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Could we really be made of Swiss cheese? Xenobiology as an engineering epistemology for biological realization

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Abstract: Besides providing potential medical and biosafety applications, as well as challenging the foundations of biological engineering, xenobiology can also shed light on the epistemological and metaphysical questions that puzzle philosophers of science. The paper reviews this philosophical aspect of xenobiology, focusing on the possible multiple realizability of life. According to this hypothesis, what ultimately matter in understanding life are its functions, not its particular building blocks. This is because there should be in theory many different ways to build the same function. The possibility of multiple realizability was originally raised in the context of AI's hypothesized capacity to realize mental functions. Because we still do not have any incontrovertible examples of digital minds, not to mention alien life of foreign biochemistry, the best way to test this philosophical idea is to examine the recent results and practices of synthetic biology and xenobiology.

”We could be made of Swiss cheese and it wouldn't matter.”

- Hilary Putnam (1975, 291)

Two different and seemingly contradictory characterizations of synthetic biology abound scientific review papers of the recent years.[1] According to the first, and arguably currently the more popular one, the goal of synthetic biology is to design and engineer novel biological systems that exhibit functions not typically found in nature.[2] Examples include engineered yeast and bacteria whose natural DNA sequences are reprogrammed so as to render the resulting cellular machinery for human purposes. This can include industrial goals like the ability to produce biofuels and vaccine components, but also “useless machines” of specific theoretical interest.[3–5] In other words, nature is made to do something that it does not normally do, but, with the help of the right set of tools mixed with a healthy dose of engineering ingenuity, it potentially could do. This approach to understanding synthetic biology has been especially prominent amongst biocircuits researchers who typically model their

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design work on traditional engineering fields like electrical engineering.[2,6]

According to the second type of characterization, the goal of synthetic biology is to design systems with natural biological functions, but to realize them in a different, alternative, or “unnatural”, way.[1,7] This approach is usually championed by people coming from chemistry and it is connected to the work on the foundations and frontiers of biology: the origin of life, astrobiology, and especially xenobiology.[8,9]

These two characterizations of synthetic biology rely on a common view that engineered artefacts have functions. Through their design they have the ability to do things which makes them intellectually interesting. What allows the comparison to naturally evolved systems is the fact that these can also be thought of as having a functional design of sorts, even if there is no conscious designer responsible for it.[10,11] While the first case of the forward-engineering of biocircuit behavior is typical to all industrial practices, the second function-equivalent approach to engineering design has also a rich history in fields like computer science.[12] For reasons that I am going to explicate in this essay, it is also of specific interest to those working on the philosophy of science.

The broadly ethical and philosophical challenges of xenobiology have been recently acknowledged.[13] However, its constructive possibilities for specific philosophical theories are yet to be properly developed. In the scientific community, it has been argued that the xenobiological goal of trying to redesign naturally occurring functions in a new, unnatural, way is a powerful tool to test our understanding of life.[8,14] This seems to rest on an implicit assumption that it is indeed possible to separate the concept of life in general, and biological function more specifically, from its material, biochemical basis. In the philosophy of science, this position is known as functionalism.[15] According to this view, what ultimately matters in the above physics/chemistry level sciences is not what material the system of interest consists of, but rather, what it does, how it functions, what kind of capacities it has in its environmental or social context, and so on.[15]

This idea has popular manifestation in many modern day sci-fi classics and also deep roots in the history of Western philosophy, going back to Descartes’ separation of the mind and the body as well as Aristotle’s notion of the four causes (material, formal, efficient, and final). Few philosophers or scientist hold on to Cartesian substance dualism anymore, and Darwin's theory of evolution by natural selection put Aristotelian teleology finally to rest.

Recent philosophy has taken a more naturalistic stance toward functions. After WWII it was common to see the emerging molecular sciences as even replacing the function-talk of higher-level sciences like psychology and functional biology. One manifestation of this reductionist tendency was to suggest identity relations between various ordinary phenomena and their underlying molecular basis.[16] Like water was empirically found out to correspond to H_2O, philosophers of science similarly argued that neuroscientific results can be used to show that psychological functions are identical to certain neurobiological mechanisms or processes. Correspondingly, the concepts of Mendelian genetics were argued to be reducible to molecular biology.[15,17]

Against this trend rose a counter-argument in the form of multiple realizability. In the late 1960's, the eminent philosopher and logician Hilary Putnam argued that mental capacities can be realized in various ways in things like mammalian brains, mollusk nervous systems and even electric circuits in digital computers.[18] Thus, they cannot be reduced to any one material medium. To exhibit a psychological function (say, pain aversion), it is enough for the system to run a certain logical program, with characteristic input-output relations. The analogy between brain "hardware" and mental "software" is easily generalized from psychology to other functionally oriented fields like biology. A simple biological example comes from genetics. In pleiotropy, one gene can influence two or more traits that are not obviously related. However, the converse can also happen: two or more genes can bring about the same phenotype. As a first approximation, multiple realizability can be likened to the latter, many-to-one relationship between the lower-level molecular basis and the higher-level function. Standard codon redundancy is another example.[11]

Philosophers have debated how to best understand multiple realizability. Is it some kind of conceptual truism or a bold empirical hypothesis? For example, it seems clear that Putnam was not totally serious with his quip about Swiss cheese quoted at the beginning of the paper; surely it would matter a lot, if we were made of homogeneous dairy product. (The claim is ambiguous on whether we can reassemble or modify the fats and proteins of the piece of cheese we are given.) The thing is how to make the hypothesis interesting. How to find the balance between cases of trivial natural variation and outright impossible claims of poorly-informed sci-fi?

Recently, philosophers of science have conducted case-studies on various biological phenomena to estimate how common it is to encounter multiply realized solution in nature.[15,19,20] What makes this data difficult to evaluate is the prevalence of functional homologies.[20] Because of common descent, many biological functions in nature are realized as they are not because of structural necessity, but because of contingent historical reasons.[11] Because our sample size of life is limited to one, the prospect of coming with independent evidence for multiple realization is seriously hampered.

This situation tends to strengthen reductionist intuitions. It is clear that the positing of identities is a useful heuristic device that can often simplify our ontological bookkeeping.[15] However, like all methodological heuristics, it is fallible and comes with potential downsides.[11] In contemporary accounts, it has become commonplace to identify genes with strings of DNA. That is, the higher-level concept of a gene or a genome and the designator of a macromolecule are used interchangeably. It is easy to see how this kind of practically-motivated use of language serves its purpose. However, the danger is that it eventually becomes so entrenched in our thinking about the living world that we do not even notice it anymore. The material basis of genetic functions, DNA, becomes to define the very phenomenon it was originally proposed to explain. Because of this, it becomes difficult to even entertain the idea that genes might be based on something else – after all, they are *defined* as bits of DNA! What else could they be?

However, as we have already seen, basing one's biological outlook on the reductionist heuristic of interfield identities is not the only available option. Xenobiologists and biological engineers often start from the opposing idea, namely, that biological functions can be realized in multiple different ways.[21] It is important to see that this is not the same thing as entertaining any kind of ontological commitment that this is always the case or that it follows from some kind of privileged first principles. Rather, it is best understood as a fruitful, yet fallible research heuristic, an intellectual stance to inquiry.[10,21]

Interestingly, the multiple realizability hypothesis of genetic functions has for some time been implicitly recognized in the scientific community as a potential source of application in biosafety engineering.[21,22] One particularly popular idea is to utilize different material mediums for genes to achieve orthogonal variants of a given engineered module. For example, non-DNA-based genomes could act as genetic firewalls in synthetic organisms, preventing them from exchanging genetic information with naturally occurring species, while at the same time ensuring their other biological functionalities.[22] This orthogonality would ensure that they remain recognizably biological and able to act at an ecological level while being semantically encapsulated.[22,23] The potential many-to-one relationship between different types of biopolymers and informational genes is thus not only a theoretical hypothesis, but also a practically-motivated engineering goal.[21]

Not any difference in realizers is enough to warrant claims of multiple realizability, however. After all, because of the prevalence of noise and natural variation in the living world, no two biological systems are exactly alike. To engineer convincing cases of alternative chemical bases of life, they should differ from natural systems in a principled way, utilizing mechanism that differ in *kind* from those found in nature.[15] For example, a change in the chiralities of common biomolecules – so-called mirror-life[24] – although interesting in its own right, might not constitute an in-principle different approach to realizing the functions of a living cell. However, using synthetic design methods, xenobiologists can push the evidence for multiple realizability, testing its limits under unfamiliar circumstances. These include not only foreign genetic base pairs, but also expanded genetic alphabets (including a recent example of a system with eight letters[25]), alternative and expanded genetic codes[26], XNA molecules with foreign backbone materials[22,27] and non-canonical amino acids (ncAAs).[26]

Alternative genetic systems provide a good test case of multiple realizability for a number of reasons. First, the functional goal of the engineering of DNA alternatives is very clear: to come up with chemical systems that have the capacity to carry and transmit genetic information. This can be further specified with more operationalized conditions. For example, in order to support Darwinian evolution, the copying mechanism should be robust, but not completely certain, so that there is room for biologically relevant mutation levels.[8]

The second interesting feature of an alternative genetic system is that the relationship between the material basis of the system and the mechanism through which it achieves its biological function cannot be neatly separated. Since we are talking about macromolecules, this of course should not come as surprising. But this means they are not mere aggregates of “passive material” where one can swap building blocks around at will.[11] As experimenters know by heart by now, coming up with a right kind of system with the right kind of building blocks that add up to a functional whole is anything but trivial. For example, in the case of artificially expanded genetic alphabets, it is highly constrained which molecules can pair with each other, not to mention mutate back and forth with A, T, C and G, as in the case of P and Z.[8]

Recently, the Romesberg lab, basing their research on a proof-of-concept work by the Kool lab, have managed to construct an expanded information storage system with an expanded alphabet that can access ncAAs. The interesting thing is that the mechanism through which the new base pairs dNaM-d5SICS and dNaM-dTPT3 are directing ncAA incorporation is not based on standard hydrogen bonding, making it “highly orthogonal” to the natural genetic alphabet.[26] They emphasize the conceptually groundbreaking features of their work, suggest that the resulting semi-synthetic organism indicates that “the ‘parts’ used by nature may not be as unique and privileged as previously assumed”.[26] The Benner lab, on the other hand, while working in the context of systems utilizing hydrogen bonds, have provided evidence that it is possible to bypass the size-complementarity mechanism of base pairing suggested by the Watson–Crick model of DNA. Some of the variants they have constructed seem to exhibit new kind of “skinny” (small base-small base) and “fat” (large base-large base) pairing potential.[28]

Because of the context-sensitivity of most biological systems, one can of course wonder whether identification of functions makes sense across different cases. Without the surrounding cellular machinery, one could hardly ascribe any function to a synthetic device, sequence, or a single molecule. It is important to note that considerations of function and multiple realization are not absolute, but are always made from a particular perspective.[11] For example, two realizers might be function-equivalent from one perspective, but not from another one – think of multifunctional enzymes whose roles are partially overlapping. The problem with natural biological systems is that identifying any function to begin with might sometimes prove difficult. This is not only due to the complexity of their interactions, but also for the fact that functional roles tend to change during evolution. For example, a trait might have been originally selected for to perform a function F, but is currently favored because of its role in realizing another function G. Fortunately, in the case of xenobiology (and engineering more generally), some pragmatic criteria for the sameness of function can be obtained by observing whether different realizers were designed with the same purpose in mind.[21] Presumably, in order to count as functional XNA, a synthetic genetic system would need to be able to realize at least some important subset of the functional properties of natural DNA. To what extent this functional alignment can be achieved remains an empirical question.

Although philosophy at its best can produce informative reflection and inspiration for the scientists, it cannot ultimately dictate what kinds of results and finding are scientifically the most interesting or important. This, rather, is settled by scientists themselves and involves restructuring and reorientation of models and theory and ever further rounds of empirical work. What forms of biochemistry provide genuinely new ways of constructing biological functions cannot be reliably predicted from the armchair. Xenobiology is still taking its first steps and most of its results are not yet definitive. But a lot of interesting proof-of-concept results have already been obtained. While the potential multiple realizability of biological functions in xenobiology should not be taken to imply that life as a phenomenon is somehow non-reductive or autonomous from chemistry, it nevertheless encourages the idea that biological theory can guide chemical engineering. Both functional and material stances can unite in the pursuit of new explorative theory.

This connects the importance of engineering to what philosophers often call modal knowledge. How can we gain knowledge about those aspects of reality that go beyond the actual? What kind of biological systems are *really* possible, and not just sci-fi? Ultimately, what alternatives are genuinely possible is down to the limitation of the natural world and its physical and chemical principles. At the moment, we are still far from fully understanding these limitation on the range of the possible.[14] The best proof of a possibility is to make it actual.[29] Combing these results with more general theories about the world, synthetic knowledge can be generalized beyond single instances of tinkering, making it an indispensable tool for generating new perspectives[30,31], and even helping to tackle questions in the philosophy of biology.[32,33]

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