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MANUFACTURED LIFE

The scientific and social challenges of synthetic biology

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Since biology became secularised and the molecular scrutiny of life began, the possibility of artificially synthesising living cells in a laboratory became a tangible possibility. Contemporary synthetic biology aspires to design and manufacture new forms of life to obtain social and economic benefits. However, we cannot rule out the possibility that the creation of synthetic life forms may also bring scientific rewards in terms of a greater understanding of biological complexity, which we would not be able to access through analytical means. It is clear, therefore, that the term synthetic biology raises expectations, but it is no less true that it also causes concern. This article starts with a critique of the identification of cells as machines and discusses the current scope of synthetic biology and efforts to standardise it. We also outline some of the social implications of attempts to manufacture life.

Keywords: biotechnology, metaphor, artificial life, synthetic life, scientific communication.

METAPHORS AND IDENTIFICATION

More than a century ago, Stéphane Leduc coined the term *synthetic biology* (Leduc, 1912). Following the materialistic – or, rather, antivitalist – current of biology at the time, Leduc sought to reproduce the forms and dynamics of living beings in the laboratory using chemical ingredients. He applied an extreme materialistic logic: «Why is it less acceptable to try to make a cell than it is to make a molecule?» (Leduc, 1912). Although the academic community rejected and ridiculed his experiments, the impact his chemical gardens had on the collective imagination, thanks to the press and literature, was remarkable. Thus, it is not surprising that Thomas Mann chose to include the surprising and enigmatic creation of artificial life as one of the favourite pastimes of the composer Adrian Leverkühn's father in *Doctor Faustus*.

«Organisms are not machines designed by external agents for a purpose. They are the result of an unintentional evolutionary process»

There were other scientists who, in various cultural contexts, also obsessively pursued the synthesis of life, including Alfonso L. Herrera in Mexico and John B. Burke in England (Peretó, 2016). All of them were convinced there was no insurmountable boundary between inert matter and life, and they also shared the desire to demonstrate that natural causes were sufficient to explain biological phenomena. Perhaps the most intellectual and scientific defence of this position was the one made by Jacques Loeb, the discoverer of artificial parthenogenesis. The observation that an unfertilised egg could start developing by changing only the chemical conditions of the environment shattered many scientific and cultural preconceptions. On the one hand, it created the possibility of investigating life from an engineering perspective through the controlled manipulation of phenomena: for Loeb, control was equivalent to understanding. On the other hand, initiating animal development with non-biological (and, even worse, non-male) factors challenged the canonical vitalist mindset, which is why Loeb was considered by his contemporaries (especially by Catholic authors) to be the most dangerous of materialists (Keller, 2002; Peretó & Català, 2012).

At the end of the nineteenth century, the scientific debate was no longer centred on whether the synthesis of life in the laboratory would ever be possible, but on

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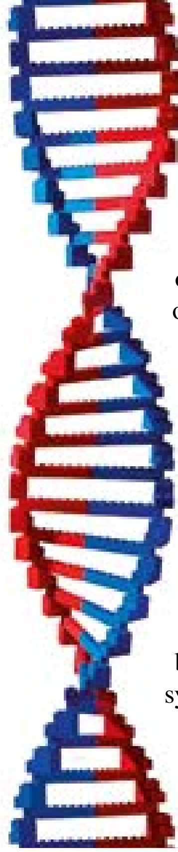
More than a century ago, Stéphane Leduc (right) coined the term *synthetic biology*. Leduc sought to reproduce the forms and dynamics of living beings in the laboratory using chemical ingredients. Although the academic community rejected and ridiculed his experiments, the impact his chemical gardens had on the collective imagination, thanks to the press and literature, was remarkable. In the picture above, one of his «osmotic productions» illustrating *The mechanism of life*, published in English in 1912.

when this extraordinary milestone would be achieved. At times it seemed very close, as indicated by the emphatic opinions of authors like Leduc, Herrera, and Burke. But the premises about the chemical composition of life which they all based their opinions on, were far removed from reality. The colloidal state, with a rather unspecific composition, was considered genuine cellular matter. At the beginning of the twentieth century, as biochemistry began to develop as a discipline separate from organic chemistry and physiology, experts started to glimpse a molecular complexity of life that made it difficult to synthesise it in the laboratory. Loeb, who with his pioneering work on protein chemistry embodies the transition from «the dark age of biocolloidology» to the basic elements of molecular biology, would insist that the ultimate goal of biology is to manufacture life. However, he reserved this ambitious programmatic goal for future generations of younger and more daring scientists (Loeb, 1906) and simultaneously strongly criticised contemporary attempts to manufacture cells in the laboratory, which he called naive and premature.

Loeb was convinced that the artificial synthesis of life would one day be achieved, based on the certainty that cells are, quite literally, chemical machines: «Living organisms are chemical machines, [...] no one can say with certainty that such machines might not one day be constructed artificially» (Loeb, 1904). That explicit machinism was, therefore, what gave rise to a synthetic biology field based on engineering, design, manufacturing, and system prediction and control. It is a very early example of a machinist ideology in biology, projecting the Cartesian dream at the cellular and molecular scale. Taking the analogy literally, machines were no longer just metaphors, but an intellectual framework driving research. But how realistic is the identification of living beings with machines?

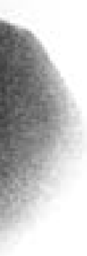
CELLS ARE NOT MACHINES

One of the most deeply rooted and explicit assumptions of contemporary synthetic biology with an engineering profile is the notion that living organisms are literally machines. There are countless examples in the literature of claimed equivalences between organisms and machines, or computers (Nicholson, 2014; Porcar & Peretó, 2016). Mechanisms comprise standardised and interchangeable components with predictable behaviours, and are designed, manufactured, and repaired by external agents. Synthetic biology considers cells to be systems consisting of parts with logical relationships between them, like those designed by industrial or electronic engineers. The use and abuse of metaphors is driven by extreme machinism and has been criticised from various perspectives (De Lorenzo, 2011; Nicholson, 2014; Porcar & Peretó, 2016). However, upon closer inspection, and in the context of a synthetic biology



that aspires to construct a more quantitative biology, contemporary machinism does not express a realistic description of what cells are like and how they function, but rather, a desire or a long-term goal. Nonetheless, it is also true that synthetic biology has revitalised forgotten – or, at least, marginalised – debates in contemporary biology, such as the discussion about what life is.

Thus, what both machines and cells have in common is that they are, from the point of view of thermodynamics, systems that are open to the flow of matter and energy. But this is as far as the identification goes: the «efficient causes» – to use the Aristotelian concept employed by the theoretical biologist Robert Rosen – are internal in living beings and external in machines. Organisms are not machines designed by external agents for a purpose, but rather, they are the result of an unintentional evolutionary process whose main driving force is the ability to persist and reproduce in each environment. This is a fundamental ontological difference between organisms and machines: the historical development of complexity and biological diversity is non-teleological, in other words, it is purposeless. Even so, the appearance of purpose and intention in living beings is evident – what Jacques Monod called *teleonomy* to avoid the identification with teleology.



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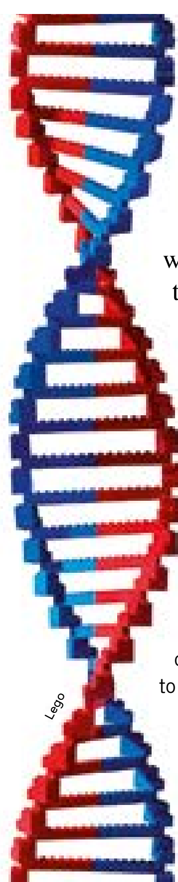
In a recent reflection, microbiologist Víctor de Lorenzo, following in Monod's footsteps, proposed the term *technonomy* (as opposed to *technology*) to refer to the appearance of design in life and to the logic of the relationships between the components of living systems without needing to adopt a strong metaphysical position implying that there is real (technological or engineered) design (De Lorenzo, 2018). That is to say, De Lorenzo advocates a return to the usefulness of metaphors and analogies while avoiding unrealistic dead ends. The fact that cells are not the result of a designer or an engineer is one thing, but it is still useful to analyse living organisms «as if» they were. We will have to evaluate the epistemological value of this approach in biological phenomenon once we have tangible results from a version of synthetic biology that is truly based on the principles of engineering. In short, once we see if it is possible to create new designs based on purposeless and non-designed entities.

Therefore, despite accepting the teleonomic and technonomic nature of life, we can still identify certain pitfalls that synthetic biology, when understood as engineering, would have to face (Porcar & Peretó, 2016). Thus, while engineer-designed systems rely on redundancy to achieve acceptable levels of robustness, life is based on degeneration – in the sense of functional synonymy – and the multifunctional character of its components. For example, because of their inherently flexible nature, proteins can have multiple functions that overlap with each other and which generate robust relationship networks. The main (adaptive) functions of cellular components often coexist with collateral, minor, non-adaptive, or neutral functions (known as promiscuous functions). In the cellular context, these are a notable source of evolutionary innovation (Tawfik, 2010) but, as we will see below, they may represent an obstacle for the development of synthetic biology based on the identification and replacement of standard and independent modules.

«One of the most noteworthy controversies related to synthetic life refers to the discussion of whether it will be possible to standardise living beings»

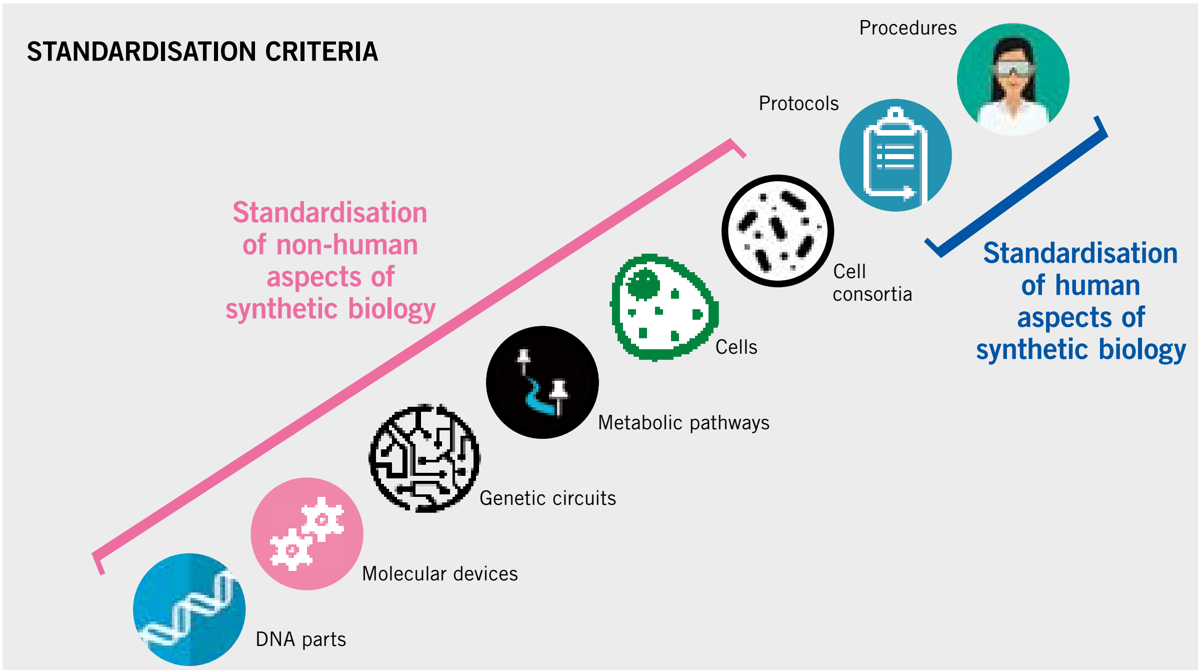
WHY STANDARDISE LIFE (IF EVEN POSSIBLE)?

One of the most noteworthy controversies related to synthetic life refers to the discussion of whether – and to what extent – it will be possible to standardise living beings. As we have just explained, living beings, despite being subject



Lego

An informal definition proposes that a standard is a piece, such as a screw or a drill bit, whose characteristics make it universal and predictable in terms of its use and functions. Many different machines can be built with a relatively small number of standard parts: assembly sets, such as Meccano or Lego, are good examples of standard systems. The idea of standardisation in synthetic biology is based precisely on the combination of well-characterised (DNA) parts. However, the predictability of biological interactions is still currently far from complete, which in turn makes it difficult to accurately predict the behaviour of synthetic organisms.



In synthetic biology we can consider different levels to which we can apply standardisation criteria. The lower end of the diagram shows processes in the standardisation of molecular and cellular systems, which allow the use of parts and modules with specific properties that can be combined and integrated into different genetic and biochemical circuits. The other end shows the practices, protocols, and procedures used by different laboratories and teams in a variety of social settings and cultural contexts, which can also be standardised. An obvious benefit of this process is the improved reproducibility of experiments.

to the laws of physics, are not exactly biomachines. However, this contrasts with the fact that synthetic biology, by definition, seeks to mechanise living beings, to modify them according to engineering criteria, to design devices that produce, for example, food, drugs, or biofuels.

The success of industrial engineering is linked to standardisation. Cars, mobile phones, or washing machines would not be possible – much less at today's cost – without standard components. But what is a standard? An informal definition proposes that a standard is a piece, such as a screw or a condenser, whose characteristics make it universal (we can buy the same screw or condenser all over the world) and predictable (a 3 mm diameter screw fits into a plastic 3 mm wide peg, no matter what brand). It can also be said that a relatively small number of parts can be used to build many different machines. Assembly kits such as Meccano or Lego are good examples of standard systems. In fact, with only a few part types and minimum skill you can build a formal replica – in the sense that only the shape is reproduced – of almost any object.

The success of standardisation in engineering justifies the search for standards in the field of biology, inspired by the principles of design. If we consider the concept of *biomachines*, albeit only as a metaphor, the interest in finding and assembling standard biological parts as the basis for synthetic biology becomes evident. The idea is exciting and arises from the analogy between the construction of a machine and the design of a totally or partially synthetic being. For example, it is clear that the pieces to create an oil-degrading bacterium are very different from mechanical or electronic components; they are not screws or chips, they are DNA pieces, genes, and protein encoders with structural, catalytic, or regulatory functions. Even so, it must be stressed that these functional products (i.e., proteins) are expected to follow – or at least we hope they will – a relational logic in their interaction and functional integration with the rest of the components of the system.
For example, if complex biological interactions were totally predictable, on-demand metabolisms could be designed. This is not yet the case, even though efforts have been made to integrate massive amounts of data derived from «omics» technologies. But, despite early successes in the computational simulation of cellular activities, the global mathematical modelling of interactions between biomolecules and the variability inherent to every metabolic process, make it difficult to predict the exact behaviour of a synthetic organism.

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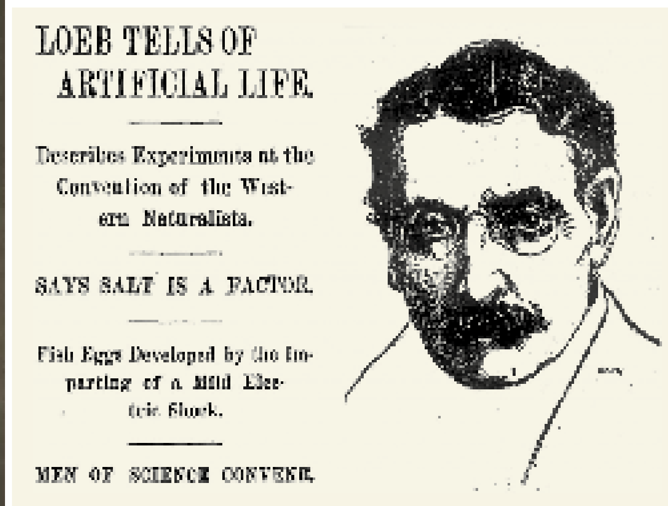


LOEB TELLS OF ARTIFICIAL LIFE.

Describes Experiments at the Convention of the Western Naturalists.

SAYS SALT IS A FACTOR.

Fish Eggs Developed by the Imparting of a Mild Electric Shock.

MEN OF SCIENCE CONVENE.

Chicago Daily Tribune

Jacques Loeb (left) was perhaps the first scientist whose research was visible in terms of media impact. In the late 19th and early 20th centuries, sensationalist headlines and articles were published about Loeb's artificial parthenogenesis. Shown above is an illustration from the *Chicago Daily Tribune*, published on 28 December 1900, devoted to the scientist and featuring a headline hinting at the creation of «artificial life».

However, the advantages of standardising living things as far as possible could be enormous: the reuse of components would make design easier and we would make sure that synthetic organisms and circuits work in a predictable way because they would have been tested thousands of times before. The difficulties in achieving these goals are closely related to the fact that, as we have already discussed, cells are not machines. Unlike machines, the technonomy of cells does not respond to our desire to build, repair, or even understand them. In addition, one detail is inherently linked to life and its origin and draws a clear boundary between cell and machine: evolutionary change. In industry, the last thing the manufacturer (or customer) wants for a given product is for it to change. We all want a car that works exactly like all other cars of the same model. A unique change only for one vehicle would hardly be an improvement. Quite on the contrary, a variation of the model standard would indicate a malfunction or the presence of a defective part. Conversely, life (evolution) plays with variability and constant change (mutations) and ultimately, with death. For living beings, being different, changing and deviating from the archetype, is the driving force of adaptation. However, this clashes with synthetic biologists' desire to design life à la carte, within standardised parameters.

«Synthetic biologists currently agree that standardisation would be enormously beneficial. But there is also a widespread feeling that it will be very difficult to achieve»

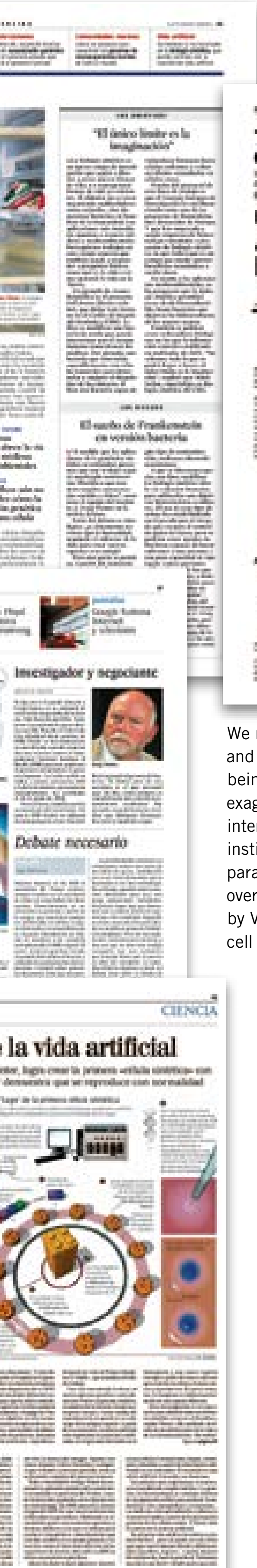
In short, the development of standards in biology is insufficient, and moreover, we still need to define sufficiently-characterised and robust biological parts. Thus, biological parts can be considered standardised when we can truly reuse these parts to generate innovation, a software engineering-like feature that characterises most advanced technologies but which is absent from current collections of biological parts, like the Biobricks™ components (Valverde, Porcar, Peretó, & Solé, 2016). However, the scientific community disagrees on the scope of the standardisation of life, whether such standardisation will only be possible under laboratory conditions or if it is also possible in more variable environments, and what the range of application of a given standard will be, given the overwhelming biological diversity. Synthetic biologists currently agree that standardisation would be enormously beneficial and would at least provide greater experimental reproducibility. But there is also a widespread feeling that this type of standardisation will be very difficult to achieve.

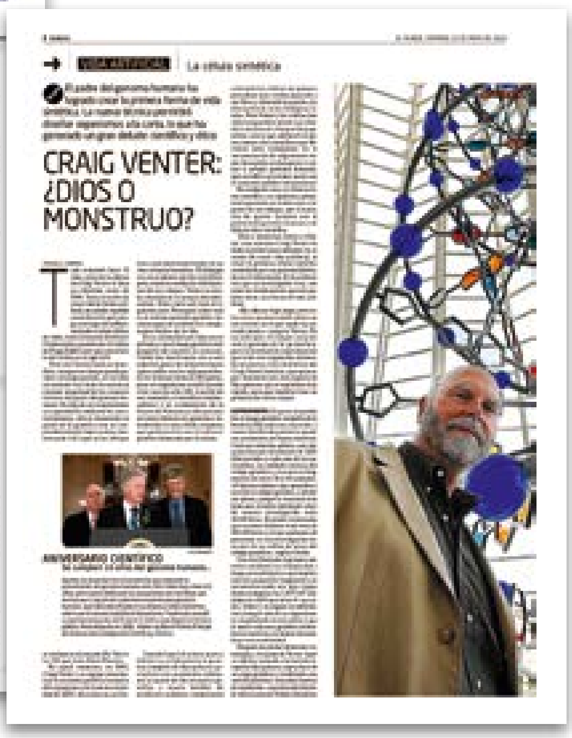
Furthermore, there is a sociological aspect inherent to standardisation processes which, like everything related to the protection of intellectual property and patents (Konig, Dorado-Morales, & Porcar, 2015), is superimposed onto other social aspects and the ethical dimension of technologies (for a specific discussion on ethics and synthetic biology, see Douglas, Powell, & Savulescu, 2013). Establishing standards implies prior discussion so that the widest cross-section of people from different cultures and traditions can reach agreements of acceptance. Thus, even within the synthetic biology community, there are many views and tensions about the strict acceptance of engineering concepts (such as the computable and modular character of a system) in the domain of living beings. Consequently, standardisation in synthetic biology also represents a controversial social challenge with its own identity.


Tendencias
El primer ser vivo creado por ordenador
Craig Venter obtiene una bacteria a partir de datos informáticos, un hito hacia la síntesis de vida artificial
vida&artes
Vida de bote
El juego de ser Dios
No seamos hipócritas
La revolución de
Ante la puerta de Tannhauser

SOME SOCIAL IMPLICATIONS OF THE MANUFACTURE OF LIFE

In addition to the social aspects linked to the standardisation process, other issues should be highlighted. MIT sociologist Kenneth Oye has formulated what is surely the best definition of the potential impact of synthetic biology in terms of its public perception: he argues that the very term *synthetic biology* «could almost have been calculated to cause a strongly negative response». In part, this is because of cultural reasons rooted in the negative perception of monsters and various mythological or literary beings, most of which, because they are artificial, are «bad» and hopelessly escape the control of their designers. At this point, mentioning Mary Shelley's novel *Frankenstein; or, the modern Prometheus* is inevitable. In the novel, a scientist's imitation of a titan triggers a whole series of heinous misfortunes. But this only (partly) justifies the negative perception that one may have had beforehand, starting from the designation of the discipline. It is true, however, that synthetic biology technologies and genetically modified organisms (GMOs) are criticised by environmental groups and by a significant part of the population. Nevertheless, in order to narrow down the debate, one must insist on emphasising the obvious fact that technologies are not inherently bad, even





We must reflect upon the relationship between scientists and communicators to prevent information from being conveyed to the public out of context, or in an exaggerated way, or so that it serves unfairly the specific interests of scientists or institutions. The case of the institute of the famous biotechnologist Craig Venter is paradigmatic: at the end of May 2010, media from all over the world were reporting on an article published by Venter's team according to which the first synthetic cell had been created. Although this milestone was later substantially moderated, in the following days much of the media reported the idea that life had been created artificially. The pictures show some examples taken from Spanish newspapers that discuss the matter in terms of «creating artificial life», «canned life», or «playing God».

«Technologies are not inherently bad, even though their use always implies assuming some risk»

though their use always implies assuming some risk. Therefore, we could suffer the consequences of misusing these technologies or of some of the risks associated with their implementation, should they materialise.

GMOs work, and synthetic organisms are also beginning to function, even though, as we have mentioned, they have limitations. The potential danger of a synthetic organism – or a GMO – justifies the well-known precautionary principle. However, for the time being, there is no evidence to suggest that synthetic organisms are any more dangerous than natural ones. But the lack of evidence for environmental or biosafety hazards does not preclude the obligation to act with caution, given the power of technology and the undoubted fact that many aspects of modified life forms are simply too difficult to predict. In addition to safety issues, there is also a socio-economic perspective (common to existing debate about other technologies) related to the effect that this newly-implemented technology would have on the labour market. For example, how would the manufacture of a microorganism capable of synthesising vanillin at a very competitive price affect the economy of the communities in Veracruz or Madagascar that hand-pollinate *Vanilla planifolia* orchid flowers? To address these ethical, environmental, and social aspects, all the parties must be integrated into a peaceful common debate based on verified data and conducted with complete transparency, following the recommendations of the responsible research and innovation (RRI) framework (Konig et al., 2015).

The need for transparency in the debate must also consider the role – or power – of the media to aggravate or sometimes (and equally necessary), to temper discussions related to synthetic life. Premeditated human interventions in life, with the aim of taking control of biological processes, represents one of the earliest historical cases of interaction between scientists and communicators and produced very disappointing results. Loeb was perhaps the first scientist whose research, especially regarding artificial parthenogenesis, was visible in terms of media impact (Turney, 1995). The sensationalism of the headlines and articles devoted to Loeb's research in the late nineteenth and early twentieth centuries led to his work being labelled «artificial synthesis of life» when he merely considered it the controlled induction of the development of an unfertilised egg through chemical manipulation of its environment. This public reaction forced Loeb to publish a note in *Science* disavowing himself from all journalistic information published about his research. Thus, the first real modern scientist's experience of media coverage linked to the creation of life – outside the pages of fantasy literature – was rather uninspiring.

Even so, throughout the twentieth century there were cases of scientists and journalists indulging each other when the media amplification of research satisfied scientists or their institutions. An example is the role of Wendell M. Stanley and the Rockefeller College at Princeton University in the dissemination of work on the crystallisation of Tobacco Mosaic Virus as a «revolutionary discovery» that crossed the border between living and inert matter (Creager, 2002). More recently, the J. C. Venter Institute showed communicative efficacy in disseminating their research on artificial minimal cells, resulting in a series of worldwide headlines featuring scientists «playing God» (see Porcar & Peretó, 2018). In this context, we must reflect upon the biunivocal relationship between scientists and communicators: the former transmitting their research in an appropriate way without exaggerations or unjustifiable extrapolations; the latter avoiding sensationalism or uncritical *churnalism*.[1] So, what could the formula be? One proposal is co-creation by synthetic biologists (as we have already seen, a remarkably sociologically heterogeneous community in terms of its science-engineering dichotomy), communicators, and the rest of society, within a general RRI framework to define both medium- and long-term strategic objectives for synthetic biology and its limits (Porcar & Peretó, 2018). In this context, dialogue to reach a consensus on the value and use of metaphors, and the revision of those that misrepresent technological reality, and which may be subject to social prejudice closer to panic than to responsible and rational risk assumption, would be worthwhile.

«To address the ethical, environmental, and social aspects of synthetic biology, all the parties must be integrated into a peaceful common debate»

REFERENCES

Creager, A. N. H. (2002). *The life of a virus. Tobacco mosaic virus as an experimental model, 1930-1965*. Chicago: The University of Chicago Press.
De Lorenzo, V. (2011). Beware of metaphors: Chasses and orthogonality in synthetic biology. *Bioengineered Bugs*, *2*(1), 3–7. doi: 10.4161/bbug.2.1.13388
De Lorenzo, V. (2018). Evolutionary tinkering vs. rational engineering in the times of synthetic biology. *Life Sciences, Society and Policy*, *14*(1), 18. doi: 10.1186/s40504-018-0086-x
Douglas, T., Powell, R., & Savulescu, J. (2013). Is the creation of artificial life morally significant? *Studies in History and Philosophy of Biological and Biomedical Sciences*, *44*, 688–696. doi: 10.1016/j.shpsc.2013.05.016
Keller, E. (2002). *Making sense of life. Explaining biological development with models, metaphors, and machines*. Cambridge: Harvard University Press.
Konig, H., Dorado-Morales, P., & Porcar, M. (2015). Responsibility and intellectual property in synthetic biology: A proposal for using Responsible Research and Innovation as a basic framework for intellectual property decisions in synthetic biology. *EMBO Reports*, *16*(9), 1055–1059. doi: 10.15252/embr.201541048
Leduc, S. (1912). *La biologie synthétique*. Paris: A. Poinat.
Loeb, J. (1904). The recent development of biology. *Science*, *20*(519), 777–786. doi: 10.1126/science.20.519.777
Loeb, J. (1906). *The dynamics of living matter*. New York: Columbia University Press.
Nicholson, D. J. (2014). The machine conception of the organism in development and evolution: A critical analysis. *Studies in History and Philosophy of Biological and Biomedical Sciences*, *48*, 162–174. doi: 10.1016/j.shpsc.2014.08.003
Peretó, J. (2016). Erasing borders: A brief chronicle of early synthetic biology. *Journal of Molecular Evolution*, *83*(5–6), 176–183. doi: 10.1007/s00239-016-9774-4
Peretó, J., & Català, J. (2012). Darwinism and the origin of life. *Evolution: Education and Outreach*, *5*(3), 337–341. doi: 10.1007/s12052-012-0442-x
Porcar, M., & Peretó, J. (2016). Nature versus design: Synthetic biology or how to build a biological non-machine. *Integrative Biology: Quantitative Biosciences from Nano to Macro*, *8*(4), 451–455. doi: 10.1039/c5ib00239g
Porcar, M., & Peretó, J. (2018). Creating life and the media: Translations and echoes. *Life Sciences, Society and Policy*, *14*(1), 19. doi: 10.1186/s40504-018-0087-9
Tawfik, D. S. (2010). Messy biology and the origins of evolutionary innovations. *Nature Chemical Biology*, *6*(10), 692–696. doi: 10.1038/nchembio.441
Turney, J. (1995). Life in the laboratory: Public responses to experimental biology. *Public Understanding of Science*, *4*(2), 153–176. doi: 10.1088/0963-6625/4/2/004
Valverde, S., Porcar, M., Peretó, J., & Solé, R. V. (2016). The software crisis of synthetic biology. *BioRxiv*. doi: 10.1101/041640

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[1] A neologism referring to journalism based on the press releases of agencies, companies, and institutions, in which the media merely reproduce the information received without contrasting or consulting the sources.