TOWARDS A NEW COVENANT WITH NATURE – STARRED BY ENVIRONMENTAL MICROORGANISMS

by Víctor de Lorenzo

A rendition of Lara Tabet's residence and how it inspired our research agenda
A bit of a background

Lara Tabet's host laboratory is located within the so-called National Center of Biotechnology, at the National Research Council (CNB) in Madrid, specifically in the Laboratory of Environmental Synthetic Biology[1], which is led by this chapter's author. The team has been working on developing tools to address major environmental problems through the genetic engineering of microorganisms, and other methods which stem from contemporary molecular biology, for a long time (de Lorenzo, 2008; Dvořák et al., 2017; Schmidt & de Lorenzo, 2012). This laboratory has undergone profound technological changes in the last few years; for a long time, we were only able to program bacteria for environmental release (e.g., for bioremediation of chemical pollution) to a minor extent and with considerable unpredictability (Cases & Lorenzo, 2005). At present, though, we find ourselves in a position to undertake the application of modern genetic engineering and rational biodesign in earnest and with much better (and quite amazing) molecular tools because of the advances made within synthetic biology (Malik et al., 2021; Rylott & Bruce, 2020). Furthermore, the same molecular methodologies – made available only recently – offer open perspectives on the use of live constructs as agents that are able to deliver solutions to the phenomenally significant problems that we face as a planet, such as climate change (de Lorenzo, 2017; de Lorenzo et al., 2016).

[1] For more information, see: https://vdl-lab.com/

It is in this context that we launched Project Madonna, with the ambition of pushing the boundaries of familiar biochemical reactions towards new transformations, thereby bringing otherwise abiotic processes, which are typical of the chemical industry, into the biological fold. The long-term vision involves connecting the naturally occurring biogeochemical cycles with the human-created industrial metabolism for the sake of a sustainable element for recycling at a global scale. Our main approach to this end involved leveraging the immense problem-solving capacity of biological evolution to resolve challenges that are both multi-objective and that require optimization (Abraham & Jain, 2005). This is not just a theoretical occurrence, but it is also a powerful tool for biotechnologists when all-rational design, from first principles, is not possible because of excessive complexity. This is exactly the case for the Madonna project, given that it attempts to break the extant walls between living and non-living matter by pushing the limits of natural metabolism forward and towards a different type of chemistry. This endeavor requires the development of new-to-nature biological agents and will even require that we revisit contemporary biology's core foundations. One specific question concerns whether or not we can modify the so-called central dogma of molecular biology i.e., DNA goes into RNA and then goes into proteins, which can then propagate into metabolism (de Lorenzo, 2014). Instead, the abiding challenge concerns whether or not we can start with a reaction that, in principle, is not biological, eventually having it become encrypted in a biological system (Ralser et al., 2021). That is basically the project's mission and we have worked hard in order to make some progress in that direction.

Where are we now? The conventional approach to having bacteria running new reactions typically includes looking for gene-encoding enzymes that catalyze similar reactions and then applying adaptive laboratory evolution, i.e., ALE (Sandberg et al., 2019) to first diversify *in vivo* and then to select gene/enzyme variants that push the reaction towards the desired outcome stepwise. In fact, ALE reproduces Darwinian evolution in a test tube; the key difference being that the selective pressure and the fitness function are imposed by the human user in this case. We should note that the stratagem here involves the 'innovation' of something that exists: there is already a gene/enzyme in place and ALE enables its cognate DNA to explore a related sequence space in the pursuit of a new solution to the selection pressure. What can we do when the reaction, which is interesting to our concerns, is altogether unrelated to any other known biochemistry? In other words: how do we create authentic 'novelty' – not just innovation (Payne & Wagner, 2019;

Wagner, 2017)? Madonna's proposition involves cyclically exposing the abiotic reaction to the biological agent (which is programmed to evolve quickly) in such a way that it enables the development of a mutual interplay. This scenario might result in the modification of the biological component's genome to the point that the reaction is recorded in the DNA eventually and is later executed by the biological, live actor. This approach is expected to operate in a manner similar to the mechanism, through which many prebiotic reactions eventually become incorporated in, and run by, diverse living systems (Ralser et al., 2021). It goes without saying that the key question at stake here is that of 'creativity', an issue that directly connects the project with our artist-in-residence's interests.

Experimental synthetic biologists meet a professional artist

It is not an uncommon occurrence to amateurishly discuss the connections between science and art in conversations over coffee with researchers. As a matter of fact, many scientists have a soft spot for specific artistic expressions (typically music) or other manifestations of plastic virtuosity. One can entertain at least two points of convergence between the two domains, one of which is definitely 'creativity'. That said, let me speculate at this point that creativity is mostly technological in the research world, not scientific proper. Science is about understanding. Technology and engineering are about doing new things, i.e., bringing otherwise non-occurring items into existence. Technology both enables and empowers science, but it is not science (Wolpert, 1994). An engineer's mindset for building a bridge or that of a biologist using CRISPR as a gene editing tool (Ahmad et al., 2018) are, in my opinion, comparable to that of a composer of a new symphony or a flamenco choreographer. Alas, the Renaissance tradition of artists-engineers (epitomized by Leonardo) diverged over the centuries into two separated and mutually alienated cultures. There is, however, a second layer of common ground between art and research: 'curiosity', i.e., the drive to wonder about how and why things function as they do, unveiling their inner logic and proposing scenarios that are new-to-nature. No wonder, then, that literature and other creative expressions have inspired scientific endeavors and that scientific views of the world have influenced the arts throughout history. The predicted consequence of all of these considerations is that if one puts creative and curious individuals together, whether it be an artist or someone from a research background, then something interesting is bound to happen. In any case: having an artist visit an experimental laboratory was as unusual and exotic as it could get, from our perspectives.

To be frank, we had never entertained the possibility of interacting with a professional artist within our own research team directly! The Madonna work program included having an artist-in-residence, but we had no clue about what that would involve in practice. It was our partner, Biofaction, who made the connections and who arranged the contact as a sort of 'blind date'. We started by inviting Lara to our seminars. She then took the time to talk to the members of the laboratory, one at a time, who explained to her what we were doing, what instruments we had, the molecular tools we used, the bacteria that we cultured, our biotechnological interests, etc. Most importantly, we explained both the interpretive frames that we systematically adopt to address reality (or at least the small portion of it that we handle) and the uncompromising way in which we deal with results when generating new knowledge in our field. She immediately became excited by what the possibilities of applying synthetic biology tools to environmental microorganisms (Martínez-García & de Lorenzo, 2017) might deliver in two specific aspects; the first being whether we can communicate with such microorganisms and tell them what to do and the second being a mirror endeavor, which was if we can empower microorganisms to tell us what to do. These generic ideas were boiled down into two distinct, but somehow connected, artistic projects that were the subject of countless discussions around assessing their technical feasibility, their safety, and the message to be shared with the general public. We were thrilled to witness how bringing an artist like Lara to our laboratory inspired her creative agenda in directions that she had never probably explored previously. We should note, though, that inspiration was bidirectional: we also discovered perspectives that we had never contemplated regarding our intimate interplay with the microbial world by talking to her.

We are us and our microbiome

The first idea that comes to mind when discussing 'bacteria' is that of infectious diseases and, therefore, of enemies-to-defeat. This long-prevailing notion has been somewhat softened over the years with discoveries about the key role played by microorganisms in cycling elements and degrading toxic chemicals in the environment, thereby enabling the production of much-appreciated foods (cheese, beer, etc.) and these microorganisms even act as catalysts in some industrial processes (Ko et al., 2020). The big change in the way in which we deal with bacteria, though, was brought about by the more recent realization of our intimate interplay with our own microbiome (Blaser, 2014). We may not see it with the naked eye, but the large microbial community that inhabit our gut – and basically any other exposed surface of our body – has an influence not only on our health, but also on our very perception of reality, our mood, and the way in which we interact with each other. When we talk, kiss, touch, hug, share objects, etc., we interchange bacteria and end up having a shared microbiome that may come to pass into our intestine and might even form part of the so-called gut-brain axis and its constant traffic of neuroactive signals (Foster & Neufeld, 2013; Foster et al., 2017). How far such an influence goes is still a matter of much contemporary research. Sharing a microbiome is even entertained to enable the fostering of group cohesion, even influencing an entire population's mood. It is fascinating to realize how modern science, genomics in particular, has challenged traditional notions of philosophical and religious anthropologies of what it is to be human. Not only do we probably share nearly 99% of our DNA with chimpanzees (Swiss Institute for Bioinformatics, 2020) (and a good 40% with bananas! (Hoyt, 2021)), but we also sustain a constant circulation of bacteria among our body, with animals (Edmonds-Wilson et al., 2015; Stewart et al., 2018), with plants, and with the rest of the surroundings which form the material reality in which we find ourselves (Talbott et al., 2020). The environmental microbiome at large works as a sort of Ariadne's thread that connects every type of life form to every other type. We are part of a continuum that encompasses the entirety of the living world in which microorganisms fill the gaps between different actors. No wonder, then, that this raises questions about the notion of the 'self'. Our comprehension of ourselves cannot simply ignore the idea that we have a whole other self inside of us: the microbiome that inhabits our body. Spanish philosopher Ortega y Gasset stated his famous aphorism in 1914 that "... I am I and my circumstance ..." but we might rightly amend it in 2022 to '... I am I and my microbiome ...' No way these notions, which were amply discussed during Lara's stay, should go unnoticed among creative and artistic minds who are not devoid of political concerns, such as our visitors!

Given the growing awareness about the aforementioned gut-brain axis, a legitimate question is whether or not the deliberate spreading of mood-influencing bacteria through a large human population could ultimately have serious social consequences, even political ones, given that our perception of reality could be modified at a large scale. We are at this point far from that scenario technically, which is itself packed with considerable safety concerns, ethical issues, and clear risks of misuse. That said, we have the artistic freedom and ability to entertain and express not-yet-born futures with all their pluses and minuses in plastic forms as well as in provoking thoughts, reactions, and debates about such possibilities. Lara grabbed the opportunity to translate the issue into a thrilling artistic performance. The practical payoff of these discussions for our own scientific agenda was a realization of the current scarcity of technologies for microbiome engineering, in addition to big gaps in our understanding of how microbial communities both work and react to the introduction of a newcomer strain and/or the acquisition of new information through horizontal gene transfer (Brito, 2021). These are currently being entertained as topics for potential future research projects. I would never have thought about these matters had Lara not been with us – one more case of mutual art-research inspiration.

A new covenant with nature?

It looks like the widespread way in which Western culture has dealt with the biological world is, ultimately, based on the mandate of Genesis 1:28 "… Be fruitful and multiply and fill the earth and subdue it, and have dominion over the fish of the sea and over the birds of the heavens and over every living thing that moves on the Earth …" Although the biblical author was unaware of the microbial role played in how life on Earth is sustained, the message was clear that the human mission involves dominance and supremacy over all of the nature that surrounds us. Can this old mandate remain the same forever, though? Reality is that unchecked growth, mostly since the industrial revolution and the Haber-Bosch reaction (Ritter, 2008), has led to a rampaging climate crisis, unmanageable overpopulation, and massive environmental degradation, including growing pollution, and an enormous volume of non-recyclable waste. Some optimists translate such grave issues into merely technical problems that can be met through scientific progress in the hopes that perpetual growth can continue indefinitely. In fact, the dire future anticipated in the famous 1972 book *The limits to growth* has not been realized, owing *inter alia* to the onset of new technologies and scientific discoveries (Meadows et al., 2013). Can this buying of time go on endlessly? Nuclear fusion is presented as the ultimate source of inexhaustible energy (Ongena & Oost, 2004), super-productive transgenic crops are often proposed as the solution to the food crisis (Borlaug, 2000), biofuels the replacement of oil (Solomon, 2010), and biomanufacturing the way to make the production of chemicals more sustainable (Zhang et al., 2017). These are all welcome developments, certainly, but they still fall under the paradigm of unchecked domination of the natural world: changing just the minimum necessary ensures that nothing really changes. Can we ever think otherwise?

Synthetic biology seems to be the battleground for two (somewhat opposing) views of what to do with the wealth of information about the living world that we have amassed over the last 20 years. In one case, the idea of engineering biology aligns with the aforementioned drive to provide robust, effective replacements to our socioeconomic/industrial settings' most undesirable components – but without questioning the system itself (Goven & Pavone, 2015). This approach basically involves genetically programming biological entities to do exactly what we want and for our own exclusive sake (Qian et al., 2018). This looks to me like the ultimate implementation of the aforementioned mandate to "… have dominion … over every living thing that moves on the Earth …" Paradoxically, though, synthetic biology is also advanced as a discipline that enables us to enter into a new partnership with nature, owing to our growing capacity to both monitor and decipher – and eventually return – signals that come from the extant natural world (Ananthaswamy, 2014; Lohr, 2021). The question that follows is whether this could make us envision a change in our interplay with the environment – and all life forms that inhabit it, microorganisms included – one not fostered by domination, but in terms of conversation and, eventually, negotiation.

The biggest asset that biological systems have to resist the sheer number of attempts to make them submit is evolution: every successful and durable genetic construct made in the laboratory is, ultimately, a compromise with mutations and constant changes. To this day, evolution is one of the few natural phenomena that we are still unable to make submit altogether. In my opinion, the starting point of our dealings with the microbial world must, therefore, be evolution – something that many think that we understand, but about which we just have scratched the surface in my view (de Lorenzo, 2018). The outcome cannot be anything other than coexistence and compromise. This may look like an extravagant, unrealistic endeavor, but in reality, we are already in the midst of a new way of looking at the biological realm, as exemplified by the contemporary shift in our view of animals in the Western world. For centuries, animals were just edible stuff to either hunt or fish, dangerous foes to avoid/kill, or living objects to tame as a work force, and as non-human companions only to a minor extent. In contrast, our societies are experiencing a growing tendency towards vegetarianism and veganism, respect for animal rights, and sympathy towards feelings that had been thought of previously as being exclusively human. Even animals that were traditionally considered to be entirely non-sentient, such as cephalopods, have turned out to be sort of motile brains that are able to dream, feel, and react to stimuli in quite a human-like fashion (Ryuta et al., 2018; Crook, 2021). Microorganisms are not yet within our scope in that respect, although the role they play in the service of humanity has occasionally been recognized, albeit just symbolically (Metaphorest Aprayer Team, 2022). Microbes were on this planet long before us and they surely have much to tell us, provided we were able to understand their language of course. There is still much to develop in what could be called the microbial world's *attentive epistemology* as a complement of both the standard hypothetical-deductive scientific method and the contemporary emphasis on data-driven research. I believe that art has a big role to play in this endeavor, given that it can grasp features of our interplay with microorganisms that are not yet amenable to formal analyses and can anticipate a new covenant with the natural world, one replete with the forms of life that we cannot see.

Long before modern physics explained the nature of time, space, and matter, various generations of artists explored and reflected upon the same big questions through a diversity of plastic, musical, and literary expressions. It is often argued that impressionism attempted to both capture and echo the energy embodied in the material world by means of effects of light and rough brushstrokes of paint that reflected the inner dynamism of objects and live things in a manner influenced by the progress of the physics of the time. Perhaps a fresh horizon and challenge for the new generation of artists will include apprehending and communicating some of biology's key discoveries from recent decades. First, that all life forms – both visible and invisible – are intimately associated, the apparent gaps among them being effectively filled by environmental microorganisms that act as go-betweens among different manifestations of such a life. Second, that the complex phenomenon that we call 'evolution' rules the interplay between the living world's rationally conscious part (rationality is something that we exclusively claim to be) and the rest. There is still much to do on both the research front and in terms of the cutting-edge artistic creativity, which are bound to walk hand in hand. Who will be the Monet, Renoir, or Cézanne of our times? What discoveries will have inspired them?

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