concept of adaptive genetic variation and how it has changed over time. I begin by providing a diachronic historical assessment of the concept of adaptive genetic variation, from Darwin to today. After setting the necessary historical context, I then review the independent modern literatures for the mechanisms of adaptive genetic variation—i.e., sexual recombination, adaptive mutation, and very briefly genetic transposition, horizontal gene transfer, and gene/genome duplication. When considered together, a common empirical pattern arises from within these independent literatures and exposes a major paradox between the available evidence on adaptive genetic variation and modern theory, thus warranting a new philosophy of biology that is based on explanatory pluralism, multifactorial analyses, and multilevel causation.

3.1 Introduction to *The Paradox of Adaptive Variation*

> "It is amazing to what great extent variation in natural populations has been neglected in the study of evolution. Amazing because natural selection would be meaningless without variation…Can high variability by itself be favored by selection because it increases the probability of the production of unusual character combinations?" (Ernst Mayr, 2005*:* xvii)

The paradox of adaptive genetic variation is one of the oldest explanatory problems in the history of evolutionary biology[43]. Because of its longevity and severity, this paradox shines a spotlight on several of the most persistent philosophical anachronisms stalling theoretical progress in greater biology. The empirical evidence reviewed herein demonstrates the need for a

[43] Nearly every great figure of twentieth-century evolutionary biology has come to recognize this paradox in passing—from Weismann, de Vries, T.H. Morgan, Fisher, Wright, Mayr, and Dobzhansky, to Muller, Mather, Sturtevant, Stebbins, J. Huxley, E.B. Ford, Maynard Smith, G.C. Williams, Kimura, G. Bell, and Gould—as will be outlined in this chapter.

multilevel and pluralistic causal model of natural selection (**Chapters 4 & 5**), thus refuting reductionistic interpretations of natural selection dynamics that used to privilege one unit or lower-level of selection (i.e., individual- or gene-level) across ecological contexts in space and time.

The crux of this paradox rests on the production of intraspecific genetic variation as "the most potent evolutionary property of populations [for] arguments about species selection" (Lloyd & Gould, 1993: 595; e.g., Maynard Smith, 1998) because of the evolvability-benefit that it generally confers as a higher-level emergent property (Folse III *et al.*, 2010; Jablonski, *Forthcoming*). When phenotypic/developmental plasticity mechanisms or demographic rescue mechanisms fail to relieve novel pressures, species tend to resort to genetic evolvability mechanisms (Gomulkiewicz & Holt, 1995; Carlson *et al.*, 2014; Bonnet et al., 2022) such as increasing global mutation or recombination rates, conserving genetic variation or utilizing cryptic genetic variation reservoirs, procuring large-grade mutational events like gene duplications or whole genome duplication events, or are more receptive to the domestication of foreign genes such as selfish transposable elements. Yet if these mechanisms are adaptive and natural selection has played a causal role in their evolutionary history, then their evolvability-benefits are generally ascribed at higher levels of biological organization.

Such empirical observations are not readily explainable by Darwinian or subsequent theoretical models of natural selection (e.g., Modern Synthetic theory, Gene's Eye Viewpoint of Evolution; see for more Agren, 2021) since they often require higher-level selective explanations, and higher-level selection remains a suspect notion for many prominent evolutionary biologists (e.g., Williams, [1966]1996; Dawkins, 1976; Coyne, 2009; Abbot *et al.*, 2011), especially concerning adaptive variation and evolvability (e.g., Barton & Partridge, 2000; Partridge & Barton, 2000; Chicurel, 2000; Poole *et al.*, 2003[44]; Sniegowski & Murphy, 2006; Lynch, 2007; Charlesworth *et al.*, 2017; Watson, 2020; Hansen *et al.*, *Forthcoming*). *The paradox of adaptive genetic variation* is thus founded as an active explanatory problem that remains unsolved to this day because many biologists within specific traditions (e.g., population genetics) still deny the realism of higher-level selection, especially considering evolvability.

Contrary to what conventional Darwinian theory predicts, there is now abundant evidence that natural selection does not invariably select to maximize individual fitness components (i.e., fecundity, survivability, viability, or mating success) but can also select for population-level features that increase population fitness (e.g., evolvability) over longer timescales and frequent spatial changes. Natural selection does not invariably reach for higher individual-fitness peaks but also *for the ability of populations to traverse and explore the adaptive landscape*. A balance between short-term and long-term evolutionary goals is thus the evolved result of many lineages.

In this chapter, I first provide a brief historical account of the paradox of adaptive genetic variation and how it has evolved into a major explanatory paradox today. After setting the necessary historical context, I then briefly review the modern evidence for genetic evolvability (i.e., adaptive mutation, meiotic recombination, horizontal gene transfer, genetic transposition,

[44] Poole *et al.* (2003*:* 163) claimed that "The concept of evolvability covers a broad spectrum of, often contradictory, ideas. At one end of the spectrum, it is equivalent to the statement that evolution is possible, at the other end are untestable post hoc explanations, such as the suggestion that current evolutionary theory cannot explain the evolution of evolvability". This chapter is a reaction to those, like Poole *et al.*, who think that evolutionary theory can adequately explain evolvability-like phenomena.

gene/genome duplication)—demonstrating how genetic evolvability mechanisms become selectively advantageous given environmental variation and over longer timescales.

This exemplifies the need for a discipline-wide shift in theoretical and explanatory strategies away from a monistic, reductionistic, or monocausal philosophy and toward a pluralistic, multicausal, and multilevel theory of natural selection (**Chapters 4 & 5**). Without these necessary philosophical developments, we cannot hope to explain complex emergent phenomena such as sex or adaptive mutation, therefore making *the paradox of adaptive genetic variation* a pressing issue for evolutionary biologists that warrants resolution.

3.2 From Darwin's *Problem of Variation* to Dobzhansky's *Paradox of Viability* (1859-1950)

> "I have hitherto sometimes spoken as if the variations—had been due to chance. This, of course, is a wholly incorrect expression, but it serves to acknowledge plainly our ignorance of the cause of each particular variation" (Charles Darwin, 1859: 131)

Darwin thought of the process of adaptation by natural selection as subdivided into two independent and sequential causal processes: (1) the generation of random heritable variation, and (2) natural selection acting upon this variation to cause differences in survivorship (Mayr, 1982). While he convincingly demonstrated the existence of the latter process by providing analogical evidence for natural selection with the existing knowledge on selective breeding, he could not explain how the first process unfolds to the liking of his contemporaries. This is known as *Darwin's problem of variation* (see for more Vorzimmer, 1972). According to the historian William Provine (1971*:* 131), "the most basic weakness of his [Darwin's] concept of evolution was the lack of an adequate theory of the production of the variations upon which natural selection acted." Thus, natural selection was a failing program in the years following Darwin's death up until the first synthesis (1883-1918)—an era known as *the eclipse of Darwinism* (Bowler, 1983)—mainly because there were many competing models of variation and adaptation.

Empirical advancements around the turn of the 20th century refined our concept of variation and led to discrediting the developmental theories of adaptation[45]. August Weismann's empirical work led to his famous *germ plasm theory* ([1892]1893)[46] that drew a strict delineation between somatic and germline variations, insisting that variation arising from heritable material was sequestered from environmental influence, leading to the refutation of *Lamarckian inheritance*[47].

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[45] I suspect that most of the theoretical advancements made in the history of biology derived from refutations of a failed programme or idea (e.g., Neutral Theory defeating adaptationism, modern ecological insights defeating Darwinian gradualism, etc.).

[46] The idea that that the production of heritable variation corresponded to the ability of a species to adapt to environmental pressures was actually first proposed by August Weismann, when he proposed the functionality of sex to lie in the furnishing of heritable variation for natural selection to act upon (Weismann, 1889). This important contribution marked the first time that the mechanisms behind heritable variation were thought to, potentially, hold adaptive functionality. Additionally, Weismann thought the adaptive functionality of recombination was met according to "the needs of the species (Weismann, 1889*:* 279)," making him one of the first evolutionists to note the possibility of selection acting on multiple levels.

[47] Weismann here was drawing the conceptual boundary of "individual" very crudely which has been challenged as unsuitable for describing individual organisms in most taxa (Buss, 1987).

Later pioneers in the field of experimental evolution, Hugo de Vries (1901-1903) and T.H. Morgan *et al.* (1915), demonstrated that new variants arise as spontaneous rearrangements of heritable material irrespective of the needs of species (what they came to call *mutations*), which ultimately refuted the idea of orthogenesis or *directed evolution*. These conceptual advances undermined the notion that the processes of variation were purposeful or directed modifications of the ontogenetic pathway, therefore setting the stage for the subsequent flourishing of natural selection theory in the first synthesis (Bowler, 2005). By the start of the first synthesis (*circa* 1918), a consensus had been reached that heritable variation arises from random changes in genetic material through mutation and/or recombination.

One of the major challenges that still needed to be addressed was how ample variation is generated for natural selection to act upon in natural populations. Evolutionary geneticists such as Theodosius Dobzhansky, E.B. Ford, and others (H.J. Muller, 1932; Sturtevant & K. Mather, 1938) were called to investigate this question from an experimental and ecological approach (ecological analyses were rather rare back then). Their conclusions independently arrived at the same parallactic recognition that mutation and sex presented a paradox to Darwinian theory, or what Dobzhansky referred to as *the paradox of viability* (Beatty, 1994):

> "A species perfectly adapted to its environment may be destroyed by a change in the latter if no hereditary variability is available in this hour of need. Evolutionary plasticity can be purchased only at the ruthlessly dear price of continuously sacrificing some individuals to death from unfavorable mutations" (Dobzhansky, 1937: 126-127).

Although early experiments by De Vries and Morgan effectively demonstrated the infrequent and often deleterious nature of mutations, by this time mutations were known to be the ultimate source of all genetic variation. Dobzhansky here recognized the conflict that this presented to Darwinian theory since selection for the genetic viability of individuals did not appear to be *invariably advantageous* (Ruse & Wilson, 2009*:* 523-4). Ecological environments were unpredictable and variable, as Dobzhansky observed, so populations must balance genetic variations that permit adaptedness to extant conditions while simultaneously allowing for future adaptation (i.e., *evolvability*). In genetic terms, he thought many genes exhibit polymorphism and are thus maintained in the population by selection favoring heterozygotes.

This came to be known as Dobzhansky's "balance hypothesis", therefore founding the concept of *balancing selection* (talked about in greater depth in Chapter 4; see for more on the sociopolitical history: Beatty, 1994).[48]

Further work by the geneticists H.J. Muller (1932) and A.H. Sturtevant & K. Mather (1938) noted that the continual shifting of genotype frequencies seen in recombinatorial states provided 'insurance' for future changes in the environment, conferring a 'flexibility' (i.e., evolvability) for the species. As Mather (1943) would go on to notice, such shifting is largely costly to individuals

[48] There is a much deeper and sociopolitical history here that is outside of the flow and scope of this manuscript, but which I will attempt to award more attention to in the future. For example, Dobzhansky and Muller fought over the chief action of natural selection, primarily for sociopolitical reasons. Muller argued that natural selection is purely an eliminative force, needing to purge the deleterious mutations from populations, which interacted with his political beliefs regarding eugenics. Dobzhansky, on the other hand, started the "balance school" that was an "optimistic, pluralistic view that sees nature as process rather than product" (Felsenstein, 1975, 589; see for more Beatty, 1994; Carvalho, 2019)

since it would separate favorable gene combinations built by past selection. He therefore saw this conflict as a tradeoff between present fitness and future flexibility, where:

> "Failure to achieve an adequate balance spells either its own (the individual) doom, on the one hand, or that of its descendants, on the other. Existing organisms must therefore have descended from those which had most adequately balanced the advantages of fitness and flexibility in the past" (Mather, 1943: 44).

Thus, *the paradox of viability* earned recognition in the synthetic era when several founders began to detect an internal anomaly between their existing causal model of natural selection and the empirical tendencies of genetic variation observed in natural populations. *The reason?* Because the Darwinian and modern synthetic model of natural selection was heavily reduced to one level of biological organization, often referred to today as *the individual selection assumption* (see **Box 5**). Even the population geneticist R.A. Fisher—who was a staunch supporter of a reductive model of natural selection because of his interest in unifying biology with physical methodology (Smocovitis, 1996)—came to see sex as the only exception to the individual selection assumption: "characters ascribed to interspecific selection should of course characterize, not species, but whole genera or families, and it may be doubted if it would be possible to point to any such character, with the possible exception,

Box 5: The Individual Selection Assumption - Reducing Natural Selection to Lower levels

The individual selection assumption has a long history in evolutionary thought (see for more Pigliucci, 2008b, Box 3; Okasha, [2006] 2013). Darwin considered individual organisms to be the primary causal unit of natural selection. The population geneticists R.A. Fisher and J.B.S. Haldane were responsible for taking this assumption mainstream (Okasha, [2006] 2013) in the synthetic era due to the influences of positivist philosophy (Smocovitis, 1996). Yet this assumption would become a central tenet of Darwinian theory following the group selection controversy of the 1960s (see for more Maynard Smith, 1998).

Under this assumption, selection is seen as primarily causing adaptations at the level of the individual organism, as opposed to higher levels of selection such as the group, population, species, or lineage. Adaptive features are thus only acquired by and passed on to successive generations through individual organisms, not groups or species. Any benefit that is ascribed to a level of selection higher than the individual is merely assumed to be an incidental effect of an aggregate, or a *by-product* of an individual-level adaptation (Williams, [1966]1996).

A slightly more reductive model of natural selection bifurcated from this assumption following the group selection controversy, in which the gene was seen as the primary causal unit of selection because genes are the long-term units of evolutionary change (e.g., Williams, [1966]1996; Dawkins, 1976). But these interpretations have garnered their own controversies (Sober & Lewontin, 1982).

Both reductive interpretations of natural selection are still taught and promulgated today, more specifically by population geneticists who grew up in an era that Gould (1983) referred to as "the hardening of The Modern Synthesis". For example, Jerry Coyne (2009*:* 29) perfectly typifies this assumption, "as evolution predicts, we never see adaptations that benefit the species at the expense of the individual," primarily because a higher-level benefit would contradict the individual selection assumption and require long-term evolutionary reasoning. However, such reductive viewpoints of selection are quickly becoming the minority among philosophers and biologists, precisely because a pluralistic, multicausal, and multilevel model can readily explain more complex biological and ecological phenomena.

as suggested in Chapter VI, of sexuality itself, which could be interpreted as evolved for the specific rather than for the individual advantage" (Fisher [1930;1958]1999: 280).

This paradox arose, in part, due to the explanatory interests of the population geneticists to explain adaptation and the resultant philosophical tools they used to accomplish their goals (Mayr & Provine, 1998). Yet technological limitations also played their role. Population and evolutionary geneticists were *confined* to performing only within-population analyses because it was nearly impossible to study the extent of genetic variation between populations using Mendelian methods (which only became possible after the advent of proper genome sequencing techniques in the 1980s). During this period, evolutionary research was therefore executed almost exclusively by studying allele frequency changes *within populations* rather than *between populations,* which led evolutionary biologists to reduce the causation of natural selection to one level (Nei, 2013; refer to **Box 1** for more). Such blatant philosophical issues would only become more evident in the following decades as a research emphasis was placed on the complex subject of sexual recombination.

3.3 The Paradox of Sexual Reproduction (1958-Present)

The first synthesis culminated in the widespread acceptance of a new model of adaptive evolution largely due to the background efforts of early evolutionary ecologists such as Dobzhansky or Ford (see Ch. 2). By the 1950s, natural selection acting on random and heritable variation became the universal explanation for adaptive evolutionary change (Mayr & Provine, 1998). But the establishment of this new model led to new problems being recognized. Several founders began to detect an internal anomaly between their reductive theory of natural selection and the available evidence on genetic variation, an issue that would reach new heights in the following decades.

Such issues particularly emerged in the research front on sex. A consensus seemed to be reached by 1958 that sex was selectively advantageous at higher levels of selection because of the evolvability benefit that it confers. For example, the geneticist H.J. Muller claimed the following when comparing the reproductive differences between sexuality and asexuality:

> "It is true that some groups of organisms, including even higher organisms, in every period of the earth's history, have dispensed with sexual reproduction in fact or in effect, and that this has given them the considerable temporary advantage of being able to multiply without having to wait for the nuisance of finding and pairing with one another first. *But these can have only a transitory splurge and are doomed to fall behind in the long evolutionary race and to disappear. They furnish an illustration of the short sightedness, the opportunism, of natural selection.* The stem forms of evolution, from which the organisms of later periods will be derived, are those that pay their tax to sexuality and are repaid in novel developments" (Muller, 1958: 153, emphasis added).

Then in the same year, another leading figure of twentieth-century biological thought, John Maynard Smith, noted that

> "The compensating advantage of the sexual process is that it *increases the range of potential variation in a population, and therefore its evolutionary plasticity* […] Now if

> the advantage of sexual reproduction is that it increases the range of potential variation in a population, *then the advantage refers to the population as a whole, and not to any particular individual in it*. It follows that sexual reproduction has been established as the rule, both in animals and plants, because selection favoured some populations at the expense of others. This forms a contrast to the examples discussed in the last chapter, in which the 'unit' selected was the individual and not the population" (Maynard Smith, 1958: 138-9, emphasis added).

A year later in 1959, some of the greatest minds in evolutionary biology convened to celebrate the centennial of Darwin's *Origins*. A legendary panel was organized to explore the evolution of sex that was chaired by Julian Huxley and Alfred E. Emerson and attended by Daniel I. Axelrod, Theodosius Dobzhansky, E. B. Ford, Ernst Mayr, A. J. Nicholson, Everett C. Olson, C. Ladd Prosser, G. Ledyard Stebbins, and Sewall Wright. Stebbins summarized the consensus they reached as a balance between short-term and long-term benefits:

> "Why is it that in higher organisms sex seems so essential and is never lost, whereas such organisms as fungi and bacteria get along for very long periods without sex or with only a very small amount of genetic recombination? [...] Some years ago, Kenneth Mather pointed out that the genetic recombination system must establish a compromise between two conflicting needs. One need is genetic insurance—generating sexual combinations that at present may have no selective value but may become essential in the future when the environment changes. The other need is to generate the largest possible number of individuals that are fit at the present time. And the balance—the compromise between these needs—is likely to be very different in different organisms.
>
> Take, for instance, a bacterial colony in which millions of individuals are produced in one day, with the generation time a tiny fraction of what it is in man. Here new genotypes can perhaps be generated in large part by occasional mutation or even successions of mutations, as in the adaptation of bacteria to streptomycin. In this case, sex is perhaps of less selective value than in the slowly reproducing higher animals. And in plants the larger, more slowly reproducing perennials and woody plants usually have a high degree of cross-fertilization and genetic recombination through a high chromosome number, whereas the weeds—the pioneers—usually have self-fertilization and sometimes asexual reproduction. This is associated with the fact that a plant in a vacant and relatively uniform habitat is most successful if it generates a large number of offspring similar to itself" (Stebbins, 1960: 126).

Thus, by 1960, it was apparent that sex held its advantages at a level of selection higher than the individual, due to the evolvability benefits generally conferred in changing ecological circumstances. However, this conclusion would only become more mystifying in the coming decade following the infamous *group selection controversy*. During this heated battle of ideas, the respected ecologist V.C. Wynne-Edwards (1962) attacked the individual selection assumption by arguing that individuals sacrifice their reproductive interests to control population growth, which he called *group selection*. This provoked the estimable John Maynard Smith (1964), Robert Trivers (1971), and G.C. Williams (1971) to conserve the theoretical traditions of Darwinian theory by branding group selection as a teleological imputation or forward-looking force that was improbably real within their reductive worldviews (Maynard Smith, 1998). From this point onwards, group selection was considered anathema within many research traditions

(and still is), further cementing the status of a reductive model of natural selection that views adaptation as a causal phenomenon that only ensues at lower levels of biological organization.

Borrello (2010) argues that the victory over group selection was not so much earned as it was self-proclaimed, and a strong climate of intimidation followed in its wake that discouraged young researchers from pursuing the idea of *group selection*. This led to the suspicion of other higher-level or emergent reasoning. When selective pressures at higher and lower levels were aligned, processes at the lower level were to be given causal priority. Only in very rare cases was a level of selection higher than the individual to be invoked, such as populations or species (Brunet & Doolittle, 2015).

Around the same time that the critics were leading their attack on group selection in the 1960s, new evidence began to put them in a precarious position. Crow & Kimura (1965*:* 448) were the first to show that sex *not only confers no immediate benefit to the individual but is actually quite deleterious to individuals*, therefore implying that sex was an unmistakable emergent adaptation that majorly contradicted their theoretical predictions.

This led many of the same critics to note that sex was *the only exception* to the individual selection assumption (similar to the Fisher quote mentioned above). G.C. Williams (1966, 125) stated, "The machinery of sexual reproduction in higher animals and plants is unmistakably an evolved adaptation". In a future letter to Maynard Smith, he came to notice the conflict that this presented: "As long as the paper [Maynard Smith, 1971a] continues to point out that there would seem to be an immediate 50% disadvantage in meiosis, and that explaining sexual reproduction is a major evolutionary problem, it will serve an important function in the book (Williams, 30 Jan. 1969)." Thus, by the end of the 1960s, many evolutionists became aware that sex was both a likely candidate for *higher-level adaptation* as well as *a costly endeavor for the individual* (Dagg, 2016), flying in the face of theoretical projections.

With the evolution of sex now seen as a major issue in evolutionary biology, Maynard Smith (1971a; 1971b; 1974; 1976; 1978) and G.C. Williams (1971; 1975; 1978; 1980; 1988; with Mitton, 1973) spent the next decade attempting to find a theoretical model that would fit for the evolution of sex. At first, their mathematical models worked within the confines of the individual selection assumption and attempted to conserve the reductive foundations of Darwinian theory. But repeated attempts to find an immediate individual benefit were either inaccurate or inapplicable to natural populations (Dagg, 2016). This led Williams (1971: 161) to concede that *"*sexual reproduction must stand as a powerful argument in favor of group selection," and Maynard Smith (1976: 257) to bemoan "one is left with the feeling that some essential feature of the situation is being overlooked" (interesting sidenote: later reflecting on this time, Maynard Smith [1998] noticed the errs of firstly conserving the theoretical traditions of Darwinian theory, as he would eventually accept sex as one of the best examples of higher-level selection because of the evolvability benefit that it confers to species). Sex was finally perceived as a *bona fide* theoretical crisis:

> "This book is written from a conviction that the prevalence of sexual reproduction in higher plants and animals is inconsistent with current evolutionary theory. My purpose is to propose minimal modifications of the theory in order to account for the persistence of so seemingly maladaptive a character. Many well-informed readers may disagree with much of my reasoning, but I hope at least to convince them that there is a kind of crisis at hand in evolutionary biology" (Williams, 1975: v).

Williams here made a call to arms that was heard around the world:

> "You may not have noticed, but the resulting crisis was heard in laboratories and lecture halls around the world. A new generation of evolutionary biologists heard the battle cry and went on the offensive" (Michod, 1995: xvi).

Thus, *the paradox of sex* was officially recognized in the 1970s and became a major explanatory problem for evolutionary biology. So grand was this paradox that Graham Bell (1982, 19) would come to later refer to it as "the queen of problems in evolutionary biology," in which he aptly summarized the entire situation at hand:

> "It was the very success of this attack [on group selection] which led population biologists to realize how embarrassing sex is. Most supposedly altruistic behaviours were quickly found either to have concealed advantages for the individual, or else to be directed towards the welfare of closely related individuals. But sex appeared to fit into neither of these categories: if it permits the rapid mobilization of genetic variation, then this may be a matter of vital concern for the population, but does not in itself concern the individual. Evolutionary biologists thus found themselves on the horns of a dilemma: either the apparently unsatisfactory hypothesis of group selection was indeed an adequate explanation for the maintenance of sexuality, or else a quite different hypothesis framed in terms of natural selection must be sought" (Bell, 1982, 47).

The unrelenting commitment of many 20th-century evolutionary biologists to a reductive model of natural selection caused many of the same to notice an implicit and profound theoretical incongruency between natural selection theory and the available evidence on the evolution of genetic variation (that was largely stemming from ecological work). Darwin's *problem of variation* (1958-1918) evolved into *the paradox of viability* (1918-1950) when the reductive formations of evolutionary theory were settled in the first synthesis. And *the paradox of viability* evolved into the *paradox of sexual reproduction* (1960-) after the individual selection assumption became entrenched in theory following *the group selection controversy*, thus raising the origin and maintenance of sex as a major explanatory issue for evolutionary biology continuing to this day.

3.4 The Evolutionary Maintenance of Sexual Reproduction Today: A Brief Literature Review

> "We do not even in the least know the final cause of sexuality; why new beings should be produced by the union of the two sexual elements, instead of by a process of parthenogenesis … The whole subject is as yet hidden in darkness" (Charles Darwin, 1862: 77, 96).

The evolution of sex is still widely regarded as one of the major unexplained phenomena in evolutionary biology (Barton & Charlesworth, 1998; Doncaster *et al.*, 2000; Otto & Lenormand, 2002; Otto, 2009; Colegrave, 2012; Lively & Morran, 2014; Neiman *et al.*, 2017; 2018; Bell, [1982] 2019). Several authors also continue to refer to sex as 'the queen of problems in evolutionary biology', highlighting the gravity of the explanatory paradox that remains unsolved (e.g., Colegrave, 2012; Neiman *et al.*, 2017; 2018; Bell, [1982] 2019).

The reasons why we have failed to explain sex are four-fold. First, sex is a metaphysically complex process whose evolutionary history entails many accompanying stages and mechanisms such as meiotic recombination, fertilization, ploidy evolution, and sexual mating strategies. In turn, we have attempted to explain such complexity from a monistic rather than a pluralistic mindset. Over the past 50 years, new hypotheses for sex were typically tested on their own merit or in comparison to other hypotheses. This has repeatedly proved to be the wrong explanatory approach to sex, as modern biologists have yet to agree on one hypothesis as capable of explaining the complete ambit of sexual processes sufficiently. A recent push has therefore been made to view the evolutionary benefits of sex from a 'pluralist' mindset, in which the hypotheses on sex are considered in unison, rather than in comparison because a complex and pervasive process as sex is likely maintained because of multiple benefits (e.g., West *et al.*, 1999; Neiman *et al.*, 2017; 2018).

Another reason why we have failed to explain sex is that we have viewed it from a monocausal and abstract standpoint. Many of the previous hypotheses for sex were modeled under simplified and restrictive assumptions that did not mirror the causal complexity of natural conditions (Otto, 2009). However, a recent push has been made by empiricists to model sex using a multifactorial approach, identifying the myriad genetic, ecological, or population factors that describe the natural conditions where sex is likely to evolve or be maintained (Otto, 2009; Lively & Morran, 2014). Such a multifactorial approach has proved to reveal more of the complex causal field of sex, making models more realistic with greater predictive power (Otto, 2009).

Yet a pluralistic or multifactorial approach may not always be useful to explain the various stages of sex. An important distinction has been made in the literature between the origins and maintenance of sex, since the causal mechanisms behind each respective stage are probable to vary considerably (Maynard Smith, 1978; Lenski, 1999). For example, some authors have suggested that many single factors acting in sequence were responsible for the early evolution of sexual processes, with each step providing a solution to one problem (e.g., Maynard Smith & Szathmary, 1995; Lenski, 1999). In this case, a multifactorial or pluralist approach would be less useful. However, others maintain that the transition to sexuality (from protoeukaryote to LECA) was made from simultaneous coevolved innovations (Goodenough & Heitman, 2014). Thus, another reason why we have failed to adequately explain sex is that we have not partitioned the relevant evolutionary stages along causal or evidential lines. While the literature is divided on how sex initially evolved, a certain consensus on the causal mechanisms behind its maintenance has manifested over the past 50 years. For this reason, each respective stage of sex likely warrants its distinctive explanatory approach. I generally limit the scope of this review to focus solely on the evolutionary maintenance of sex for this reason, not its origins.

The last issue has yet to be adequately recognized within the research traditions of sex. We have traditionally attempted to view and model the costs/benefits of sex at one level of biological organization, *within-species at the individual level*. However, many of the inherent costs and benefits of sex do not follow the theoretical projections of reductive models, making the evolutionary origins and maintenance of sex difficult to explain (Otto, 2009; S. Meirmans *et al.*, 2012; Hartfield & Keightley, 2012; Lehtonen *et al.*, 2012; Lively & Morran, 2014; Neiman *et al.*, 2017; 2018; Bell, [1982] 2019; cf. Stelzer, 2015). The immediate costs to the individual seemingly outweigh the benefits when compared with asexual reproduction. And this problem is further compounded by the near-ubiquity (Vrijenhoek, 1998) and the high conservation of sex across the eukaryotic spectrum (and similar popularity of parasexuality in prokaryotes or fungi)

because these are typical markers of strong and pervasive selection (Hartfield & Keightley, 2012). It follows that any analysis of sex must first consider the cost-to-benefit ratio, since the greater the costs, as well as the immediacy of these costs, the greater the benefits must be to mollify negative selection and explain the long-term maintenance of sexual processes (S. Meirmans *et al.*, 2012; Lehtonen *et al.*, 2012).

3.5 The Costs of Sex

The individual costs of sex are many (Otto, 2009; Lehtonen *et al.*, 2012; Meirmans *et al.*, 2012; Neiman & Schwander, 2011). When compared to the rapid rates of asexual reproduction, sex takes time and energy to find, attract, and mate with a partner; sex increases the risk of predation or infection by sexually transmitted diseases; sexual species forego the opportunity to gather resources when reproducing. Also, in many facultatively sexual species (i.e., species capable of switching between sexual and asexual reproductive modes), it takes more time and energy to switch from mitotic to meiotic reproductive modes (Otto, 2009).

One of the more serious costs is known as the 'two-fold cost' of sex (e.g., Maynard Smith, 1978; Williams, 1975; Gibson *et al.*, 2017). G.C. Williams referred to this as the 'cost of meiosis', which speaks to the transmission disadvantage imposed on sexual females since asexual female mutants transmit twice as many genes at the same or less energetic cost per offspring than sexual females (Lehtonen *et al.*, 2012). However, Joshi and Moody (1998) mathematically demonstrated that there is no cost of meiosis in dioecious species (there is in hermaphrodites) but found a two-fold cost of sex in the *cost of males*.

The *cost of males* proposed by Maynard Smith (1971a) is perhaps the more articulate and germane reading of the two-fold cost of sex (Lehtonen *et al.*, 2012). Assuming a 1:1 sex ratio, asexual females invest 100% of resources into clonal daughters while sexual females invest only 50% of their resources on females and waste the other 50% on males, which should lead to double the frequency of asexuals relative to their sexual counterparts. This is not to say that males contribute nothing to the sexual process, as they do contribute genetic material, but it does mean that there is an inherent cost to halving the number of reproductively viable members in a population due to resource distribution. Although few experimental studies have examined the *cost of males* directly, Gibson *et al.* (2017) found a large and immediate fitness disadvantage of sexual mutants in a seminatural population of the New Zealand mud snail (*Potamopyrgus antipodarum*) that was consistent with this hypothesis. However, it is doubly important to consider the ecological conditions in the case of the *cost of males*, as most species are strongly affected by resource distribution, resource supply, and the sharing of resources between asexual and sexual competitors[49] (i.e., *niche overlap*; Stelzer, 2015).

Another major cost of sex is recombination load, or the breaking of favorable genetic combinations (Barton & Charlesworth, 1998; Otto, 2009; Roze & Michod, 2010; Whitlock *et al.*,

[49] Psychological research indicates that biological males are more likely to engage in riskier behavior. For this reason, males may also be advantageous in the same way that somatic activity performs the 'riskier' metabolic activity while germ cells maintain healthier DNA; what is known as *the disposable soma hypothesis*. Another off-topic thought that I have on this subject is that the benefit (or one of the benefits) of sexual selection lies in the constant selective pressure applied to behaviorally sexual species, causing more adaptive evolution even in times of environmental stability, since selective pressure is the direct causal agent of natural selection.

2019). Given certain genetic backgrounds, such as in the presence of positive epistasis or genetic dominance, recombination destroys positive associations among alleles and reduces individual fitness, which in turn should cause negative selection against sexual mutants per the individual selection assumption (Nei, 1967; Maynard Smith, 1978; Lewis, 1987; Otto, 2009; Lehtonen *et al.*, 2012). This cost, however, may be beneficial in a different ecological circumstance.

3.6 The Benefits of Sex

There are two sides to the coin of sexual reproduction, dependent on ecological circumstances. Although the destruction of genetic associations by recombination is costly in some circumstances due to recombination load, this has been found to provide a benefit following environmental changes when species are less adapted to extant circumstances (Otto, 2009; Lively & Morran, 2014; Sharp & Otto, 2016). This is because the causal efficacy of natural selection is reduced when advantageous alleles become associated with deleterious alleles at linked loci due to drift, what is known as *Hill-Robertson interference* (Hill & Robertson, 1966; Felsenstein, 1974; Hartfield & Keightley, 2012). Recent evidence has shown that recombination breaks apart groups of linked loci and expands the range of gene combinations exposed to selection, including deleterious genetic linkages (or *selective interference*; Sharp & Otto, 2016), thereby increasing the strength of selection relative to drift (Goddard *et al.*, 2005; Mcdonald *et al.*, 2016; Neher *et al.*, 2010; Sharp & Otto, 2016).

This benefit remains the oldest and most intensely investigated explanation for the maintenance of sex, first proposed by August Weismann in 1889. Weismann (1889) hypothesized that sex provides novel and mostly advantageous genetic variation from the shuffling of genes during meiosis, which in turn increases the causal efficacy of natural selection and facilitates adaptation. After a hundred years of observation and scrutiny, Weismann's hypothesis remains the dominant explanation for sex (Maynard Smith, 1978; Barton & Charlseworth, 1998; Burt, 2000; Barton, 2009; Otto, 2009; Becks & Agrawal, 2012; Hartfield & Keightley, 2012; Colegrave, 2012; Roze, 2012; Bell, [1982]2019). Indeed, there is no shortage of evidence that the genetic variation produced during sexual recombination increases the rate of adaptation relative to asexual reproduction, especially in novel or complex environments, which has been demonstrated theoretically (Hadany & Comeron, 2008; Otto, 2009; Hickey & Golding, 2018) and experimentally (Colegrave, 2002; Kaltz & Bell, 2002; Goddard *et al.*, 2005; Grimberg & Zeyl, 2005; Gray & Goddard, 2012a; 2012b; Lachapelle & Bell, 2012; Masri *et al.*, 2013; Luijckx *et al.*, 2017; Chu *et al.*, 2017; see for more Becks & Agrawal, 2012; Lively & Morran, 2014). Additionally, outcrossing—or the interbreeding of unrelated individuals—has also been observed to facilitate greater rates of adaptation relative to self-fertilization, suggesting that the mixing of genetic material between lineages is the facilitatory action that begets the adaptation (Lively & Morran, 2014; Goldberg *et al.*, 2010).

However, one very important caveat needs to be noted. The proposed benefit of Weismann's model does not always follow in space and time. In some environments, recombination may decrease the amount of genetic variation in a population (Allen & Lynch, 2008; Gorelick & Heng, 2010). Even in cases where sex increases genetic variance, such an increase may be disadvantageous in the short term due to genetic slippage (Lynch & Deng, 1994). Similarly, higher rates of outcrossing or genetic shuffling are favorable only in novel environments when populations are not sufficiently adapted to their environment or when genetic associations are

negative, as the rates of outcrossing have been noted to decrease as fitness plateaus or when positive genetic associations increase (Allen & Lynch, 2008; Otto, 2009; Gorelick & Heng, 2010; Becks & Agrawal, 2012; Roze, 2012). When considered alone, Weismann's hypothesis, like the other hypotheses for sex, is not precise enough to explain the evolutionary maintenance of sex and recombination *in its entirety*. Sex does not always facilitate adaptation by outcrossing, nor is the facilitation of adaptation the only corroborated benefit of sex. Such a biologically complex process as sex likely requires a multifactorial and pluralistic approach, and other hypotheses either refine Weismann's original idea or explain the evolution of sex in different terms (Hartfield & Keightley, 2012).

Other explanations include the hypotheses that recombination reduces the probability of fixing deleterious mutations (or *Muller's Ratchet*; Muller, 1964; Jain, 2008); unites beneficial alleles from different lineages to facilitate adaptation through synergistic epistasis *(the Fisher-Muller model*; e.g., Fisher, 1930; Muller, 1932; Park & Krug, 2013; Scheuerl & Stelzer, 2017); reduces genetic hitchhiking associated with selective sweeps (e.g., Maynard Smith & Haigh, 1974; Hartfield & Otto, 2011); or defends against coevolving parasites (*Red Queen hypothesis*; e.g., Jaenike, 1978; Hamilton, 1980; Gibson *et al.*, 2017). Several recent studies have demonstrated that antagonistic coevolution with parasites could provide the continuous environmental pressure required to selectively maintain sex in the long term despite high costs to the individual (Morran *et al.*, 2011; Hartfield & Keightley, 2012).

When taken together, most of the hypothetical models that attempt to explain the maintenance of sex do imply an advantage at higher levels of organization over longer timescales, ascribing the main benefit of sex to be a genetic evolvability mechanism that allows species to adapt to constant environmental pressures (like parasites), variable or stressful environments, or long-term evolutionary obstacles (Wagner & Draghi, 2010; Bell, [1982] 2019). For example, prior work has demonstrated that sexually-bred *Chlamydomonas* lines resulted in increased fitness variance relative to asexual lines, in which an initial decrease in the mean fitness was shown to be offset by an eventual increase in long-term fitness (Colegrave *et al.* 2002; Kaltz & Bell, 2002), but this effect was seen only in laboratory settings (Allen & Lynch, 2008). Similar results were later observed in yeast by Goddard *et al.* (2005) and *Chlamydomonas* again by Lachapelle & Bell (2012) and Lagator *et al.* (2014), whereby recombination caused an initial increase in the rates of evolutionary rescue of sexual populations when placed in a novel, stressful environment. But this beneficial effect was not sustained as the populations adapted to their environment over time, leading to a fitness decline (Lagator *et al.*, 2014). In agreement with these findings, there is increasing evidence that the standing and cryptic genetic variation achieved through the sexual process plays a vital role in the evolutionary rescue and survival of species (Lachapelle & Bell, 2012; Bell, 2017; Uecker & Hermisson, 2016). Yet perhaps the best empirical example of the benefits of sex derives from Goldberg *et al.* (2010). They demonstrated that the short-term advantages of self-fertilization within the nightshade plant family (*Solanaceae*) are offset by strong species selection for obligate outcrossing, due to the higher rates of extinction amongst self-fertilizers in the long-term. These recent findings strongly suggest that recombination affords a major evolutionary benefit when species enter new habitats or following environmental changes, allowing them to evade extinction.

However, it must again be cautioned that such a complex process as sex likely confers more than one benefit, often at varying levels. According to Muller's *ratchet* (Muller, 1964), sex reduces the likelihood of fixing deleterious mutations due to drift, thereby improving individual fitness.

This 'masking' effect of sex has long been thought to be one of the major advantages of sex, first recognized by Sturtevant & Mather (1938) and Fisher (1930). For example, diploidy has been noted to improve the viability of individual offspring since diploids mask the phenotypic consequences of deleterious recessive mutations (called *lethal equivalents* in genetic nomenclature). However, this benefit is seen only in the presence of frequent genetic mixing (Otto, 2017; Scott & Rescan, 2017), as haploidy appears to be advantageous when species have less-frequent genetic mixing and more mutation since selection can purge the deleterious alleles faster than in diploids, allowing for greater rates of adaptation. These results demonstrate that sex is an efficient strategy for sorting beneficial from deleterious mutations (Mcdonald *et al.*, 2016), acting as both a buffer system that increases robustness at the individual level while also facilitating adaptation and evolvability at a higher level of selection. New philosophies such as pluralistic or multilevel explanations are therefore warranted to explain the complexity of sex.

3.7 Explaining the Maintenance of Sex

> "This nuisance is created by attempting to explain sex in too abstract a fashion, as though it were an ideal process whose mere material manifestations could be neglected, so that we are led into speculations whose worth cannot be established" (Bell, 1982: 160).

This brief review of the literature on the evolutionary maintenance of sex shows the problems and solutions acknowledged by researchers today. In particular, the maintenance of sex has proved incredibly difficult to explain given its causal complexity. Despite these difficulties, much epistemic progress has recently been made by simple transitions towards a pluralistic or multifactorial explanatory approach, thus paving the way for new models that could lead to more accurate predictions of sex and explain the major causal forces underlying its maintenance.

For example, it is now widely appreciated that the costs and benefits of sex shift over space and time thanks to recent ecological insights (Becks & Agrawal, 2012; Sharp & Otto, 2016; Neiman *et al*., 2018; Bell, [1982] 2019). In some environmental circumstances, sex may inflict grave costs on the individual and preclude its evolution or evolutionary maintenance, especially when species are well-adapted to their environment and genetic associations are positive (Allen & Lynch, 2008; Gorelick & Heng, 2010). In other instances, the benefits of sex may outweigh the costs when species are pressured to adapt to novel, harsh, or capricious environments, thereby maintaining sexual processes. Yet while these are the general trends from evidence, there are many external variables to consider that affect the likelihood of sex evolving.

Sex can also be maintained because of a reduction, circumvention, or inapplicability of costs due to developmental or genetic constraints, ecological differentiation, or life-history traits (Meirmans *et al.*, 2012; Lehtonen *et al.*, 2016). Populational characteristics such as inbreeding, population size, and the mutation rate can also affect the evolutionary maintenance of sex (Lively & Morran, 2014)—but all of which are also heavily dependent on environmental conditions. Thus, given all the necessary conditions that need to be considered, the best way to explain the evolution of sex is through a species-specific multifactorial approach that takes into account the broad ambit of causal conditions on a case-by-case basis (Meirmans *et al.*, 2012).

The Second Synthesis has underlined much of the progress seen within the research front on sex. We have undergone an important shift in perspective from asking the general question of *why*

has sex evolved, or examining the beneficial and costly functions of sex independent of environmental influence, to asking the more specific ecological question of *what conditions allow for sex to evolve*? This shift has been crucial for our understanding of sex, and largely influential for evolutionary biology as a whole, because it shifts our focus away from solely investigating the general benefits (or costs) of biological features, to attempting to map the complex causal field underlying the evolution of these features *in an ecological context*—which generally allows for more accurate predictions (Otto, 2017). Approaching the evolution of biological features from this perspective lends itself to a multifactorial approach that more accurately parallels the evolutionary process in nature since rarely do we see the causal forces working in isolation to explain the entire evolutionary history of a biological feature or trait.

According to the sexpert Sally Otto (2017), we need a multilevel and dynamic model of natural selection that can explain the evolutionary maintenance of sex for higher-level reasons (such as increased variability) that is, in turn, also capable of explaining the opposite biological pattern of selection acting at the behest of the individual, such as pushes for decreased recombination or selection for haploidy in the presence of frequent genetic mixing (Otto, 2017). However, our current model of natural selection is currently incapable of availing these suggestions due to its monistic and reductive nature, keeping the *paradox of sexual reproduction* an active problem for modern evolutionary biology.

We now find ourselves at an epistemic juncture where we can confidently assert that higher-level selective processes have played a major causal role in the evolutionary maintenance of sex. This conclusion is accepted by most researchers today since higher-level selection appears to be the best way to explain why the action of genetic mixing occurs in a vast amount of species, despite individual fitness costs (Stanley, 1975b; Nunney, 1989; Otto, 2009; Goldberg *et al.*, 2010; Becks & Agrawal, 2012; Lively & Morran, 2014; Sharp & Otto, 2016; Neiman *et al.*, 2018; Whitlock *et al.*, 2019; Bell, [1982] 2019). What is therefore recommended to resolve the long-standing *paradox of sex* is (a) a multilevel and dynamic model of natural selection that views selective pressures and subsequent adaptation as varying over space and time and at multiple levels, coupled with (b) a multifactorial approach towards the natural conditions that influence the likelihood of sex evolving, and (c) a pluralist approach towards the hypotheses for sex. Interestingly, these recommendations do not *only* apply to the evolution of sex. A similar explanatory paradox has also arisen within the adaptive mutation literature.

3.8 *The Paradox of Adaptive Mutation*

Around the same time that *the paradox of sex* was becoming widely recognized within the evolutionary biology community, similar trends were sprouting in the literature on mutational dynamics. Although mutations were largely believed to be random and arise independently of selective influence during the first synthesis (Fitzgerald & Rosenberg, 2019), several experimental studies performed in the 1960s-80s found increased mutation rates in stressed populations, despite the largely deleterious effect that mutations would likely have on an individual's phenotype. Such strange findings led to the bifurcation of two models in the 1990s that ultimately quarrel over the explanation of the underlying causation and dynamics of mutation—*the non-adaptive vs. adaptive models of mutation*.

The conventional *non-adaptive* approach comprises *Drake's model* (Drake, 1991) and Lynch's *Drift-Barrier Hypothesis* (Lynch, 2010; Lynch *et al.*, 2016) that attempt to conserve as much of the modern synthetic model of natural selection as possible. These models maintain the individual selection assumption through the idea that natural selection acts to invariably drive mutation rates down to as low a value as possible *in every ecological context*, because new mutations are deleterious to the individual phenotype (Hershberg, 2015).

The adaptive approach, on the other hand, derived from early experimental evidence performed on *E. coli* and suggested that increased mutation rates were advantageous to populations placed in a novel environment. Thus, the lively non-adaptive vs. adaptive debate today centers around one consequential question: *how does natural selection influence the mechanisms of mutation?*

Yet a step before reaching the epistemic juncture of presupposing the influence of natural selection on the mechanisms of mutation, the question was not *how natural selection acts on the mechanisms of mutation*, but ***if*** *natural selection acts on the mechanisms of variation altogether*. Past models of mutation looked vastly different from our modern models, and understanding the conceptual development leading up to modern models provides a useful context to contrast their validity.

3.9 Early Models of Mutation

American geneticist A. Sturtevant (1937) reasoned early on that the genes that affect the underlying production of mutation and determine the absolute rates of mutations (i.e., what we now refer to as *modifier genes*) are themselves subject to mutation and therefore may be subject to natural selection. He suggested that such modifier genes could evolve to fixation because of their genetic associations with a fitness-affecting mutation at other loci (Raynes & Sniegowski, 2014). However, this idea was buried during the first synthesis since the processes of natural selection and variation were largely believed to be separate causal processes that operate independently of one another (Mayr, 1982).

Following the first synthesis, selective influence was seen to not affect the mechanisms of genetic variation, and hence variation was believed to be generated randomly (Fitzgerald & Rosenberg, 2019)[50]. Of course, several theoretical exemptions were tagged onto this model following observations in the mid-twentieth century. For example, external influences could potentially influence the mutation process, but only in the form of singular events such as radiation or the application of other environmentally induced mutagens. Yet the environmental effects of natural selection were never seen as a viable force working on mutation—a theoretical conclusion that would become entrenched following several classic experiments performed in the wake of World War II.

The frequent usage of penicillin in WWII led to antibiotic resistance which perplexed biologists, and the molecular mechanisms underlying mutation were largely unknown at this time

[50] Biologists often refer to variation as a 'random' process (e.g., Charlesworth *et al.*, 2017), yet 'random' has multiple meanings in evolutionary biology (see for more Gayon, 2005; Merlin, 2010; Millstein, 2011).

(Hershberg, 2015)[51]. This prompted several studies by Luria and Delbrück (1943), Newcombe (1949), and Lederberg and Lederberg (1952), who found that the resistant mutants were present in the population before the introduction of the antibiotics, rather than arising in response to the selective pressure of the antibiotics. These findings were interpreted as evidence that selection does not affect mutation rates and bolstered the notion that all mutants arise as random replication errors concerning their selective consequences (i.e., are *undirected*), therefore maintaining the modern synthetic concept of *random variation* (Maisnier-Patin & Roth, 2015).

However, early attempts at pinpointing the causal mechanisms behind mutations responsible for specific phenotypes were often challenging due to noisy data (a confound noted by Luria & Delbruck in their 1943 paper). As Shapiro (1984) would point out, these experiments used immediately lethal selective agents (i.e., virulent phages or streptomycin) and thus could only produce mutants in the absence of selection. Their statistical analyses of the variation in mutant frequencies were not particularly informative about the regulation of the mutagenic process, precisely because any reasonably complex system would appear stochastic. Despite these methodological shortcomings, many biologists still tout these studies as established knowledge (e.g., Charlesworth *et al.*, 2017).

This conclusion remained popular until the late 1960s, 70s, and 80s when experimental findings began to erode the idea that mutations are random, as several studies indicated that mutation rates were *non-randomly influenced by the environment and subject to selection* (e.g., Witikin, 1967; Cox & Gibson, 1974; Gross & Siegal, 1981; see for more Fitzgerald & Rosenberg, 2019). Such findings finally liberated the conceptual divide between natural selection and variation, leading to the eventual bifurcation of two distinct approaches to mutation in the 1990s that debated an entirely new question: *if natural selection does indeed affect the mechanisms of mutation, what effect does it have on these mechanisms?*

3.10 The Non-Adaptive Models of Mutation – Drake's Model and The Drift Barrier

The non-adaptive models of mutation were the more theoretically conservative approach to explaining this exciting new observation. Many biologists tried to reconcile such a new contradictory conclusion with other tenets of the modern synthetic model, conserving its theoretical foundations. If natural selection *does* influence the mechanisms of mutation, then it must do so in a way that aligns with the modern synthetic model of adaptive evolution. Natural selection must favor the lowering of mutation rates since most mutations are deleterious to the individual, per the individual selection assumption (Kimura, 1967; Drake, 1991; Dawson, 1998; Lynch, 2010; Lynch *et al.*, 2016; Charlesworth *et al.*, 2017; Hershberg, 2015).

John Drake (1991) first proposed his model as a non-adaptive approach. To explain the observation that mutation rates appear to be fine-tuned, Drake argued that the mutation equilibrium is reached when the benefit of lowering mutation rates parallels the energetical cost of continuing to do so (e.g., Kimura 1967; Drake 1991; Dawson 1998)[52]. Under this

[51] The Luria & Delbruck (1943) and Lederberg and Lederberg (1952) studies were also prompted by claims that the antibiotic resistance was due to Lamarckian mechanisms, which were quickly and effortlessly dismissed as a viable explanation.

[52] *The neutral theory of evolution* (Kimura, 1968; 1983) and *the nearly neutral theory* (Ohta, 1973) provided one of the greatest advances in our knowledge of mutational dynamics since the first synthesis. A vast amount of

interpretation, natural selection causes both the decrease in the mutation rate as well as the eventual plateau of this decrease to save energetical resources. However, recent advances in whole-genome sequencing have made our measures of absolute mutation rates more precise, and several studies have observed higher mutation rates than predicted by Drake's model (Lee *et al.*, 2012; Sung *et al.*, 2012).

Another non-adaptive approach was recently proposed by the geneticist Michael Lynch, referred to as The *Drift-Barrier Hypothesis* (Lynch, 2010; Lynch, 2011; Lynch *et al.*, 2016). Under this interpretation of mutational dynamics, the lower limit on mutation rates is not offset by the energetical costs as suggested by Drake's model, but rather by genetic drift. This model is best summarized by Sung *et al.* (2012):

> "…the drift-barrier hypothesis predicts that the level of refinement of molecular attributes, including DNA replication fidelity and repair, that can be accomplished by natural selection will be negatively correlated with the effective population size (N_e) of a species. Under this hypothesis, as natural selection pushes a trait toward perfection, further improvements are expected to have diminishing fitness advantages. Once the point is reached beyond which the effects of subsequent beneficial mutations are unlikely to be large enough to overcome the power of random genetic drift, adaptive progress is expected to come to a standstill. Because selection is generally expected to favor lower mutation rates as a result of the associated load of deleterious mutations, and because the power of drift is inversely proportional to Ne, lower mutation rates are expected in species with larger N_e" (Sung, *et al.*, 2012).

The drift barrier is predicated on the assumption that the vast majority of mutations are deleterious and are therefore indirectly selected against through associations with the deleterious alleles generated elsewhere in the genome, similar to earlier models proposed by Kimura (1967). As mutation rates are lowered, selection to further reduce mutation rates becomes weaker, until a point is reached in which selection is no longer strong enough to counteract the action of genetic drift (Lynch, 2010; Lynch *et al.*, 2016). Supporting the model, Lynch argues that many per-base mutation rates inversely correlate with the effective population size (N_e) found in both prokaryotes and eukaryotes (Lynch, 2010; Sung *et al.*, 2012; Lynch *et al.*, 2016).

While the non-adaptive models do well to explain and predict the lower-bound limits of mutation rates, there have been numerous observations of mutation rates that exceed far above their minimum predictable threshold. Increasing literature is now dedicated to explaining this unusual phenomenon, similar to *the paradox of sex*.

3.11 Recognizing the Paradox of Mutation: The Adaptive Mutation Controversy

Some of the same findings in the late 1960s, 70s, and 80s that led biologists to rethink the 'randomness' of mutations also suggested an alternative interpretation from the conservative non-adaptive models (Hershberg, 2015; Fitzgerald & Rosenberg, 2019). Rather than invariably

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potentially adaptive genetic variation was now thought to be held in natural populations as *nearly neutral* variation, and most new mutations were now conceived to have little to no effect on an organism's phenotype, emancipating the effects of selection to purify individually deleterious mutations and therefore relaxing the individual selection assumption. However, the resultant theory that was constructed out of these findings (e.g., mutation-selection equilibrium) still neglected the actions of ecological heterogeneity and stress in evolution, denying the role that ecology played in maintaining and procuring genetic diversity (Nevo, 2001).

driving mutation rates down to as low a value as possible and selecting against all mutations in every ecological context, natural selection may favor the increase of mutation rates and mutator alleles, hypermutator mechanisms, or certain kinds of mutation over others when environments change.

This new hypothesis came from Cox and Gibson's (1974) famous *E. coli* experiment that suggested that higher mutation rates were advantageous in variable environments. Several subsequent studies by Shapiro (1984), Cairns *et al.* (1988), and Cairns & Foster (1991) found similar results when they observed manipulated strains of *E. coli* mutating advantageously following their placement in a novel environment on a growth-dependent plate. These findings surprised researchers because they indicated that mutations may not occur by spontaneous

mechanisms and may adapt the cells to their environment (see for recognized errors of these studies Hershberg, 2015; Maisnier-Patin & Roth, 2015)[53].

Box 6: Why Adaptive Mutation is Not Lamarckism or Directed Mutation

Biologists continue to liken adaptive mutation and evolvability to the developmental programmes of Lamarckism or directed mutation (e.g., Charlesworth *et al.*, 2017). There is some evidence to suggest that Lamarckian mechanisms of 'soft' inheritance— i.e., the heritable transmission of variations that arise during development— may hold some evolutionary significance, in the same way that phenotypic plasticity mechanisms influence the evolutionary process in the short-term (Lind & Spagopoulou, 2018; Bernatchez, 2016; Zhang *et al.*, 2018). However, there is insufficient evidence to suggest that the heritable effects of Lamarckian mechanisms are long-lasting and therefore contributable to permanent evolutionary adaptation in the long-term (Charlesworth *et al.*, 2017; Futuyma, 2017b; Eichten & Springer, 2015; Iqbal *et al.*, 2015). In contrast, adaptive mutation does have a robust literature in support, and since changes in genetic composition are relatively fixed, adaptive mutation mechanisms do affect the evolutionary process in the long-term.

In a similar vein, adaptive mutation is not arguing for the same theoretical conclusions as directed mutation. Whether or not the effect of increased mutations directed towards a specific area of the genome is generated through an innate, site-specific mutagenic stress response (i.e., what is often referred to as directed mutation) is still up for debate and requires more empirical attention, as there is insufficient evidence to support this model today (Fitzgerald & Rosenberg, 2019). But this matter is independent of adaptive mutation, which strictly argues that populations vary in their dynamics of mutation, and that this variance is largely dependent on context. Adaptive mutation argues that environmental pressures can cause a global increase in the rate of mutations in a population to direct adaptation through an increased probability that an advantageous mutation will occur but does nothing to say that an advantageous mutation will occur indefinitely nor at a specific site. In turn, adaptive mutation models still accept that (1) the concomitant mutational load associated with increased mutation rates, and therefore that (2) the mutational process maintains a level of stochasticity or randomness, since the subsequent phenotypic effect of mutations cannot be predicted or directed by the evolutionary process. Thus, in comparison, they main difference between adaptive mutation and directed mutation models is that the latter does not conceive of any randomness in the mutational process and therefore suffers as a teleological imputation, since innate mechanisms are seen to recognize the environmental pressure put on specific genes and can cause an advantageous mutation at this one specific loci of an individual. When juxtaposed, the concept of adaptive mutation is not merely conceptually distinct from the psuedoconceptual models of Lamarckism or directed mutation, but more importantly, adaptive mutation has a robust literature in support.

Another major observation led to more puzzling conclusions. Several biologists in the 1980s and 90s found that approximately 1% of all-natural bacterial isolates were extreme hypermutators, with approximately 10–30% being weak mutators (Gross & Siegel, 1981; LeClerc *et al.*, 1996; Matic *et al.*, 1997; Hershberg, 2015). This led some biologists to ask *why such a high frequency of hypermutating bacteria is maintained within these populations.* The unlikely explanation that *mutators accelerate adaptation in asexual populations* became the accepted explanation for this phenomenon (Sniegowski *et al.*, 1997; Taddei *et al.*, 1997; Giraud *et al.*, 2001; Notley-McRobb *et al.*, 2002).

The *paradox of adaptive mutation* was thus beginning to be recognized approximately 20 years after the paradox of sex became a consensus (Rosenberg, 2001; Fitzgerald & Rosenberg, 2019), but only by a select few biologists within a few research fronts (particularly microbiologists). Despite costs to individual fitness, mutator alleles appeared selectively advantageous following environmental changes, providing some populations with a higher-level advantage to combat novel environmental pressures. These conclusions eventually caused the adaptive

models of mutation to split off from the non-adaptive models. While the non-adaptive models of mutation kept with much of modern synthetic theory, the adaptive models of mutation were advertised as a different and novel approach to understanding the underlying causation and dynamics of mutation. The non-adaptive models do well to explain and predict the lower-bound limits of mutation rates, yet they run into issues when attempting to explain the converse finding, of mutation rates that exceed far above their minimum predictable threshold. In the following section, I concisely review the evidence for adaptive mutation, which validates the realism of *the paradox of adaptive mutation*, and then conclude with a prescriptive argument for how to resolve this paradox, similar to those previously given in the section on sex.

3.12 Review of the Modern Literature on Adaptive Mutation[54]

The adaptive model of mutation has been extensively studied and reviewed over the past 20 years from various perspectives, with a vast and often abstruse literature at hand (Foster, 1999; 2000; Rosenberg, 2001; Roth *et al.*, 2006; Lynch, 2007b; Baer *et al.*, 2007; Barrick & Lenski, 2013; Maisnier-Patin & Roth, 2015; Hershberg, 2015; Lynch *et al.*, 2016; Fitzgerald *et al.*, 2017; Fitzgerald & Rosenberg, 2019). Several proponents of adaptive mutation argue that global mutation rates have been fine-tuned by natural selection to maximize the long-term survival and evolvability of populations (Rosenberg, 2001; Denamur & Matic, 2006; Galhardo *et al.*, 2007; Martincorena *et al.*, 2012; Paul *et al.*, 2013; Fitzgerald & Rosenberg, 2019). Others have disagreed with this claim on the basis that there is not enough supporting evidence (Roth *et al.*, 2006; Lynch, 2007b; Lynch *et al.*, 2016; Maisnier-Patin & Roth, 2015; Hershberg, 2015).

However, I argue that the literature substantiates both viewpoints to a certain extent. Recent studies have provided sufficient evidence to suggest that mutation rates are not 'fine-tuned' to maximize the long-term survival of populations, but that they are more dynamic and highly responsive to changing environmental conditions than previously assumed (Bonnet et al., 2022), with this "flexibility" (i.e., *evolvability*) also affecting the long-term survival of populations over time (Engelhardt & Shakhnovich, 2019; Swings *et al.*, 2017; Ram & Hadany, 2012). Mutation rates are more plastic, in both an evolutionary and mechanistic sense, than previously assumed.

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[53] It is important to note that Cairns & Foster (1991) did not find any mutations to be directed to the genes that grant the greatest fitness benefit (e.g., directed mutation), since unselected mutations outside the loci of interest were also accumulated (Cairns & Foster, 1991). Certain researchers, such as Charlesworth *et al.* (2017) have wrongly labelled the Cairns experiments (Cairns *et al.*, 1988; Cairns & Foster, 1991) as evidencing directed mutation—or an increased mutation rate in a specific and targeted DNA sequence in response to environmental pressure. Cairns & Foster (1991) clearly state that the mutations were *not directed* to the genes that would afford the organisms the greater fitness benefit and instead saw a genome-wide increase in mutations or the absolute mutation rate (see for more **Box 6**).

[54] The literature on mutational dynamics is exceptionally broad. Many of these studies define mutation or mutation rate differently. Some have focused on the substitution rate rather than mutation rate. But most studies cited in this section strictly measure nucleotide substitutions. I, therefore, take a broad approach to review this vast literature, broadly defining 'mutation' here as any genetic changes in the DNA sequence that are not horizontally transferred, with important aberrations to be considered later in the review on gene/genome duplication or genetic transposition. Moreover, I will place a special emphasis here on mutation rate evolution, since this is how the adaptive vs. non-adaptive debate is typically framed.

The optimal mutation rate is known to depend on a number of genetic, populational, and/or ecological factors including genome size, effective population size, presence of recombination, or environmental variability. Given these factors, it is not surprising that mutation rates vary greatly within and between populations (this variance has also been found to extend to within-genomes, which will not be covered here).

Empirical studies have repeatedly observed faster adaptation due to a global increase in per-base mutation rates from error-prone DNA (and sometimes RNA) polymerase activity, particularly in asexual prokaryotic lineages (LeClerc *et al.*, 1996; Tenaillon *et al.*, 2000; Travis & Travis, 2002; Tanaka *et al.*, 2003; Rattray & Strathern, 2003; Gerrish *et al.*, 2007; Rajon & Masel, 2011; Million-Weaver *et al.*, 2015; Tenaillon *et al.*, 2016; Ragheb *et al.*, 2019; Arenas & Cooper, 2013; Lenski, 2017). Mutators tend to produce offspring with relatively higher genetic variation, which in most cases leads to greater phenotypic diversity and increases the likelihood that a beneficial phenotype will evolve. An increase in phenotypic diversity is therefore important when a population is exposed to stressful or novel environments, which is thought to prompt an increase in the frequency of the mutators alleles within a population (Loh *et al.*, 2010; Swings *et al.*, 2017).

Hypermutation (i.e., an observed increase in mutation rates) has been commonly observed in microorganisms when placed under great selective pressure, especially in pathogens (Swings *et al.*, 2017; Wiser *et al.*, 2013). A much higher prevalence of hypermutators has been found to exist in natural bacterial populations (Gross & Siegel, 1981; Hall & Henderson-Begg, 2006) such as *E. coli* (LeClerc *et al.*, 1996; Matic *et al.*, 1997; Denamur *et al.*, 2006), *Pseudomonas aeruginosa* (Marvig *et al.*, 2015; Oliver, 2015), *Salmonella* (LeClerc *et al.*, 1996), *Staphylococcus aureus* (Iguchi *et al.*, 2016), *A. baumannii* (Hammerstrom *et al.*, 2015), and others (see for more Swings *et al.*, 2017). The high mutation rate of HIV has also allowed for its continual evasion of the immune system (Rambaut *et al.*, 2004). But hypermutation is not domain-specific to prokaryotes or viruses. Similar findings have been exhibited in pathogenic eukaryotes under extreme stress, despite hypermutation being a less common strategy for adaptation in eukaryotes due to ploidy evolution and recombination of eukaryotic cells (Thompson *et al.*, 2006). These include *S. cerevisiae* (Voordeckers *et al.*, 2015; Liu & Zhang, 2019), the parasite *Plasmodium falciparum* (Lee & Fidock, 2016; Gupta *et al.*, 2016), and the fungal pathogen *Candida glabrata* (Healey *et al.*, 2016). Hypermutation has also been found to play a similar role in cancer development and proliferation, since it expands the genetic range of a cancerous cell that is necessary to overcome barriers to tumor progression (Coelho *et al.*, 2019), allowing them to adapt to therapeutic pressure by enhancing their mutability (Russo *et al.*, 2019). A greater understanding of the hypermutation process in yeast and bacteria may thus yield valuable insights into curbing cancer proliferation (Natali & Rancati, 2019). These findings suggest that higher mutation rates confer a selective advantage at many levels of biological organization, allowing individual cells, populations, or species to adapt away from environmental stressors and survive.

The best example of this last observation derives from recent studies on microbial resistance to our antibiotics (AMR). The World Health Organization has consistently included AMR in their top 10 list of threats to global health for nearly two decades, and this growing concern has been primarily directed at microbes that can evolve quickly out from under our defenses (i.e., evolvability). Recent studies have convincingly demonstrated that the evolvability observed in these bacteria has been the result of ingrained genetic mechanisms that switch to transient

hypermutator states when under pressure (Mehta *et al.*, 2019; Pribis *et al.*, 2019; Blázquez *et al.*, 2018; Couce *et al.*, 2015; see for more Windels *et al.*, 2019). One such study by Ragheb *et al.* (2019) took a novel approach to investigate AMR by inhibiting evolution in several strains of bacteria through the inactivation of the highly-conserved DNA translocase protein *Mfd*[55]. The function of *Mfd* was thought to be in transcription-coupled repair that initiates the nucleotide excision repair of bulky lesions of DNA at sites where RNA polymerases have stalled. Yet recent evidence has also observed *Mfd* increases mutagenesis when under environmental stress (Million-Weaver *et al.*, 2015; Martin *et al.*, 2011; Wimberly *et al.*, 2013; Pani & Nudler, 2017), suggesting that *Mfd* is multifunctional. Ragheb *et al.* (2019) therefore inactivated *Mfd* in several mutant strains of *Salmonella typhimurium* and *Bacillus subtilis*, finding a 2- to 5-fold lower mutation rate that corresponded to antibiotic resistance levels of 6- to 21- fold lower than those seen in the wild-type strains with active *Mfd*. The most surprising finding, however, was that *Mycobacterium tuberculosis* mutant strains lacking *Mfd* were found to be nearly 1,000x less likely to evolve antibiotic resistance than the wild-type strains, hinting at the crucial role that *Mfd* plays in *tuberculosis* AMR. These results suggest that inhibiting genetic evolvability mechanisms that accelerate evolution (through a supposed 'anti-evolution' drug) could provide a pragmatic and supplementary treatment option to curb AMR development and other pathogenic infections. Moreover, the high conservation of *Mfd* across the prokaryotic domain indicates that it has been selectively maintained over time and suggests that prokaryotic species have multifunctional evolvability mechanisms that can switch to hypermutator states (through moonlighting proteins such as DNA and RNA polymerases) when under strong selection.

Such transient hypermutation states have been observed in several species of bacteria, and the evolvability afforded by these mechanisms appears to be causally connected to the evolutionary survival of these species in the long term (e.g., Windels *et al.*, 2019; Swings *et al.*, 2017; Tenaillon *et al.*, 2016; Couce *et al.*, 2015; Maclean *et al.*, 2013; Wielgoss *et al.* 2013). Mathematical analyses have also theoretically demonstrated that stress-induced mutator alleles (i.e., transient hypermutation or evolvability mechanisms) are favored by natural selection over mutators that constitutively increase mutation rates in both variable and constant environments (Ram & Hadany, 2012), with further work also showing that these stress-induced mutators may increase the rate of adaptation without jeopardizing the mean fitness of well-adapted asexual populations (Ram & Hadany, 2014).

Due to the Second Synthesis, recent experimental and methodological advances now allow for studies that can finally shed light on the long-term fate of mutators (Barrick & Lenski, 2013). One of the more interesting findings from Richard Lenski's famous *long-term evolution experiment* (LTEE) was that multiple populations of *E. coli* evolved elevated point-mutation rates (~100x) at various times of the LTEE, which caused the subsequent adaptation and increased complexity observed in these populations (Sniegowski *et al.* 1997; Blount *et al.* 2012; Wielgoss *et al.* 2013; Tenaillon *et al.* 2016; Lenski, 2017). One such study found that hypermutator populations initially adapted faster to their novel environment and exhibited a higher mean fitness in the long-term over those populations that retained their ancestral mutation rate (Wiser *et al.*, 2013). Loh *et al.* (2010) found similar results by manipulating the high-fidelity DNA polymerase I of *E. coli* to express varying mutation rates across a variable environment.

[55] *Mfd* has also been found to promote DNA repair and transcription fidelity in response to UV radiation, but does the opposite in the presence of antibiotics, suggesting that the kind of environmental pressure applied begets different functions from Mfd.

Mild mutators eventually outperformed the wild-type and extreme-mutator strains through the "hitchhiking" model of mutator evolution—that is, mutator alleles being carried to a high frequency through the genetic associations they have with the adaptive mutations they generate, which is a common explanation for the presence of mutator modifiers in populations (Good & Desai, 2016; Raynes & Sniegowski, 2014). While more research is certainly warranted to understand better the long-term dynamics of hypermutation (outside model organisms), the burgeoning research front on *evolutionary rescue* is beginning to reveal similar trends.

The important role that adaptive mutation plays in the evolutionary rescue of populations has only recently come to light (Osmond *et al.*, 2020; Anciaux *et al.*, 2019; 2018; Bell, 2017; Carlson *et al.*, 2014; Orr & Unckless, 2008; 2014; Gonzalez *et al.*, 2013; Gonzalez & Bell, 2013; Bell & Gonzalez, 2011; Bell & Gonzalez, 2009), largely because of the effects of rapid anthropogenic climate change (Alexander *et al.*, 2014; Lindsey *et al.*, 2013). Both standing genetic variation and *de novo* variation are essential for the evolutionary rescue of natural populations (Gomulkiewicz & Holt, 1995; Ramsayer *et al.*, 2013). While recombination and standing genetic variation are already known to play a vital role in evolutionary rescue (Bell, 2017; Carlson *et al.*, 2014), the production of *de novo* mutation appears to be more salient in the rescue process. This is because mutation affects both standing and *de novo* variation. Higher mutation rates are therefore used as a predictive measure in correspondence with a greater probability of evolutionary rescue (Osmond *et al.*, 2020; Orr & Unckless, 2014; Martin *et al.*, 2013; Anciaux *et al.*, 2019; 2018)[56].

Although few experimental studies have directly manipulated the mutation rate to test these predictions (Bell, 2017; Carlson *et al.*, 2014), there is ample theoretical (Anciaux *et al.*, 2019; 2018; Osmond *et al.*, 2020; Greenspoon & Mideo, 2017; Taddei *et al.*, 1997) and indirect empirical evidence to support this conclusion (e.g., the AMR studies). For example, species diversity is known to be a determinant of the likelihood of species extirpation from climate change (Alexander *et al.*, 2014), and an increasing number of empirical and theoretical studies have drawn a strong positive correlation between rates of mutation and diversification (Hua & Bromham, 2017). Moreover, recent studies have identified the superiority of *genetic rescue* over other types of rescue (e.g., demographic, developmental) in combating species extinction from climate change, indicating that the introduction of novel genetic variation into a threatened gene pool is the faciliatory action that begets new adaptation in evolutionary rescue (Hufbauer *et al.*, 2015). Thus, it is commonly reasoned that when threatened populations can no longer combat climate change with phenotypic plasticity mechanisms or demographic rescue strategies (such as increased gene flow, migration, or dispersal methods), pressure is put on a species to evolve through genetic adaptation from *de novo* genetic variation (Carlson *et al.*, 2014; Alexander *et al.*, 2014; Gonzalez *et al.*, 2013; cf. Merilä & Hendry, 2014).

However, raising mutation rates is not always an advantageous strategy in evolution. High mutation rates have been observed to drive a population to extinction from the acceleration of Muller's ratchet, mutational meltdowns, exceeding the lethal mutation rate, or if the error threshold for fitness is exceeded (Gerrish *et al.*, 2007). For these reasons, natural selection likely

[56] Contra this position, Ferriere & Legendre (2013) maintain that low genetic variation may attenuate the threat of evolutionary suicide and small population sizes may facilitate escape from evolutionary traps.

imposes upper-bound limitations on the mutation rate to avoid species extinction in natural populations.

The most consistent finding from the literature on mutational dynamics is that they are heavily dependent on species-environment relationships, which limits the upper bounds of mutation rates. Tenaillon *et al.* (2016) noted that an initial increase in the frequency of hypermutators in several populations—one caused by a DNA mismatch repair mutation and another caused by a transposable element—was met with an eventual plateau of hypermutability and even led to a decline in some populations following accruing mutational load. Experimental studies on bacteria have consistently found this same evolutionary trajectory: when populations encounter a novel environment or any changes in their environment that result in a low mean fitness or a fitness reduction (i.e., from environmental stress), hypermutator states and mutator modifiers are favored to facilitate adaptation (e.g., Desai & Fisher, 2011; McDonald *et al.*, 2012; Wielgoss *et al.* 2013; Good & Desai, 2016; Swings *et al.*, 2017). But following sufficient adaptation to the new environmental conditions, the opportunity for further improvement is offset by the cost of deleterious mutations. A lowered mutation rate is favored once the fitness gains from reducing mutational load become greater than the gains associated with beneficial mutations from a high mutation rate (Lenski, 2017; Raynes & Sniegowski, 2014). Sprouffske *et al.* (2018) also found that while higher mutators accumulated more genetic diversity, this increase in diversity conveyed benefits only for milder mutating populations. Milder mutators were better at adapting and surviving over higher mutators, even when placed in a novel environment with persistent chemical stressors applied, suggesting that there is an upper bound limit to the mutation rate that even stressed populations may not cross.

3.13 Explaining Adaptive Mutation

Our knowledge of the underlying causation and dynamics of the mutation process has progressed tremendously since the first synthesis. Contrary to the Darwinian concept of *random variation* that drew a causal divide between the production of variation and natural selection, it is now widely appreciated that selection influences the mutation process through modifiers (Otto, 2014). This has led to the important alteration of our causal structure of evolutionary theory from assuming "variation as a predominantly random process" to "random variation (that arises irrespective of selective needs) that can be affected by non-random selection." Perhaps more importantly, recent work has convincingly demonstrated that natural selection does not invariably push mutation rates down to as low a value as possible, but may favor an increase in mutation rates, mutator alleles, and/or biological mechanisms that switch to hypermutator states when populations become less adapted to their environmental circumstances to save evolvability, despite immediate fitness consequences in offspring viability at the individual level.

There remains considerable debate over whether ancestral mutation rates are "low" because of their individually deleterious effects (Lynch, 2007b; Lynch *et al.*, 2016; Maisnier-Patin & Roth, 2015; Hershberg, 2015; Raynes & Sniegowski, 2014) or "high/fine-tuned" to maximize the long-term survival of populations (Fitzgerald *et al.*, 2017; Fitzgerald & Rosenberg, 2019; Denamur & Matic, 2006; Galhardo *et al.*, 2007; Martincorena *et al.*, 2012; Paul *et al.*, 2013). However, I believe this debate runs independently of what the evidence implies. There is less evidence to

suggest that ancestral mutation rates are fine-tuned to maximize future benefits, as many recent mutation accumulation studies have observed a "low" ancestral mutation rate in bacteria and single-celled eukaryotes (Barrick & Lenski, 2013; Raynes & Sniegowski, 2014). But there is increasing evidence to suggest that genomes have multifunctional dynamic evolvability responses that can switch to transient hypermutation states or release genetic constraints (through changes in genetic architecture), thereby allowing mutator alleles to more easily evolve when populations are placed under pressure to adapt to novel environmental conditions (more on this in Chapter 5).

The non-adaptive models, therefore, do well to explain the lower bound limits of mutation rates. But like the evolution of sexual reproduction and recombination rates, the optimal mutation rate varies greatly in space and time, as it depnds on numerous genetic, populational, and ecological factors. When species become less adapted to their extant environmental circumstances, higher mutation rates are favored (either by selection for mutator alleles or by switching to transient hypermutator states) to generate more genetic variation and increase the likelihood of generating a beneficial mutant, but only to a given point. Upper-bound limits to mutation are set by the concomitant mutational load and other limits to the beneficial effects of high mutation rates. The optimal mutation rate therefore evolves between these lower- and upper bounds set by multilevel selection and drift, with many causal factors explaining the movement and variance of rates between these two bounds.

Under this pluralistic view of mutational dynamics, natural selection plays a primary role but at multiple levels of biological organization. Several authors have interpreted these findings as a tension between opposing effects of selection (Lenski, 2017; Wielgloss *et al.*, 2013; Good & Desai, 2016), with mutator alleles being thought to arise from "second-order" or "indirect" selection through genetic hitchhiking with the beneficial mutations they produce (Tenaillon *et al.*, 2016; Good & Desai, 2016; Raynes & Sniegowski, 2014)[57]. However, given the individually deleterious effects of mutation and the necessity of generating new variation at the population level, the best interpretation of these findings is that the optimal mutation rate is set by selection acting at different levels. Individual selection pushes for lower mutation rates to maintain the genetic viability of offspring while higher-level selection pushes for higher mutation rates to generate variability. While "second-order selection" offers a potential explanation for the initial evolution of mutators, higher-level selection is the only logical explanation for why transient hypermutation mechanisms *persist* in prokaryotic genomes. Thus, as with the paradox of sex, resolving the lesser-known *paradox of mutation* likely requires a similar pluralistic, multifactorial, and multilevel approach to natural selection.

3.14 Other Novel Mechanisms of Adaptive Genetic Variation

Recent technological advances in modern genetics, such as improved genomic sequencing techniques, have illuminated the profoundly generative roles of transposable elements (TEs),

[57] A beneficial mutator allele may arise through genetic hitchhiking and receive a founder effect in a new niche. Here I am not arguing against the validity of such an observation. Instead, I argue that maintenance selection at a higher level remains the most empirically probable explanation for the existence (and mostly *persistence*) of mutator alleles.

horizontal gene transfer (HGT), and gene duplications (GDs) or whole-genome duplication events (WGDs or polyploidization) in the facilitation of adaptive genetic variation, that go beyond the traditional conceptual boundaries of mutation and recombination. Yet, while our knowledge of these mechanisms has grown immensely as of late, relatively little is still understood about the evolutionary causes that govern these mechanisms. Nonetheless, these mechanisms exhibit similar empirical trends to that of sexual reproduction and adaptive mutation, thereby permitting the construction of a general and causative conceptual model to explain their evolution existence and persistence.

3.15 Transposable Elements (TEs)

Transposable elements—i.e., interspersed repetitive DNA sequences—have long been thought to facilitate evolutionary innovation and adaptation (Britten & Davidson, 1969; Chao *et al.,* 1983; Rech *et al.,* 2019). Laureate Barbara McClintock (1961) was the first to speculate on the vital functions of mobile elements in maize. Nevers & Saedler (1977) extended this hypothesis to possibly explain their evolutionary function:

> The prevalence of IS sequences and controlling elements in organisms as diverse as *E. coli*, *Zea mays* and Drosophila suggest that they may be of general biological significance… Whether they exert control functions at these positions or are simply kept in reserve as prefabricated units for the evolution of new control circuits remains unclear. (Nevers & Saedler, 1977*:* 114)

A popular hypothesis for the function of TEs among researchers is that they are "kept in reserve" because of their future evolutionary benefits (e.g., Kleckner, 1981; Barroso, 2012; Fedoroff, 2012; Brunet & Doolittle, 2015). Indeed, it does appear that TEs make up a proportionate amount of prokaryotic and eukaryotic genomes and store a vast amount of genetic variation (Cordaux & Batzer, 2009). Although previously considered "junk DNA", results from the ENCODE Project Consortium (2012) have demonstrated that a vast majority of TEs are functional, primarily affecting developmental processes and gene expression.

While TEs have been observed to alter patterns of gene expression in response to short-term stressors (Elbarbary *et al.,* 2016), there is mounting evidence that these sequences also have long-term consequences in genetic novelty or genome evolution (Fedoroff, 2012). In some instances, TEs have acted as modifier genes that cause hypermutability (e.g., Tenaillon *et al.,* 2016). Higher rates of transposition are also positively correlated with higher rates of deletions and duplications through homologous recombination (Chao *et al.,* 1983). Thus, like mutators, they have been shown to rise to fixation from selective sweeps, either due to their direct influence on an adaptive mutation or as a by-product.

TEs have also been shown to play a role in adaptive evolution (Rech *et al.,* 2019; Casacuberta & Gonzalez, 2013). For example, in *D. melanogaster*, the insertion of an *Accord* retrotransposon in the upstream region of the Cyp6g1 gene caused transcript up-regulation and led to increased resistance to several insecticides (Daborn *et al*, 2002; Chung *et al.*, 2007). However, TEs are largely driven by sexual or mutational dynamics, with some studies on *S. cerevisiae* demonstrating that TE loads decrease rapidly under asexual reproduction, making them more likely to evolve (Bast *et al.*, 2019).

Several researchers have questioned the role that selection has played in the evolution of TEs, branding such claims as part of a 'pan-adaptationist' program (Koonin, 2016; Sarkar, 2015). Others have suggested that TEs are prime examples of a species-level function due to their facilitation of adaptation (Brunet & Doolittle, 2015). While the former's viewpoint of natural selection dynamics leaves out the possibility that selection is acting to maintain TEs (or TE modifiers) to facilitate adaptation, more evidence is needed to establish a causal connection between TEs and species' survival over time. It should be noted that, if selection does act to maintain or proliferate TEs, then selection likely acts on the genes responsible for TE domestication and proliferation (similar to modifier genes) and not TEs directly, hence why they may be considered non-functional in a sense (Doolittle & Brunet, 2017). Given the available evidence, TEs are merely candidate examples of higher-level selection and the *paradox of adaptive variation*.

3.16 Horizontal Gene Transfer (HGT)

Horizontal gene transfer—or the sharing of genetic material between unrelated organisms—is now recognized as an important mechanism for generating novel variation and facilitating adaptation in bacteria and archaea (Soucy *et al.*, 2015; Kobras & Falush, 2019). The generative role that HGT has played in early eukaryotic evolution is also beginning to be revealed (Embley & Martin, 2006; Husnik & McCutcheon, 2018). HGT mechanisms have been observed to facilitate speciation since the acquisition of foreign genes indubitably causes divergence among a recipient and its relatives, which has been noted to do so even in the presence of gene flow between populations causing sympatric speciation (Arnold & Kunte, 2017)[58].

While there is some evidence to suggest that every transfer event carries potential fitness costs to the individual, many recent observations suggest that the benefits of adaptive trait transfers often offset these costs, therefore facilitating adaptation and increasing mean fitness in the long-term (Baltrus, 2013; Soucy *et al.*, 2015; Arnold & Kunte, 2017). For example, HGT is a formidable mechanism for AMR, as one study found that *Rhodobactercapsulatus* were able to transfer antibiotic resistance to bacteria of a different phylum (Christen *et al.*, 2012). Another set of studies found that an antifreeze protein that allows fish to adapt to icy water was horizontally transferred to herring, smelt, and sea raven species (Graham *et al.*, 2012). HGT events were noted to enable the survival of red alga *G. sulphuraria* in hot, metal-rich, and acidic environments (Schönknecht, 2013). Indeed, there is much evidence to support the claim that HGT events generate innovative characters and facilitate adaptation to novel environmental pressures (Husnik & McCutcheon, 2018)

However, the process of packaging, traveling (or better described as 'free-flowing'), and domesticating HGTs from an incipient to a recipient is not a well-understood process, and HGTs may initially function as selfish genetic elements. Once integrated into a recipient-genome, these independently existent elements are often expressed at low levels and are typically nearly neutral to the host (Park & Zhang, 2012). However, these elements can later provide novel combinations of genetic material upon which natural selection can act in times of environmental change or novelty, during which the transferred material potentially produces a beneficial phenotype and

[58] The observation of HGT causing genetic divergence even in the presence of gene flow largely detracts from the modern synthetic model of speciation that focuses on allopatric speciation (Arnold & Kunte, 2017).

becomes domesticated by the host (Soucy *et al.*, 2015). These selfish elements can act as a vast gene reservoir in times of environmental harshness, especially in prokaryotes (Rankin *et al.*, 2011; Broaders, 2013; Kobras & Falush, 2019).

3.17 Gene Duplications (GD) and Whole Genome Duplication (WGD)

Gene duplications represent a kind of large-scale mutation that has been recently acknowledged to play an integral role in the functionalization and formation of novel genes (Kondrashov, 2012). Several theoretical models have been proposed to explain the dynamics and presence of gene duplications (reviewed in Innan & Kondrashov, 2010). Older models worked within the confines of the individual selection assumption, stating that gene copies may protect their mother genes from the accumulation of deleterious mutations, thereby providing a slight fitness advantage (Haldane, 1933; Fisher, 1935)—but the advantage conferred by these models is thought to be nearly insignificant (Innan & Kondrashov, 2010).

Adaptive hypotheses are a better fit for the evidence, as several studies have found an abundance of adaptive gene duplications in response to adaptation in stressful or variable environments, with some appearing to come with an added cost to fitness (Kondrashov, 2012). Additionally, many bacteria have been observed to duplicate genes and amplify expression as an adaptive response to antibiotic treatments (Kondrashov & Kondrashov, 2006; Craven & Neidle, 2007; Sandegren & Andersson, 2009). But it needs to be noted that the opposite pattern of gene duplication, or reductive evolution and gene loss, has also recently been recognized as a major facilitator of adaptation and diversification (Shen *et al.*, 2018), suggesting its evolutionary value is multifactorial.

Likewise, whole genome duplication events (i.e., also referred to as *polyploidization*) are large-scale mutations whereby the entire genome is duplicated. This changes the ploidy number of a species, which in turn often drastically increases the genetic variation and genome size of a population. WGD events have since been documented in prokaryotic and eukaryotic organisms but are more commonly found in plant genomes (Van de Peer *et al.*, 2017).

The large-scale phenotypic effects of WGDs make them extremely costly in many circumstances, typically leading to an evolutionary ‘dead end.’ Nevertheless, WGDs may provide a large-scale adaptive advantage by drastically increasing genetic variation in a short period, conferring the polyploid an initial selective advantage (Van de Peer *et al.*, 2017). Indeed, it has been suggested that the ability to procure a WGD event in response to environmental changes affords certain species an evolvability benefit, as it has been repeatedly observed that polyploids have a higher stress tolerance (Madlung, 2013; Ramsey, 2011; Diallo *et al.*, 2016). Moreover, sequencing data from a large number of plant genomes and transcriptomes suggest that WGD events are more common during major ecological or environmental changes, such as extinction events, as a number of these events appear to have occurred during the Cretaceous-Paleogene or K-Pg boundary (Van de Peer *et al.*, 2009; Lohaus & Van de Peer, 2016; Kagale *et al.*, 2014). Supporting this suggestion, Mable *et al.* (2011) have found a correlation between the presence of WGDs events during periods of climate change and unstable environments. These results suggest that even the large-scale consequences of WGD events may allow some species to evade extinction during periods of intense environmental change.

3.18 Empirical Considerations

Evolution has engineered multiple strategies for adaptation to new environmental challenges, some of which lie outside the scope of this chapter but need to be acknowledged because of their relation to adaptive genetic variation. Phenotypic or developmental plasticity mechanisms modulate genetic variation into phenotypic variation (i.e., G-P map) and generate crucial phenotypic heterogeneity through epistatic or regulatory changes, developmental trait plasticity, or epigenome plasticity (Payne & Wagner, 2018). And dispersal strategies allow some populations to simply avoid challenges by moving into a new ecological niche (Travis *et al.*, 2013). However, when dispersal or developmental mechanisms fail to relieve the novel pressures placed on populations, evidence indicates that rescue strategies commonly rely on genetic adaptation to avoid extinction (Carlson *et al.*, 2014; Payne & Wagner, 2018; Gomulkiewicz & Holt, 1995). Thus, while the primary focus of this paper only explains part of the adaptation story, which may lead some to view it as 'reductionist' in a very shallow sense (e.g., Fusco & Minelli, 2010), genetic adaptation remains a significant part of how species evolve and adapt over time, if not *the most important factor* of adaptation.

Due to the limited scope of this chapter, I have left out several important considerations. First, increasing evidence is beginning to reveal the significance of cryptic genetic variation (Zheng *et al.*, 2019) and mutational robustness (Draghi *et al.*, 2010) in the adaptation process, primarily because they affect the production or conservation of novel adaptive variation (which I talk more about in Chapter 5). Secondly, I also omit how the mechanisms of genetic variation act in tandem. For example, recombination has traditionally been thought to limit mutation rate (cf., Cobben, 2017), or horizontal gene transfer to interfere with the spread of mutator alleles (cf. Ram & Hadany, 2019). More research is surely needed to understand how the mechanisms act in concert with each other under a pluralistic perspective. Thirdly, it is well-established that other evolutionary forces interact strongly with the processes of genetic variation, such as gene migration (Brown & Pavlovic, 1992).

I should also note that the studies reviewed here have their empirical limitations. Most of the studies of sex reviewed here used model species such as yeast or simple eukaryotic organisms. And most of the adaptive mutation studies mentioned above also use simple single-celled organisms, such as *E. coli*. More research is therefore warranted to confirm these trends using more complex organisms and community ecostructures (Hendry, 2019).

Lastly and quite importantly, this chapter does not review the evolutionary origins of the mechanisms of genetic variation since its primary goal was to demonstrate the causal role that natural selection plays in their maintenance. The literature has indicated four potential hypotheses that could explain their initial evolution: (1) they may confer an initial benefit by increasing mean population fitness in the short-term (e.g., Wagner & Draghi, 2010); (2) they could initially evolve through genetic hitchhiking on another directly selected trait or *"second-order selection"* (e.g., Futuyma, 2017b); (3) they may arise from neutral or nearly neutral processes (Agrawal, 2006); or (4) they may initially arise within genomes as selfish genetic elements that propagate themselves at the expense of or neutral to the individual until environmental change occurs and the selfish element is domesticated by the host because it provides novel genetic variation (e.g., Brunet & Doolittle, 2015; Soucy *et al.*, 2015). Another viable suggestion is that environmental stimuli over longer timescales may be relatively

predictable by evolution, therefore negating any time constraint on the evolution of individually deleterious features (Palmer *et al.*, 2013). Empirical studies support the claim that ecological variables appear to shift often and rapidly, which may make them more predictable, especially in certain variable environments (Grant & Grant, 2002).

3.19 Solving the Paradox of Adaptive Variation: Towards a Pluralistic Theory of Natural Selection

Over the last 163 years of research in evolutionary biology, we have observed the strong preference of Darwinian natural selection to select for biological features that enhance the probability of individuals surviving to reproductive age, leaving more descendants to the next generation, or DNA repair mechanisms that enhance offspring viability. However, 163 years is only a blip in the long history of biological evolution on earth. Indeed, the paradox of adaptive variation is an active issue for evolutionary biology precisely because we failed to view evolution in space and time, which is when adaptive genetic variation becomes causally manifested and selectively advantageous.

Now that we have the technological capabilities to view 'evolution in action' over longer periods and frequent spatial changes, new evolutionary patterns are finally being revealed. These include the strong preference of natural selection to produce, conserve, or domesticate novel genetic variation when species undergo harsh, novel, or capricious environments, allowing them to combat present or future challenges and evade extinction, sometimes in lieu of individual fitness. However, natural selection theory cannot explain these recent findings because of the reductionistic and monistic philosophical zeitgeist that built this theory (Ch. 2).

The reductive viewpoint of natural selection that has dominated evolutionary thought since its conception has caused many of the same architects of modern evolutionary theory to appreciate the implicit and profound *paradox of adaptive variation*. The paradox of adaptive variation thus exists as one of the oldest, most pressing theoretical and explanatory paradoxes in modern evolutionary biology, precisely because of (a) its historical precedence, being recognized by nearly every great evolutionary theorist *post*-Darwin; (b) the amount of contradictory evidence available in the literature today that does not fit with the theoretical projections of Darwinian natural selection; and (c) the central yet underdeveloped causal relationship between variation, natural selection, and evolvability that has yet to be fully explained by theory. Due to its longevity and severity, this paradox shines a particular spotlight on the anachronisms stalling progress in biology, and science more generally.

The Second Synthesis between evolutionary biology and ecology—and, more specifically, the greater emphasis that evolutionary biologists now place on *empirical realism*—has demonstrated the need for a new philosophy of biology; one that is grounded in explanatory pluralism, multifactorial analyses, and multilevel causation. Moving away from asking *why sex has evolved* (i.e., cost-benefit ratio) to the ecological question of *what conditions allow for sex to evolve* has been crucial for our understanding of the evolutionary history of sex, as well as for improving predictive trends in evolving populations (Otto, 2017; e.g., Rushworth *et al.*, 2020). It allows for the complete mapping of the complex causal field underlying the evolution of sex in natural ecosystems. Complementary to this switch to a more *empirically real* approach has been a switch in explanatory tactics toward explanatory pluralism, as sex is the "prime example of explanatory

pluralism in biology" (Fehr, 2001; see for more Neiman *et al.*, 2017; 2018). However, divisions within this research front still exist, where those trained in ecology tend to call for explanatory pluralism, while population geneticists remain conservative and call for a general, reductive model of sex (Meirmans & Strand, 2010).

Philosophers of biology have been arguing for such general advancements for nearly three decades now (e.g., Dupré, 1993; Mitchell, 2003; Okasha, [2006]2013; Godfrey-Smith, 2009; Anjum & Mumford, 2018). However, these works have largely failed to attract the attention of the common biologist and change the perceptions of the consensus, evidenced by the reductive viewpoints of evolution that are still being promulgated in most textbooks used to teach evolution to younger generations (e.g., Futuyma, 2017b; Hartl & Clark, 2006; cf. Zimmer & Emlen, 2020). I believe biologists have largely overlooked these seminal works of philosophy because they were empirically inadequate in the evidence used to support their theoretical and philosophical proposals. However, on the other hand, I also find most of the theoretical descriptions and prescriptions given by empiricists to be largely lacking from the holistic and perspicacious viewpoint typically awarded from an intimate knowledge of the history and philosophy of biology. Both groups have something invaluable to offer the other (Laplane *et al.*, 2019). We must resolve the history of ostensible conflict between science and philosophy if we are to progress our knowledge (Anjum & Mumford, 2018; Dupré, 1993; Pigliucci, 2019). On these grounds, this chapter is the empirical and historical foundation from which I can next construct my philosophical and theoretical recommendations to finally resolve the paradox of adaptive variation, using advances from the philosophy of science to organize all the necessary empirical phenomena into a coherent causal explanatory structure that fits well within the existing structure of evolutionary theory.

To account for the paradox of adaptive variation, I foresee a reformulation of natural selection theory towards pluralism (Ch. 4-5), that integrates the concepts of **maintenance selection** as the type of selection most commonly acting to maintain the adaptive genetic mechanisms over time (Ch. 4); **species selection** as the level that natural selection is most commonly operating at to maintain these mechanisms over time; **multilevel selection** to explain how selection operates between various levels; and **evolvability** as a probabilistic dispositional property that is a determinant of higher-level selection akin to individual fitness (i.e., what selection is *selecting for* in species; Ch. 5). Integrating these new models into natural selection theory should finally allow for the abjective explanation of the evolutionary history and the effective prediction of future evolutionary trends of the mechanisms of adaptive genetic variation—as well as, perhaps, other *evolvability-like* or emergent biological features.

3.20 Chapter 3 in Summary

The conceptual and causal relationship between natural selection and variation is foundational in theory, given that both are central to our understanding of adaptive evolution. While past models have assumed that the production of variation is random and independent of selection, we now know that the mechanisms of variation are under selective influence from the environment. Past reductive models have also assumed that natural selection operates invariably at the individual level. However, recent evidence strongly suggests that natural selection operates at multiple

levels of biological organization, favoring different levels in different ecological contexts over space and time. The *paradox of adaptive variation* is therefore revealed as a major theoretical problem for modern evolutionary biology that can be finally and simply be resolved by a philosophical transition towards a pluralistic model of natural selection.

Theory and Philosophy

Our neurons must be used for more substantial things. Not only to know but also to transform knowledge; not only to experience but also to construct.

Santiago Ramon y Cajal

Induction for deduction, with a view of construction

August Comte

Chapter 4 – Towards a Pluralistic Theory of Natural Selection: *Maintenance Selection*

Science progresses through the integration and organization of new knowledge into inductive theoretical structures that can causally explain and predict natural phenomena. In chapters 4 & 5, I consider the theoretical implications of the paradox expounded in the last chapter and argue for the theoretical emendations necessary to account for these recent trends, grounded in a contemporary philosophy of science outlined in Chapters 1 & 2. Natural selection theory must pluralize and integrate the concepts of **maintenance selection** as the type of selection most commonly acting to maintain evolvability mechanisms over time (this chapter); **species selection** as the level of selection that is the most causally relevant for these mechanisms (Ch. 5); **multilevel selection** to explain how selection operates between various (sometimes conflicting) levels (Ch. 5); and **evolvability** as a new probabilistic dispositional property that is a higher-level determinant of selection akin to individual fitness (i.e., what selection is *selecting for* in populations and species; Ch. 5). Several different types of pluralism are therefore warranted to update and improve the causal explanatory range of natural selection theory.

4.1 Towards a Pluralistic Theory of Natural Selection

When significant pressure is put on a species to evolve when their respective environment changes, this pressure is predominantly relaxed through the adaptive evolution caused by mechanisms of genetic variation. As previously demonstrated in the last chapter, lineages have evolved an array of mechanisms to perform such a function, like meiotic recombination in eukaryotes or stress-induced mutation in prokaryotes. However, modern evolutionary theory is ill-equipped to explain the evolution of these mechanisms given its vestiges of past reductionism and monism. A movement towards theoretical and explanatory pluralism is thus warranted to integrate all the necessary explanatory components into theory.

Pluralism means something different to different people, in different eras or epochs of intelligentsia, and in different locales of knowledge production or organization. Uncoincidentally, this is also the primary insight and driver behind pluralism, the idea of *differences* between people and methods, often in space and time. Science is now embracing pluralism at its core. Pluralism now dictates how science is done, how sub-disciplinary scientists organize under a broad and arbitrary banner like “physics” or “biology”—with crosstalk happening within these broad disciplines, as well as between them, like evolving populations

exchanging genetic information in a manner that is hard to ontologically categorize. Pluralism is thus the natural progression of maturing fields of knowledge and inquiry (Mitchell, 2003).[59]

Science progresses not only through the accumulation of more knowledge but also through the integration and organization of such knowledge into inductive theoretical frameworks that can causally explain and predict natural phenomena. In particular, the history of evolutionary biology demonstrates that progress is made through the reciprocal development of empirical methodology, mathematical modeling, and the theoretical construction of verbal or philosophical causal-explanatory models[60]. Like the first synthesis, the Second Synthesis has progressed us to an epistemic juncture where novel empirical anomalies and recent developments in the modeling of natural selection mandate the reformulation of natural selection theory *towards pluralism*.

In Chapter 1 & 2, I outlined the recent transitions in the philosophy of science towards explanatory pluralism, multilevel explanations, and multicausality. In Chapter 3, I exposed *the paradox of adaptive variation* as a major theoretical paradox of evolutionary theory, elucidating the philosophical anachronisms that have pervaded biological thought since Darwin.

In Chapters 4 & 5, I offer a normative argument for the resolution of the paradox of adaptive variation through the reformulation of natural selection theory to account for changes in the causal dynamics of natural selection, which are largely dependent on ecological interactions and at multiple levels of selection. This includes the integration of **maintenance selection** as the type of selection that is causing the maintenance of these mechanisms over time; **species selection** as the most causally relevant level of selection that is acting to maintain these mechanisms; **multilevel selection** to explain how selection operates between various levels; and **evolvability** as a new higher-level dispositional property that is a determinant of selection akin to individual fitness (i.e., what selection is *selecting for* in species). Integrating these concepts into natural selection theory should finally allow for the abjective explanation of the evolutionary history and the effective prediction of future evolutionary trends of the mechanisms of adaptive genetic variation—as well as, perhaps, other evolvability-like or emergent biological features.

4.2 The Ontology of Natural Selection

Natural selection is a cornerstone of modern biological thought. No other concept in biology can rival its capacity to causally explain the great peculiarities of organic life on Earth—*and likely beyond*. Charles Darwin conceived of his theory of natural selection as a causal theory in which external causes imposed by environments shape the features of organisms. This is precisely the causal pattern that Darwin intended to capture by calling his theory "*natural selection"*. Darwin thought that organisms did not exist independent of their selective environments, with their environments not only selecting for adaptive variants but also causing the generation of novel

[59] In the philosophical literature, a pluralism of sorts has been developing on the topic *of pluralism* (see for a good overview Muszynski & Malaterre, 2021).

[60] It needs to be noted that scientific progress can, in a broader sense, also be achieved by theoretical conservatism. This does not represent the current state of evolutionary biology, where an influx of empirical findings now contradicts our epistemological structures to a degree that warrants theoretical action and revision.

variants[61] (see for more Winther, 2000). *Darwinian natural selection* thus became viewed as an external, incremental, and complex process of natural environments 'selecting for' the individual organisms that are the best adapted to their environmental conditions.

Nevertheless, our understanding of natural selection has come a long way since Darwin, with the philosophical notion of natural selection developing divergently within various sub-disciplines of evolutionary biology (see Ch. 2). This is where philosophy can be of great use in the context of modern biology, acting as a bridge between these various conceptions of natural selection. An incredible amount of philosophical effort has been dedicated to the ontology of natural selection (and fitness) over the past forty years (Sober 1984; Brandon 1990; Matthen & Ariew 2002; Walsh, Lewens & Ariew 2002; Bouchard & Rosenberg 2004; Millstein 2006; Pigliucci & Kaplan 2006; Brandon & Ramsey 2006; Walsh 2007, 2010; Ramsey 2013; Pence & Ramsey, 2013; Birch, 2016; see for more Gildenhuys, 2019). For this reason, I will not attempt to chronicle the expansive literature here, but I shall instead narrow my focus to a generalizable ontological account of natural selection.

The principles of natural selection popularized by Richard Lewontin in his famous paper *The Units of Selection* (1970) attempt to capture the core causal factors of evolution by natural selection in a highly concise manner. Lewontin argues that populations of individuals will undergo adaptive evolutionary change by natural selection when three necessary and sufficient conditions are met:

> (C1) Different individuals in a population have different morphologies, physiologies, and behaviors (*phenotypic variation*).
>
> (C2) Different phenotypes have differential rates of survival and reproduction in different environments (*differential fitness*).
>
> (C3) There is a correlation between parents and offspring in the contribution of each to future generations (*fitness is heritable*)

> (Effect) A population will undergo adaptive evolutionary change by natural selection.

These principles attempt to capture the complete causal field of natural selection while invoking, both implicitly and explicitly, many complex causal processes including development, reproduction, survival, and inheritance (see for more Gildenhuys, 2019). Lewontin's principles succeed as a general heuristic for the representation of natural selection, employed for their pedagogical utility because they neatly distill the main factors of natural selection. However, due

[61] An idea that has, in part, since been found to be true. In the second essay, I corroborated the trend of natural environments selecting for more or "better" genetic variation. However, Darwin conceived of the environment as having a direct causal influence on individual variations, rather than having an indirect effect on genetic modifiers, due to his ignorance of genetic inheritance. This is why we cannot fully say that Darwin was correct in his initial interpretation.

to their simplified and abstract nature, there are several known issues with these principles when applied in complex and natural biological settings (Gildenhuys, 2019; Godfrey-Smith, 2007).

One of the known issues with Lewontin's principles and later extensions of his original model (e.g., Maynard Smith, 1991; Godfrey-Smith, 2007) is the omittance of the causal workings of *maintenance selection*. These models typically focus on the causal dynamics of directional selection, since they hone their focus on natural selection *causing evolutionary change*. But evolutionary change is not a necessary prerequisite for natural selection to act as a cause of evolution.

4.3 *The Paradox of Stasis*

Change is the fundamental idea of evolution. Evolutionary biologists primarily study biological change over time, but species are not always changing. The causes of evolutionary stasis have therefore taken a backseat to those of directional selection, despite the long periods of morphological stasis that are reflected in the fossil record that warrant explanation—a problem known as *the paradox of stasis*[62] (Simpson 1944; Lewontin 1974; Gould & Eldredge 1977; Williams 1992; Hansen & Houle, 2004; Futuyma, 2010; Haller & Hendry, 2014).

Elements of evolutionary stasis are proper a focal of modern evolutionary biology, such as developmental, genetic, or ecological constraints that limit the possibilities of evolution[63], inter-populational gene migration that precludes genetic divergence and speciation, evolved robustness and phenotypic plasticity mechanisms that afford species resistance to perturbations with no concomitant alteration in their genetic architecture, or DNA/RNA repair mechanisms that maintain the genetic viability of populations. These elements relate in that they cause evolutionary stasis and trait uniformity over time rather than causing evolutionary change and genetic divergence.

But what about natural selection? Can natural selection cause the persistence and stabilization of biological traits, features, or processes over time? Does natural selection have to be directional? Or can natural selection still be an evolutionary cause *without actually causing evolution?* The idea of selection acting to maintain traits over time has taken on many forms in the history of evolutionary biology as balancing, stabilizing, disruptive, nonlinear, negative or purifying selection. However, the commonalities between all these phenomena of selection have never been fully recognized in the literature. This is not to say, however, that components of maintenance selection have never been or are not today a proper focus of evolutionary biology.

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[62] An interesting suggestion that may explain *the paradox of stasis* is fluctuating selection (Bonnet & Postma, 2018). Because fitness landscapes are not constant over time, selection that fluctuates in strength and direction may bring average selection coefficients to zero and slow down longer-term evolutionary adaptation (Bell, 2010).

[63] The idea of constraints, and maintenance selection more generally, requires a type of counterfactual thought. Constraints help explain why certain traits *did not* evolve, especially in the presence of pressures. For example, to explain why other primates have not evolved a similar capacity for bipedalism, or why tetrapods did not evolve more than five fingers and toes, likely has to do with the developmental processes underlying these traits. This is why evolvability is commonly conceived as a developmental phenomenon that loosens developmental and genetic constraints, allowing for trait evolution (e.g., Brown, 2014).

This is to say that all the components of maintenance selection have never been fully appreciated *in unison, under pluralism*, and this is reflected in the philosophical literature since most ontological and causal accounts of natural selection primarily focus on the causal field of directional selection (i.e., variation, heritability, and fitness differences). In the following sections, I rework the principles of natural selection to include the causal phenomenology of maintenance selection that is otherwise lacking in the philosophical and biological literature. A bit of tidying up natural selection theory is in order.

4.4 Integrating Maintenance Selection

> "I regard it as unfortunate that the theory of natural selection was first developed as an explanation for evolutionary change. It is much more important as an explanation for the maintenance of adaptation" (Williams, 1966*:* 54).

Being the strict externalist that he was, Darwin would have been surprised to hear that his theory was taken to typically correspond to evolving populations since he constructed a selective explanation for the stable polymorphisms exhibited in flowering plants. He once recounted, "the benefit which heterostyled dimorphic plants derive from the existence of the two forms is sufficiently obvious…Nothing can be better adapted for this end than the relative positions of the anthers and stigmas in the two forms" (Darwin, 1877*:* 30). To Darwin, natural selection did not only drive populations to evolve monomorphic adaptations but also to retain polymorphisms (i.e., *balancing selection*). Darwin thus considered his theory of natural selection *as capable of explaining a lack of evolutionary change* as well as directional selection (Gildenhuys, 2019).

Nevertheless, new research initiatives in the twentieth century placed a special emphasis on directional evolutionary change. The primary explanatory interest of the population geneticists in the first synthesis was how natural selection results in adaptive evolutionary change (Mayr & Provine, 1998). Of course, notions of maintenance selection were always a proper focus of evolutionary research. Models of stabilizing and balancing selection have been around for nearly a century now. Alfred Russell Wallace insisted that 'natural elimination' was a more apt term for natural selection, emphasizing the causal effects of negative or purifying selection (Smith, 2012). However, evolutionary biologists have historically placed a research and explanatory precedence on the causal dynamics of directional selection over maintenance selection[64] (in line with G.C. Williams' quote above). As a consequence, we have never had a workable philosophical notion of maintenance selection, and thus never had a comprehensive ontological and causal account of natural selection[65].

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[64] One likely reason why a precedence has been granted to directional over maintenance selection is due to their relative causal influences. Recent findings suggest that directional selection may be more common than stabilizing selection in nature (Bonnet & Postma, 2018).

[65] Our relative neglect of maintenance selection is also likely a major reason why the paradox of adaptive variation exists as such an explanatory problem, since you cannot see these mechanisms as adaptations except in light of maintenance selection.

Determining whether a population is undergoing maintenance selection warrants a different set of principles from directional selection. In the case of directional selection, there is variation in the correlations of competing heritable traits to the mean fitness of the population, causing the more successful traits to increase probabilistically in frequency and rise to fixation. Variation among competing traits (fitness differences) drives this type of selection, causing changes in allele frequency.

In the case of maintenance selection, however, *variation* is not a necessary condition for causation. For example, natural selection can cause a trait to be at complete fixation with no variation, which is to say that the frequency of the loci responsible for the adaptation in the population is near 100% (e.g., stabilizing selection). In another sense, maintenance selection may also conserve variation at a trait locus, whereby selection acts to maintain this variation rather than causing competition between this variation (e.g., stable polymorphisms from disruptive or balancing selection). This amounts to variance among traits, but the variance is sustained and should continue to be inherited (have a nearly perfect *heritability* of 1). The consequence of this causal effect of maintenance selection differs from the causal effect of directional selection in that *the variation is sustained as the adaptation rather than being the cause of adaptation*.

The two principles that generally must be satisfied for there to be any causation of selective maintenance are as follows:

(C1) The trait (or *traits* regarding disruptive or balancing selection) is inherited by nearly every member of the population (has a high heritability of approximately 1);

(C2) And if this trait is causally connected to the fitness at any level of biological organization in a given environment, which is to say that the correlation between the trait and evolutionary survival of an entity at one level of biological organization is *nonzero*;

(E) Then the biological trait will undergo maintenance selection, with selective pressures from the active ecological context maintaining the loci responsible for the adaptive trait, keeping the population at a stable equilibrium and/or purifying any disturbances made to the inheritance of this trait (e.g., from a deleterious mutation).

Traits under maintenance selection are therefore selectively maintained *if and only if* there is a causal connection between the heritable adaptive feature and the evolutionary survival of a biological entity at any level of biological organization, with any disturbance in the development of the given adaptation (e.g., from mutations) resulting in catastrophic phenotypic effects, fitness detriments, and/or unviable offspring. The maintenance of adaptation therefore requires the perpetual causation of selective environments, acting as a conservative force that eliminates new mutations through purifying or negative selection (see how to evaluate for maintenance selection **Box 7**).

The findings from ecology expressed in Chapter 2 are beginning to reveal the intensity of natural environments to constantly act on biological traits and features. Further findings from evo-devo also suggest that maintenance selection can act on life history traits and/or developmental processes. For example, Emlen *et al.* (2005) found differences within a beetle lineage's ability to retain or resorb their thoracic horns into adulthood. These findings imply that there is some

differential maintenance of specific developmental structures, suggesting that lineages vary in their ability to maintain biological features or structures over time—which is a marker of potential selection (see **Box 7**).

Box 7: Evaluating for Maintenance Selection

Although producing different evolutionary outcomes, the commonality between balancing, stabilizing and disruptive selection is selection acting to maintain traits because of their fitness values within an ecological context. When a population is already sufficiently adapted to their environment, selection acts as a conservative force that eliminates new mutations to preserve the current adaptedness of the population (Bell, 2009). This force is called *negative* or *purifying selection*, and is typically a marker of *maintenance selection* acting on populations to preserve adaptedness.

Yet maintenance selection can be difficult to distinguish from positive selection or neutral evolution. However, there are several definable and testable biomarkers of maintenance selection working on biological features and, at a more macro-level, acting on populations. These include (i.) genetic signatures of negative/purifying selection acting at a genomic region, (ii.) disturbances made to a trait cause a subsequent reduction in fitness, and/or (iii.) persistent homology in lineages.

Marker (i.) embodies the effects of negative selection acting on *ultraconserved* genomic regions. Genomic regions that are highly conserved, both within a species and between species in a lineage, should have less genomic change than other regions under positive selection or drift. The reasoning behind this is that regions that are thought to be essential for biological function and development, such as protein-coding genes or regulatory genes that control transcription and cellular development (called *ultraconserved* genomic regions: see for more, Bejerano *et al.*, 2004; Reneker *et al.*, 2012) likely undergo negative selection *when there is strong pressure to maintain their fitness consequences*. Thus, at a local level, negative selection may cause the frequent purging of mutational disturbances in any given genomic region that is essential for biological function. In comparison, novel environmental pressures cause positive selection to typically alter the mean fitness value of a trait, while negative selection acts to maintain traits at a stable equilibrium over time, generally caused by already sufficient adaptation to an environment (or environments). Thus, the signature of positive selection is a genomic region that is changing more rapidly than the background rate, with greater genetic divergence, which could result from mutagenesis, general evolvability mechanisms, or relaxed maintenance selection since mutations in these regions are less likely to be purged and more likely to persist and be inherited (see for more Stajich, 2013). In contrast to positive selection, the signature of negative selection is a slowly evolving genetic region, relative to the rest of the genome, because most ensuing mutations will be purged, exhibiting fewer genetic changes than observed elsewhere in the genome (i.e., *background selection*). However, a slowly evolving genomic region may also be the consequence of neutral evolution. In this case, we can use the normal background rate of evolution as a standard to distinguish between these two states, with drift corresponding to a region evolving near the genome-wide average and negative selection corresponding to regions that evolve below the average.

Marker (ii.) is more difficult to test but is perhaps the best way to detect if maintenance selection is working on trait, if done correctly. If one can perturb the trait and credibly demonstrate, with controls in place, that the original state has higher fitness than the perturbed states, then the original state was in all probability an adaptation under maintenance selection. For example, one such study found that by altering widowbird tail lengths, longer tails enhance male reproductive success and were therefore strongly maintained as adaptations (Stearns, 2013). Marker (iii.) relates to the identification of highly conserved homologies within species, lineages, kingdoms, or domains. If a trait is homologous, then this is a possible indicator of an adaptation that has been kept under constant maintenance selection. However, this is to keep in mind the processes of genetic or developmental constraints, which may also play a causal role in maintenance of homologous traits.

At the macrolevel, the definable and testable markers of maintenance selection *working on populations* are (i.) selectively imposed stable equilibriums, and (ii.) low global mutation or recombination rates. Marker (i.) relates to selectively induced and relatively stable trait equilibriums with little to no allele frequency change at the loci in question (from stabilizing, balancing, or disruptive selection). For example, in the case of stabilizing selection, the fittest genotype in the population is fixated with a heritability of nearly 1. In consideration of marker (ii.), negative selection can either have a broad impact on global mutation/recombination rates of a population, decreasing rates to as low a value as possible if the population is already well adapted to their environment. A low global mutation/recombination rate is therefore a signature of maintenance selection acting to maintain a population's adaptedness to their environment, with the exception of evolvability mechanisms, to be explained in the next section.

4.4 The Balance of Natural Selection: Directional and Maintenance Selection

Evolutionary biologists have historically disagreed on whether natural selection acts purely as a positive force that causes adaptation and directional evolutionary change or as an eliminative force that removes deleterious variants. This debate is still lively in the philosophical literature today (Sober, [1984]1993; see for more Martinez & Moya, 2011; Birch, 2012). Without getting into the intricacies of this debate, I think the empirical literature supports the conceptualization of natural selection as both types, or else we need a wildly different causal interpretation of natural selection than we have today. Both types of natural selection capture separate causal processes (or *directives*) of selection but share similarities in their causal attributes and effects—both require an environment to favor a given variant.

The earliest proponent of the "balancing concept of natural selection", as I call it, was Theodosius Dobzhansky (1937). As mentioned in Chapter 3, Dobzhansky recognized 'the paradox of viability' when he noticed that many natural populations harbor an extensive amount of genetic variation through *heterosis* (AKA *heterozygote advantage*). Although heterosis causes lower-fitness individuals to be maintained in a population, since high-fitness heteozygotes give rise to lower-fitness homozygotes in every generation, heterosis appeared to be maintained in a large number of natural populations because of its long-term evolvability benefits, thus striking a balance between present individual viability and long-term population evolvability (see for more Carvalho, 2019).

The balancing concept was furthered by the two doyens of late-20th-century evolutionary thought, G.C. Williams (1966) and John Maynard Smith (1978). In his now-famous *Adaptation and Natural Selection*, Williams wrote, "natural selection is the only acceptable explanation for the genesis and maintenance of adaptation" (Williams, 1966*:* V)—thus recognizing the two distinct directives of natural selection. As noted in Chapter 3, Williams and Maynard Smith were particularly interested in the evolution of sex, with the latter finally conceding to higher-level selection as a likely causal reason for the maintenance of sexual reproduction (Maynard Smith, 1998).

Around the same time, similar lines of thinking arose within the mutation literature. Leigh (1970) inferred from Kimura's (1967) work on mutation rate evolution that many asexual species appear to strike a balance between the selection for a lower mutation rate to preserve *adaptedness* and an increased rate to facilitate *adaptability* (or what is better known today as evolvability). Leigh utilized the evolutionary trade-off between adaptedness/adaptability to explain why mutation rate appear to be far above the physiologically-feasible minimum in many asexual species.

Strictly delineating between the *genesis* and *maintenance* of adaptations, per Williams, or the adaptedness/evolvability evolutionary trade-off, per Leigh, is part of a long tradition that continues today among students of sexual reproduction (e.g., Bell, [1982]2019), adaptive mutation (e.g., Ram & Hadany, 2012; 2014; 2019; referred to as "stability vs. variability" in Radman *et al.*, 1999), both sex and mutation (e.g., Lenski, 1999), and those that study the "bi-modality between evolvability and robustness" (e.g., Masel & Trotter, 2010; Altenberg, 1994;

Lenski *et al.*, 2006). Graham Bell (2009) perfectly exemplifies the balance concept of selection in his recent compendium on natural selection:

> "There are two broad categories of natural selection. In the first place, it will be a conservative force that eliminates new mutations so as to preserve the current adaptedness of the population. This is called purifying selection. Secondly, it will be a progressive force that favours new mutations when the environment changes. This is called directional selection. These categories are not exclusive. Both internal and external change will occur in every generation, eliciting both purifying and directional selection in different degrees on different characters" (Bell, 2009, 22).

Under similar sentiments, Richard Lenski (1999) reiterated the importance of maintaining the genesis/maintenance divide in the sex literature, cautioning that, while a pluralistic view of sex may aid in the explanation of its current utility and pervasiveness, the origins of sex likely entailed one selective factor acting sequentially rather than simultaneously. Its maintenance, however, likely entails a multicausal explanation.

Ram & Hadany (2012; 2014; 2019) use Leigh's adaptedness/adaptability distinction to explain the observed appearance of stress-induced mutagenesis, theoretically demonstrating that SIM mechanisms may overcome the adaptedness/adaptability trade-off by increasing the rate of complex adaptation without reducing the mean population fitness. In this sense, *adaptedness* and *evolvability* are not mutually exclusive from each other and can be achieved simultaneously by selection (Ram & Hadany, 2014).

Thus, an interesting commonality—that is not coincidental—between all these authors' strict delineation between directional and maintenance selection is their research interests in the evolution of sex, mutation, and more broadly in adaptive genetic variation. This is because students of adaptive genetic variation must appreciate the salience of variation in the grander process of adaptation, noticing the long-term evolvability benefit typically conferred from the production, conservation, or domestication of novel genetic variation.

Sex and its evolvability benefits have thus been historically framed as the quintessential example of maintenance selection, as recognized by many of the greatest minds in evolutionary thought *post*-Darwin. Its near-ubiquity (Vrijenhoek, 1998) and strong conservation across the eukaryotic spectrum (and similar popularity of parasexuality in prokaryotes or fungi) are typical markers of strong and pervasive selection (Hartfield & Keightley, 2012). Maintenance selection thus appears to be the best explanation for the observed conservation and ubiquity of sexual processes.

Such conceptual and causal distinctions are rarely expressed explicitly. Here I conceptually distinguish between these two types of natural selection, *directional* and *maintenance selection*, to categorize their phenomenological similarities while also highlighting the primary causal reasons why they vary, contingent on species-environment relationships in space and time. Making such an explicit distinction thus compartmentalizes similar phenomena (environments favoring a variant) while in turn highlighting the differences between these processes: directional selection is in effect when populations are adapting to new circumstances, and maintenance

selection is in effect when populations are already well-adapted to their environments, acting to preserve the *adaptedness* of the population. Species-environment relationships are thus the primary causal factors that can be used to infer and predict future selective states of natural populations.

Yet like most things in biology, the conceptual parameters constructed here are not rigid and entail multiple phenomenological overlaps. The general idea of maintenance selection is the conservation of adaptation in a given environment, but most biological species exhibit an innate ability to thrive in varying environments and across frequent spatiotemporal changes. Maintenance selection has likely played a salient causal role in the preservation of biological features or processes that facilitate further or future adaptation (Nunney, 1989; Bell, [1989] 2019). This is especially true in variable environments, where preserving "adaptedness" means maintaining features that enhance a species' ability to navigate a changing adaptive landscape and adapt to novel environmental stimuli. Today, we call this notion *evolvability*. In this sense, maintaining *adaptedness* and *evolvability* are not mutually exclusive of each other and can be achieved simultaneously through selection (Ram & Hadany, 2014).

4.5 Chapter 4 in Summary

In this chapter I introduce the need to pluralize natural selection theory, based on the evidence reviewed in chapter 3. Philosophers and scientists have generally conceived of the ontology of natural selection as strictly causing directional evolutionary change, rather than causing evolutionary stasis and trait maintenance. In this chapter, I briefly update the principles of natural selection to include the causal workings of *maintenance selection*, alongside directional selection. I then briefly elucidate the history behind the balance concept of natural selection, which see natural selection as a balance between the two opposing forces of *maintenance* and *direction* and introduce the phenomenological overlap of the two in consideration of *evolvability*.

Chapter 5 – Towards a Pluralistic Theory of Natural Selection: Species and Multilevel Selection *for Evolvability*

Evolvability is an unusual concept. Its *unusualness* stems from its *long past but short history* in evolutionary thought, despite its unambiguous role in the evolutionary process. Darwin assumed that all extant species hold some capacity for evolution, going so far as to suggest that some species may be better at evolving than others (Sansom, 2008). In the synthetic era, theorists formalized the latter notion that species vary in their response to natural selection dependent on the production and conservation of *genetic variation* (e.g., Fisher's [1930] *Fundamental Theorem*; Dobzhansky's [1937] *Balancing Hypothesis*), therefore establishing the conceptual foundations of *genetic evolvability*.

Yet for a variety of reasons, evolvability was initially "taken for granted" and built within evolutionary theory as "a given premise" (Hansen, 2016, 83). For starters, the causal mechanisms behind the production and conservation of novel genetic variation—i.e., from mutation or recombination—were assumed to be the result of "random" or stochastic processes separate from selective influence[66]. A causal boundary was drawn between (1) *the random or stochastic mechanisms that produce heritable variation* and (2) *the process of natural selection acting on this variation to cause adaptation* (Mayr, 1982). These became independent and sequential causal events in the adaptation process, implying that most species were continuously replenished with sufficient variation for natural selection to subsequently act upon "without any need for special mechanisms generating new variability" (Charlesworth *et al.*, 2017, 8).

However, the assumption that the production of novel genetic variation is *random* and independent of selection has been subtly overturned in the last 60 years, despite the curious reluctance of some theorists to accept such explicit conclusions. New evidence arising from microbiology, ecology, and experimental biology has established that mutation and/or recombination modifier genes are not only *exposed to the direct influence of selection* (Otto, 2014), but most species exhibit greater flexibility to cause adaptive genetic changes in response to selective pressures than previously supposed (Swings *et al.*, 2017; Fitzgerald & Rosenberg, 2019), often with no observable benefit to individual organisms.

This leads us to the main reason why evolvability was initially overlooked. Evolvability is an emergent dispositional property whose manifestation is causally relevant at higher levels of biological organization over longer stretches of time and frequent spatial changes—with several biologists viewing evolvability as *the best example* of an emergent biological adaptation (Lloyd

[66] Although mutations were known to be sometimes caused by external but non-selective forces such as UV radiation or the application of other environmentally induced lethal mutagens.

& Gould, 1993; Maynard Smith, 1998; Folse III *et al.*, 2010). Yet empirical limitations and methodological constraints have naturally obscured the causal complexity of biological systems for the majority of evolutionary research. Early genetics research was often limited to within-population analyses (Nei, 2013) and performed within restrictive spatiotemporal parameters (Ford, 1964; Levins, 1968; Endler, 1986), therefore concealing the complex evolutionary and selective dynamics of natural populations. As a result, evolutionary theory was initially constructed in an abstract vacuum that was not particularly representative of evolution in nature (Otto, 2009; Hendry, 2017).

The divisions between theory and empiricism were further exacerbated within the 20th-century scientific zeitgeist of *logical positivism,* which favored the mathematical reductionism of theoretical population genetics (Smocovitis, 1996). Evolvability was therefore *imperceptible* or largely ignored by evolutionary theorists who placed a premium on reducing biological causation to one privileged level or lower levels of biological organization. Biologists clinging to these theoretical traditions still doubt the empirical realism and/or theoretical significance of evolvability for precisely the same reasons (e.g., Barton & Partridge, 2000; Partridge & Barton, 2000; Chicurel, 2001; Poole *et al.*, 2003[67]; Sniegowski & Murphy, 2006; Lynch, 2007b; Charlesworth *et al.*, 2017).

Yet now in the age of evolutionary ecology where we can readily observe how evolutionary and selective dynamics unfold in the space and time of capricious ecosystems, and/or construct real-world experimental parameters that simulate these natural contexts, evolvability is beginning to be revealed as a major evolutionary process. As demonstrated in **chapter 3**, evolvability explanations are essential to explain why some species survive when others go extinct within *the evolutionary rescue* research front (Gomulkiewicz & Holt, 1995; Carlson *et al.*, 2014; Bell, 2017). A clear causal link has been established between genetic evolvability mechanisms and the evolutionary survival of species or lineages—e.g., from meiotic recombination (Bell, [1982] 2019), stress-induced mutagenesis (Ram & Hadany, 2012; 2014; 2019), hypermutation (Swings *et al.*, 2017), horizontal gene transfer (Soucy *et al.*, 2015), transposable element domestication (Brunet & Doolittle, 2015), and gene duplications/whole-genome duplication events (Van de Peer *et al.*, 2017). The observed ubiquity and conservation of these genetic evolvability mechanisms across biological domains point to higher-level selective processes such as *species or lineage selection* as the underlying causal reasons why these mechanisms are maintained in the long-term, thereby facilitating adaptive evolution through the production, conservation, or domestication of novel genetic variation when environments change, often with no observable benefits to individual organisms or *selfish genes.*

Thus, the *unusualness* of evolvability in the history of evolutionary thought is precisely what makes it an interesting concept. The reasons why a central process such as evolvability can go relatively unnoticed in theory shed specific light on the philosophical anachronisms that have

[67] Poole *et al.* (2003*:* 163) made the claim that "The concept of evolvability covers a broad spectrum of, often contradictory, ideas. At one end of the spectrum it is equivalent to the statement that evolution is possible, at the other end are untestable post hoc explanations, such as the suggestion that current evolutionary theory cannot explain the evolution of evolvability". Evolutionary theory, and in particular natural selection theory, is not equipped to explain the existence of higher-level selective features such as evolvability.

been stalling theoretical progress for over a century. Today, philosophers of biology generally agree that complex biological phenomena such as evolvability—which are only just being revealed by superior empirical methodologies—justify a switch in theoretical tactics away from explanatory reductionism, monism, and monocausal modeling towards a theory that embraces pluralistic, multilevel, and multicausal explanations (Dupré, 1993; Mitchell, 2003; 2009; Potochnik, 2017; Anjum & Mumford, 2018).

However, the ensuing chapter has little to do with *the realism of evolvability* (hopefully, that was already demonstrated in Chapter 3). For those evolutionary biologists who derive from empirically rich traditions, the central role of evolvability in the evolutionary process is self-evident. Yet I also take issue with how evolvability is presented by progressives on the other side of the spectrum who operate under the banner of *The Extended Evolutionary Synthesis* (Laland *et al.*, 2014; Pigliucci & Muller, 2010), which will be the primary focus of this chapter.

Evolvability has been referred to as "a cornerstone of the EES" (Pigliucci, 2008b, 75; Pigliucci & Muller, 2010) because (i.) development was ostensibly missing from the Modern Synthesis, and (ii.) evolvability is largely construed as a developmental phenomenon by most in the evolvability research front (Ibid; Hanson, 2016; Hansen *et al.*, *forthcoming*; Nuño de la Rosa, 2017). However, the historicity of (i.) is in question (Futuyma, 2017; *forthcoming*), and here I reject (ii.) that evolvability is largely a developmental phenomenon. Evolvability may very well be "the proper focus of evo-devo" (Hendritske *et al.*, 2007), but *evo-devo is not the proper focus of evolvability*. Genetic evolvability has always been, and shall remain, the central focus of evolvability thought.

Hansen *et al.* (*forthcoming*) continue in the tradition of placing a strong emphasis on development and broadly argue for *an unrestrictive or "anything goes" type of pluralism* for the evolvability concept, following similar philosophical prescriptions by Nuño de la Rosa (2017), Brown (2014), and Pigliucci (2008b). But a budding concept such as evolvability does not benefit from an overly broad type of *pluralism, explanatory or methodological*. New concepts benefit from a *restricted pluralism*, where we can still accept the many different viewpoints of evolvability, but leave space for further conceptual refinements and causal distinctions made between these (oftentimes competing) viewpoints.

Here I suggest the utility of maintaining the ultimate/proximate causal distinction (i.e., *Weismann's barrier*) of modern genetic theory to build a more accurate causal picture of adaptation by *evolvability* (c.f. Uller & Laland, 2019; Laland *et al.*, 2011). *Why?* Because drawing a causal distinction between *genetic evolvability* and the more recently emphasized *non-genetic* (or *evo-devo*) *evolvability* grants us taxonomic clarity. It organizes similar phenomena while also maintaining a concreteness in conceptual parameters that should be preferable to broad conceptualizations of evolvability that categorize all evolvability-related explanandum under the same conceptual umbrella—*i.e.*, phenotypic plasticity, developmental plasticity, epigenetic variation, the genotype-phenotype map, modularity, robustness, evolutionary capacitance, and adaptive genetic variation. Re-organizing the evolvability concept by making further causal refinements is thus a must if evolvability is to progress into a mature concept within the background of modern evolutionary theory.

5.1 The Neglected Long Past of Genetic Evolvability

> "Concepts such as evolvability, for instance, did not exist in the literature before the early 1990s… [T]he majority of the new work concerns problems of evolution that had been sidelined in the (*Modern Synthesis*) and are now coming to the fore ever more strongly, such as the specific mechanisms responsible for major changes of organismal form" (Pigliucci & Muller, 2010: 4, 12).

But evolvability was never "sidelined", at least in the same way as the other proposed novel concepts of the *EES*, nor was it inexistent in the literature before the 1990s. Early theorists and empiricists—such as Weismann, Fisher, Ford, Wright, and Dobzhansky—granted evolvability a central role in their investigations when they were attempting to model how populations respond to selection. However, given the limitations imposed by the methods and instruments contemporary to their time, they were never able to effectively reveal evolvability dynamics, so they instead built the evolvability concept implicitly within their theoretical models (e.g., Fisher's *Fundamental Theorem*, Dobzhansky's *balancing hypothesis*, or Wright's *Shifting Balance Theory*). As discussed in Chapter 1, we also need to consider the broader scientific zeitgeist, i.e., *logical positivism*, that favored reductionistic interpretations of biological phenomena (Smocovitis, 1996), thus concealing the emergent nature of evolvability.

This is why evolvability can be said to have *a short history but a long past*. Many recent historiographies on evolvability have suffered from historical revisionism and presentism by neglecting its *long past*. These historiographies—often briefly mentioned at the start of reviews—are subjectively directed towards the authors' *present* conceptualization of evolvability. For example, the quantitative geneticist Thomas Hanson (2016; and more recently, Hansen & Pelabon, 2021) gave a brief historical account of evolvability, but only as it is conceived in developmental biology today, claiming that evolvability is a relative newcomer to evolutionary biology because development was "black-boxed" during the Modern Synthesis (cf. Futuyma, 2017; Chapter 13). He goes on to note that this all began to change in the 1970s and 1980s due to the renewed interest in evolutionary constraints, setting the stage for evolvability to become an official research front. Brigandt (2015), Minelli (2017), and Porto (2021) made similar historical assertions, seeing the history of evolvability as relatively new because of their evo-devo lens.

Yet the issue with these historical accounts is that they fall under the fallacy of *presentism*. They regard evolvability and its history as it is most commonly presented today, as a developmental phenomenon within the context of modern biology. They entirely disregard the intellectual contexts that incubated evolvability, thus excluding a significant portion of the history of evolvability thought.

This is a misuse of history because it falsely promotes certain conceptualizations of evolvability over others. Today, this has manifested into the precedence given to an evo-devo approach of

evolvability over its more historically considered notion of *genetic evolvability*. How scientific ideas are conceptually constructed influences their perceived history, yet good history and science rely on the opposite to be true. *History should influence how scientific ideas are conceptually constructed.* Thus, we need an accurate philosophical history of evolvability to help inform its conceptual construction within evolutionary theory today.

Evolvability *as an idea* has a much deeper history that is indeed quite relevant to its modern conceptual construction. The philosopher Massimo Pigliucci (2008b) was the first to give an historical account of evolvability *as an idea*, no matter what the biologists back then were calling it (for an example of a nominal history of evolvability, see Crother & Murray, 2019). Surprisingly, few authors have since followed in his footsteps. Here I provide a brief historiography of evolvability *as an idea* that is not currently acknowledged by those in the evolvability research front.

Indeed, evolvability defined in the simplest and least controversial sense merely as *the capacity for species to evolve* has been a putative assumption since the onset of Darwinian theory, therefore holding no specificity or relevance in modern conversations. Darwin certainly flirted with the more controversial idea that domestic and wild populations with greater variety would outperform others because they were more adaptable (Sansom, 2008), but he never explicitly touted this idea[68]. Several years after Darwin's passing, August Weismann became the first to explicitly note several crucial aspects of evolvability[69]:

> "Thus in amphigonic [sexual] reproduction two groups of hereditary tendencies are as it were combined. . . The object of this process is to create those individual differences which form the material out of which natural selection produces new species" (Weismann 1889*:* 272).
>
> "[T]he communication of fresh ids [genes] to the germplasm implies an augmentation of the variational tendencies, and thus an increase of the power of adaptation. Under certain circumstances this may be of direct advantage to the individual which results from the amphimixis, but in most cases the advantage will be only an indirect one, which may not necessarily be apparent in the lifetime of this one individual, but may become so in the course of generations and with the aid of selection. For amphimixis must bring together favourable as well as unfavourable variations, and the advantage it has for the species lies simply in the fact that the latter are weeded out in the struggle for existence, and that by repetition of the process the unfavourable variational tendencies are gradually eliminated more and more completely from the germ-plasm of the species" (Weismann 1904*:* 223).

Here we see the first explicit association made between **(a)** the production of novel variation (from recombination), **(b)** variation in the ability (or *power* as expressly stated) to adapt between species, and **(c)** the subsequent beneficial effect this would have on a biological entity *higher*

[68] Thomas Huxley also once mentioned in a letter that 'saltations' (i.e., large-effect mutations) may be under selective influence because they are adaptive following environmental change (taken from Vorzimmer, 1972).
[69] I credit Weismann as the progenitor of evolvability because he was the first to explicitly mention this idea in an academic setting and therefore made it known.

than the individual. This was the first instance that the mechanisms behind heritable variation were considered to hold some adaptive value. Burt (2000*:* 338) has since interpreted these passages to mean that sex does not function to increase mean fitness directly, but rather "increases the variance of fitness, and thus the response to selection, and mean fitness after selection."

After the neo-Darwinian era, many biologists retreated into a developmental viewpoint of evolution—an era called the "eclipse of Darwinism" (Bowler, 1983). Developmental theories of adaptation, such as *Lamarckian* or *Orthogenetic theory*, superseded natural selection theory. Within this intellectual context, "adaptability"—a progenitor term for evolvability—was gained from organismal plasticity responses that tended towards Lamarckian inheritance (e.g., Baldwin, 1896; Osborn, 1896). However, Lloyd Morgan (1896) presented an eerily modern account of the evolvability process that did not suffer from any Lamarckian connotations, in which organismal plasticity or developmental mechanisms were seen as transitory responses that allow time for genetic mechanisms to cause adaptive evolution at the population level[70].

Following the delegitimization of these developmental theories in the synthetic era, the population geneticist R.A. Fisher formalized Weismann's ideas with his *fundamental theorem of natural selection.* This theorem (in the vein of physical reductionism [Smocovitis, 1996]) mathematically demonstrated that the rate of change of mean fitness is equal to the genetic variance of a species. It follows from Fisher's theorem that the potential of a species to respond to selective pressures is contingent on the amount of genetic variation (or more precisely, *additive genetic variation*), which became a crude measurement of evolvability that is still in practice today by quantitative geneticists.

Like Weismann, the evolutionary geneticist Theodosius Dobzhansky was an early empirical investigator into the origins and nature of genetic variation in natural populations. Due to his empirical work, Dobzhansky was perhaps the closest to acknowledging modern conceptions of evolvability:

> "But nature has not been kind enough to endow the organism with the ability to react purposefully to the needs of the changing environment by producing only beneficial mutations where and when needed. Mutations are random changes. Hence the necessity for the species to possess at all times a store of concealed, potential, variability" (Dobzhansky, 1937*:* 1).
>
> "A species perfectly adapted to its environment may be destroyed by a change in the latter if no hereditary variability is available in this hour of need. Evolutionary plasticity can be purchased only at the ruthlessly dear price of continuously sacrificing some individuals to death from unfavorable mutations" (Dobzhansky, 1937*:* 126-127).

In a letter from Mayr asking what his (Dobzhansky's) crowning scientific achievements were, he replied with the idea that "a population can cope with diversity of environments either by having

[70] Thank you to the late Patrick Bateson (2017) for these references, although his discussion of "adaptability" made no mention to the current notion of evolvability.

genetic variety or by having genotypes with adaptively flexibly manifestations" stood as one of his best (Dobzhansky, 15 Dec. 1970; found in Carvalho, 2019), thus revealing the central role that evolvability always played in his investigations.

Similar to Weismann, Dobzhansky also recognized the beneficial effect that the production and conservation of genetic variation would have at a level above the individual, which he called *group selection* (later influencing Wynne-Edwards to do the same). Dobzhansky would go on to argue that populations with increased variation would eventually outcompete populations with lower variation because of the fitness advantage it would eventually confer, despite the short-term fitness costs to the individuals within the population (Borrello, 2010). As noted in the third chapter, future students of sex carried on the legacy of Dobzhansky and Weismann, noting the evolvability benefit that was afforded to sexually reproducing species (e.g., Maynard Smith and G.C. Williams).

Evolutionary ecologists built off the observational work started by Dobzhansky in the latter half of the twentieth century (including his prized student, Richard Lewontin). The concepts of "adaptability" or "environmental flexibility" captured the general idea of evolvability when ecologists would discuss how a population survives and adapts in multiple or changing environments, and how this was tied to populational properties of standing genetic variation (e.g., Levins, 1968; Lewontin 1974; Endler, 1986, 48).

Quite interestingly, evolvability appeared to grow divergently as a concept in domains outside of evolutionary biology in the 1980s before being re-introduced into the evolutionary biology literature[71]. Evolvability, or 'evolutionary adaptability'—however it was referenced—became an important concept in early machine learning strategy, being described as an inherent trait of biological systems that was desirable for machine learning systems to solve a problem in more efficient ways. Michael Conrad (1985) set up a 'trading zone' between these two disciplines and re-applied the principle of evolvability back into biological terms, noting the key differences between digital computing and biological systems, with the former opting for programmability as opposed to evolvability.

This work led Richard Dawkins' (1988) to recognize the importance of evolvability when experimenting with his computer program "Blind Watchmaker", publishing his findings in a chapter in *Artificial Life* titled "The Evolution of Evolvability". In his simulations, Dawkins uncharacteristically demonstrates how some embryologies have more potential to generate variation and evolve than others. This is significant because he not only recognizes that variation is produced through evolvability systems, but that there is variation among the evolvability systems themselves in their ability to produce variation, making them most likely under selection in the long term and at a higher level:

[71] Crother & Murray (2019) note that, "The irony comes from the fact that the early development of evolvability came from the machine learning/artificial intelligence research programs that looked to biological systems to inform them about developing machines that could evolve. Dawkins (1988) flipped that by noting that his artificial system is a "powerful analogy" that teaches us "something important about real biology."

> "A title like The Evolution of Evolvability ought to be anathema to a dyed-in-the-wool, radical neo-Darwinian like me. . . As the ages go by, changes in embryology that increase evolutionary richness tend to be self-perpetuating. . . I am talking about a kind of higher-level selection, a selection not for survivability but for evolvability. . . It now seems to me that an embryology that is pregnant with evolutionary potential is a good candidate for a higher-level property of just the kind that we must have before we allow ourselves to speak of species or higher-level selection" (Dawkins, 1988: 239, 253-254).

Dawkins here helped found the developmental approach to evolvability, yet his conception of evolvability was odd by today's standards. Today most developmental approaches use organismal-level explanations, yet Dawkins here appealed to a developmental approach of evolvability that also required higher-level selective explanations (to be explained in section 5.6).

However, while several authors have arbitrarily credited Dawkins with popularizing the term *evolvability* and expanding the idea (e.g., Pigliucci, 2008; Payne & Wagner, 2018), Nuño de la Rosa (2017) used modern computational analytical tools to assess the conceptual development of evolvability over time and found that it was actually Houle (1992), Wagner & Altenberg (1996), and Kirschner & Gerhart (1998) that officialized evolvability as a true research front. From this point onwards, the moniker *evolvability* would come to represent a complex web of ideas revolving around the production and conservation of variation. Between 1990 to 2017, the term 'evolvability' has been referred to 967 times in journal articles, with associated cocitations numbering 17,466 (Nuño de la Rosa, 2017). Different definitions of evolvability have thus diverged within the many subdomains of biology, flooding the literature and causing conceptual confusion as to *what evolvability is or explains* (Section 5.2).

The history presented here is often not discussed by students of evolvability today, for several reasons. Firstly, evolvability as a developmental phenomenon has overshadowed all other considerations of evolvability. Thus, when new students arrive at the evolvability literature (often from *evo-devo*), they are met with only a snapshot of its history. It becomes clear, almost immediately, that many students of evolvability are arguing from deep-seated presuppositions or *a priori* ideas about evolvability. Yet when one broadens their historical inquiry and knowledge to include the conceptual history of variation alongside evolvability, then it becomes clear that evolvability thought has a much deeper history than is commonly presented.

As discussed in Chapter 3, there is also a taboo against talking about concepts that involve higher-level selective explanations. Evolvability, from its first conception, has been associated with natural selection at higher levels of biological organization. Weismann, Dobzhansky, and later Maynard Smith and Williams could not find a way to argue around this point. There are many good sociological reasons, then, to shy away from any conception of evolvability that may involve higher-level selective explanations, since it is still considered anathema in some circles of biology (Borrello, 2010). The evo-devo wing of evolvability tends to try and distance themselves from any selective explanation precisely for this reason (section 5.7). In the coming sections, I present an argument as to why we should not shy away from selective explanations of evolvability, especially higher-level selective explanations, but rather embrace them as useful explanatory tools for evolvability.

In sum, the original notion of evolvability as relating to adaptive genetic variation—i.e., *genetic evolvability*—would eventually become superseded by a far more general and broad view of evolvability that instead focused on the phenotypic consequences of transient "evolvability" mechanisms. This transition was likely due to the concomitant expansion of developmental evolutionary biology in the 1980s and 90s, around the same time that evolvability became popularized (Nuño de la Rosa, 2017).

5.2 Evolvability Theory Today: The Issue(s) with Evolvability

Within the past thirty years, understanding why biological entities vary in their capacity or propensity for evolution—*i.e., evolvability*—has bloomed into a central research front within evolutionary biology, catching the attention of biologists from every major sub-discipline (Nuño de la Rosa, 2017; e.g., Houle, 1992; Wagner & Altenberg, 1996; Kirschner & Gerhart, 1998; Gerhart & Kirschner, 1997; 2007; Earl & Deem, 2004; Pigliucci, 2008b; Brookfield, 2001; 2009; Wagner & Draghi, 2010; Arenas & Cooper, 2013; Brown, 2014; Minelli, 2017; Payne & Wagner, 2018; Porto, 2021; Riederer *et al*., 2022; Hansen *et al.*, *forthcoming*). Despite the influx of work that describes or mentions evolvability, it remains more conceptually fuzzy now than it did when it was first popularized 30 years ago, evidenced by the diversity or "plurality" of conceptions of evolvability, or by the large volumes dedicated to explaining such diversity (e.g., Hansen *et al.*, *forthcoming*).

Yet we are no closer to agreeing on *what evolvability is*; that is, *what are the bearers of evolvability* (the entity possessing the capacity to evolve, e.g., traits, individuals, populations), *what biological features make up the causal basis or causally contribute to evolvability* (developmental systems, genetic systems) and how do they differ in their *causal attributes,* such as *causal influence* (Lewis, 2000) or *causal specificity* (Woodward, 2010), and finally, *what phenomenon should evolvability be conceptualized to explain?*

Different definitions of evolvability flood the evolutionary biology literature today (see for extensive lists: Pigliucci, 2008b; Brown, 2014; Minelli, 2017; Nuño de la Rosa, 2017; Porto, 2021; Hansen *et al.*, *forthcoming*), and even outside the traditional scope of evolutionary biology—such as biotechnology and AI research (Bloom *et al*., 2006; Lehman, Wilder, & Stanley, 2016), computer science (Valiant, 2007; Turney, 1999), or medical research on microbial resistance and cancer development (Davies & Davies, 2010; Gillings & Stokes, 2012). This issue is further exacerbated by the number of phenomenologically similar yet nominally different concepts that emanate from all walks of biology, that describe aspects of the general idea of evolvability without any explicit mention of evolvability, including *evolutionary capacitance or cryptic genetic variation* (Paaby & Rockman, 2014: Rutherford & Lindquist, 1998)*, environmental flexibility or species invasion* (Lee & Gelembiuk, 2008), *evolutionary rescue* (Bell, 2017), *error-prone polymerases* (Rattray & Strathern, 2003), *adaptive mutagenesis* (Morreall *et al.*, 2015), *genetic charge* (Le Rouzic & Carlborg, 2008), *option value* (Jump *et al.*, 2009), or *bet-hedging strategies* (Villa Martin *et al.*, 2019)—to name a few.

Brookfield (2001; 2009), Love (2003), Pigliucci (2008b), and Brigandt *et al*., (*forthcoming*) mark the conceptual confusion surrounding evolvability as likely the result of the term being used to refer to multiple distinct, but overlapping, phenomena related to the production or storage

of novel variation (both genetic and phenotypic) and its consequent effects on adaptation. It is for this reason that most in the evolvability research front agree on the prescription of a broad and *unrestrictive pluralism* for evolvability to solve its conceptual issues (e.g., Hansen *et al.*, *forthcoming*[72]; Nuño de la Rosa, 2017; Brown, 2014). These broad models of evolvability encompass all evolvability-like phenomena under the same conceptual umbrella—e.g., phenotypic plasticity, developmental trait plasticity, epigenetic variation, G-P map, modularity, robustness, evolutionary capacitance, genetic evolvability.

While it is true that the eclectic assemblage of definitions and associated concepts certainly speaks to the need for an anything-goes type of pluralism for evolvability, or something similar across multiple domains, taking such a broad and inclusive approach exacerbates the issue(s) with evolvability. What these broad conceptions of evolvability often gain in generality (e.g., are easily understood, increased explanatory breadth) they lose in specificity (e.g., explanatory/predictive power, causal adequacy, theoretical coherency). Much of the conceptual confusion surrounding evolvability is caused by this lack of specificity, which in turn hinders the capacity of evolvability to exist within the theoretical background of modern evolutionary theory, like an oversized puzzle piece.

For example, definitions of evolvability have ranged across a spectrum from the most general to the most specific. In its broadest sense, evolvability is exactly as it sounds: '*the ability to evolve*' (Turney, 1999; Yang, 2001). Such broad conceptions have almost no utility or relevance in modern discussions since every extant species is agreed to have some capacity for evolution.

Others later noted that the diversity in a species' ability to evolve is not the salient aspect of evolvability, but rather their ability to evolve *adaptively* is what makes evolvability different and important (Wagner & Altenberg, 1996; Hansen, 2006)—which led to the revised definitions of evolvability as a *response to selection* (e.g., Flatt, 2005; similar to Fisher, 1930) or *evolutionary potential* (Wagner, 2005; Sterelny, 2007; Brown, 2014). This revision marked a distinction between a neutrally descriptive term of evolvability, such as that conceived by Turney (1999) and Yang (2001), to a normative concept of evolvability that constitutes some form of improvement. As such, evolvability has become a proxy for any observable phenomena related to *evolutionary potential*, marking any sort of long-term improvement. It is thus commonly used as an explanatory trashcan for experimentalists to dump their hypothetical extrapolations when the traditional theory cannot readily explain their findings.

For example, Woods *et al.* (2011) conducted a longitudinal study of four genetically distinct "clonal" strains of *E. coli*. They found that (a) lower initial-fitness strains eventually outcompeted higher-initial fitness strains and (b) that changes in the epistatic interactions between the strains *likely* played a causal factor in this result. It was later claimed that the result was exciting because "it was generally thought that an increased mutation rate meant you were

[72] Quite confusingly, in their chapter Brigandt *et al.* (*forthcoming*) generally argue for a pluralistic and broad model of evolvability, but then go on to note that: "It is practically necessary for many scientific investigations to have an account that more concretely specifies the bearer of evolvability (p. 9) … A generic definition only stating that evolvability is a capacity of a population would not accomplish this. Interrelations of these kinds between conceptions of evolvability applied to diverse bearers appear commonly for different research questions" (p. 11).

more evolvable. This shows genetic background is another really important aspect of evolvability" (D. Rozen in Milton, 2011).

The authors extrapolated from their findings that the lower-fitness strains eventually outcompeted the higher-fitness strain because they were more *evolvable*, owing to their operational definition of evolvability as *the expected degree to which a lineage beginning from a particular genotype will increase in fitness after evolving for a certain time in a particular environment*. The lower-fitness strain was therefore deduced to have a greater potential to evolve in the future since it became the eventual winning strain. But we must be critical and ask ourselves, is this the best way to think of evolvability? Putting aside the clear methodological issues with choosing such a circular definition of evolvability, can the authors even claim to understand the underlying causal factors that led to the result, and should they be considered *evolvability*?

Indeed, other likely explanations exist that would not fall under the conceptual umbrella of 'evolvability', in any traditional sense (see for more Milton, 2011). Perhaps mutational bias played a causal role, as the eventual winning strain could have been biased to head down this mutational pathway and evolve the beneficial allele (spoT allele) that led to the fitness increase. This is a likely explanation because the eventual winning strain did so 6/20 times when their evolutionary trajectories were "replayed", with the eventual losers never evolving this beneficial mutation.

Even if we are to grant the authors that some element of the genetic background played a causal role in the eventual winning strain's trajectory, perhaps owing to genetic constraint plasticity or epistatic interactions, then we should still hesitate to call this *evolvability*. This kind of "evolvability", whatever its causal basis, patently differs from the evolutionary potential gained from, say, stress-induced mutagenesis or the cryptic genetic variation exhibited in sexually reproducing species.

5.3 Non-Genetic (or Evo-Devo) Evolvability

To expand on these issues, let us consider the most popular cluster of evolvability conceptions, *the evolutionary developmental biology (evo-devo) concept of evolvability* (Nuño de la Rosa, 2017). Richard Dawkins (1989) and Peter Alberch (1991) jumpstarted the evo-devo concept of evolvability with their initial focus on development, effectively defining evolvability as a "property of embryological systems, i.e., certain types of developmental systems are better at evolving" (Alberch, 1991: 9).

Parallel to the maturation of developmental biology as a major biological sub-discipline in the 1990s, accumulating evidence began to clarify how certain developmental properties, at the organismal level, influence a population's ability to respond adaptively to novel environmental challenges. Some of these new observations seemed counterintuitive, like imposing certain constraints in variation promoted evolvability in virtual organisms (e.g., Rasmussen *et al.*, 1990). Or perhaps more unexpected was the finding that greater robustness—i.e., intrinsic resistance to change—actually promotes a greater build-up of variation and enhances evolvability indirectly (outlined in Kirschner & Gerhart, 1998).

With their two publications in top journals, Wagner & Altenberg (1996) and Kirschner & Gerhart (1998) propelled the evo-devo approach into the mainstream and made development the proper focus of evolvability theory (Nuño de la Rosa, 2017). The authors broadly emphasized the role that development plays in the production or structure of phenotypic variation, defining evolvability as *the capacity to generate heritable adaptive phenotypic variation* (influencing others to do the same: e.g., Payne & Wagner, 2018; Minelli, 2017; Porto, 2021). They argue that properties of developmental systems—such as the G-P map, protein versatility, weak linkage, compartmentalization or modularity, developmental trait plasticity, exploratory behavior, or the epigenome—were related to evolvability since they bias the amount and kind of phenotypic variation expressed in evolutionary systems so that more favorable and nonlethal kinds of variation are made available to natural selection in times of need.

These approaches have been referred to as *non-genetic evolvability* since they go beyond the mechanisms of genetic change, from mutation or recombination, to focus on the organizational and structural mechanisms of organisms that influence and optimize variation production in complex systems (Wagner & Laubichler, 2004). Of course, many "non-genetic" mechanisms may be underpinned by genetic processes, as rightly recognized by many in the evolvability research front. However, the organizing theme of evo-devo evolvability is the special emphasis that it places on the production or structure of phenotypic variation since "phenotypic variation is the selectable material of natural selection"[73] (e.g., Brookfield, 2001; Payne & Wagner, 2018).

For example, significant research attention within the evolvability research front has been directed towards the modularity of the G-P map and how phenotypic robustness promotes evolvability (G. Wagner & Altenberg, 1996; Kirschner & Gerhart, 1998; A. Wagner, 2005; Masel & Trotter, 2010; Wilder & Stanley, 2015; Pavlicev, *forthcoming*). This work has convincingly shown that most species have an innate "evolvability" to (a) buffer lethal mutations and (b) reduce the number of mutations needed to produce phenotypically novel traits. Both observations correspond to the way that genetic variation is modulated (compartmentalized) and turned into phenotypic variation by the G-P map.

However, despite its success to discover new and exciting phenomena related to evolvability, the evo-devo approach has perpetuated and, in some cases, exacerbated the conceptual issues with evolvability. Several have argued that the broadness of the evo-devo concept is a virtue, thus focusing on the explanatory breadth of evolvability to capture multiple overlapping phenomena (e.g., Pigliucci, 2008b; Nuño de la Rosa, 2017; Brown; 2014; Payne & Wagner, 2018; Brigandt *et al.*, *forthcoming*). Taking such a broad approach to evolvability has in turn distracted us from the complete causal field of evolvability, including upstream causal events like genetic evolvability.

[73] The assumption "phenotypic variation is the selectable material of natural selection" underdetermines the causation of natural selection, and in many considerations, runs parallel to the *random variation assumption* mentioned at the start, since it assumes that genetic mechanisms are stochastic and selectively unimportant.

5.4 Drawing a Causal Distinction Between Non-Genetic and Genetic Evolvability

Because of its emphasis on development and phenotypic variation, the evo-devo concept often fails to delineate between short- and long-term evolvability phenomena. This is to say that the evo-devo concept ***does not delineate*** between the mechanisms that generate genetic, long-term, and heritable change from the mechanisms that generate non-genetic and non-heritable (or *transiently heritable*) change, such as epigenetic variation or stochastic gene expression. Both types of mechanisms contribute to the evolvability of populations, but *they contribute in different and significant ways*. Non-genetic evolvability mechanisms generate phenotypic heterogeneity without creating genetic variation, making these changes more transient in the evolutionary process.

For example, in a recent review of evolvability published in *Nature Review Genetics*, Payne & Wagner (2018) considered four non-genetic mechanisms that create phenotypic heterogeneity as "evolvability mechanisms"—i.e., stochastic gene expression, errors in protein synthesis, epigenetic variation, and protein promiscuity[74]. According to the authors, the phenotypes created by these non-genetic mechanisms "may themselves be heritable, eventually made permanent by mutation or epigenetic modification, or they may simply 'buy time' for a population to adapt in other ways to an environmental change" (Payne & Wagner, 2018*:* 25)[75].

The authors go on to demonstrate this point by arguing that epigenetic modifications can create phenotypic heterogeneity from the changes in the protein conformations of prions. For example, the prion [PSI^+] in *S. cerevisiae* is an aggregated conformation of the translational suppressor Sup35 protein, which causes reduced translational fidelity. Some of these errors reveal cryptic genetic variation, producing adaptive phenotypes that are transiently heritable for several generations in response to pressures. The authors suggest that these epigenetic modifications of prions "buy time" for mutation and recombination mechanisms to catch up and cause an adaptive, long-term, heritable change.

In the causal story of evolvability extrapolated by the authors, the non-genetic mechanisms that cause phenotypic heterogeneity are the salient causal aspects that lead to the ensuing *evolvability*. The *causal emphasis* is put on the phenotypic variation generated, even though the authors confusingly recognize the secondary or "conditional" causal role that the non-genetic mechanisms play by "buying time" for mutation and/or recombination mechanisms to catch up and cause adaptive and long-term change. Alas, this is an example of how most causally conceive of the evolvability process today. Their attention is put on the biological mechanisms *downstream* from genetic evolvability mechanisms.

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[74] Most of the non-genetic mechanisms mentioned by Payne & Wagner (2018) mary be better served under the conceptual umbrella of *phenotypic plasticity*—or the ability of an organism to change its phenotype in response to changes in the environment (Pigliucci, Murren, & Schlichting, 2006*:* 2363). Phenotypic plasticity mechanisms are genetically ingrained mechanisms *that reflect non-genetic adaptive changes.* Every mechanism that these authors have thus classified as non-genetic 'evolvability mechanisms' functions better under the concept of phenotypic plasticity since their evolvability-related effects are rather transient in comparison.

[75] The underlying causal mechanisms governing these processes are not well understood, and they may as well be the result of genetic contributions (Mërila & Hendry, 2014; Birney *et al.*, 2016; Lappalainen & Greally, 2017). We are thus left to assuming some amount of epistemic risk when we claim to know the causal basis for the observed phenotypic heterogeneity.

What is being neglected by the evolvability research front is the upstream disparity in causation, or a disparity in the mechanisms that cause genetic evolvability *between species*, rather than all species having the same capacity to produce, conserve, or domesticate genetic variation. Indeed, if every species had the same capacity for genetic evolution[76], and most of the differences of variation existed at the organismal-developmental level, then the most salient aspect of evolvability, as well as the direct causal element of evolvability, would be non-genetic evolvability mechanisms that modulate invariable or stochastic genetic variation that subsequently turns into phenotypic heterogeneity.

However, species do not exhibit the same capacity for genetic evolution due to selective reasons. Mutation and/or recombination rates are incredibly variable throughout taxa and levels of biology, often dependent on numerous causal factors, including selection (Lobkovsky *et al.*, 2016; Swings *et al.*, 2017). It has been widely appreciated in microbiology that natural selection *can causally intervene and influence the mechanisms of genetic variation, with some species being more genetically evolvable* since at least the 1960s (Fitzgerald & Rosenberg, 2019).

This seems to be a point that is strangely absent in most considerations of evolvability (e.g., Brown, 2014; Brigandt *et al.*, *forthcoming*). For example, Nuño de la Rosa & Villegas (2019) note that the G-P map governs how "random genetic mutation" translates into non-random, structured, and possibly adaptive phenotypic variation for characters exhibited by particular types of organismal systems. What is missing from these considerations is the fact that there is *non-random* discriminate sampling in the processes of mutation/recombination themselves, with the variation in these processes being best attributed to *between populations* because of the interlevel conflicts that typically accompany the emergent benefits (i.e., the individual-level costs of recombinatorial and mutational load; to be expanded in Section 5.6).

Such a disparity strongly suggests that higher-level natural selection acting on mutation/recombination modifiers is an upstream causal event from the generation of phenotypic heterogeneity that needs to be distinguished from other downstream causal events of evolvability, such as those pertaining to *non-genetic evolvability*. This also suggests that causal distinctions can be made between the amount of causal influence (Lewis, 2000) or specificity (Woodward, 2010)[77] that these two types of evolvability exhibit, with early indicators suggesting that genetic evolvability is more causally influential and causally specific than non-genetic evolvability.

We see similar obsevobservationsations when we draw parallels between other literatures with similar explanatory goals, such as the evolutionary rescue research front. Developmental mechanisms (and dispersal methods) might be initially sufficient to relieve minor pressures and allow for population persistence. Yet when too great of pressures are applied, populations generally shift their strategies to facilitate adaptive evolution through genetic changes (Carlson *et*

[76] Constant, Invariable, or stochastic genetic evolution is often a presupposition for other failed notions such as the random variation assumption or the molecular clock.

[77] Relating to causal specificity, most students of evolvability are the first to recognize how little is still known about the underlying mechanisms of the G-P map, or how genetic variation is turned into phenotypic variation. There seems to be an element of *epistemic* and/or *aleatory* risk involved with accepting evo-devo conceptions of evolvability (in a similar but less-dire case as that presented by Biddle, 2015). The ontological causal relationship between non-genetic evolvability mechanisms and their ensuing evolvability-related effects remains a major question mark. This suggests that non-genetic mechanisms may be less causally specific than genetic evolvability mechanisms since we have a clear causal relationship between genetic evolvability and its effects on adaptation.

al., 2014; Mërila & Hendry, 2014). Indeed, such a distinction is important to make in the evolutionary rescue research front, exhibited by the work that attempts to establish the time frames over which genetic change versus existing phenotypic plasticity will be most important for population persistence (Chevin *et al.* 2013, Kovach-Orr & Fussmann 2013; sources drawn from Hendry *et al.*, 2018).

The available evidence thus implies an ontological and causal distinction between the direct causal elements of genetic evolvability (e.g., evolvability mechanisms like HGT, stress-induced mutation, or meiotic recombination) that generate genotypic heterogeneity, and the non-genetic causes that influence how effective genetic evolvability mechanisms are at producing adaptive phenotypic changes (structural causes) or the developmental mechanisms that produce phenotypic heterogeneity and "buy time" for genetic evolvability mechanisms to cause adaptive evolution. This is because non-genetic evolvability mechanisms appear to be *conditional elements* of genetic change (i.e., structural causes), rather than the direct causal elements (or what is called a *triggering cause* in the causal literature) of evolvability[78]. Non-genetic mechanisms certainly aid in the facilitation of adaptive evolution, but their role is better cast as *conditional* rather than *causal*. Like a silencer to a pistol, conditional non-genetic mechanisms likely evolved to augment and modulate the mechanisms of genetic variation.

Other examples include the influence of the G-P map on evolvability since it promotes greater evolvability *but also greater robustness* (Pavlicev, *forthcoming*). The G-P map is best described as a structural cause that eases the selective constraints of genetic mechanisms, which in turn allows for the direct causation of genetic mechanisms to generate more adaptive mutations in the future (Masel & Trotter, 2010). Likewise, Brown (2014) noted that weak constraints on developmental traits afford a greater probability that traits can evolve in response to environmental demands. Such constraints only make the probability of a beneficial mutation of a trait more likely, whereas the direct causal action of evolvability is contingent on the genetic mechanisms (that are also probabilistically dependent but upstream causal events).

The causal distinctions that abound between genetic and non-genetic "evolvability" mechanisms—such as differences in causal influence and downstream effects, causal specificity, and/or spatial location—strongly suggest that we must maintain something like the ultimate/proximate causal distinction between genes/development (i.e., *Weismann's barrier)* in the evolvability concept, contrary to what several progressives have argued (c.f. Uller & Laland, 2019; Laland *et al.*, 2011). For precisely the same reasons why we drew a distinction between development and genetics in evolutionary biology over a century ago (i.e., *Weismann's barrier*), and why we still view the explanatory utility of Lamarckian or soft inheritance as inferior to hard-inheritance structures, are precisely the same reasons why we should draw a similar distinction between *shorter-term phenotypic evolvability from developmental mechanisms* and *longer-term higher-level genetic evolvability*.

If evolvability is to become a mature causal explanatory model, we must have a good grasp of its causal relations. When we are constructing a causal explanatory model, especially one that

[78] The distinction made here is similar to what Mackie (1965) refers to as the predisposing causes (causal conditions that set the stage for an event to occur) from triggering causes (causes that trigger the event's occurrence), which is a common distinction made in the medical literature (e.g., smoking increasing the probability of causing cancer).

attempts to capture the complete causal field of a complex phenomenon such as evolvability, we must make further causal distinctions so that we can accurately and precisely model and replicate this process in the future. Maintaining such a causal distinction between non-genetic vs. genetic evolvability thus organizes similar phenomena while also achieving a concreteness in conceptual parameters, which should be preferable from the typically broad conceptual model of evolvability that hastily categorizes all the evolvability-related explanandum under one conceptual umbrella. We need to reemphasize the *evolvability gained from genetic changes* rather than the nondescript evolutionary potential gained from non-genetic, non-adaptive developmental processes.

5.5 Reemphasizing Genetic Evolvability (and the role of selection)

The majority of the focus of the evolvability research front since its onset 30 years ago has been on the role that development plays in the adaptation process, or on the *phenotypic* side of the G-P map. Hendritske *et al.* (2007) even deemed "evolvability as the proper focus of evolutionary developmental biology." But while evolvability may be the proper focus of developmental biology, *genetic evolvability remains the proper focus of evolvability.*

Evolvability unquestionably lives at both sides of the G-P map. But by focusing too greatly on development and phenotypic variation, those in the evolvability research front have routinely overlooked the most important causal factor of evolvability, which is *evolvability by adaptive genetic variation*. Standing genetic variation[79] or the input of new or "better" genetic variation from selectively maintained genetic mechanisms are upstream causal events that need to be distinguishable from non-genetic evolvability processes.

Re-emphasizing genetic evolvability could partly resolve some of the primary questions and issues surrounding evolvability theory. For example, every major review of evolvability has attempted to breach the topic of the *evolution of evolvability*, or what are the causal mechanisms of evolution underlying evolvability (e.g., Pigliucci, 2008b; Sansom, 2009; Brown, 2014; Hansen, 2016; Minelli, 2017; Payne & Wagner, 2018; Porto. 2021; Hansen *et al.*, *forthcoming*)? At the forefront of these discussions is the curious and often controversial relationship between evolvability and natural selection. *Does evolvability entail or imply natural selection? Is evolvability a selectable property?*

A few have (rather cautiously) granted natural selection a causal role in the evolution of evolvability (Love, 2003; Earl & Deem, 2004; Colegrave & Collins, 2008; Pavličev & Cheverud, 2015). Some have argued that evolvability evolves through neutral or non-adaptive (spandrel) processes (Wagner & Altenberg, 1996; Turney, 1999; True & Haag, 2001; Lehman & Stanley, 2013; Brown, 2014; Payne & Wagner, 2018). However, most stay passively agnostic on this subject. Wilder & Stanley (2015, 2) exemplify this sentiment: "There is no consensus across work on whether selection can favor evolvability."

[79] Like most things in biology, there is some phenological overlap between non-genetic and genetic evolvability mechanisms. Genetic variation is not only maintained and conserved by sex, but also by developmental mechanisms, which sometimes releases cryptic genetic variation. In another sense, sexual processes could even be considered developmental mechanisms.

I am prone to agree with the consensus that it is harder to point to an unequivocal example of evolvability evolving through selection, only when it is considered a developmental phenomenon. Evo-devo primarily investigates phenomena in the short term at the individual-organismal level, which has led to evolvability being viewed as primarily a developmental phenomenon that facilitates phenotypic heterogeneity among individuals.

Because of the heritability element implied in *genetic* evolvability mechanisms, and because of the long-term or emergent explanations necessary to account for such mechanisms, genetic evolvability is that much more likely to be a robust product of selection in most evolutionary histories happening over an extended amount of time (through maintenance selection). Genetic evolvability has therefore been overlooked *because other lines of research that are directly contributable to evolvability have been overlooked*. Genetic perspectives of evolvability—like those given by Radman *et al.*, (1999), Earl & Deem (2004), or Colegrave & Collins (2008)—are seldom referenced by those in the evolvability research front, and if they are, then they generally take a backseat in perspective.

What the evolvability research front has yet to fully appreciate is that a HUGE literature exists outside of the developmental purview of evolvability, that does not fly under the traditional 'evolvability' banner but *is directly contributable to evolvability theory.*

Take microbiology as an example. Microbiology is beginning to shed light on the underlying biochemical mechanisms of evolvability, providing a robust yet neglected empirical literature rife with examples of evolvability. This is a typical criticism cast at evolvability by those that read (or *half-read*) the evolvability literature and claim that there is no good empirical evidence for evolvability (e.g., Charlesworth *et al.*, 2017; Sniegowski & Murphy, 2006). Evolvability needs to be linked to a clear-cut biological mechanism (Crother & Murray, 2019). Several mechanisms have been proposed, such as heat-shock proteins acting as evolutionary capacitors (Rutherford & Lindquist, 1998; Love, 2003), non-genetic evolvability mechanisms like epigenetic variation or protein promiscuity/versatility (Payne & Wagner, 2018), or others (cf. Crother & Murray, 2019; Arenas & Cooper, 2012; Colegrave & Collins, 2008; Sansom, 2008).

While many of these examples provide a reasonable attempt at demonstrating evolvability, many or most of them fall short because they do not provide a full-scale report, from start to finish, of a biological mechanism that caused future or further evolvability. This highlights a major problem for the evolvability research front. Without an unequivocal empirical example of evolvability available, evolvability will continue to be an epistemological soup that moves wantonly from one understanding to another. The development of evolvability into a mature conceptual model *necessitates* a deeper understanding of the lower-level biochemical, molecular, and physiological processes underlying evolvability, precisely because understanding evolvability's causal basis provides increased explanatory depth and predictive power of evolvability processes, accounting for how the evolvability processes occur and why they lead to adaptive evolution.

The best exemplar candidates of evolvability, then, derive from *genetic evolvability* because of its historicity and supporting evidence. Genetic evolvability has been readily observed for over a century, as most species have been observed to have some capacity to adapt to environmental pressures due to the production of novel genetic variation or the conservation of standing genetic variation. With the advent of proper genome altering techniques, our understanding of genetic evolvability has only intensified as experimental biologists have been toying with the expression

or function of DNA/RNA polymerases and repair enzymes and mapping their evolutionary consequences.

One such microbiological study mentioned in chapter 3 provides good evidence for evolvability. Ragheb *et al.*, (2019) exposed bacteria to several types of antibiotics and inhibited their expression of the DNA translocase protein *Mfd*—which is known to promote DNA repair *and* mutagenesis dependent on environmental conditions—thereby causing severe declines in their global mutation rates and precluding their evolvability. Given that *Mfd* is highly conserved across prokaryotic and eukaryotic domains, these findings point to *Mfd* and other DNA/RNA polymerases as likely contenders for stress-induced evolvability mechanisms that are conserved through maintenance selection. *Why is this study more important than past studies?* Because rather than demonstrate how a gain-of-function promotes greater evolvability, which is more common but also more difficult to assess, this study showed how a *loss-of-function leads to less evolvability.* Maintenance selection is easier to identify using this novel approach, which is probably the main causal force acting on evolvability mechanisms (with the gain-of-function approach typically used to identify directional selection). For this reason, the combined effects of maintenance selection and evolvability have likely been concealed *because we have been focusing on the wrong type of selection, using the wrong methods.*

What is currently unacknowledged by those in the evolvability research front is that this study, and many of the other studies reviewed in chapter three[80], *are unequivocal examples of selection for evolvability*—they satisfy all the necessary conditions for maintenance selection outlined in chapter four. Given that these mechanisms are clearly genetic mechanisms, the *heritability condition* is easily satisfiable. The *causal connection condition* is also satisfied, as the focal evolvability features in these studies caused some populations to survive over others[81].

As demonstrated in the last paper, the causal connection between modifiers and a species' likelihood of evading extinction (i.e., species *survival*) has only recently been recognized by the evolutionary rescue research front. Recombination and hypermutation have been shown to cause the *evolutionary rescue* of species following environmental change (Gonzalez *et al.*, 2013); rates of TEs are likely causally connected to a species extinction rate (Brunet & Doolittle, 2015); HGT has been observed to allow species to evade extinction; and WGD events have been observed in the fossil record to increase in prevalence during mass-extinction periods, suggesting that they offer a large-grade mutational benefit to species in times of great need. In sum, there are biological mechanisms related to the production or conservation of genetic variation that causally affects the survival of biological populations and species over time.

The issues of (i.) *the evolution of evolvability* and (ii.) *linking a biological mechanism to evolvability* have thus been answered, in part, when it is conceived as *genetic evolvability*.

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[80] One can surely disagree on the methodology of such studies provided, or on the actual validity of the outcome that was measured (e.g., species extinction or survival). But if we agree on the experimental validity of these studies, that the causal relationships found in these studies were indeed *real*, then we must accept this as a case of natural selection, or else we need an entirely new ontological understanding of natural selection.

[81] In a private conversation I had with a reputable evolutionary geneticist, they saw the increased mutations rates as a by-product of metabolic processes or other mechanisms, rather than a directly selected evolvability mechanism. What they fail to appreciate is that these considerations do not matter. The mere fact that these mechanisms provided an evolvability benefit in a given environment (or, rather, a shift in environment) that then led to the survival of certain populations over others is enough to claim that natural selection has occurred, or likely has occurred many times in the past, because it satisfies as the necessary causal conditions for natural selection.

Selection does play a causal role in evolvability, and often many of the evolvability-type mechanisms ingrained in the genome, such as the multifunctionality of DNA/RNA polymerases to repair but also "malfunction" when necessary, are so well conserved that maintenance selection is the best explanation for their persistence across domains. The adaptive and often selective nature of evolvability should thus be kept in the conceptual model of evolvability, rather than see evolvability as strictly a product of non-adaptive, non-genetic mechanisms that enhance evolvability.

This brings us to the main reason why genetic evolvability has been overlooked *because most of the contemporary focus on evolvability has been placed at lower levels, disregarding macroevolutionary or ecological perspectives.* The reason why we have neglected the explicit and intimate relationship between selection and evolvability is because we need higher-level selective explanations to explain most genetic evolvability phenomena.

The relative disconnect between ecology and evolvability is evidenced by the lack of macroevolutionary perspectives offered in evolvability reviews or compendiums. In the few instances that they have been considered, they have generally taken a backseat to evo-devo considerations (e.g., Pigliucci, 2008b; Jablonka, *forthcoming*). Given that evolvability is primarily manifest when environments change, one would think that ecology would play a central role in evolvability theory. Yet ecology is one of the missing pieces in evolvability theory, that once considered, opens the door to a new understanding of evolvability, one that recognizes the profoundly causal explanatory role of higher-level selection to select for and maintain genetic evolvability mechanisms.

5.6 Macroevolutionary Evolvability: Species Selection and Multilevel Selection

> "Some evolutionists argue that natural selection can act only on properties that are advantageous to the individual (e.g. Williams, 1986). Evolvability is advantageous to the species. Do not, therefore, let the concept of evolvability mix into biological thinking. This dictum is wrong on two counts…" (Conrad, 1990: 77).

There is strong evidence to imply that selection plays an important causal role in evolvability, especially when we consider *genetic evolvability*. But at what level of biological organization or timescale are the effects of evolvability generally seen? Indeed, the entire dialogue of evolvability hinges on these essential questions. Brigandt *et al.* (*forthcoming*) recognize this in their recent chapter:

> "The complexities mentioned so far should make it obvious that there is not one unique, privileged timescale for evolvability. Instead, different approaches will choose a timescale that is relevant to their methodological perspective and research question, while ensuring that the timescale used to measure the stimulus condition (e.g., the period during which an average selection differential obtains) matches the timescale for the ensuing manifestation of a population's or taxon's evolvability…evolvability may well be distinctive as a disposition. One reason is that plasticity, organismal robustness to environmental perturbation, and phenotypic variability primarily pertain to short-term effects. In contrast, we have seen that evolvability also captures long-term evolutionary

> potential, thereby accounting for change and innovation across longer timescale" (Brigandt *et al., forthcoming*).

And how they explain such long-term or macro-evolvability:

> "From a paleontological perspective, species and higher taxa can exhibit evolvability by having lower extinction rates and by possessing the ability to undergo adaptive radiations and diversify (Love, 2003; Sterelny, 2011) … Although extinction events have a destructive effect in the short run, one may explore whether it is possible (and under which conditions it is possible) for extinctions to accelerate evolution in the long run. Prior extinction events might have selected for taxa that can rapidly occupy vacated niches, taxa have a high evolvability with respect to future extinction events as a possible stimulus condition of macro-evolvability (Lehman and Miikkulainen, 2015)" (Brigandt *et al., forthcoming*).

Despite their recognition that evolvability may be related to the differences in extinction rates (i.e., a higher-level fitness metric), they still do not see selection as a viable causal mechanism behind evolvability:

> "Selection can act on actual variation, but not the potential for variation: 'the basic problem with the evolution of evolvability is that selection cannot act on potentials or abilities – only on results. It can act on a fit phenotype but not on the ability to produce a fit phenotype per se' (Watson 2020)" (Brigandt *et al., forthcoming*).

As here recognized by the authors, what timescale we choose to view evolvability has very real consequences for what level we ultimately perceive evolvability (and largely evolution) to hold its causative effects. For example, population and quantitative genetics view evolvability as a higher-level property since they frame it in historical terms as the ability of *a population* to respond to selection (i.e., variations of Fisher's *fundamental theorem*). In contrast, evolutionary developmental biologists generally frame evolvability as a developmental property *of organisms* that permits the generation of novel phenotypic variation or biases the generation of different individual phenotypes: "In evolutionary developmental biology, the focus is on how the configuration of development for organisms from a certain taxon permits the generation of novel and functional phenotypic variants or biases the generation of different phenotypes" (Brigandt *et al., forthcoming*). Similarly, Wilder & Stanley (2015, 14) note "Populations become evolvable when greater exploration is promoted, and individuals become evolvable when selection is for phenotypic variation. These observations highlight the importance of population-level evolvability."

Evolvability as defined in evo-devo is a property of *individual organisms* and their capacity to generate functional phenotypic variants. However, evolvability operating at different levels of biological organization causes different evolutionary outcomes, with higher-level evolvability causing genetic changes that remain more fixed in the long-term and thus are more evolutionary significant. *Why*? Because adaptive variation primarily manifests at the populational level, hence why populations are thought to evolve and not individuals (Love, 2003). Evolvability is best conceived as an ontological property of higher-level entities, as an emergent property of individuals within populations. This is why genetic evolvability generally conflicts with the evo-devo approach, since how they view the manifestation of evolvability differs (e.g., genetic vs.

phenotypic change), causing different causal perspectives of evolvability operating at different levels of biological organization.

It is important to note that evolutionary biologists have primarily modeled evolution at the population level since at least the Modern Synthesis. This is not a coincidence, but rather signifies something more profound, that the causation of evolution primarily occurs at the populational level (see why Ariew, 2008)[82]. Thus, because individuals cannot evolve, then they logically do not have the capacity for evolvability[83]. This is not to say that individuals cannot contribute to evolvability processes or that individual-level variation is *inconsequential*, just that the primary causal effects of evolvability are often expressed at levels higher than the individual (Wilder & Stanley, 2015).

Nuño de la Rosa & Villegas (2019) and Brigandt *et al.* (*forthcoming*) both disagree with this assumption because, as they argue, evolvability in developmental terms does not view one individual organism as the bearer of evolvability, but rather evolvability refers to one *type* of developmental system that is evolvable (not a *token*; see for more Brigandt *et al.* (*forthcoming*)[84]. For this reason, many students can appreciate evolvability as an abstract and flexible concept that refers to causal processes at various levels of biological organization.

Indeed, it is ontologically possible that evolvability is causally relevant at multiple levels of biological organization, what could be called *multilevel evolvability*. The *first principle of natural selection* is that, wherever there is variation (that is heritable), there can also be natural selection. Extending this principle to capture evolvability at multiple levels: wherever *there is variation in the processes that generate heritable variation*, then there can be evolvability by natural selection. There is now abundant evidence for variation in mutation rates *between clades down the hierarchy to genes* (i.e., genomic "hotspots"). However, just because such variation in mutation rates exists at many levels *does not imply* that each level has the same evolvability, or that the variation was specifically selected for the advantage of evolvability at that level.

New phenomena are typically defined by their *causal effects or consequences*, and the evolvability of individuals is important insofar as it produces adaptive changes at the population level. Individual-level variation is not the salient causal aspect of evolvability, yet rather *the variation of individuals within a population*, creating *diverse and evolvable populations*. Take frequency-dependent selection as an analog. The salient causal aspect of frequency-dependent selection is *the variation between individuals within a population*, rather than individual-level variation, since it depends on the relative frequency of a genotype within a population and not the individuals' ability to vary. The causal field consists of population- and individual-level processes, but the evolutionary consequences are often ascribed to populations. In instances of evolvability, the adaptive consequences of variation between individuals are manifested at the

[82] Here I note populations as the primary ontological level of evolution. It is important to note that, throughout this thesis, I use "populations" and "species" as interchangeable terms. I do so because the question of which level of evolutionary causation is most causally relevant includes several ongoing philosophical debates (i.e., the species problem) that lie outside of the feasible scope of this thesis.

[83] This is important to keep in mind given the scientific virtue of *theoretical coherency*, because most of the theory we have built up over the years has revolved around population thinking.

[84] Yet all short-term evolvability mechanisms may well be the result of long-term selection explanations, since they are ingrained in the genome to react to short-term stressors.

population level. Evolvability is not an individual-level phenomenon, then, since individuals are not the ones receiving the evolvability benefit[85].

This highlights why evolvability primarily exists as a higher-level emergent property, since it has new causal consequences that are not present in the lower-level properties upon which they depend, and the higher-level properties downwardly affect lower-level individuals, sometimes deleteriously. For example, *the paradox of adaptive variation* demonstrates how evolvability manifestations could cause deleterious effects at the individual level by decreasing the viability of individual offspring while simultaneously causing adaptive consequences at the population level. This is not only a signature of an emergent property but a very strong indicator that evolvability was selected for its higher-level advantages.

Evolvability mechanisms such as modifier genes are good examples of lower-level features causing higher-level or emergent consequences because they tend to have low heritabilities (in the quantitative genetics sense) at the individual level comparable to their high heritabilities at the species level. This is truly indicative of what we refer to as a species-level feature (a.k.a., an *aggregate feature*, see Goldberg, 2014) since the feature varies little within species but varies greater between species, thus allowing for natural selection at a higher level. Indeed, mutation and recombination rates have been observed to vary *within species*, as well as *within genomes*. Yet the variance tends to be greater and is more easily identifiable *between species* than at these lower levels since the heritability of lower-level features is generally low. For example, the amount of TEs has been found to vary relatively little within populations but varies greatly between populations (Brunet & Doolittle, 2015). For these reasons, modifiers are easily attributable as lower-level features with species-level consequences since there is greater variation in these lower-level features at the species level.

As demonstrated in chapter three, such an empirical trend is readily observable in the adaptive genetic variation literature. In stable environments or following sufficient adaptation, global mutation or recombination rates tend to drop or be lower than average. However, when a population is stressed or environments change, then we typically see an uptick in global mutation or recombination rates. From a multilevel perspective, the best way to view this scenario is that natural selection is shifting its adaptive interests along hierarchies to value individual-level survival over population-level evolvability in stable environments while valuing the latter in variable or novel environments.

This is why we typically see the trend of decreasing fitness (which is generally a measure of individual-level selection; see for more Graves & Weinreich, 2017) inversely correlated with evolvability in the adaptive genetic variation literature, at least initially. If evolvability were an individual-level phenomenon, then we would see no such trend or tradeoff. Minor pressures may be resolved through individual-level variation (i.e., *phenotypic plasticity or developmental mechanisms*). Yet the evolutionary rescue literature continues to demonstrate that when greater pressures are applied, individual-level variation is insufficient to relieve great pressures, causing populations to rely on genetic evolvability mechanisms by shifting their mutation/recombination

[85] Most in the evolvability research front seem to agree with this conclusion. Only recently have several philosophers started to deviate from this conclusion. I suspect this is due to them wishing to place their evo-devo approach well within the theoretical traditions and conceive of evolvability as an individual-level phenomenon.

rates to better adapt to novel environmental stimuli (Carlson *et al.*, 2014)—what are likely remnants of past selections for evolvability.

Comparative evidence from behavioral ecology (or evolutionary psychology) shows similar trends in emergence, in that a tradeoff exists between different levels contingent on environment-species relationships (Wade, 2000). "Weird" evolutionary strategies such as cooperation or insect colonization are generally understood as selectable in unpredictable or harsh environments (Sober & Wilson, 1998; Okasha, [2006]2013). Facultative species aggregate in harsh environmental conditions but disaggregate in favorable conditions. Life-history studies have also recently demonstrated how environmental variation might select for different optima in offspring

Box 8: A (Brief) History of Higher-Level Selective Explanations and Evolvability

The levels of selection debate is one of the most fundamental—and equally controversial— discourses in the history of evolutionary biology that centers around the question: *at which level of the biological hierarchy does the process of natural selection typically operate*, or, to which level or levels may we attribute the benefits of natural selection (i.e., adaptations) to hold their causal manifestations. The mathematical models of Fisher and Haldane in the early twentieth century focused on within-species natural selection, and thus their models could not envisage adaptations at a level of selection higher than the individual (Nei, 2013). By the mid-twentieth century, it became apparent to many biologists that higher-level adaptations—or features that appear to confer a benefit for the "good of the species"—were present in the tree of life, but there were no theoretical models capable of explaining how such features might arise (Okasha, 2014: 201). Thus, without a readily available explanatory strategy, group selectionist arguments were easily discounted.

G.C. Williams (1966) was perhaps the most vociferous opponent of higher-level selective explanations, altering attitudes towards them for decades to come. He thought the idea of group selection was tenable, likely because of his interest in sex, but thought of it as a relatively "weak" evolutionary force, since individuals have a faster rate of turnover than groups. He instead saw group-level features as *fortuitous group benefits*, or features that incidentally benefit groups, but selection did not cause their initial evolution. For example, Williams thought there was an evolvability-type benefit behind the evolutionary maintenance of sex, but he thought this was unlikely the reason *why sex evolved in the first place*. In his eyes, the higher-level advantage of sex did not evolve out of higher-level selection, but rather as an incidental side effect (*spandrel*) of individual-selective processes.

Species-selection theory was thus promoted by Stanley (1975a;b) as an alternative to *group selection theory*, marketed as a selective explanation for higher-level features of biological species that did not conflict with the time constraints of the *individual selection assumption*. Group selection failed because it worked within the time-constraints of individual selection, focusing on how lower-level individual interactions create emergent variation and differential 'fitness' at a group level. Species selection, in contrast, was built on the idea that species themselves are 'individuals[1]' and therefore evolve in a similar fashion to individual selection, yet over greater geological time scales. What thus led to the gradual acceptance of *species selection theory* over *group selection theory* was the simple distinction that it made over evolutionary timescales (Goldberg, 2014). D.S. Wilson (1997; Wilson & Wilson, 2007) has expanded this framework to include the idea of *multilevel selection*-that is, that natural selection can operate at multiple levels simultaneously. The philosopher Samir Okasha ([2006]2013) has since expanded this framework from a mathematical perspective. See Folse III *et al*. (2010) for a good overview.

Interestingly, genetic evolvability has long been considered as the best example of a species-level adaptation. This is why Lloyd & Gould (1993) referred to intraspecific genetic variation as "the most potent evolutionary property of populations [for] arguments about species selection (p. 595)" or why Sniegowski & Murphy (2006: R832) said that "because populations, not individuals, evolve and adapt, it follows that evolvability-as-adaptation must be the consequence of selection among populations rather than selection[1]." Genetic evolvability perfectly demonstrates how selection can act higher levels of selection over longer timescales, because of the conflicts between levels.

size (reviewed in Marshall *et al.*, 2018; Cameron *et al.*, 2021). For example, Marshall *et al.* (2008) showed that unpredictable environments might select for greater "bet-hedging" (i.e., evolvability) strategies, whereby mothers conceive offspring of variable size to increase the chances that some of these offspring are suited to the prevailing conditions. Cameron *et al.* (2021) thus recently demonstrated the effectiveness of using a multilevel approach to explain why such variability in offspring size exists.

Using higher-level or emergent explanatory strategies in the case of evolvability is thus *not discretionary*, but *absolutely necessary*. We *need* higher-level selective explanations like species selection to capture the adaptive consequences of evolvability since they are typically expressed at higher levels of biological organization (Goldberg, 2010), while also *needing* multilevel selection theory to explain how adaptive interests shift along with these levels (i.e., inter-level conflicts or tradeoffs).[86]

From a different perspective, the fact that there is variation amongst *individuals within populations* points to the possibility that this could explain its initial evolution or even short-term selection for evolvability. When individuals vary in some respective trait, there is an increased causal efficacy of selection *in the short term*. Natural selection can operate more quickly on individuals within a population than on a population itself, hence why multiple levels of biological organization may not only be a happenstance of biology, but also an adaptation in and of itself. I would call this idea *global evolvability*—the notion that evolvability mechanisms operate at multiple levels of biological organization to streamline evolution at every level[87]. Indeed, if evolvability operated at just the individual level, or just at the populational level, this would be less advantageous than if it operated at multiple levels with less causal constraints between levels (i.e., upwards and downwards causation). This is not to fall prey to teleology by claiming that evolution was indubitably selected for global evolvability because it was advantageous for higher-level biological entities. But there is some evidence to suggest that multilevel causal interactions do exist. I suspect that most higher-level properties of populations, species, or taxa first evolved through individual-level selection operating within populations until they were selected over longer periods and/or following extinction-type events (i.e., macroevolutionary transitions).

Just like population genetics cannot reduce all the causal processes (mutation, selection, drift, migration) to within-population analyses and believe that this explains all evolutionary change, students of evolvability cannot conceptualize evolvability as a broad-set process that causes similar evolutionary changes at every level of biological organization. Massive and important causal distinctions abound between all the kinds of evolvability mechanisms, most notably at what level they cause adaptive change. Evolvability at the population level produces causal changes that are much longer lasting and thus more evolutionary significant than evolvability at lower levels. Ironically, the population genetic viewpoint may be the best marketer of evolvability, since a population-level viewpoint of evolvability should be the principal way to view evolvability.

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[86] It is less clear, however, if we need *a multilevel evolvability concept* since there is less evidence for the causal import of individual or lower-level evolvability. But what is clear is that we need multilevel causal strategies to make sense of the readily demonstrable evolvability as emergent properties of populations.

[87] If the realism of *global evolvability* is true, then this could be interpreted as evidence for *the Gaia hypothesis*.

In sum, evolvability is thus best considered at the ontological level of populations, since the causal effects of variation are also best considered as an emergent, aggregate property of individuals *within a population*, allowing evolvability to ensue at the populational level. Populations are the primary causal bearer of evolvability manifestations. As noted by Wilder & Stanley (2015), Brookfield (2009), and Love (2003), it makes no sense as to why selection on individuals should maximize evolvability, but every sense to view it as an emergent property of population or specie. For this reason, we need new explanatory strategies like species selection or multilevel selection to explain the emergent causal manifestations of evolvability. Yet there is one last element to consider: the conceptual role of evolvability in natural selection theory. In the following section, I argue that evolvability functions best within natural selection theory *as a higher-level fitness component.*

5.7 Evolvability as a Dispositional Fitness Determinant of Species

The parallel between evolvability and fitness feels so natural that you see it arise inadvertently within many biologists' reasoning on evolvability. For example, Dawkins (1988) first recognized this connection when he remarked, "I am talking about a kind of higher-level selection, a selection not for survivability but for evolvability" (p. 218). In a similar vein Colegrave & Collins (2008) pose the question, "But are there characteristics of organisms that function not to increase their fitness, but instead to increase evolvability? That is, are there traits that are selected and maintained because they increase the ability of a population to respond to natural selection?" (p. 464). In a recent review of fitness, Graves & Weinrich (2017) appreciate that "alleles affecting traits like sex, evolvability, and cooperation can cause fitness effects that depend heavily on differences in the environmental, social, and genetic context of individuals carrying the allele" (p. 399).

A primary theme of this thesis is how selection is not as short-sighted as previously supposed, using evolvability as an exemplar of a longer-term and higher-level adaptation. Under this purview, evolvability has real ontological and epistemic ties to the concept of biological fitness, only at higher levels. However, students of evolvability do not view evolvability and fitness as familial concepts owing to the evo-devo slant in the literature that disregards the external causal influences of ecological environments on evolvability. In the following I will highlight the similarities between evolvability and fitness, arguing that the evolvability concept functions best within evolutionary theory as *an extrinsic probabilistic dispositional fitness determinant of species.*

All agree that both evolvability and fitness are *dispositional properties* (Love, 2003; Brown, 2014; Nuño de la Rosa & Villegas, 2019; Brigandt *et al., forthcoming*). By reference to the "ability of a population" to either respond to selection or evolve, most conceptions of evolvability frame it as a disposition. *But what kind of disposition is it? A probabilistic or deterministic disposition? An intrinsic or extrinsic disposition? A disposition that holds its causal basis in genes, organisms, or populations?* As demonstrated in the last section, an answer to the last question has already been achieved, with populations being *the primary causal bearer of evolvability mechanisms*. However, the former question is more difficult, and I will philosophically unpack it in the following. Thankfully, philosophers of science have built a useful toolkit that allows for the comparison of various aspects of dispositions (see **Box 9**). Answering these questions is thus important if we wish to draw comparisons between competing

models of evolvability, figuring out which kind of disposition evolvability *is* and should be conceived *as*.

Box 9: Biological Dispositions

A dispositional property is a capacity, ability, or potential to exhibit some future outcome under certain causal conditions. This marks the primary distinction between a dispositional property and a non-dispositional or "categorical" property, in that a dispositional property need not be manifest while a non-dispositional property is always manifest.

For example, different types of glass exhibit different levels of fragility. The fragility of a glass window is its disposition to break under certain causal conditions (e.g., a rock thrown at the window). This window exhibits fragility irrespective of any actualized event, even if it never breaks. This is why something can be "disposed" to break even if it never truly breaks, even if it *never truly manifests*. Such "fragility" is thus thought to explain a persisting or future state of a window (Mumford, 1998). In contrast, a non-dispositional property of a window, such as its shape or size, is always manifest.

Philosophers of science have recently devoted much interest in dispositional properties because of the central role that they presumably play in the understanding and explanation of scientific phenomena. Philosophers have built a useful framework for the identification and understanding of dispositional properties within the broader literature on *causation*, using dispositions as an *explanans* for difficult *explanandum*, to make causal generalizations, and to predict future causal states. This is to say that dispositions are *causally potent* in that they causally explain the occurrence of a given manifestation. For example, using the diverse toolkit now in philosophical practice, scientists can now identify particulars of varying properties and make accurate predictions about the properties (e.g., about the propensity of a window to break if we know its fragility).

Dispositional properties are common in every science (Mumford, 1998) but especially in biology (Hüttemann & Kaiser, 2018). This is because the phenomena explored in biology is generally more variable and thus their properties are not always manifest. Pure categorical or deterministic dispositional properties are rare in biology for this reason, since their nature must be imbued with causality from more absolute sources or laws of nature. The lawless-ness of biology makes it so that properties are generally contingent on spatiotemporal context and multiple interacting environmental factors. In line with the philosophical movement away from causal determinism and towards a probabilistic model of causation, it makes more sense to now cast most biological properties as *probabilistic dispositions*. Biology is thus a science rife with probabilistic dispositions by nature of its complex explanandum.

Biological examples of dispositions include phenotypic or developmental plasticity, protein foldability, or the pluripotency of cells. For example, holders of the BRC1 allele exhibit a greater propensity to manifest breast cancer, but this does not predetermine cancer. Whether or not the cancer actually manifests depends on multiple other developmental factors. But the greater probability of manifesting cancer caused by the BRC1 gene represents a *probabilistic disposition*, with the carcinogenic disposition explaining the higher frequency of breast cancer found in holders of the BRC1 allele.

Some philosophers have gone so far as to conclude that all properties are dispositions or at least bestow some aspect of being dispositional (called *pure dispositionalism*; see for more Mumford, 1998; Orilia & Paoletti, 2020). This is more likely to be true in biological domains, where the phenomena explored is generally caused by multiple interacting factors. However, the philosophical status of dispositions has always remained a persistent concern in these conversations, as they are sometimes deemed inferior to non-dispositional or "categorical" properties (Lange, 1994). This is partly due to their relatively elastic or intangible nature (perhaps also a reason why biology has been concomitantly deemed an inferior science in history). Because of this, dispositions usually always come with some added conceptual confusion, making the phenomena they describe and measure more difficult to pinpoint than non-dispositional properties. This is a major reason why evolvability and fitness are some of the most metaphysically confusing concepts in biology.

Evolvability is also accepted by most philosophers to be *probabilistic in nature*. Probabilistic dispositions lie in contrast to deterministic dispositions (a distinction made by Mackie, 1977) since a probabilistic disposition may or may not be manifest after its (*necessary but not sufficient*) causal conditions have been satisfied (Brigandt *et al.*, *forthcoming*; Nuño de la Rosa & Villegas, 2019; Brown, 2014)[88]. Evolvability need not manifest in a higher rate of evolution (or, in the case of genetic adaptive evolvability presented here, need not manifest in a *higher rate of adaptive evolution*) because two populations with identical evolvability in the same environment may follow different evolutionary outcomes merely due to chance. This is to say that more evolvable populations may or may not evolve adaptively even when the causal conditions are ripe for them to do so, merely that they *probabilistically will*.

Biological fitness, for comparison, follows exactly the same rule. High-fitness individuals may or may not survive and out-reproduce lower-fitness individuals, but over time they *probabilistically will*. Many philosophers have recognized that evolvability exhibits many of the same characteristics and problems as fitness (e.g., Love, 2003; Brown, 2014; Brigandt *et al.*, *forthcoming*): (1) They both reflect causal propensities that help explain future evolutionary outcomes (more on this later); and (2) due to their *probabilistic dispositional* nature, they are both extremely difficult concepts to conceptualize and measure, since dispositional properties are, by definition, not readily observable properties, and the probabilistic aspect adds another layer of confusion and difficulty[89]. Yet for most philosophers, this is where the similarities stop.

The primary distinctions often made between *fitness* and *evolvability* are in their spatial locations, i.e., *are they (a) intrinsic or extrinsic properties of (b) organisms or populations (i.e., causal bearers)?* Most students of evolvability ***do not*** view evolvability and fitness as familial concepts precisely because they see evolvability as *(a)* an *intrinsic* property *of (b) individual organisms*, owing to the evo-devo slant in the evolvability literature[90]. Fitness, in contrast, is often conceived as an epistemic tool used to measure *extrinsic* causal influences of selective environments.

For reference, an intrinsic property lives innately within a natural kind, remaining the same regardless of the external conditions imposed on it. In contrast, an extrinsic property is not inherent to the natural kind, and its value (or degree or measurement) does depend on the conditions surrounding said property. According to Brigandt *et al.* (*forthcoming*), *extrinsic* means that "some features external to the bearer of the disposition are relevant to the disposition being present, including the way in which the bearer interacts with other objects" (p. 13). This is

[88] Evolvability may, *prima facie*, appear to be a categorical or deterministic disposition when in consideration of sexual recombination, since recombination is technically always manifest in sexual species. However, dispositions are generally defined by their manifestation, and novel environmental conditions do not invariably entail higher rates of adaptation from sexual processes, signifying that it is still a probabilistic disposition.

[89] Yet the recent movement to classify fitness as a *probabilistic dispositional property* is thought to resolve many of its past metaphysical shortcomings and misunderstandings[89], known as *the propensity interpretation of fitness* (Rosenberg & Bouchard, 2021; Mills & Beatty, 1979). What this really signifies, to me, is that we have shifted our models of causation to better fit our explanatory needs. In turn, this has made it easier to conceptualize fitness.

[90] I know from personal correspondence and through my attendance at the *2019 evolvability conference* held in Oslo that most biologists in the evolvability research front do not think evolvability holds any connection to fitness, presumably because they disregard the link between selection and evolvability altogether and rather see evolvability as an intrinsic property from the lens of evo-devo.

to say that an intrinsic property holds its causal basis "internally" while extrinsic properties hold their causal basis from environmental or outside factors.

Brown (2014), Nuño de las Rosa & Villegas (2019), Brigandt (*forthcoming*), and most students of evolvability generally conceive of evolvability as *an intrinsic dispositional property*, rather than an extrinsic property, precisely because they view evolvability as a developmental phenomenon that lies outside of selective influence[91]. Focusing on developmental mechanisms (e.g., the G-P map) as the causal basis of evolvability *accents features internal to individual organisms* (Brigandt *et al.*, *forthcoming*). "The evolvability of an organism is its *intrinsic capacity* for evolutionary change… it is a function of the range of phenotypic variation the genetic and developmental architecture of *the organism* can generate" (emphasis added; Yang 2001, 59). Such a perspective often lies implicitly within most modern conceptions of evolvability today[92].

Yet behind the evo-devo position, there is minimal evidence to suggest that evolvability is an intrinsic property, unaltered or uncued by external causal sources (see Wilder & Stanley, 2015). For example, Lehman & Stanley (2013), using evolutionary simulators, showed how the evolvability *of organisms* could evolve through passive or non-adaptive processes such as drift or founder effects. Individuals were classified as "evolvable" when they received a founder effect from an undiscovered niche. This suggested that evolvability may inevitably evolve through drift in genotypic space accompanied by the passive tendency of evolution to accumulate new niches. But these computational models were overly restrictive in their parameters and unrepresentative of natural conditions, honing their focus in the short-term on how *organisms* may become more evolvable, not populations[93].

Empirical findings generally imply the opposite. For example, Loh *et al.* (2010) found that mutator strains of E. coli were the most frequent winners over the wild-type and antimutator strains, implying that the greater probability of developing selectively advantageous mutations was the primary reason why these strains won out, rather than the initial growth advantage conferred by the mutator itself (i.e., the founder effect). This finding aligns with most of the available evidence on evolvability reviewed in chapter three. Genetic evolvability mechanisms that increase the probability of securing a beneficial variant are generally prompted by external sources such as a change in environmental conditions or novel selective pressures.

What is perhaps more surprising is the general concern that many philosophers have raised over attributing a property as "intrinsic", especially in biology (Brandon, 1990)[94]. Smith (1977) claimed that the location of transient dispositions is not fundamentally intrinsic. If a disposition can be manifested or lost in changing environmental circumstances, then those circumstances

[91] Love (2003) offers a more philosophically pragmatic and agnostic approach to evolvability, recognizing that the causal basis of evolvability is comprised of both intrinsic and extrinsic factors.

[92] It is curious to me why students of evo-devo are so readily open to ascribing evolvability, or any developmental phenomena for that matter, as an intrinsic property. Do not most developmental properties *require an external stimulus to manifest*? Developmental theory, from psychology to biology, *revolves around the influence that an environment has on some causal bearer*. Developmental mechanisms may be "intrinsic" in the sense that they represent an internal feature of an organism, but the manifestation of such a disposition is still *determined or "turned on" by external factors*.

[93] I also am dubious in how they are defining natural selection and selective pressures, since the benefits of founder effects are securely rooted in selective explanations of evolvability.

[94] Further demonstrating the need for methodological disunity between the sciences.

that elicit such an effect cannot be claimed as *intrinsic*, suggesting that a wider net of causal conditions serves as the basis for the disposition. "It appears impossible to ascribe a disposition of an entity without (at least) an assumed environment; certain dispositional properties with the intrinsic structure of the entity manifesting the disposition" (Love, 2003, 1022).

In a very broad sense, almost too broad to hold any relevance, all dispositions can be considered intrinsic since they are *latent but manifestable properties* of a natural kind. This elucidates the metaphysical difficulty of dispositions. Every disposition is intrinsic in some sense, in that they remain an internal feature of biological systems. But every biological disposition also likely holds some external aspects in their causal bases. So, a clearly articulated distinction between intrinsic/extrinsic dispositions is unreachable in biology, merely because there is no hard distinction between a biological kind (gene, organisms, species, etc.) and their surrounding environments. Biological kinds are their environment, and their environments retain causal aspects of biological kinds, pointing to the utility of a pluralistic and reciprocal model of causation in biology. This underlies the reason *why* biology is a science of *probabilistic dispositions* (see **Box 9**). Most biological effects or manifestations are probabilistic in nature because of the myriad of external influences operating to instantiate any given manifestation. All probabilistic dispositions are then, *to a degree, extrinsic*, because this is what makes them probabilistic in the first place[95].

For example, many diseases once thought as *genetically determined* are now known to be affected by environmental factors, to a degree. Huntington's disease (mutation in HTT gene) is an example of a *less extrinsically based disposition* since environmental factors still influence its manifestation but less so than, say, holders of the BRC1 allele manifesting into breast cancer. Yet the seminal thing to note is that Huntington's disease, while being a relatively innate and genetically predetermined disease, is still causally influenced by external cues; extrinsic causal sources still *comprise its causal base*. Even Phenylketonuria (PKU), once thought of as a more genetically deterministic disposition, has been found to be sensitive to subtle environmental changes such as diet[96].

What this more urgently suggests is that we need to rethink the intrinsic vs. extrinsic distinction in the philosophy of biology, as it is irrelevant in natural biological contexts (Brandon, 1990). The important distinction we must make between dispositions in biology is *how extrinsically-causative is the dispositional property?* To what *degree of extrinsicality* are biological dispositions?[97] In the case of evolvability, the question we should be asking ourselves is *how extrinsically-motivated are evolvability mechanisms?*

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[95] This goes back to semantics. If a property is indeed not readily influenced by external sources, then its manifestation is already predetermined, and thus should be considered as *a categorical or deterministic dispositional property* (I write "readily" because, like I said before, all biological features are likely influenced by their environment). It follows that *all probabilistic dispositions will be extrinsically motivated.* If not, then they are better described as a deterministic dispositional property. By virtue of evolvability being a *probabilistic* disposition underscores the importance of external influences in its manifestation.

[96] Other possible examples of deterministic dispositions in biology include chronic variable immunodefiency (cvid), chronic granulomatous disease, or X-linked (Burtons) agammaglobulinemia. However, these have also been found to be influenced by developmental factors.

[97] It should be noted that I am not the first to make this argument. Robert Brandon has made a similar argument in his criticism of Michod's attribution of intrinsic properties to genotypes (Brandon, 1990, 27-30).

If we get to the bare metaphysical bones of evolvability, it is curiously *centered around the idea of external causation*. Evolvability is relevant given what environmental circumstances? Changing environments? Novel environments? When species or individuals need to adapt to some novel environmental pressure, correct? Indeed, this is evolvability's virtue: *that evolvability is causally manifested and prompted by novel environmental stimuli.*

A crucial yet often overlooked aspect of dispositions, in both metaphysics and the sciences, is the causal external influence that varying environments have on dispositions, or their relevant *background conditions*. This is to say that a disposition may not only vary in its degree or propensity to manifest in one given causal environment, relative to other similar dispositions, but it may also vary in its degree across different causal environments. Consider that the fragility of window **A** and the fragility of window **B** may have the same capacity to break in environment **C**. However, their fragility may vary in environment **D**—perhaps **A** has a lower freezing point than **B**, and **D** represents a colder environment, making **B** more fragile than **A** in **D**. A rock thrown at **A** and **B** may therefore cause drastically different results in **C** versus **D**. This situation represents a *multi-track* disposition—the same disposition can yield multiple outcomes in multiple environments. In the case of a *multi-track probabilistic disposition*, there can be many different manifestation probabilities in different environments.

Similarly, evolvability has been shielded as an important disposition of species precisely because we have, historically speaking, primarily researched evolutionary dynamics *in stable background conditions* (for more see Ch. 2). Evolvability properties likely remain latent within genomes until new stimulus conditions arrive—i.e., novel selective pressures or environmental changes—causing evolvability mechanisms to manifest their full potentiality. This is why they are *extrinsic probabilistic* dispositional properties—external causal cues (abiotic or biotic selective pressures) are often necessary to turn on the evolvability mechanisms, facilitating adaptive evolution by increasing the probability of securing a new adaptation through an increased rate of mutation and/or recombination. Evolvability mechanisms are indeed intrinsic in the sense that they lie latently within genomes, but this is what makes them dispositions. W*hat brings about the manifestation* is the crucial idea of dispositions, and for evolvability to manifest often requires some sort of external stimulus. Evolvability is thus more accurately conceived as *a highly-extrinsic dispositional property*, rather than an "intrinsic" dispositional property because (a) there are no purely intrinsic properties in biology and (b) *the very idea of evolvability* is centered around the external causation from surrounding ecological environments.

Brigandt *et al.* (*forthcoming*) curiously make this point using their example of protein foldability. Protein foldability was originally thought to be an intrinsic dispositional property that manifested irrespective of external cues. But upon further investigations performed in the 1980s and 90s, external stimuli such as chaperone proteins were found to play important roles in the manifestation of protein conformational structures, thus illuminating the important role of external stimuli on the causal manifestation of protein foldability. The authors conceded that evolvability "is not solely an intrinsic property of a population, but is also dependent on the population's environment; the disposition of evolvability's causal basis is partly extrinsic" (p. 16). Yet to me, this feels like a half-hearted attempt to recognize the inevitable: that evolvability is primarily an extrinsic disposition.

It is perplexing, then, that most students of evolvability cling to the idea of evolvability as an intrinsic dispositional property[98]. I suspect the main reason for this is because *they have separated it from the external causal influences of natural selection* (e.g., Pigliucci & Muller, 2010), further perpetuating this viewpoint as a presupposition until it became *a priori* consensus without any real logic or evidence in support. Yet evolution in light of ecology now renders this position untenable. The fundamental insight deriving from the Second Synthesis is that ecological factors play a substantially greater role in the evolutionary history of all biological features than previously thought, especially in the case of *evolvability*.

Thus, what this fruitless debate over *intrisicality/extrinsicality* demonstrates is that whatever scope of investigation we are choosing has very real implications in how we view aspects of evolvability (what is called *selective bias*). This was correctly recognized by Brigandt *et al.* (*forthcoming*: 28): "Adopting a particular definition of evolvability or deciding on a specific bearer of evolvability is a methodological choice; once this choice is explicitly recognized, then it increases clarity about the relevant manifestation and causal basis". Within the restricted lens of evo-devo, evolvability is often seen as unrelated to fitness because it is an "intrinsic" dispositional property. But in a more holistic viewpoint of evolvability that integrates the perspectives from all walks of biology (e.g., evo-devo, microbiology, ecology), as well as the history and philosophy of science/biology, evolvability is more clearly attributed as an *extrinsic dispositional property*. This is why choosing the disciplinary lens in which to view evolvability matters to our conceptualization of evolvability and its most salient causal aspects, because under the holistic purview, then the ontological connection between evolvability and biological fitness becomes apparent.

For this reason, evolvability and fitness are familial concepts[99]. Like fitness, evolvability carries information not merely about how evolutionary outcomes ensued but how they might have ensued were things different. This is the mark of *a selective-based explanation*—they explain how biological features have evolved by natural selection, in reference to the differences in ecological pressures on varying causal bearers (genes, organisms, populations) at a given time that increases the probability of a particular evolutionary outcome (see for more Brown, 2014). It also functions as a *contrastive explanation* because it clarifies the causal reasons why an outcome occurred (or more probabilistically occurred) in contrast to another (Love, 2003; cf. Witteveen, 2019). For example, after identifying and measuring the evolvability of populations, we can use this measurement to reliably predict which populations may survive over others that go extinct (either competing or relative populations), as demonstrated by the evolutionary rescue experiments discussed in chapter 3. Evolvability therefore functions as an important component

[98] There is some weird determinism going on behind the evo-devo position.

[99] In fact, the "internal" aspect of evolvability points to the likely need for a selective explanation. Internal mechanisms suggest that selection has ingrained them into the genome at some point in the evolutionary past. The fact that dispositional properties represent intrinsic potentials whose manifestations are expressed in the future also points to the necessity of using long-term or higher-level explanations, that which evo-devo explanations cannot readily give. This is how evolvability and species selection are connected, since longer-term selection is required to explain why these properties are maintained over evolutionary time. With every repeatable round of environmental changes (since environmental change is the only *certainty* in biology) then evolvability mechanisms—whether they be developmental or genetic—become domesticated by selection into the genome, with higher-level selection acting to maintain and alter these processes over time. This is not to say that non-adaptive or drift processes play no role in their evolutionary history. But it is to say that that selection has, in all probability, played a far greater role in their initial evolution and maintenance than non-adaptive processes, like with most biological features.

of population or higher-level fitness. But it is only one component because, like fitness, it is always a function of a specific environment (or rather many environments) composed of many abiotic and biotic factors (Weber 1996, 428-9; Hendry, 2018; Graves & Weinreich, 2017)[100].

In conclusion, evolvability is best conceived as *an extrinsic probabilistic dispositional property of populations, as a capacity of populations* (causal bearer) to evolve adaptively as *a function of selection acting on the genetic system* (causal basis), causing higher rates of adaptive evolution (manifestation) in probabilistic terms when placed in a stressful environment (specific causal conditions). In comparison, fitness is also an extrinsic probabilistic dispositional property that is generally instantiated at a lower level of biological organization. Given their similarities in the known particulars of dispositions, and the fact that they both entail a *selective explanation*, evolvability and fitness should now be viewed as familial concepts, with evolvability being a higher-level fitness component able to explain why certain populations, species, or taxa survive where others go extinct. I suspect that much of the metaphysical confusion surrounding evolvability can be resolved by conceiving of evolvability in this way, granting it a central and robust causal explanatory position within modern evolutionary theory.

5.8 Prescribing a Restrictive Pluralism to Solve Evolvability's Conceptual Issues

Many argue for a broad or *unrestricted "anything-goes" type of pluralism* to resolve the conceptual issues with evolvability, which is often overly inclusive of overlapping phenomena since they include developmental evolvability mechanisms alongside genetic evolvability mechanisms without drawing any major causal distinctions between the two types or other typologies (Hansen *et al.*, *forthcoming*; Nuño de la Rosa, 2017; Brown, 2014). Yet rather than taking such an inclusive approach, it may prove more useful to compare and contrast the various merits of competing accounts of evolvability to enhance its conceptual clarity and allow for its successful integration into modern evolutionary theory.

Such a rationalist strategy has been referred to as *restricted pluralism*, more commonly recognized in the economics literature when strictly contrasted with an *anything-goes type of pluralism* (Marques & Weisman, 2008) because it tolerates a heterogeneity of viewpoints within some sort of homogenous cluster, while simultaneously calling for the discrimination of the heterogeneity within such a cluster. This is to say that *restricted pluralism* allows for the comparison of competing models, ideas, or hypotheses based on any sort of demarcationist criteria, thus allowing space for the construction of more nuanced and complex theoretical models. Restricted pluralism is thus a rational reaction to an ever-increasing ontological

[100] One last issue should be mentioned. Fitness and evolvability are generally couched in ontological as well as quantitative terms. Yet fitness is generally definable as a function of how well an entity is adapted to an environment, meaning that fitness is easily measurable in a stable environment. Evolvability, on the other hand, becomes a salient aspect of species when they are less adapted to their respective environment. When fitness is located as a measurement of individual-level selection (relative or absolute fitness), then it will generally always be inversely correlated with evolvability. Even population fitness is still couched in terms of individual-level selection, meaning that a low population fitness can also yield a high evolvability and *vice versa*. This is also a major reason why many biologists have overlooked the connection between the fitness and evolvability.

complexity found in most sciences today. And a complex concept such as evolvability likely necessitates taking such a nuanced pluralistic approach.

Restricted pluralism goes hand-in-hand with the building philosophical literature on *scientific theoretical virtues,* which acts as the objective criteria to reliably sort through similar yet competing ideas. Philosophers of science have recently devoted much attention to systematizing the scientific theoretical virtues (Kuhn, 1977; Brock & Durlauf, 1998; Keas, 2018; Schindler, 2018). Indeed, this is an excitingly novel approach to theoretical argumentation in the sciences. Instead of arguing for a scientific theory (or a promising hypothesis) by demonstrating its underlying *empirical adequacy* or other strictly epistemic virtues (e.g., Popper, 1959), which is the most common practice in science today and throughout history, we can now compare and contrast the various scientific virtues—those of an epistemic, non-epistemic, or pragmatic nature—of a theoretical model within a neat and orderly standardized framework (e.g., Baedke, 2020).

Thanks to ecology and other empirically rich traditions that have allowed for the investigation of causally complex evolutionary dynamics over longer periods and frequent spatial changes, *genetic evolvability* is now an epistemically virtuous concept. There is now an abundance of evidence underlying genetic evolvability. However, what also sets *genetic evolvability* apart from *non-genetic evolvability* is the non-epistemic virtue of *theoretical coherency* (or what Keas [2018] calls *universally coherent)*. *Theoretical coherency* is a non-epistemic virtue because it relates to how our knowledge is structured and how new knowledge can be best integrated within a prevailing scientific paradigm. When constructing a novel concept, we must pay heed to the existing theoretical structure; to how well the novel concept sits with most of our modern theoretical structure of evolution[101]. Yet the novelty of a promising concept often blinds us to thinking about how its theoretical coherency.

It is important to remember that scientific concepts are social constructs, subjectively framed to integrate homogenous phenomena or data under a common, normalized representational model that is externally valid. The "goalposts" of our models (or *conceptual parameters*) can always be moved following new observations and evidence. Often the more rigid the parameters of a concept are drawn, the easier it is to understand its causal workings in a specific context, which in turn generally enhances its understandability within the larger causal picture of putative theory. When concepts lose their rigidity, they become subject to *ad hoc* reasoning (Schindler, 2018), and they also tend to lose their meaning and procure confusion[102]. This is precisely what is happening in the evolvability literature today.

Genetic evolvability maintains *Weismann's barrier* and thus keeps with the causal criteria of modern genetic theory better than its alternatives[103]. Non-genetic evolvability, in contrast, places

[101] This is also a likely reason why evolvability was initially built within evolutionary theory and neglected for so long.

[102] In no other science, I think, is this better appreciated than in biology due to the immense conceptual and phenomenological overlap.

[103] There are, however, several aspects of genetic evolvability that are *incoherent* with our existing theory, and excitingly, this is where theoretical progress should happen. The reductive atmosphere that born the Modern Synthesis and modern evolutionary theory has been, time and time again by ecology, proven to be too abstract and unrealistic of natural parameters. We must move towards a pluralistic, multilevel, multicausal model of natural

too great of an emphasis on development and not enough emphasis on genetic evolvability. And while development clearly plays an integral role in the evolvability process, there is not enough evidence to discharge *Weismann's barrier*. Until we find more evidence demonstrating how developmental or non-genetic evolvability mechanisms influence the evolutionary process in the long term, *Weismann's barrier* is here to stay.

It is thus problematic to encompass all the mechanisms of evolvability under one conceptual umbrella, without making any further distinctions. In the first place, the generality of these definitions makes it difficult for biologists to form a proper quantification of evolvability; one that can be used in theory by quantitative and population geneticists (Hansen *et al.*, 2011) or as a standard for experimental practice and comparison. These are important for the prediction of evolutionary outcomes in natural populations (Pigliucci, 2008b; Palmer & Feldman, 2012). Often in the history of science, we have seen a tradeoff between the explanatory breadth (how many phenomena a concept can explain) and the predictive power of scientific theories. When too wide of an explanatory net is cast, predictive power becomes more difficult.

Yet generality of explanation (i.e., explanatory breadth, explanatory consistency) is still considered by many to be a hallmark of good science. However, the history of science indicates that as scientific disciplines grow and mature, they evolve to form more specific explanations that better explain the causal field of complex phenomena—*they often tend towards explanatory pluralism at a discipline-wide level* (Dupré, 1993; Mitchell, 2003; 2009). Yet scientists still instinctively lean towards this generality when constructing new conceptual models, which is a significant deterrent to forming better, more accurate, and more predictive causal explanatory models, especially in a discipline with a casually complex explanandum like biology. For these reasons, some sort of broad pluralism is indeed warranted at the discipline-wide level of biology. But pluralism should not be overly prescribed, which is often the case under an *unrestrictive or "anything goes" type of pluralism*.

This is why we must first reach a consensus within the evolutionary biology community as to what constitutes *evolvability* and set our sights away from any broad or unrestricted type of pluralism for the time being. Scientific concepts benefit from a restrictive pluralism while in their infantile stages, to first construct a sturdy conceptual parameter around one or a few readily observable phenomena and then build out from this foundational point. Explanatory pluralism generally follows once a concept is established and advanced, as standardized methods become further refined enough to investigate more peripheral phenomena related to the concept.

One needs to look no further than natural selection theory as the perfect example of this trend. Natural selection *was not ready to be pluralized* until the recent synthesis between evolutionary biology and ecology. We simply did not know enough about selective dynamics until we began to incorporate ecological analyses in evolutionary biology, which is why natural selection theory was initially best served by the philosophies of *explanatory monism* and/or *reductionism*. Early progenitors of evolutionary theory were therefore not doing a disservice by reducing or *monizing* natural selection to lower causal levels; rather, their *modus operandi* was aligned with the best

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selection if we wish to explain complex adaptations, like those surrounding genetic evolvability (i.e., sex and adaptive mutation; see for more Distin, *forthcoming*). For these reasons, we must conserve several remnants of genetic theory, such as *Weismann's barrier*, while calling for the general theoretical progress away from the reductionistic causal modeling of biology old.

interest of biology during their time, within their intellectual zeitgeist (i.e., logical positivism), and with their technological limitations or scarce epistemic reservoir.

For these reasons, taking a more narrowed or *restrictive pluralistic* approach is not only in the best interest of the evolvability concept given the available evidence but also in the best interest of evolutionary theory more generally. This calls for the further refinement of the evolvability concept, cutting up its conceptual parameters to arrive at a more accurate causal picture of evolvability within the broader scope of evolutionary dynamics.

5.9 Chapter 5 in Summary

Variation is the lifeblood of all evolutionary processes, yet evolvability is the causal reason *why variation is important*. Advances in the empirical sectors of biology are beginning to reveal evolvability as a major ontological component of the evolutionary process. How a central process such as evolvability can go relatively unnoticed in theory following over a century's worth of scientific research shines a particular spotlight on the philosophical anachronisms that have been stalling progress in biology, as well as greater science more generally.

Because evolvability exists as an emergent adaptation at higher levels of biological organization that manifests given environmental variation, its recent elucidation marks an historical turning point in biological research, away from the outdated *reductionism* that was originally taken from the physical sciences and towards an *emergent philosophy* that captures biological change *in space and time*. Biology has therefore won its autonomy from the other sciences, being gifted its own philosophy of science (i.e., the philosophy of biology), in part thanks to *the disunity of science movement*. These recent advancements are therefore the cause as well as the effect of the Second Synthesis. Just like the first major synthesis led to the legitimization of biology as a major scientific discipline, the Second Synthesis (*circa* 1980-) has led to the autonomization of biology from the other sciences and has spurred the development of a distinct philosophy of biology.

Conclusion and Future Directions

> "Intellectual progress usually occurs through sheer abandonment of questions together with both of the alternatives they assume ... We do not solve them: we get over them. Old questions are solved by disappearing, evaporating, while new questions corresponding to the changed attitudes of endeavor and preference take their place" (John Dewey, 1910: 19*, The Influence of Darwin on Philosophy, and other essays in contemporary thought*).

Evolution in space and time is now at the forefront of evolutionary considerations thanks to the Second Synthesis between ecology and evolutionary biology. It is a remarkable fact of history that we knew *relatively little* about how evolution and selection truly unfold in nature until recent times. We are no longer asking *if natural selection is operating* but *how natural selection is operating in natural populations*, marking an important shift in our thinking that has underscored an explosion of new knowledge on how selection varies in strength, direction, form, and most recently *level*, all dependent on ecological conditions.

Evolution in light of ecology has thus shifted us away from *evolution as a population genetic or statistical phenomenon*, to a biology that embraces *empirical realism* and views evolution as it should be viewed, as an ecological phenomenon that ensues *in space and time*. In this period, we have gone from defining natural selection in statistical and reductive terms as "the differential survival and reproduction of individuals with particular traits over their competitors, leading to non-random associations between phenotype and fitness within a generation (Lande & Arnold, 1983; Frank, 2012; Morissey, 2014; taken from Henshaw & Zemel, 2016)" to an ecological definition that embraces all forms of causation (i.e. maintenance & directional) at every level of biological organization: "ecological environments favoring the features of a biological entity (genes, individuals, populations) that are causally connected (in probabilistic terms) to the survival and reproduction of said entity in space and time[104]". This thesis thus illuminates a novel way to look at the causal actions of natural selection, as a balancing act between present and future needs, and between conflicting/cooperating levels of selection, operating in space and time.

Ecological insights have continually demonstrated the failures of causally representing complex biological phenomena using simple, idealized mathematical models. However, this is not to say that population genetics is a useless venture, nor that it cannot improve in light of ecology. Simplified, reducible, monocausal modeling has its uses in certain epistemic contexts, like standardizing empirical work or in simple demonstrations of evolutionary processes (which is useful for instruction). However, population genetics is not the *end all be all* that several high-status proponents suppose it to be (e.g., Lynch, 2007a; Charlesworth *et al.*, 2017; read for more

[104] This can also mean the favoring of biological features that transcend ecological environments, such as the case with evolvability features.

Millstein, 2013), and ecological insights should often be granted epistemic precedence due to their closeness to nature.

Evolvability is the perfect example of how we, as a discipline, have neglected several key causal aspects of evolution that warrant acknowledgment. For starters, genetic evolvability is a selectable property, thus demonstrating that selection can causally intervene in variational processes and is not effectively *random*, as was assumed by modern synthetic theory. Secondly, evolvability exists as an emergent property that has been overshadowed by the backdrop of reductive philosophies. This is why the paradox of adaptive variation is also the forgotten history of evolvability thought since it demonstrates how evolvability has been overshadowed in reductionistic atmospheres of evolutionary biology. Thirdly and lastly, evolvability is a dispositional property that manifests given environmental variation, which is why we need to view *evolution in space and time* to effectively reveal its presence. A large body of work has shown how evolvability is caused by environments that vary over space and time (see Ch. 3; Draghi & Wagner, 2009; Crombach & Hogeweg, 2008; Steiner, 2012; Palmer & Feldman, 2011; Hansen *et al.*, *forthcoming*), and although biologists have always been studying *evolvability as an idea*, the conceptual rise of evolvability over the past forty years demonstrates the profound shift offered by an EST perspective[105].

Even within the last few days when I have been putting the finishing touches on my thesis, a new publication in *Science* provides unwavering support for the primary arguments of this thesis. Bonnet *et al.* (2022) performed a meta-analysis of 19 long-term studies showing that the average estimate of the additive variance in relative fitness, $V_A(w)$, was two- to four- times larger than previous estimates, suggesting that most natural populations harbor an extensive amount of genetic variation that allow them to respond to changing environmental conditions *in the short-term* (see for more comments on the research: Walsh, 2022). Commenting on the research findings, Timothee Bonnet remarked, "This research has shown us that evolution cannot be discounted as a process which allows species to persist in response to environmental change. What we can say is that evolution is a much more significant driver than we previously thought in the adaptability of populations to current environmental changes." This study provides some of the most convincing evidence to date that most species have a greater evolvability to cause adaptive evolution than previously supposed. The evidence for genetic evolvability keeps stacking. I have merely scratched the surface of the vast empirical literature in support of the conclusions reached in this thesis. This is emerging knowledge.

The core parts of this thesis thus fit together to make one long argument against the outdated ways we used to look at evolution and at biology. Not only is the paradox of adaptive variation the perfect exemplar of the philosophical anachronisms that have been stalling theoretical progress for the better part of the last century, but sexual reproduction also stands as the best example of *pluralism in biology*, giving us an idea of how to resolve the paradox and further progress biology. And the paradox of adaptive variation also runs parallel to the history of

[105] Other conceptual transitions also demonstrate the important shift towards an EST perspective prompted by *the second synthesis*. The Darwinian notion of gradualism has been subtly overturned by the recent fact that evolutionary and ecological dynamics can play out on similar timescales. As mentioned in chapter 2, the realization of *eco-evolutionary dynamics* is thus a profound transformation in biological thought, because it realizes that biological systems are products of their ecological surroundings and *vice versa*.

evolvability, explaining how and why evolvability phenomena have been overlooked in a biology that neglects evolution *in space and time*.

However, the Second Synthesis is incomplete. The overflowing epistemic reservoirs turned out by the empirical ongoings of *normal science* (*sensu* Kuhn) have yet to be turned into a cohesive theory like that seen in the first synthesis. The first synthesis saw the unification of knowledge between the various biological subdisciplines (e.g., paleontology, systematics, morphology, and genetics) because the bridge builders (e.g., Dobzhansky, Fisher) noticed a profound gap in the communication between these disciplines. The dissenters were quibbling over the same phenomenology but from different *causal perspectives*. Likewise, the Second Synthesis is, in part, the consequence of the selective attenuation of biological subdisciplines to neglect key causal information that lies outside of their traditional purview (Potochnik, 2017). Today, profound gaps in communication still exist between the various subdisciplines of biology, perfectly demonstrated within the evolvability research front (e.g., population genetics vs. evo-devo)[106].

Closing this gap and synthesizing the wide body of extant knowledge requires a different approach to that offered in the first synthesis. Indeed, Smocovitis (1996) noted that the word *synthesis* gestures towards unification and the general positivist idea of *theoretical unity*. Yet the kind of unity our forebearers called for is likely different than the kind required today. The causal complexity of most biological phenomena demands pluralist ontologies and methodologies. Thus, we need a *synthesis*, a unification of theory and knowledge between the various subdisciplines, but one grounded in *pluralism*.

Progressing Biology

Over the last century, the baton of scientific achievement has been passed from the *physical sciences* over to *the biological sciences*. Biology has become the leading science of the 21st century. However, biology as a discipline has yet to realize its full scientific potential. In this thesis, I have given a broad overlay of the profound historical transitions that have ensued in modern biological practice, remaining an unfinished critique of the underlying philosophies that have stalled theoretical progress in biology for over a century.

Biology is unlike any other scientific discipline, hence why we need *scientific disunity* (Dupré, 1993; Cartwright et al., 1996; Cartwright, 1999). We have never undergone a paradigmatic revolution as described by the philosopher of science Thomas Kuhn in his famous *Structure of Scientific Revolutions* (1962). Biological theories are not *incommensurable* between competing or parent-offspring "paradigms", as theory is generally built cumulatively and progressively. Biologists have been building upon the same theoretical core of adaptation, inheritance, and variation since the formalization of modern biology in the synthetic era (Smocovitis, 1996).

New conceptual ideas or theoretical additions have been consistently uploaded into evolutionary theory through the "synthesis" with other biological subdisciplines (Futuyma, 2017a;

[106] This is why the history of evolvability is of particular interest to not merely biologists, but to all scientists as well. Evolvability not only demonstrates why we need new theory in biology, but also why we need to construct a new scientific process in general.

forthcoming). Population biology was added in the 1960s, microbiology in the 1970s, ecology in the 1980s, evo-devo and conservational biology in the 1990s, systems biology in the 2000s—so on and so forth. Each synthesis has brought a new understanding of the evolutionary process, all revolving around the same theoretical core ideas as before (with a rotating yet refined emphasis put on one concept over another: e.g., selection vs. variation vs. neutral evolution). Biology is thus not a discipline of *scientific revolutions* but *syntheses*, with the first synthesis receiving the most attention (and equal *misunderstanding*) today because it was our founding synthesis—but we have progressed theory a lot since then.

One reason why we have seen so many syntheses in the history of biology, and why we see the rising tensions today, is because of the subject matter we investigate. Biological systems are singular in their causal complexity. Biological causation is context-dependent because the phenomena we explore are extremely variable in space and time (why there are no such things as *laws* in biology). Our causation also tends to be multifactorial, multilevel with upwards and downwards causation between biological levels of organization, with a myriad of evolutionary variables (e.g., life-history, population dynamics) that affect biological features in the present (see for more Mitchell, 2003). Add onto this the notion of *reciprocal causation*, that organisms influence their environment and *vice versa*. Biological causation is indeed very *messy* (see for more Anjum & Mumford, 2018).

Such causal complexity invites the divergence of the various subdisciplines. Causal ideas arrive from many places in biology, precisely because we investigate the same causal phenomena from various perspectives (i.e., *adaptation*) using different methodologies (e.g., ecology vs. microbiology). In her brilliant book *Idealization*, philosopher of science Angela Potochnik (2017) convincingly demonstrates how and why scientists selectively attenuate their research agendas to a particular cause or causal pattern of interest. Their investigations result in the construction of oversimplified and idealized causal models, that disregard other important causal information that lies outside of their chosen periphery. Perhaps no other science is this better appreciated than biology. Biologists routinely over-emphasize and/or neglect key causal information that lies outside the traditional scope of their discipline, due to the messy causation inherent to biological systems, which then manifests in continual calls for theoretical progress and new syntheses (irrespective of their value to biology).

In the case presented throughout this thesis, I believe there is a significant place for evo-devo to make profound insights where population genetics has overstepped and limited their research focal. But on the other hand, evo-devo has, in many ways, overstepped its boundary and neglected important causal information deriving from modern genetics and ecology. To explain such a causally complex world as we have in biology, we likely need an integrative pluralism (Mitchell, 2003; 2009). But in the instance of evolvability, before we can reach any such integrative point, we first need *a restrictive pluralism* to identify the core causes of evolvability.

This is why proponents of an *Extended Evolutionary Synthesis* (Laland *et al.*, 2014; Pigliucci & Muller, 2010) are right to call out the fact that biological theory is having a hard time keeping up with the waves of new evidence coming in from all walks of biology (e.g., Uller & Laland, 2019). There is no question that we do need new explanatory and theoretical strategies to explain the causal complexities that are only just being revealed by our superior empirical methodologies. Yet I see this as a symptom of the scientific process in general, and not something that is terribly specific to biology.

Progressing Science

Technological progress over the past half-century has underscored the explosion of new knowledge in every scientific discipline, which is consequently having a hard time being translated back into theory. For this reason alone, I have a growing suspicion that the rising dissension between biologists has less to do with metaphysical or epistemological concerns, and more to do with the inadequacies of how the scientific process is structured itself.

For example, we still communicate and verify science using nearly the same journal system as we did 350 years ago. Such methods were suitable for knowledge production and dissemination back in the time of snail-mail and when 'horsepower' actually pertained to horses. But in our modern context, these methods are due immediate reformation. With the amount of new information being constantly turned out by the scientific machine, theoretical progress is stalled by having such a slow uptake process and no unified set or standard for theory to become concretized and/or upended.

Scientific fact and theory are also based on consensus, yet we have no practical means for surveying the opinions of scientists, despite living in a technologically capable world. Scientists must resort to reading between the lines of esoteric and extensive literatures, quite literally guessing where theory currently stands. Until this issue is resolved then every major scientific discipline can expect repeated and unwarranted attacks upon its theoretical mainframe, especially in evolutionary biology.

The abstractness of evolutionary theory lends itself to more attacks than perhaps any other scientific theoretical structure (as implicitly noted by Welch, 2017; Futuyma, *forthcoming*). Evolutionary theory is too esoteric for any scientist working outside the traditional scope of evolutionary biology to pick up our literature and understand where our knowledge currently stands and how it maps back into theory (perfectly exemplified by those esteemed biologists who found success in their respective discipline and mistook their success for knowledge of evolution, i.e., "*The Third Way of Evolution"*). Students of evolution do not know where evolutionary theory currently stands because *we, as a discipline, do not know where our theory currently stands.*

These intellectual battles are thus beneficial to the scientific process because they illuminate the core tenets of theory, and perhaps illuminate the philosophical tenets that are due reformation. Still, it would be helpful to have a standardized representation of theory that scientists could continually argue and update, that happens outside of the traditional bounds of "normal science" or empirical efforts. If science had something like the Stanford Encyclopedia of Philosophy, that organizes all putative knowledge into a consensual theoretical core for each respective science, then it would see more progress in the next five years than it did in the previous five hundred.

The main issue, then, is not the fault of progressives or conservatives, but the scientific process more generally. Biological theory mimics the phenomena we study; we have an ever-changing, amorphous theory. Slight theoretical modifications are constantly "being added" or advocated, but are they understood or integrated? Because we have no good means of surveying the opinions of scientists, scientists are constantly shooting at an ever-changing and imperceptible theory, literally guessing where the edges of theory lie. If we had a set or standard for forming

and maintaining theory, then this would allow for more accurate critiques and streamline theoretical progress. Therefore, modern science needs a massive makeover, or else the history of science will continue to be one of slow, ineffectual theoretical progress, as demonstrated by the history and present of *evolvability*.

Future Directions

The Second Synthesis will culminate when there is an agreement reached in the evolutionary biology community—including quantitative and population geneticists—that our past models of evolution have been overly abstract and reductive to represent the complex causal dynamics of evolution and selection typically found in nature, thus placing a greater research emphasis on the realism and external validity of our causal models. A consensus must be reached for there to be any sort of scientific or theoretical progress.

As I mentioned in the preface, this is an unfinished project. The completion of this project merits more research into specific areas that I could only gloss over in this thesis, such as the philosophical issues of *biological individuality, emergent causation, pluralism, scientific explanation*—ad infinitum. But the hard part is done. I have completed the structural foundation of my argument. Now I intend to extend upon those foundations, to progress science alongside evolutionary thought.

This thesis will mark my introduction to the sciences and, sometime in the near future, will hopefully change how biologists look at the history, present, and future of biology. Yet my other wish is to set this work as a foundation to build out and up from, utilizing the evolvability concept as an exemplar of why scientific methodology needs to change and how to update it to meet modern epistemic demands. Epistemological and methodological issues surrounding the evolvability concept shine a particular spotlight on the areas of science that warrant progress, such as the communication gap between the various subdisciplines of biology (e.g., evo-devo and ecology).

What science needs is a new way of communicating. The journal system has proved to be inefficient and ineffectual. We must set up trading zones between disconnected yet relevant research clusters to enable greater crosstalk. We need a new method for forming, validating, and maintaining theory that speeds up the theoretical process while keeping the selective and critical sieve of science to weed out the undeserving work.

Because I have been following the research on evolvability for many years now, and because I was lucky enough to find such an important and interesting concept to centralize my research, I am thus in a position to make generalizable prescriptions for how the scientific process should change. Most philosophers today criticize the scientific process from afar, without getting their hands dirty on some issues of scientific worth. Yet I have positioned myself not only to notice the profound changes that science needs to make, but also to garner the respect of living scientists and inspire real change, given that my work is largely scientific. This was, after all, my original intent when I first chose evolvability as my research focal over seven odd years ago.

Now it is time for science to adapt and evolve by altering its foundational philosophies, much akin to the evolvability process in biology. Thus, evolvability is the perfect metaphorical and literal example of *how* and *why* science needs to change.

Resumen en Castellano

Evolución en el espacio y el tiempo: la segunda síntesis entre la ecología, la biología evolutiva y la filosofía de la biología

El conocimiento científico está progresando a un ritmo sin precedentes nunca visto en la historia. Los avances tecnológicos significan que la máquina científica produce nuevas evidencias y conocimientos a un ritmo alarmante, aportando nuevos métodos de investigación, nuevas formas de ver viejos problemas o fundando disciplinas de investigación e investigación completamente nuevas. En biología, la investigación molecular, ecológica y experimental novedosa ha generado una explosión de información muy detallada que aún no se ha integrado completamente en los marcos teóricos. Se necesita tiempo para estructurar y organizar nuevos conocimientos, traducirlos en teoría y mantenerlos a lo largo del tiempo. Aquí es donde la filosofía, y quizás lo que es más sorprendente, la historia, se convierten en empresas abundantemente útiles.

Esta tesis doctoral es, por lo tanto, tanto un ejercicio de historia y filosofía de la ciencia como se basa en la ciencia pura y la biología evolutiva, aunque está destinada a ser consumida por el biólogo común. La filosofía tiene mucho que ofrecer a las ciencias, particularmente en el ámbito de la construcción teórica y la causalidad. En esta tesis, utilizo conocimientos filosóficos e históricos para aclarar cuestiones conceptuales en torno a la selección natural; unir los intereses explicativos de disciplinas previamente divididas (es decir, ecología, biología evolutiva e historia y filosofía de la biología); aclarar cómo el secular debate sobre los niveles de selección es una disputa por el reduccionismo; tallar la naturaleza en sus articulaciones y 'limpiar' nuestra estructura teórica proporcionando parámetros conceptuales explícitos, mejorando así la consistencia interna de la teoría evolutiva; y lo más importante, dar un paso atrás y ver el discurso científico desde un punto de vista holístico e identificar las actitudes o métodos predominantes que están frenando el progreso científico en biología. El progreso biológico actual requiere un conocimiento íntimo de la historia y la filosofía de la biología.

Por ejemplo, preguntar cómo y por qué las especies se adaptan a su entorno sigue siendo el principal objetivo explicativo de la biología evolutiva. Pero en esta tesis, mostraré cómo las actitudes y presuposiciones predominantes de la ciencia han causado que los biólogos descuiden aspectos clave de la adaptación y enmarquen la selección natural bajo una luz causal limitada. Los restos de la envidia de la física abundan en la práctica biológica moderna debido a las influencias del positivismo lógico en la ciencia del siglo XX, que se expresa claramente en las principales disciplinas teóricas de la población y la genética cuantitativa. El reduccionismo explicativo y el monismo son mentalidades atractivas que pretenden reducir la diversidad de explicaciones a un número reducido de teorías o leyes matemáticas en un nivel de discurso privilegiado. Pero la búsqueda de modelos explicativos monocausales de fenómenos naturales absolutos ("leyes") no es una estrategia de trabajo en biología debido a la complejidad causal y la

restricción espaciotemporal de los fenómenos biológicos, y muchos han cuestionado su utilidad incluso en física. La biología no es física ni debe pretender serlo. Las teorías biológicas como la selección natural deberían reflejar la complejidad ontológica de los sistemas biológicos y ecológicos, actuando en múltiples niveles de organización biológica y variando en el espacio y el tiempo dependiendo de una miríada de factores ecológicos. Esto exige una nueva filosofía de la biología que se base en el pluralismo, la multicausalidad y la emergencia. En esta tesis, proporciono una hoja de ruta sobre cómo la biología puede hacer la transición hacia estas filosofías.

Por lo tanto, considero que los avances recientes en ecología, biología evolutiva y filosofía de la biología sientan las bases para otra importante síntesis biológica, a la que me refiero como la Segunda Síntesis porque, en muchos aspectos, es análoga a los objetivos y resultados de la primera síntesis (pero es importante distinta de lo que algunos han autoproclamado como la síntesis evolutiva extendida). Con el desarrollo general de una filosofía distintiva de la ciencia, la biología ha emergido legítimamente como una ciencia autónoma.

En esta tesis, ofrezco una reconstrucción histórica de las fuerzas filosóficas, tecnológicas y naturales que condujeron a la Segunda Síntesis, con la esperanza de reconocer los avances significativos que han alcanzado a la biología en la última generación. Luego ofrezco mis recomendaciones normativas, prescribiendo una teoría pluralista de la selección natural que puede explicar fenómenos emergentes complejos (como la capacidad de evolución) para finalmente resolver la paradoja de la variación adaptativa. Lo hago construyendo un puente entre la gran biología y la historia/filosofía de la biología, enfocando los principales logros de los historiadores y filósofos durante la última generación y cómo estos avances pueden modernizar el pensamiento biológico.

La primera síntesis legitimaba la biología; la Segunda Síntesis de la biología autonomizada. Ahora es el momento una vez más de organizar y estructurar nuestro nuevo conocimiento en un marco teórico coherente, utilizando las estrategias teóricas sugeridas por los filósofos para representar una nueva forma de ver la evolución de la vida en la tierra.

En el Capítulo 1 de esta tesis, titulado “Una breve historia de las filosofías de la ciencia”, utilizo la historia de la ciencia para demostrar cómo los científicos han construido estructuras epistemológicas en forma de modelos causales (teorías o leyes) que se han abstraído de lo innato. complejidad causal del mundo natural. Desde entonces, las ciencias han descubierto un mundo natural que es tan rico y complejo en su causalidad como irregular e indeterminado. Esto es particularmente cierto en las ciencias biológicas, donde examinamos fenómenos causales que tienen lugar en sistemas multicomponentes, multinivel y evolucionados mientras construimos modelos causales que están restringidos espaciotemporalmente debido al capricho de los ecosistemas circundantes. La teoría de la selección natural se erige como el ejemplo por excelencia de una teoría moderna que se beneficiaría de la transición desde filosofías pasadas de la ciencia y/o conceptos de causalidad que se adaptaron a una época en la que la física clásica reinaba como modelo para las otras ciencias a seguir, hacia una filosofía pluralista que impone un mayor realismo empírico y adopta modelos multicausales/multinivel para adaptarse mejor a sus necesidades explicativas (Cap. 4).

La historia, si es vista como depositaria de algo más que una mera anécdota o cronología, junto con la filosofía, si es vista como un método para la construcción del conocimiento que se basa en el empirismo científico y no en la justificación a priori, puede dilucidar los anacronismos de la ciencia moderna y procurar una transformación decisiva en metodología científica, particularmente en las ciencias biológicas y evolutivas. En el capítulo uno, examino brevemente la influencia general que las filosofías subyacentes de la ciencia y los conceptos de causalidad han tenido en la práctica biológica en el pasado y argumento por qué tales filosofías ya no son útiles en el contexto de la biología moderna.

Las filosofías de la ciencia, a menudo expresadas implícitamente dentro de los paradigmas científicos predominantes, han tenido un tremendo impacto en la forma en que se realizó la ciencia en los últimos siglos. Los filósofos están continuamente inventando nuevas o mejores formas de hacer coincidir los modelos causales con los fenómenos naturales. Esto incluye el reciente alejamiento del determinismo causal hacia un modelo probabilístico de causalidad; un movimiento que es particularmente relevante en las ciencias biológicas. La causalidad biológica es excepcionalmente compleja y, a menudo, sin ley, lo que implica procesos causales en múltiples niveles de organización biológica y en diferentes contextos espaciotemporales. Un cambio tan importante en las filosofías ha sido, en parte, estimulado por recientes hallazgos empíricos de la ecología.

En el Capítulo 2, titulado “La segunda síntesis entre la ecología y la biología evolutiva”, aclaro la síntesis reciente entre la ecología y la biología evolutiva, y demuestro cómo tal síntesis ha iniciado una segunda síntesis biológica importante.

El cambio es la idea fundamental de la evolución. Explicar el extraordinario cambio biológico que vemos escrito en la historia de los genomas y los yacimientos fósiles es la principal ocupación del biólogo evolutivo. Sin embargo, es un hecho sorprendente que para la mayoría de la investigación evolutiva, rara vez hemos estudiado cómo se desarrolla la evolución típicamente en la naturaleza, en ambientes ecológicos cambiantes, en el espacio y el tiempo.

Esto ha dado como resultado una biología que aún no se ha dado cuenta de su potencial científico. Una división implícita pero marcada entre los esfuerzos teóricos y empíricos ha acosado a la práctica biológica desde sus orígenes modernos. La primera gran síntesis de la biología, es decir, la Síntesis Moderna (alrededor de 1918-1956), unió las subdisciplinas de la biología y las organizó en un marco teórico y matemático coherente de la evolución, lo que condujo a la legitimación de la biología como disciplina científica y la selección natural. como una teoría científica respetable. Sin embargo, mientras que la ecología desempeñó un papel importante en la eventual aceptación (y predominio) del punto de vista de la evolución genética de poblaciones en la era sintética, desempeñó un papel menor en el desarrollo de la teoría evolutiva hasta la década de 1980, cuando comenzamos a estudiar sistemáticamente la teoría evolutiva. dinámica de las poblaciones naturales en el espacio y el tiempo. Como resultado, la teoría de la evolución se construyó inicialmente en un vacío abstracto que no representaba la evolución en la naturaleza.

Desde entonces, la biología evolutiva ha experimentado un cambio profundo en el pensamiento sobre la evolución impulsado por su reciente síntesis con la ecología. La visión ecológica ha descrito un mundo biológico que es inconmensurablemente complejo, con relaciones causales que se extienden desde la macromolécula más pequeña hasta la ecosfera más grande, entrelazadas entre especies simbióticas y dependientes de muchas causas que interactúan que varían en el espacio y el tiempo.

Unificar la ecología con la biología evolutiva ha hecho progresar así nuestro conocimiento de la teoría de la selección natural. Ya no nos preguntamos si la selección natural está operando en las poblaciones naturales, sino cómo afecta la selección natural a las poblaciones naturales en contextos espaciotemporales. Tales avances profundos han revelado recientemente cómo la selección natural varía en fuerza, dirección, forma y, más sorprendentemente, el nivel de organización biológica, todo dependiendo de las condiciones ecológicas. Las dinámicas causales de la selección natural ya no se pueden reducir a niveles inferiores de organización biológica (es decir, individuos, genes egoístas) en escalas de tiempo más cortas, sino que se han ampliado para incluir la adaptación en todos los niveles y escalas de tiempo.

La historia causal de la selección natural, y de la evolución en general, es por lo tanto incompleta. Reducir la selección natural a una unidad o nivel privilegiado ha ocultado históricamente su compleja dinámica causal. Pero el reconocimiento reciente de esta tendencia por parte de varios biólogos dentro de líneas específicas de investigación subyace al aumento sustancial de estudios experimentales u observacionales que examinan cómo varía la selección en el espacio y el tiempo. Sus hallazgos recomiendan que el campo causal de la selección natural no se puede modelar adecuadamente utilizando modelos simples, reducibles, lineales o monocausales, sino que requiere un cambio de filosofía (capítulos 4 y 5). La selección provoca la adaptación en múltiples niveles de organización biológica, con diferentes presiones selectivas que provocan diferentes respuestas selectivas en el espacio y el tiempo, y la selección cambia así sus intereses adaptativos en el espacio y el tiempo, siendo inaplicable la aptitud individual como medida universal para la selección en el espacio y el tiempo. . Por lo tanto, un cambio metodológico y epistemológico hacia el pluralismo no es una vergüenza para la biología evolutiva. En cambio, es la marca de una ciencia que reconoce y supera sus fallas, se desarrolla fuera de los límites de otras ciencias (por ejemplo, la física) y finalmente madura hasta convertirse en una ciencia autónoma con su propia filosofía.

En el Capítulo 3, titulado “La paradoja de la variación genética adaptativa”, llamo la atención sobre lo que quizás sea el problema con más historia en la historia de la biología evolutiva: la paradoja de la variación adaptativa. Nuevos hallazgos que comenzaron a fines de la década de 1950 comenzaron a desafiar las interpretaciones reduccionistas de la selección natural de que (1) la variación se genera independientemente de la exposición a entornos selectivos y, por lo tanto, es aleatoria, y que (2) la selección natural opera estrictamente a nivel individual. Una creciente literatura empírica en los últimos 60 años ha expuesto las inexactitudes de estos dos supuestos, dada la creciente evidencia de que la producción, conservación o domesticación de la nueva variación genética es adaptativa después de frecuentes cambios ambientales o factores estresantes, pero adaptativa a niveles de selección más altos. que el individuo.

En este capítulo, intento revisar exhaustivamente el concepto de variación genética adaptativa y cómo ha cambiado con el tiempo. Comienzo proporcionando una evaluación histórica diacrónica del concepto de variación genética adaptativa, desde Darwin hasta la actualidad. Después de establecer el contexto histórico necesario, reviso la literatura moderna independiente sobre los mecanismos de la variación genética adaptativa, es decir, la recombinación sexual, la mutación adaptativa y, muy brevemente, la transposición genética, la transferencia horizontal de genes y la duplicación de genes/genomas. Cuando se consideran en conjunto, surge un patrón empírico común dentro de estas literaturas independientes y expone una gran paradoja entre la evidencia disponible sobre la variación genética adaptativa y la teoría moderna, lo que garantiza una nueva filosofía de la biología que se basa en el pluralismo explicativo, análisis multifactoriales y multinivel. causalidad.

Ahora que tenemos las capacidades tecnológicas para ver la 'evolución en acción' durante períodos más largos y cambios espaciales frecuentes, finalmente se están revelando nuevos patrones evolutivos, incluida la fuerte preferencia de la selección natural para producir, conservar o domesticar nuevas variaciones genéticas cuando las especies se someten a duras condiciones. ambientes caprichosos, novedosos o caprichosos, lo que les permite combatir los desafíos presentes o futuros y evadir la extinción, a veces en lugar de la aptitud individual. Sin embargo, la teoría de la selección natural no puede explicar estos hallazgos recientes debido al espíritu filosófico reduccionista y monista que construyó esta teoría (Cap. 2).

El punto de vista reduccionista de la selección natural que ha dominado el pensamiento evolutivo desde su concepción ha hecho que muchos de los mismos arquitectos de la teoría evolutiva moderna aprecien la paradoja implícita y profunda de la variación adaptativa. La paradoja de la variación adaptativa existe, por lo tanto, como una de las paradojas teóricas y explicativas más antiguas y apremiantes de la biología evolutiva moderna, precisamente debido a (a) su precedencia histórica, reconocida por casi todos los grandes teóricos de la evolución posteriores a Darwin; (b) la cantidad de evidencia contradictoria disponible en la literatura actual que no encaja con las proyecciones teóricas de la selección natural darwiniana; y (c) la relación causal central, aunque subdesarrollada, entre la variación, la selección natural y la capacidad de evolución que aún no ha sido completamente explicada por la teoría. Debido a su longevidad y gravedad, esta paradoja destaca especialmente los anacronismos que están paralizando el progreso de la biología y la ciencia en general.

La Segunda Síntesis entre biología evolutiva y ecología (Cap. 2) —y, más específicamente, el mayor énfasis que los biólogos evolutivos ahora ponen en el realismo empírico— ha demostrado la necesidad de una nueva filosofía de la biología; uno que se basa en el pluralismo explicativo, análisis multifactoriales y causalidad multinivel. Pasar de preguntar por qué ha evolucionado el sexo (es decir, la relación costo-beneficio) a la pregunta ecológica de qué condiciones permiten que evolucione el sexo ha sido crucial para nuestra comprensión de la historia evolutiva del sexo, así como para mejorar las tendencias predictivas en la evolución poblaciones.

En los Capítulos 4 y 5, considero las implicaciones teóricas de la paradoja expuesta en el Capítulo 3 y abogo por las enmiendas teóricas necesarias para dar cuenta de estas tendencias recientes, basadas en una filosofía de la ciencia contemporánea que se esbozó en los capítulos

primero y segundo. Estos incluyen la integración de cuatro conceptos en la teoría de la selección natural: la selección de mantenimiento como el tipo de selección que actúa más comúnmente para mantener los mecanismos de evolución a lo largo del tiempo; la selección de especies como el nivel de selección más causalmente relevante para estos mecanismos; selección multinivel para explicar cómo opera la selección entre varios niveles (a veces en conflicto); y la capacidad de evolución como una nueva propiedad disposicional probabilística que es un determinante de selección de nivel superior similar a la aptitud individual (es decir, qué selección está seleccionando en poblaciones y especies).

En el Capítulo 4 titulado "Hacia una teoría pluralista de la selección natural: selección de mantenimiento", presento la necesidad de pluralizar la teoría de la selección natural, con base en la evidencia revisada en el Capítulo 3. Los filósofos y científicos generalmente han concebido la ontología de la selección natural como estrictamente causando un cambio evolutivo direccional, en lugar de causar estasis evolutiva y mantenimiento de rasgos. En este capítulo, actualizo brevemente los principios de la selección natural para incluir el funcionamiento causal de la selección de mantenimiento, junto con la selección direccional también. Luego elucido brevemente la historia detrás del concepto de equilibrio de la selección natural, que ve a la selección natural como un equilibrio entre las dos fuerzas opuestas de mantenimiento y dirección, e introduzco la superposición fenomenológica de las dos en consideración de la capacidad de evolución.

En el Capítulo 5 titulado "Hacia una teoría pluralista de la selección natural: Especies y selección multinivel para la capacidad de evolución", abogo por un concepto novedoso de capacidad de evolución, como un determinante de aptitud emergente de poblaciones o especies que se manifiesta cuando cambian los entornos.

La variación es el elemento vital de todos los procesos evolutivos, pero la capacidad de evolución es la razón causal por la cual la variación es importante. Los avances en los sectores empíricos de la biología están comenzando a revelar la capacidad de evolución como un componente ontológico importante del proceso evolutivo. Cómo un proceso central como la capacidad de evolución puede pasar relativamente desapercibido en la teoría después de más de un siglo de investigación científica pone de relieve los anacronismos filosóficos que han estado estancando el progreso en biología, así como en la ciencia en general.

Debido a que la capacidad de evolución existe como una adaptación emergente en niveles más altos de organización biológica que se manifiesta en una variación ambiental dada, su aclaración reciente marca un punto de inflexión histórico en la investigación biológica, alejándose del reduccionismo obsoleto que originalmente se tomó de las ciencias físicas y hacia una filosofía emergente que captura el cambio biológico en el espacio y el tiempo. Por lo tanto, la biología ha ganado su autonomía de las otras ciencias, siendo dotada de su propia filosofía de la ciencia (es decir, la filosofía de la biología), en parte gracias a la desunión del movimiento científico. Estos avances recientes son, por lo tanto, tanto la causa como el efecto de la Segunda Síntesis.

Concluyo esta tesis señalando cómo ha surgido legítimamente una nueva perspectiva de la evolución en los últimos 40 años. La evolución en el espacio y el tiempo está ahora a la

vanguardia de las consideraciones evolutivas gracias a la Segunda Síntesis entre la ecología y la biología evolutiva. Es un hecho notable de la historia que sabíamos relativamente poco acerca de cómo la evolución y la selección realmente se desarrollan en la naturaleza hasta tiempos recientes. Ya no nos preguntamos si está operando la selección natural sino cómo está operando la selección natural en las poblaciones naturales, marcando un cambio importante en nuestro pensamiento que ha subrayado una explosión de nuevos conocimientos sobre cómo la selección varía en fuerza, dirección, forma y, más recientemente, nivel. , todo dependiente de las condiciones ecológicas.

La evolución a la luz de la ecología nos ha alejado así de la evolución como un fenómeno genético o estadístico de poblaciones, a una biología que abraza el realismo empírico y ve la evolución como debe ser vista, como un fenómeno ecológico que sucede en el espacio y el tiempo. En este tiempo, hemos pasado de definir la selección natural en términos estadísticos y reductivos como "la supervivencia y reproducción diferencial de individuos con rasgos particulares sobre sus competidores, lo que lleva a asociaciones no aleatorias entre fenotipo y aptitud dentro de una generación" a una definición ecológica. que abarca todas las formas de causalidad (es decir, mantenimiento y direccional) en todos los niveles de la organización biológica: "ambientes ecológicos que favorecen las características de una entidad biológica (genes, individuos, poblaciones) que están causalmente conectados (en términos probabilísticos) con la supervivencia y la reproducción. de dicha entidad en el espacio y el tiempo". Esta tesis, por lo tanto, ilumina una nueva forma de ver las acciones causales de la selección natural, como un acto de equilibrio entre las necesidades presentes y futuras, y entre los niveles de selección en conflicto/cooperación, en el espacio y el tiempo.

Los conocimientos ecológicos han demostrado continuamente las fallas de representar causalmente fenómenos biológicos complejos utilizando modelos matemáticos simples e idealizados. Sin embargo, esto no quiere decir que la genética de poblaciones sea una empresa inútil, ni que no pueda mejorar a la luz de la ecología. El modelado simplificado, reducible y monocausal tiene sus usos en ciertos contextos epistémicos, como la estandarización del trabajo empírico o en demostraciones simples de procesos evolutivos (lo cual es útil para la instrucción). Sin embargo, la genética de poblaciones no es el final, ya que varios defensores de alto estatus suponen que es, y las ideas ecológicas a menudo deben tener precedencia epistémica debido a su cercanía con la naturaleza.

La capacidad de evolución es el ejemplo perfecto de cómo nosotros, como disciplina, hemos estado descuidando varios aspectos causales clave de la evolución que merecen reconocimiento. Para empezar, la capacidad de evolución genética es una propiedad seleccionable, lo que demuestra que la selección puede intervenir causalmente en los procesos variacionales y no es efectivamente aleatoria, como suponía la teoría sintética moderna. En segundo lugar, la capacidad de evolución existe como una propiedad emergente que ha sido eclipsada por el telón de fondo de las filosofías reduccionistas. Es por eso que la paradoja de la variación adaptativa es también la historia olvidada del pensamiento de la evolutividad, ya que demuestra cómo la evolutividad ha sido eclipsada en las atmósferas reduccionistas de la biología evolutiva. En tercer y último lugar, la capacidad de evolución es una propiedad disposicional que se manifiesta en

una variación ambiental dada, por lo que necesitamos ver la evolución en el espacio y el tiempo para revelar efectivamente su presencia. Una gran cantidad de trabajo ha demostrado cómo la capacidad de evolución es causada por entornos que varían en el espacio y el tiempo (ver Capítulo 3), y aunque los biólogos siempre han estado estudiando la capacidad de evolución como una idea, el aumento conceptual de la capacidad de evolución en los últimos cuarenta años demuestra la cambio profundo ofrecido por una perspectiva EST.

Las partes centrales de esta tesis encajan para hacer un largo argumento contra las formas obsoletas que solíamos ver en la evolución y la biología. La paradoja de la variación adaptativa no solo es el ejemplo perfecto de los anacronismos filosóficos que han estado estancando el progreso teórico durante la mayor parte del siglo pasado, sino que la reproducción sexual también se erige como el mejor ejemplo de pluralismo en biología, dándonos una idea de cómo para resolver la paradoja y seguir avanzando en biología. Y la paradoja de la variación adaptativa también corre paralela a la historia de la capacidad de evolución, explicando cómo y por qué los fenómenos de capacidad de evolución se han pasado por alto en una biología que descuida la evolución en el espacio y el tiempo.

Sin embargo, la Segunda Síntesis está incompleta. Los reservorios epistémicos desbordantes generados por los procesos empíricos de la ciencia normal (sensu Kuhn) aún no se han convertido en una teoría cohesiva como la que se ve en la primera síntesis. La primera síntesis vio la unificación del conocimiento entre las diversas subdisciplinas biológicas (por ejemplo, paleontología, sistemática, morfología y genética) porque los constructores de puentes (por ejemplo, Dobzhansky, Fisher) notaron una brecha profunda en la comunicación entre estas disciplinas. Los disidentes discutían sobre la misma fenomenología pero desde diferentes perspectivas causales. Asimismo, la Segunda Síntesis es, en parte, la consecuencia de la atenuación selectiva de las subdisciplinas biológicas para descuidar la información causal clave que se encuentra fuera de su ámbito tradicional. Hoy en día, aún existen profundas brechas en la comunicación entre las diversas subdisciplinas de la biología, perfectamente demostradas dentro del frente de investigación de la capacidad de evolución (por ejemplo, genética de poblaciones versus evo-devo).

Cerrar esta brecha y sintetizar el amplio cuerpo de conocimiento existente requiere un enfoque diferente al ofrecido en la primera síntesis. La palabra síntesis apunta hacia la unificación y la idea positivista general de unidad teórica. Sin embargo, el tipo de unidad que pidieron nuestros antepasados probablemente sea diferente del tipo que se requiere hoy. La complejidad causal de la mayoría de los fenómenos biológicos exige ontologías y metodologías pluralistas. Por lo tanto, necesitamos una síntesis, una unificación de la teoría y el conocimiento entre las diversas subdisciplinas, pero que se base en el pluralismo.

Por lo tanto, la biología evolutiva se encuentra actualmente suspendida en una etapa intermedia del progreso científico que exige la organización e integración de las reservas de conocimiento desbordantes, producidas por su reciente síntesis con la ecología, en un marco teórico coherente y unificado, tal como se vio en la primera síntesis. Aquí es donde los avances recientes en la filosofía de la biología pueden ser de gran utilidad, actuando como un puente entre subdisciplinas de la biología previamente divididas e inventando nuevas estrategias teóricas para

organizar y acomodar el conocimiento dividido. Más recientemente, los filósofos han recomendado la transición de filosofías obsoletas que se derivaron originalmente del positivismo lógico (es decir, monismo, reduccionismo y/o monocausalidad) y hacia una filosofía distinta de la biología que puede capturar la complejidad natural de los sistemas biológicos multifacéticos dentro de diversos ecosistemas, uno que abarca las filosofías emergentes del pluralismo, la emergencia y la multicausalidad.

Luego discuto cómo podemos progresar en biología. Una de las principales razones por las que hemos visto tantos llamados al progreso teórico hoy en día es por el tema que investigamos. Los sistemas biológicos son singulares en su complejidad causal. La causalidad biológica depende del contexto porque los fenómenos que exploramos son extremadamente variables en el espacio y el tiempo (por qué no existen leyes en biología). Nuestra causalidad también tiende a ser multifactorial, multinivel con causalidad ascendente y descendente entre niveles biológicos de organización, con una miríada de variables evolutivas (por ejemplo, historia de vida, dinámica de población) que afectan las características biológicas en el presente. Agregue a esto la noción de causalidad recíproca, que los organismos influyen en su entorno y viceversa. De hecho, la causalidad biológica es muy complicada.

Tal complejidad causal invita a la divergencia de las diversas subdisciplinas. Las ideas causales provienen de muchos lugares en biología, precisamente porque investigamos los mismos fenómenos causales desde varias perspectivas (es decir, adaptación) utilizando diferentes metodologías (por ejemplo, ecología versus microbiología). Los científicos atenúan selectivamente sus agendas de investigación a una causa particular o patrón causal de interés. Sus investigaciones dan como resultado la construcción de modelos causales demasiado simplificados e idealizados, que ignoran otra información causal importante que se encuentra fuera de su periferia elegida. Quizás ninguna otra ciencia se aprecie mejor que la biología. Los biólogos habitualmente enfatizan demasiado y/o descuidan la información causal clave que se encuentra fuera del alcance tradicional de su disciplina, debido a la causalidad desordenada inherente a los sistemas biológicos, que luego se manifiesta en continuos llamados al progreso teórico y nuevas síntesis (independientemente de su valor para biología).

Termino la conclusión con una discusión de las direcciones futuras que se pueden tomar. La Segunda Síntesis culminará cuando se alcance un acuerdo en la comunidad de biología evolutiva, incluidos los genetistas cuantitativos y de poblaciones, de que nuestros modelos anteriores de evolución han sido demasiado abstractos y reductivos para representar la compleja dinámica causal de la evolución y la selección que se encuentran típicamente en la naturaleza. poniendo así un mayor énfasis de investigación en el realismo y la validez externa de nuestros modelos causales. Es necesario llegar a un consenso para que haya algún tipo de progreso científico o teórico.

Sin embargo, la ciencia también necesita adaptarse para satisfacer las demandas modernas. La ciencia debe adaptarse y evolucionar alterando sus filosofías fundamentales, muy similar al proceso de evolución en biología. Por lo tanto, la capacidad de evolución es el ejemplo metafórico y literal perfecto de cómo y por qué la ciencia necesita cambiar.

Glossary

Anything-Goes Pluralism: All theories and perspectives are equally valid, and the greatest understanding of a scientific phenomenon is achieved by an unlimited proliferation of theories, concepts, and/or perspectives.

Disinterestedness (Mertonian norm): Expresses the idea that scientists should work only for the benefit of science; not for their own professional or personal gain.

Disunity of Science Movement: A philosophical movement starting in the 1980s (from the so-called *Stanford School*) that recognized the explanatory autonomy of separate scientific disciplines, making them irreducible to other scientific disciplines (i.e., physics).

Empirical Realism: A philosophy of science that encourages the designing of empirical studies to best match natural settings, in the hope of achieving externally valid causal models.

Epistemic Juncture: A point in space and time of academic epistemology, or a given scientific discipline, relating to where the knowledge currently stands on a given subject or more broadly where the edges of theory lie in a science.

Explanatory Monism: A philosophy that emphasizes a singular explanation for any given scientific phenomenon or the unification (i.e., reduction) of explanations into a singular explanatory model.

Explanatory Pluralism: A philosophy that emphasizes multiple explanations for any given scientific phenomenon.

External Validity: Is the extent to which scientific theories or explanations are assume dot be accurate (or *more accurate*) representations of the causal patterns found in nature.

Logical Positivism: A form of positivism, originally developed by members of the Vienna Circle, which considers that the only meaningful philosophical problems are those which can be solved by logical analysis and scientific inquiry, placing a special emphasis on the mathematization of scientific disciplines and their eventual reduction to physics.

Natural Selection (old statistical definition): The differential survival and reproduction of individuals with particular traits over their competitors, leading to non-random associations between phenotype and fitness with a generation.

Natural Selection (new definition in light of ecology): ecological environments favoring the features of a biological entity (genes, individuals, populations) that are causally connected (in probabilistic terms) to the survival and reproduction of said entity in space and time.

Organized Skepticism (Mertonian norm): Expresses the idea that the acceptance of all scientific work should be conditional on assessments of its scientific contribution, objectivity, and rigor.

Presentism: In historical methodology, presentism is the viewing of historical ideas in the context of present-day attitudes or perspectives. It is a wrong way to look at history because it does not take into context the sociopolitical, moral, or scientific attitudes that gave rise to the historical idea.

Reductionism: A philosophy that aims to reduce the diversity of explanations to a small number of theories or mathematical laws at a privileged level of discourse.

Restrictive Pluralism: A type of pluralism that allows for the comparison of competing models, ideas, or hypotheses based on any sort of demarcationist criteria, thus allowing space for the construction of more nuanced and complex theoretical models.

Synthesis: The unification of separated scientific domains that previously had little to no crosstalk, building towards a coherent and unified theory.

Unity of Science Movement: A philosophical movement that derived from logical positivism, that argued for the unification (i.e., reduction) of scientific phenomena into a small number of theories or laws. As an ‘over-arching metascientific hypothesis’, unity of science was synonymous with epistemic reductionism, which maintains that the unification of all scientific terminology, laws, and theories should be reduced to physics in the long run.

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