REWRITING THE SYMPHONY OF LIFE WITH SYNTHETIC METABOLISM – CAN ENZYMES PLAY MUSIC?

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The 21st century poses challenges to humankind that require a major leap forward in designing technologies that can be extended towards – and that can take advantage of – the realm of living cells. We are experiencing a fundamental transition of biology, similar to the one that chemistry underwent some 100 years ago when it morphed from a rather descriptive science into the productive science of synthetic chemistry we know today (Yeh & Lim, 2007). Among other ambitions, synthetic biology (and synthetic metabolism in particular (Cros et al., 2022; Erb et al., 2017) seeks to transform cells into living factories by both rewriting and upgrading their metabolism (Nielsen, 2017; Nielsen & Keasling, 2016; de Lorenzo et al., 2018) using cutting-edge genome and gene modification tools (Zhao et al., 2021). Through these modifications, which comprise the core of the field termed "metabolic engineering", the modified cells can produce chemical building blocks for a greener, more sustainable future (Chen et al., 2020). However, even bacteria (which are among the simplest living organisms) are incredibly complex and unpredictable.

We tame environmental bacteria in the Systems Environmental Microbiology group in order to develop sustainable alternatives to conventional industrial processes. To this end, we modify bacterial cells to render them capable of performing tasks that they could not execute previously (Volke et al., 2020; Weimer et al., 2020). We often deal with processes that do not occur naturally (complex metabolic pathways leading to novel compounds, for instance) (Cros et al., 2022). One of the main questions that we want to address in our work concerns the extent to which we can update the periodic table of life. All known living organisms are formed essentially from carbon, hydrogen, oxygen, nitrogen, phosphorous, and sulfur. Our goal is to incorporate new 'notes' (chemical elements) into the music

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of life (Nieto-Domínguez & Nikel, 2020; Pardo et al., 2022). Including new chemical atoms opens up a new world of products that we can produce with our microbial cell factories. However, finding efficient ways to biologically produce compounds, not only novel ones but also those that carry xeno-elements, is a daunting task. It usually starts by taking a good look at the highly diverse sea of life and fishing for key chemical elements (and the pathways that incorporate them into metabolism) from different species – such as genes or proteins. With these elements at hand, we want to build a synthetic metabolism that plays a desired 'melody' (the production of our compounds of interest) without 'dissonances' (no by-products). We need to learn and to understand the 'natural' metabolism's notes, instruments, and sounds in order to expand the cell's inherent metabolic 'music' to something new-to-nature – and even towards a new SinFonia, which is not a misspelling, but is rather the name of one of our group's major, EU-funded projects (Calero et al., 2020).

SinFonia aims to rewrite the metabolic music of a living cell, ideally leading to the production of fluorochemicals (chemicals that contain the element fluorine). These compounds appear in several forms in modern industry; for instance, they are the building blocks for different types of materials and constitute the key components of an increasing number of both pharmaceuticals and agrochemicals. In fact, many widespread products such as the polymer Teflon™ (polytetrafluoroethylene), the antidepressants Celexa™ (citalopram) and Prozac™ (fluoxetine), or the herbicide Treflan™ (trifluralin) contain fluorine in their molecular structures (Mei et al., 2019; Harsanyi & Sandford, 2015). Thus, the production of fluorochemicals is a particularly challenging – and exciting – goal of modern metabolic engineering. Fluorine is not even an element that is commonly found in living cells (O'Hagan, 2008). Thus, we need to fine-tune this new element, fluorine, into the natural melody of the cell in order to create our new-to-nature products, but this usually leads to dissonance. Our mission is to adjust the cell's molecular instruments, the enzymes, and the overall melody in order to incorporate a new 'chemomusical note', fluorine, within the symphony of life. At present, after years of effort, our research group has managed to assemble a pathway by encoding enzymes that can effectively take a mineral fluorine salt and can convert it into an organic fluorinated compound. This is the starting point for developing the bio-based production of valuable fluorochemicals. This was the project's status when Eduardo Reck Miranda, a composer, first joined our group.

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The idea of mixing science and art was, of course, very appealing – although we were probably a bit skeptical about the outcome of a collaboration of this sort, looking at the project from a retrospective point of view. As scientists, we face challenges on a daily basis, and we often need to change our perspectives in order to solve them; however, we remain scientists no matter what (which, in practical terms, means that we resort to the same set of tools and strategies when addressing a problem, more or less). We hoped that someone from a completely unrelated field, and someone as creative as an artist, would reveal a different and hitherto unexplored perspective of our routine work. In addition, art impacts the public perception in ways that go beyond what the usual channels for science dissemination can reach. Therefore, we were somehow expecting that the collaboration might boost the awareness of our projects, goals, and results. However, the connection between science and art has also been shown to achieve something beyond our imagination.

Making these wishes a tangible reality appeared challenging in the beginning. As the artist-in-residence was a musician, we thought that music seemed to be a self-contained universe – with its own rules and language – but one that is not possessed of an immediate translation into the physical, concrete world in which science operates. Historically, art and science went hand in hand, and it was hard sometimes to tell the difference between them. Leonardo da Vinci's transformative work comes immediately to mind. Visual artists like him wanted to understand the mechanism that lay behind what they saw in their environments. Nevertheless, five centuries have passed since da Vinci's era and science and art have since evolved far beyond what renaissance society could even have imagined. In contrast to the connection between science and visual art, the translation of science into music was, to us, a goal that was more difficult to approach. Under these circumstances, how might we establish a fluid dialogue between these two realms? What kind of output could organically merge metabolic engineering and music? Those were some of the questions that we asked ourselves before the collaboration began.

Nevertheless, all of our concerns vanished when we met Eduardo Reck Miranda. He was not only a talented artist, but also an expert on productively bringing science and music together. He already had several ideas on how to approach the biological problem from an artistic perspective, and we had fascinating discussions about selecting and customizing the strategy most suitable to our enzymatic pathway's ability to bring fluorine to life. In our opinion, the residency's deep core involves translation. While genes are

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translated into proteins as part of the flow of information in virtually any living cell, the artist-in-residence skillfully translated our proteins into... music (Miranda, 2020). The goal of developing a more sustainable process for fluorochemicals was another layer of translation, and the global process can be seen as expressing science in terms of the language of music. In fact, converting the project's goal into music was one of the residency's most exciting challenges. This is probably because a goal is something that is relatively arbitrary so we could not rely on a more structured approach, much like the one applied to the translation of amino acid sequences. In our case, we decided to go from a 'metal-sounding' composition that slowly turns into something more 'melodic' in successive cycles. This evolution represents the transition from the current hazardous environmental processes, by which fluorochemicals are produced, to establishing more sustainable procedures. Of course, we were aware that 'metallic' or 'melodic' are very subjective concepts, but we understood that subjectivity was also a part of this crosstalk between biotechnology and music.

This idea was one of our contributions, as scientists to the residency, although in general terms our participation was focused on selecting among the proposals made that fit the best with our enzymatic pathway for fluorination with consultation from the artist-in-residence. We also provided all of the data required for the translation, including the amino acid sequences and the enzyme kinetics. Transforming an enzyme into music and sound implied an actual mental shift. We are used to looking at them in structures and models, but we never actually get to hear them.

Surprisingly, one of the collaboration's most interesting moments was an idea that did not end up becoming part of the project. During the discussions on converting an amino acid sequence into music, the artist suggested the possibility of walking the opposite path, turning a musical composition into an amino acid sequence, and expressing and studying this new protein. We ruled out the practical implementation of the idea, because producing a catalytically active protein or even a soluble from a piece of music is technically very challenging. However, the concept is fascinating. Proteins in nature are not a random chain of amino acids. On the contrary, they obey strict rules that we do not fully understand yet, but we do know that only certain sequences of amino acids can form viable proteins. Interestingly, the same overall concept applies to music: musical composition is not a succession of random sounds. There are rules, both explicit and implicit, and an underlying structure, which is particularly perceptible in classical music. Is it possible to create a dictionary that translates the rules of music into the

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rules of the protein world? An answer to this question would be a remarkable achievement from both a scientific and artistic perspective.

Another enlightening experience took place when we invited the artist to present his work during our weekly laboratory meetings, which are usually characterized by hardcore scientific discussions. This was the first time that the whole team was exposed to this sort of collaborative project. We were delighted to see the results that were achieved in the multiple interactions that Eduardo Reck Miranda had with other research groups and, of course, this presentation whetted our appetite to experience such a collaboration ourselves. The only regrettable fact of this fascinating endeavor was that it took place remotely, because of the COVID-19 pandemic. Therefore, we missed the experience of having the artist physically sharing the laboratory setup with us and connecting with those group members that were not directly involved in the residency's activities. However, we enjoyed what has been an enlightening experience for all of us, even with the remote 'residency'.

Our research also transforms natural organisms into cellular factories, changing and extending their format similarly to transforming DNA-encoded enzymes into music. Listening to the sound indicates harmony, but with elements of dissonance, much like if a bit of the chaos that is intrinsic of living organisms had invaded the musical universe. This is something particularly meaningful for us, because 'chaos' – when applied to life – is not the absence of order, but an order that we do not yet fully understand. Based on the laws of chemistry and physics, the building blocks of life (nucleic acids, proteins, carbohydrates, lipids, and cofactors) interact, thereby developing a network of such complexity that our current capacity to predict outcomes is limited at best. This unpredictability, which looks like an apparent chaos, was also somehow translated by the artist, and made its way into the final music piece. The result led us to reflect upon how we might tune the music of life without dissonance and disruption. However, it is not only a matter of lack of knowledge: one may also ask if chaos is not an intrinsic (and even necessary) part of life. After all, the laws of biology are not deterministic, but probabilistic; living organisms are also not static, since life is about change and evolution.

The residency was also interesting as a way to broaden our own knowledge horizons. We learned that communication between art and science is possible and smoother than expected. Another take-home message was the need for synergies in the achievement of our goal. Prior to the residency, we used to view art as a tool to communicate science's message. This experience has changed our perspective: now we appreciate the collaboration between

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music and science from a different perspective, and we recognize this interaction as a powerful approach to develop novel auditory art. As scientists, this led to a change of standpoint – zooming out in order to get a different angle from our work, and then zooming back in to solve a challenge. Conversely, the experience also highlighted the differences between the two worlds: the scientific work needs to be continuously validated by natural reality, whereas art – in this case, music – can fly more freely. In fact, this difference, which defined the work dynamics, was explained previously with the artist making the proposals and the scientists narrowing the possibilities in order to fit the experimental data.

The residency's final output was very interesting, even though the development process was probably the best part of the collaboration. Hosting an artist-in-residency in a laboratory environment would be welcomed by us anytime, as it opens up a laboratory's creativity and diversity of perspectives. Changing one's perspective might allow new endeavors and projects. At the research level, it is unlikely that the composer's methods will be applied to our daily work. What we mean is that converting proteins into music will not be useful for our research, but the concept that biological information can be meaningfully translated into other forms of information is an inspiring idea that we will not soon forget. Therefore, we would like to highlight the view that art is not useful only for science communication, but also in the exploration of possible crossovers and in extending the scope of both research and art. Having an open position for an artist-in-residency who explores music as an art form, compared to (future) product or industry design, indicates the closer relationship between art and biological research, particularly given that we are both trying to create a physical product. Overall, we would definitely recommend having an artist or designer in residency in laboratory environments. It enriches all viewpoints. The key is to have open-minded scientists that do not view the resident's presence as additional work, but rather as an outstanding opportunity. Artists and scientists look at the same coin, called nature, from different sides and work together to complete the picture. For us personally, it has been a unique and very gratifying experience.

By way of closing, it is worth remembering one of the most iconic quotes by the German philosopher Friedrich Nietzsche – who has been already cited by Eduardo Reck Miranda – "without music, life would be a mistake". As researchers, we would not go so far as to claim that this is the case, but after this residency we can claim that music is closer to life sciences than we were inclined to think at the beginning.

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