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UNREALISTIC MODELS

Synthetic fictions: turning imagined biological systems into concrete ones

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Abstract
The recent discussion of fictional models has focused on imagination, implicitly considering fictions as something nonconcrete. We present two cases from synthetic biology that can be viewed as concrete fictions. Both minimal cells and alternative genetic systems are modal in nature: they, as well as their abstract cousins, can be used to study unactualized possibilia. We approach these synthetic constructs through Vaihinger's notion of a semi-fiction and Goodman's notion of semifactuality. Our study highlights the relative existence of such concrete fictions. Before their realizations neither minimal cells nor alternative genetic systems were any well-defined objects, and the subsequent experimental work has given more content to these originally schematic imaginings. But it is as yet unclear whether individual members of these heterogeneous groups of somewhat functional synthetic constructs will eventually turn out to be fully realizable, remain only partially realizable, or prove outright impossible.

Keywords Fiction · Models · Synthetic biology · Modality · Semifactuality · Unrealisticness

1 Introduction

Scientific models are unrealistic in various ways. The epistemic status of these simplified and highly idealized, and thus strictly speaking false depictions of reality, has become a central philosophical question. To make sense of the seeming falsity of models, several philosophers have entertained the idea of likening models to literary fictions. They have typically highlighted the fictional nature of such idealized mathematical models as the harmonic oscillator, the Lotka–Volterra predator and prey system, Carnot's ideal steam machine, economic theories of the firm, and artificial neural network models, to name just a few examples of a potential list that could go on

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and on. What is puzzling about these models is that the systems that they appear to be describing cannot strictly speaking exist. For instance, the harmonic oscillator model assumes, among other things, that the string is massless, the bob is a point mass, and there is no friction. The Lotka–Volterra model, in turn, assumes that the populations increase or decrease continuously (although actual populations consist of discrete individuals), the environmental conditions do not change, the prey population finds enough food at all times, and so on. Thus, these models posit systems with properties that any known real systems do not, or even cannot, have. How should such model systems be understood? Invoking fiction provides one solution to this problem: these model systems could be imaginary systems, or "imagined-objects" (Godfrey-Smith 2006; Frigg 2010; Frigg and Nguyen 2016; Salis 2019).[1]

The fictionalist solution to how these models can represent worldly target systems thus casts them as nonconcrete, imagined systems (Godfrey-Smith 2006; Frigg 2010; Frigg and Nguyen 2016). The idea is that, if mathematical models are not to be identified with their targets or their contingent material instantiations (e.g. particular equations on a blackboard), they might be thought of as some kind of imaginary constructs that resemble works of literary fiction. However, such a focus on the ontological status of models tends to overshadow another important locus of fictionality and unrealisticness, namely the cases in which the *target* of the model is a non-existent system. In this article, we wish to rehabilitate this latter notion of fiction because of its important function in science. There is a prominent class of scientific models, whose main purpose is not to provide scientific explanations of actual phenomena, but rather to explore unactualized possibilia. Interestingly, models studying such possibilia may also be concrete things, and hence they could be considered, we argue, as concrete fictions.

We will study concrete fictions through two examples from synthetic biology: minimal cells and alternative genetic systems. Apart from modeling such systems in conceptual and theoretical terms, the scientists studying them also seek to materially realize them. We call these biological constructs synthetic fictions and analyze their various fictional and modal aspects. The research practice of synthetic biology shows that it can be more fruitful to approach fiction in terms of modality (i.e. possibility) than verisimilitude (i.e. outright falsity). This is because the difference between the fictional and the actual is often not fixed, but dependent also on available technologies. We argue that many synthetic fictions are *semi-fictions* and may later on find partial or alternative realizations through *semifactual* strategies. That these biological realizations remain often only partial, or incomplete with respect to the functions sought for, indicates that although they are concrete, their existence is only relative. Another aspect of their relative existence is due to their dependence on the technological apparatus and laboratory conditions needed for their construction and continued functioning. In other words, although concrete, the synthetic constructs we study still

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[1] Another way of approaching such systems in terms of fiction would be to address them as fictional descriptions of real systems (Toon 2012; Levy 2015). We do not discuss this alternative as it leads to cumbersome analysis of modeling as it does not really recognize such objects as models. We focus on those accounts that take as their starting point the idea that models are surrogate systems (Swoyer 1991) or indirect representations (Weisberg 2007; Godfrey-Smith 2006). For a critical view on various fictionalist epistemologies of modeling, see Magnani (2012).

embody a fictional dimension. Indeed, we claim that one of the advantages of viewing synthetic constructs as concrete fictions is the recognition of the laborious processes through which scientists seek to realize some fictional, though theoretically and empirically grounded ideas. Through these processes, scientists are probing whether those imagined systems are biologically possible, giving also more theoretical flesh to the original imaginary speculations. Consequently, establishing a biological or any other possibility is not just a question of imagination—what is fictional may, or may not, prove to be realizable.

We proceed as follows: before addressing two at least partially realizable biological fictions, minimal cells and alternative genetic systems (Sect. 3), we will discuss fiction in philosophy of science (Sect. 2). In Sect. 4, we analyze the fictional character of these synthetic constructs and argue for why we think that the fictional perspective should be widened to cover also concrete fictions, and what implications this move has for the discussion of fictional modeling. Section 5 concludes the article.

2 Fictions within philosophy of science

2.1 Vaihingerian fictions

Writing about Vaihinger's classic *The Philosophy of 'As if'* (1924), Fine (1993) anticipated the revival of the notion of fiction within the context of modeling, observing that "the industry devoted to modeling natural phenomena, in every area of science, involves fictions in Vaihinger's sense" (p. 6).[2] Vaihinger understood fiction through its deviation from reality. These deviations are due to "thought-processes" and "thought-constructs" that contradict reality, or even themselves, but are nevertheless "intentionally thus formed in order to overcome difficulties of thought by this artificial deviation" (Vaihinger 1924, p. xlvii). Vaihinger continues: "These artificial thought-constructs are called Scientific Fictions and distinguished as conscious creations by their "As if" character" (ibid.). In highlighting the artificial character of fiction, Vaihinger invokes to the etymology of fiction in the Latin fictio, and *fingere,* that is the activity of constructing, forming, conceiving, inventing and so on, referring also to the products of such creative activities.

Indeed, fictions are omnipresent in Vaihinger's view. Art, science and the social world are permeated by fictions. Vaihinger discusses as fictions artificial classification, abstractive fictions, and schematic, paradigmatic, symbolic, legal, personificatory, summational, heuristic and mathematical fictions. He considers also various kinds of concepts or theoretical constructs as fictions such as the atom, infinity, the Absolute, and Kantian things in themselves. Many methods are fictional as well: e.g. the method of abstract generalization, the method of unjustified transference, and mathematics as a method of thought.

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[2] At the time of its writing, neither Fine's article on Vaihinger nor Vaihinger's work awakened too much interest among philosophers of science. Fine (1993) is reprinted in Suárez's collection on fiction (2009), in which several authors discuss or refer to Vaihinger. Mäki (1980) discusses Vaihinger, but rather in relation to positivist philosophy of science.

Given the inclusive way Vaihinger talks about fiction, it is difficult to think of any dimension of human language and thought that would not, ineluctably, involve fiction. Yet, Vaihinger warns of taking fictions for real things, of "personificating" or "hypostatizing" them. Fictions are best used, knowingly and reflectively, as provisional scaffolding for thinking, providing useful thought-constructs that eventually should be abandoned in the quest for "real knowledge".[3] Consequently, a fiction cannot be verified, it can only be justified, for, at best, it presents an expedient, though "circuitous approach" (1924, p. 88) on the way to knowledge.

Despite the abundance of fictions that Vaihinger enumerates and analyzes, his general characterization of fiction, i.e. his "logic of fictions", is straightforward. There are two kinds of fictions: real fictions and semi-fictions. Both kinds of fictions are in contradiction with reality, and generally understood to be so. Additionally, real fictions are in contradiction with themselves. While semi-fictions are "historically provisional", real fictions are "logically provisional" (p. 80). Vaihinger further explains the distinction in the following way: "semi-fictions are in conflict with the objective state of affairs, while with real fictions we get essentially formal mistakes in thought, logical mistakes" (p. 81). Semi-fictions may be discarded as the investigation proceeds, but they may also develop into real fictions. We are interested in the opposite movement, that of turning semi-fictions into concrete things that shows, we argue, the scientific, semifactually anchored, character of some semi-fictions. While they amount to "a deviation from reality", as Vaihinger puts it, they do not need to be false, but point instead toward unactualized possibilities. But before turning to study this insight, we take a look at the recent discussion of models and fictions where the notion of fiction has gravitated from the consideration of non-existent targets towards scientists' imaginings without too much explicit notice.

2.2 Fictions as imagined-objects

In contrast to viewing fictions in terms of their falseness, the contemporary discussion has focused on their imaginary nature. Godfrey-Smith's (2006) seminal article on model-based theoretical strategy has provided a starting point for several articles addressing fiction (e.g. Frigg 2010; Knuuttila 2017; Salis 2019). In discussing models as indirect representations, Godfrey-Smith (2006) comes up with two perspectives on fiction that do not necessarily align. On the one hand, and in accordance with Vaihinger, he approaches models as tightly constrained systems through the study of which modelers seek to understand complex real-world systems. Godfrey-Smith notes that this strategy of model-based science has characteristic strengths and weaknesses, and possibly a "historical signature". Importantly, it has one epistemic advantage in particular: the modal reach of modeling. Godfrey-Smith studies the work of Maynard Smith and Szathmáry (1995) on major transitions in evolution that proceeds stage by stage through presenting "idealized causal mechanisms", i.e. models. If these "how possibly" models, Godfrey-Smith points out, "work at all, [they] would work just as

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[3] Vaihingerian fictionalism has been given both anti-realist (e.g. Fine 1993) and realist readings (e.g. Mäki 1980).

well in a range of nearby possible worlds that happen to be inhabited by different organisms." (p. 732).

On the other hand, Godfrey-Smith views model systems as particular kinds of nonconcrete things, as "'imagined concrete things'—things that are imaginary or hypothetical but would be concrete if they were real" (2006, pp. 734–735). In other words, "they do not exist, but at least many of them might have existed and if they had, they would have been concrete, physical things, located in space and time [...]" (2009, p. 101). In the aforementioned quote Godfrey-Smith comes close to the prospect of realizing unactualized possibilities but falls back on the position that model systems are non-existent nonconcrete things.[4]

The current discussion has picked the latter notion of fiction that has provided a seemingly convenient way of handling the ontological question of what kind of objects nonconcrete model systems are—i.e. imagined-objects—and how they might represent. While in the case of concrete physical models, the material 3-D object is recognized as the model, in the case of nonconcrete models like mathematical models, the model is the imagined-object generated by a model description, e.g. a set of equations (Frigg and Nguyen 2016, pp. 225–242, see also Salis 2019).

Kendall Walton's pretence theory of fiction has been especially influential (e.g. Barberousse and Ludwig 2009; Frigg 2010; Frigg and Nguyen 2016; Salis 2019; Toon 2012; Levy 2015). A partial explanation for Walton's popularity among philosophers of science is due to his antirealist answer to the puzzling ontological nature of fictions: there are no such things as model systems. The basic idea of Walton's pretence theory is that humans can imagine various kinds of things by making use of a diversity of objects as props. Accordingly, scientists can be seen to use models as props to envisage imaginary or ideal systems. Nearly anything can function as a prop, but it becomes such only as a result of rules for its use, i.e. "principles of generation" that are part of a "game of make-believe". Thus what is fictional becomes synonymous with what is "true in the appropriate game of make-believe" (Walton 1990, p. 34).

Frigg (2010) uses Walton's theory to formulate an account of fiction and scientific representation. According to this account, model descriptions serve as props that "p-represent" an imagined system that then "t-represent[s]" a target system (Frigg 2010). Three things are crucial in this construal of representation. First, representation is indirect in that whatever we often empirically treat as models (e.g. equations, diagrams or scale models) are considered model descriptions that create in the minds of scientists an imagined entity that represents the target system. Second, this imagined entity typically has also features that are not contained in the model description (and, presumably, the other way around). Third, the fictional model system has no existence of its own, it is just something imagined in a scientific game of make-believe. Obvi-

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[4] In Godfrey-Smith's thinking the two perspectives are two sides of the same coin since he combines the notion of indirect representation by Weisberg (2007) with Giere's analysis of model-based representation (Giere 1988). Consequently, a model description specifies a model system, understood as an imagined system that then provides a candidate for representation in terms of resemblance (Godfrey-Smith 2009).

ously, the question then becomes that of explaining how such imagined entities are supposed to (t-)represent actual targets.[5]

In a later series of articles, Frigg and Nguyen (e.g. 2016, 2018) have developed the account presented in Frigg (2010) into a fully-fledged account of scientific representation. Their DEKI account of scientific representation is a rather complicated amalgamation of resources drawn from Walton as well as from Goodman (1976) and Elgin (e.g. 2004), covering both material (i.e. "concrete") models and non-physical (i.e. "nonconcrete") models. Exemplification and denotation are two of the key constituents of the DEKI account; a (representational) vehicle both *Denotes* a target system, and *Exemplifies* some properties. These properties, or related ones, are *Imputed* to a target through a *Key* that translates the exemplified properties to properties that can be ascribed to a target.

In the case of 3-D models, such as the Phillips-Newlyn hydraulic model of macroeconomy, there is a concrete object that exemplifies, under interpretation, the features to be imputed (Frigg and Nguyen 2018). However, the case of nonconcrete models, such as mathematical models, is trickier, since there is no concrete model object providing the "base" for representation. Instead, it is the imagined-object that becomes the locus of representation (as in Frigg 2010). Frigg and Nguyen are explicit on this: "By mandating those involved in a certain game to imagine certain things, the model description generates *the imagined-object that serves as the vehicle X of a representation as*." (2016, p. 13, emphasis added).[6] In other words, models are objects that represent by exemplifying, and the notion of fiction is employed to explain how mathematical models and other nonconcrete models can achieve this. (DEKI does not address fictional targets in particular, since it aims to be a general account of representation, whose targets can be actual or fictional systems).

In contrast, fiction does not play any prominent part in Frigg and Nguyen's treatment of concrete models. Imagination only enters in the symbolic rendering of the material object into a Z-representation, for example, turning the physical hydraulic machine into an economy-representation. Frigg and Nguyen explain: "In the concrete case X [i.e. the representational vehicle] is a physical object and claims about X are true or false; the imagination only comes into play when explaining how X becomes a Z-representation." (Frigg and Nguyen 2016, p. 238). While this seems reasonable with regard to the Phillips-Newlyn machine, the cases of minimal cells and alternative genetic systems pose specific challenges. Are we supposed to imagine how particular realizations of minimal cells or alternative genetic systems become minimal cell-representations or alternative genetic system-representations, for the purpose of imputing their properties to minimal cells and alternative genetic systems? That the DEKI account becomes unduly convoluted in the case of synthetic fictions is due to the fact that it is first and foremost an account of representation, yet the fictionality

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[5] For a critique, see Knuuttila (2017) and Salis (2019). Both Knuuttila and Salis point out, though approaching scientific modeling from different directions, that for a model to represent the model descriptions should be considered as parts of models.

[6] To be more specific, Frigg and Nguyen consider the nonconcrete model to be composed of both the vehicle X and interpretation, although in many cases the interpretation boils down to a simple identity, see e.g. Frigg and Nguyen (2016, p. 238).

of synthetic systems is not primarily related to the problem of how to turn them, by imagining, into representations of yet another kind of (material) things or systems.

It does seem, then, that for all its sophisticated machinery, the DEKI account does not readily account for the evolving, self-referential, and simultaneously concrete and fictional nature of synthetic systems. What is distinctive about minimal cells and alternative genetic systems is that they are initially very schematically imagined systems referring to unactualized possibilia *before* (at least partially) successful attempts to realize them. Once realized, they furnish their own targets, to be worked on in successive rounds of experimentation and modeling, remaining still partially fictional for reasons that will become clearer in our discussion of these synthetic constructs below.

3 Synthetic fictions[7]

3.1 Minimal cells

The project of constructing artificial and minimal cells dates back at least to the 1950s. The notion of an artificial cell does not refer to any specific physical entity, or “an attempt to reproduce biological cells,” as one of its pioneers has put it (Chang 2007). “It is an idea involving the preparation of artificial structures of cellular dimensions” performing some tasks of cells, where “different approaches can be used to demonstrate this idea” (Chang 1972). While most artificial cells can only mimic certain behaviors of cells, the idea of a minimal cell is more ambitious: “a minimal cell is a hypothetical biological system that possess only the necessary and sufficient attributes to be considered alive” (Gil 2011, pp. 1065–1066). Alternatively, minimal cells have been characterized as “the simplest collection of interacting molecules that can show signs of cellular life, under specific environmental conditions” (Ehmoser-Sinner and Tan 2018, p. 12). Such a cell would need to have, first, a metabolism for maintaining life, second, a genetic program, and, third, a boundary that separates the cell from its environment (e.g. Acevedo-Rocha et al. 2013, p. 276; Xavier, Patil and Rocha 2014, p. 487). These three requirements are usually considered a part of a minimal definition of life, although there exists a considerable latitude as to what is included in such definitions (see Knuuttila and Loettgers 2017a). What these considerations already hint at, however, is that the minimal cell is not going to be very minimal.

There are two principal methods of creating minimal cells, the *bottom-up* and the *top-down* method. The bottom-up method is the more demanding of the two. It aims to approximate a minimal cell by assembling one such candidate from biomolecules such as proteins, lipids, carbohydrates, nucleic acids etc. Protocells are examples of this line of research. They are compartmentalized self-organized aggregations of abiotic components that have been used as models to study the emergence of life characteristics such as self-organization and replication, and, more generally, the transition towards living cells. One of the foci of this line of research has been on encapsulating genetic and metabolic material within vesicle membranes. A milestone in this line of research

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[7] Knuuttila and Loettgers (2017b) refer to synthetic biology constructs as synthetic fictions in their study of synthetic genetic circuits.

was the protocell in which the researchers succeeded to implement RNA replication within a fatty acid vesicle (Adamala and Szostak 2013, pp. 1098–1100). The basic motivation of the bottom-up approach is to construct minimal cells from nonliving material, and so being able to answer, at least partially, the puzzle concerning the origin of life. But this goal has still remained beyond the reach of scientific research.

A more restrained goal than creating a minimal cell would be that of estimating a minimal genome that would contain the smallest number of genetic elements sufficient to build and support a free-living cellular organism in an ideal environment (see Mushegian 1999, p. 709; Acevedo-Rocha et al. 2013, p. 273). The first functional minimal cell, JCVI-syn3.0, created in the J. Craig Venter Institute (Hutchison et al. 2016), was a result of a *top-down approach* that begins with an existing cell and tries to reduce its genome to the minimum number of genes required to maintain cellular life. In fact, although the JCVI-syn3.0 cell is a reduced version of the *Mycoplasma mycoides* bacterium, it is actually a minimized version of an earlier synthetic version of the *M. mycoides*, called JCVI-syn1.0 (Gibson et al. 2010).

JCVI-syn1.0 was hailed as the first synthetic cell. The design process of JCVI-syn1.0 went as follows. First, the scientists picked the sequenced genomic data of a cell, whose sequence was already very small (*M. mycoides*). Then they further designed the genome by deleting some genes and adding others including the watermarking of the genome by adding sequences that would distinguish it from the natural *M. mycoides* sequence. The names of the researchers, their URL and even some famous quotes were added. This modified genome was chopped into 1100 pieces that were sent to a DNA-synthesis company. Yeast cells that are among the workhorses of synthetic biology, were used to stich the overlapping synthesized fragments together into a synthetic genome that was through laborious trial and error procedures transplanted into *M. capricolum* bacteria. When the synthetic genome took over (some) of the recipient cells, the resulting JCVI-syn1.0 cells provided a proof of a principle that genomes can be designed on a computer, synthetized in laboratory, and booted up to produce a self-replicating cell controlled by a synthetic genome (see American Association for the Advancement of Science 2016).

One of the original aims of creating synthetic cells was to eventually succeed in engineering a “minimal cell”. This goal was reached in 2016 with the JCVI-syn3.0 cell that only contained what researchers called essential and quasi-essential genes (the latter genes are not essential yet needed for robust growth) (Hutchison et al. 2016). The JCVI-syn3.0 cell is a minimized version of the JCVI-syn1.0. With improved transposon methods (involving foreign genetic sequences) the functions of genes were disrupted in order to find out which ones were essential for the functioning of the bacterial cell. The resulting JCVI-syn3.0 cell contained only 473 genes, yet the function of about 30% of the genes remained unknown. The researchers of the Venter team conclude: “That we have no clear idea of the functions performed by 149 of 473 genes in the minimal gene set makes it clear how incomplete our knowledge of the cellular biology really is” (Glass et al. 2017, p. 9).

What is important to notice is that researchers do not believe any minimal cell to be exhibited. They rather stress the conceptual or imaginary nature of the synthetic cell. For example, Chang (1972) refers to the notion of artificial cells as an idea (see above), and other researchers discuss minimal cells and minimal genomes as concepts (e.g. Mushegian 1999; Koonin 2000; Delaye and Moya 2010; Acevedo-Rocha et al. 2013; Xavier et al. 2014; Glass et al. 2017). Xu et al. (2016, pp. 516–532) consider minimal and artificial cells as theoretical cells, while Moya et al. (2009, p. 225) canvass "different minimal hypothetically viable cells". Ehmoser-Sinner and Tan (2018) explain: "While it is uncertain whether the minimal cell ever existed, or is still in existence, in the natural environment, this idea has spurred researchers into seeking to identify, or even create, the minimal cell" (p. 12). The authors of the JCVI-syn3.0 cell considered their creation as an instance of a real minimal cell, summarizing their achievement in the following way: "No longer are we limited to working with imaginary minimal cells or naturally occurring organisms with small genomes as surrogates. A minimal cell[8] has now been constructed" (Glass et al. 2017, p. 10). Moreover, in their original article published in *Science*, the scientists of the J. Craig Venter Institute refer to JCVI-syn3.0 as "a working approximation to a minimal cell" (Hutchison et al. 2016, aad6253-1).

Another important observation concerns the fact that the minimality of an organism's genome depends on its environment. Glass et al. (2017) discuss mycoplasma bacteria as "near-minimal cells" that were recognized as such even before the genomic era. Already Morowitz (1984) suggested that they could be used as models for understanding basic principles of life. As discussed above, *Mycoplasma mycoides* functioned as the template organism for JCVI-syn3.0 (via JCVI-syn1.0). What is interesting about mycoplasmas is that they were not originally so simple but evolved from other more conventional bacteria through a massive gene loss as a result of adopting parasitic lifestyles in nutrient-rich stable environments (e.g. Woese et al. 1980), such as e.g. human urogenital tract. The environment of their synthetic cousin JCVI-syn3.0 is even more ideal, a stress-free laboratory environment, where the growth media provides all needed nutrients. Finally, there can be different kinds of minimality that do not go hand in hand. Multiple studies have shown that the genome size does not often correlate with the complexity of other cellular features of an organism (see Xavier et al. 2014). The minimality in the components does not imply the simplicity of interactions.

3.2 Alternative genetic systems

Alternative genetic systems are synthetically designed chemical structures that are conjectured to have the ability to carry and transmit genetic information—arguably some of the most important and basic functions of any living system. Given that all known life is based on DNA (and RNA), successful alternative realizations of genetic systems would amount to a ground-breaking scientific and technological achievement. Although such xenobiological alternatives are foreign to Terran biology, the basic ontological toolkit of synthetic biologists constructing them consists of chemical elements that obey known chemical and physical principles. It is only at the level of biologically functional macromolecules and their purported ability to support life that things become (partially) fictional.

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[8] Glass et al. (2017) write interchangeably about 'minimal genomes' and 'minimal cells'. This suggests that they think of a cell with a minimal genome as an approximation of a minimal cell.

Many of the alternative genetic systems that are currently being studied are based on permutations and reconfigurations of the classical Watson–Crick model of DNA. Changes to this structure can be classified into two main categories: those targeted at the backbone material (so-called *xeno nucleic acids*, or XNAs) and those targeted at the nucleobases (artificial or expanded genetic alphabets). Thus, models for alternative genetic systems consist of molecular building blocks, like hexose sugar in place of the natural deoxyribose backbone of DNA, or as yet unfamiliar, but chemically synthesized, alternative genetic alphabets, like P and Z in place of, or as complements to, the natural nucleotides A, T, C and G. Natural evolution has opted for a certain structural design in DNA, but as far as we know, there might be other ways to implement genetic material, too.[9]

Although no living self-sustaining xeno-organism exists yet, many alternative genetic systems have already been constructed, be they XNA-based systems or unnatural genetic alphabets (see, e.g., Anosova et al. 2016; Benner et al. 2016). For example, in the case of TNA, the natural deoxyribose backbone of the DNA molecule has been replaced with the molecule threose, while PNA would stand for peptide nucleic acid (Anosova et al. 2016, p. 1012). Alternative genetic alphabets range from single nucleobase changes to systems consisting of completely new foreign base pairs (Marlière et al. 2011; Malyshev et al. 2014). Unnatural base pairs can also be merged together with the A-T and C-G pairs, forming artificially expanded genetic information systems (Zhang et al. 2017).

Most recent developments include the so-called *hachimoji*[10] system of eight genetic letters, forming the alphabet GACTPZSB (Hoshika et al. 2019). According to a recent report in *Science*, the system is designed to strike a delicate balance between structural stability and mutability. Like natural DNA and RNA, it is able to maintain its overall structure while its particular building blocks change, making it a “mutable information storage system” (Hoshika et al. 2019, p. 363). A system with these properties is central to Darwinian evolution.[11]

Of course, in and of themselves, these artificial genetic systems cannot be taken as definitive proofs about the nature of the genetic basis of life on Earth, or elsewhere in the universe. Rather, we suggest that they are like synthetic minimal cells in that they are best seen as more or less successfully realized concrete fictional model systems that can be used to explore the range of biologically feasible possibilities. Though some theoretical models have been used to explore the in-principle viability of these kinds of

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[9] Already some years before Watson and Crick’s discovery of the exact structure of the DNA molecule in 1953, Schrödinger (1944) had proposed that genes could be made up from a certain kind of as-yet-unknown aperiodic crystal. Although his hypothesis about the actual material medium of the genetic material turned out to be false, the general structural insights associated with it are still appreciated by working synthetic biologists (Karalkar and Benner 2018; Hoshika et al. 2019).

[10] Inspired by the Japanese words for “eight” and “letter”.

[11] Although no self-sustaining life is yet based on the GACTPZSB system, as an alphabet it nevertheless already surpasses in size a famous imaginary case from sci-fi. In the Steven Spielberg movie *The Extraterrestrial* from 1982, E.T.’s genome is said to consist of a six-letter genetic alphabet, featuring a foreign base pair in addition to the two familiar pairs found in the DNA of Terran life. In this regard, E.T. comes closer to an earlier achievement of the Foundation for Applied Molecular Evolution, the six-letter system GACGPZ (Benner et al. 2016). https://blogs.scientificamerican.com/news-blog/artificial-life-was-steven-spielber-2009-02-15/ (Link last accessed 20.11.2019).

molecules (e.g., Wagner 2005; Henderson et al. 2019), this work is now complemented and seriously refined by concrete wet-lab probing of these constructions by synthetic biologists and chemists.

At the current stage, these systems have a distinctly partial existence. On the one hand, they are chemically synthesized material entities exhibiting many important desiderata of a functional genetic molecule. On the other hand, it is not yet clear whether they can support life to its fullest, especially when it comes to developmental and multi-generational evolutionary processes. Successful incorporations of foreign bases have been reported in some constrained cases, like the replacement of thymine by 5-choloruracil in a laboratory strain of *E. coli* (Marlière et al. 2011). However, to achieve completely self-sustaining life that fully incorporates alternative genetic molecules is a big challenge. Recently, researchers managed to have *E. coli* cell read and sustain the pair d5SICS–dNaM as an extension of its natural genetic system, providing a proof of principle that "increased" genetic information can be both stored and retrieved by the resulting "semi-synthetic organism" (Zhang et al. 2017).

4 Synthetic semi-fictions and the semifactual strategy

Of the different philosophical notions of fiction discussed above, Vaihingerian semi-fictions seem most useful in capturing the fictional, yet concrete and partially realizable character of synthetic models. Although being at variance with what is actually the case, semi-fictions are not *in principle* contradictory with what we know about possible reality.[12] At the very least, there are no nomological reasons to deem them impossible. In other words, their nonexistence in the (known part of the) actual world may be a contingent fact. One way to look at synthetic biology is through its distinctively modal research practice that materially explores biological possibilities (Elowitz and Lim 2010; Knuuttila and Loettgers 2017b; Koskinen 2017). What may begin as a more general idea, as a scientific fiction, provides a concept and impetus for various attempts at concretely realizing it. However, such scientific semi-fictions need to be restricted in scope and keep many factual elements unchanged in order to point towards biologically realizable possibilities. In the case of modeling, such factual parts can amount to explicitly stated parameters and highly situational factors, but also the background knowledge, e.g., general scientific theories and empirical regularities play a role.[13] Minimal cells and alternative genetic systems can be viewed as particular kinds of scientifically constrained semi-fictions: synthetic fictions.

The scientifically constrained nature of many synthetic fictions can be further analyzed, we suggest, by the notion of *semifactuality*. Possibilities are often linked to the idea of counterfactuals. Whereas counterfactuals as standardly conceived address

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[12] Though semi-fictions can of course turn out to be false. The phlogiston element is a case in point. From our current epistemic situation, it seems to provide a borderline case between a semi-fiction and a real fiction.

[13] Semi-fictions are related to "anchored possibilities" in the empirical literature on human counterfactual thought. There are certain cognitive and social factors that affect what people prefer to keep immutable when considering a particular fictional situation, although these boundaries are not categorically immovable (Byrne 2005, pp. 171–173).

"what-if-things-were-different" questions, semifactuals highlight what might stay the same in the face of certain changes, taking rather an "even-if-things-were-different" line of approach to inquiry.

The term "semifactual" goes back to Goodman (1947, 1954), who used it to denote a conditional with a false antecedent, but a true consequent. He viewed semifactuals in relation to counterfactuals, stating that "in practice full counterfactuals affirm, while semifactuals can deny what is affirmed by the counterfactuals." (Goodman 1947, p. 115). The examples Goodman (1947) gives are "Had the match been scratched, it would have lighted" for the counterfactual, and "Even if the match had been scratched, it still would not have lighted" for the semifactual. On closer inspection, one can distinguish between two types of semifactuals (McCall 1983). First, there is the case in which no connection between the antecedent and consequent exists, and the consequent is true regardless of the truth of the antecedent. But in the second case, a connection exists, and the antecedent can be viewed as an alternative way of generating the consequent.

The earlier literature on semifactuals is rather thin. We propose a new reading of semifactuals that seeks to give more substance to the notion in a pragmatic and naturalistic context. Previous authors like Goodman treated semifactuals as linguistic constructions. We acknowledge that history, and draw some inspiration from it, but analogously to how counterfactuals are treated in contemporary philosophy of science, we do not want to limit our understanding of science to sentences (or propositions). Indeed, in the more recent literature, semifactuals have been given, besides their metalinguistic interpretation, a possible worlds reading (Barker 2006). According to this reading, semifactuals highlight how an important factual aspect of the actual world would hold even in nearby possible, but slightly different worlds. Semifactuals thus point to a converging picture of some aspect of reality; to different historical trajectories or causal processes leading to the same outcome (McCall 1983).

Drawing inspiration from the possible worlds reading, we suggest a third interpretation of semifactuality as the exploration of the potential multiple realizability of biological (and also other) systems. Under this interpretation, some higher-level function or organizational feature in the actual world is kept invariant while its underlying material makeup is being varied as in the case of our examples of minimal cells and alternative genetic systems. A familiar example comes from a philosophy of mind context where multiple realizability is used to argue that it is possible to hold mental properties fixed while their physical or neural realizers are manipulated (Pernu 2014, p. 529). The semifactual formulation of this idea would be: Even if the realizer was (at least partially) different, the property of interest would still hold. Thus, while the semifactual strategy highlights the invariance of some factual components of many semi-fictional models, it also employs in model construction counterfactual changes or partially fictional realizers.

While the philosophical tradition has related fiction largely to thought processes and imagination, technoscience has provided a new material scaffolding for fictional thinking and theoretical reflection. Novel technologies prompt researchers to adopt a modal mode as they acquire new ways to effectively manipulate nature. From a cognitive standpoint, directing one's attention to a possibility in the world—or, indeed, recognizing it *as* a possibility to begin with—is correlated with how controllable the target is assumed to be (Byrne 2005, p. 100). The rapidly advancing toolkit of biological engineering, and the consequent capabilities on intervening in the living world makes it easier to see possibilities where they earlier remained hidden. In contrast to previous armchair/work desk/dry lab approaches, synthetic biology can experimentally study alternative biological designs that are not found in nature, but which could nevertheless realize familiar biological functions, when concretized (see Koskinen 2019b). Both minimal cells and alternative genetic systems keep some fundamental biological functions fixed, while their naturally evolved material realizers, or at least some important parts of them, are changed. We suggest that such synthetic systems allow us to draw semifactual inferences in that they employ modal "even if" reasoning in constructing novel biological systems or parts to implement familiar functions.

Thus, instead of ontologizing the concept, or viewing semifactuals solely from a linguistic perspective, we suggest that they are best understood in terms of particular types of modelling/research strategies. We want to know whether something that is true of the actual world also holds in nearby, but different possible worlds. XNA systems, should they prove as functional as RNA/DNA, provide a relatively straightforward example of a semifactual strategy. The actual known world has genes made out of DNA. A possible alternative world has genes made out of XNA. Because in the actual world we only have one kind of genetic molecule, the only realistic way of testing out alternative possibilities is to construct them in a lab. Because the function of these XNA molecules is purported to be the same as that of DNA-based genes, successful synthesis and incorporation of XNA molecules would amount to showing the multiple realizability of genes. Accordingly, in the study of minimal cells the goal of the various lines of investigation is to develop a minimal artificial cell that would nevertheless be able to fulfill at least some basic requirements for qualifying as a living thing (in addition to possibly also modifying these requirements).

The semifactual research strategy has a number of epistemic benefits. Firstly, it restricts the search space for biological possibilities. Just compare the semifactual strategy to a purely blind-shot exploration where no clear actual world function is kept fixed as a goal. Semifactuals thus provide a ready-made standard for evaluating success. Secondly, and as mentioned above, since semifactuals are also attached to the actual world, modal inferences drawn from them tend to be more connected and robust, both biologically and conceptually. For example, a successful realization of an XNA-lifeform would show that it is not necessary to have DNA to support life; in other words, we would know that DNA is contingent as a material medium for genes. Thus, by achieving knowledge about a possibility, we also learned something new about the actual world.

The semifactual strategy can generate understanding of the robustness and generality of various biological functions—to the extent that they can or cannot be multiply materially realized. The (supposedly) multiply realizable character of biological systems is also importantly related to their modularity, a cornerstone of the synthetic biology practice. Alternative genetic systems like XNA (pick your favourite in place of the "X") or the eight-letter *hachimoji* DNA provide a nice example of how synthetic biologists proceed in a modular manner, in addressing one central part of biological organization at a time. The research on minimal cells, in turn, takes it for granted that there are genes that are responsible for the development of cell structures and the regulation of their behavior—and can leave it open how exactly they are constituted.

In view of considering minimal cells as fictions, Vaihinger's discussion of Goethe's original plant and original animal proves intriguing.[14] Vaihinger approaches Goethe's discussion as a fictive judgement that all plant and animal species should be regarded "'*as if* they had been formed according to the standard of an animal or plant archetype" (1926, p. 267). In the same vein he notes that Lotze's "hypothetical animal" should rather be considered as fictional. While *the* complete minimal cell can best be considered as a theoretical fiction, it is important to note that this fiction can have different kinds of realizations. Indeed, one central motivation for discussing minimal cells has precisely been the attempt by bioengineers, biochemists and biophysicists to create such cells in laboratories. As these usually rudimentary ideas can be realized very differently, the minimality of an actual biological system is always of a relative nature. For example, for biological reasons, one cannot strive to construct *the* minimal genome, but just a minimal genome of a particular organism. The estimates of the shared minimal sets of genes have dropped eventually to even zero as more genomes have been added to comparison. In their study of 1000 genomes, Lagesen et al. (2010) found out that there "is an incredible diversity within these genomes with essentially no genes being conserved across all prokaryotes" (p. 607).

Moreover, minimal sets of genes vary considerably in terms of gene number and even identity not only between different organisms but also in the same organism in different conditions. Consequently, the notion of a minimal gene set is relativized not only to the organism in question but also to its environment and so the condition of ideal (laboratory) environment is typically added to the definition of a minimal cell (e.g. Mushegian 1999; Koonin 2000; Glass et al. 2017). The same kinds of considerations apply also to alternative genetic systems whose foreign metabolic needs are only satisfied in a highly artificial laboratory environment. One intriguing theoretical question, then, that these semi-fictional constructs raise, is *when* should we count a synthetic system as a living entity, or an essential part of such an entity.

5 Conclusions

Synthetic biology investigates the realizability of biological possibilities: various organizational principles and mathematical and other models are turned into synthetic constructs that are not only scaffolds towards a better understanding of already existing actual biological entities (Elowitz and Lim 2010; Knuuttila and Loettgers 2017b; Koskinen 2017). Rather, these synthetic constructs extend the boundaries of biological knowledge also beyond natural evolution on Earth. For example, minimal cells provide insight into how life could have evolved from non-living materials, and how life could be defined. Artificial genetic alphabets address, among other things, the question of whether the genetic code would need to be RNA/DNA-based, or if that is simply a contingent fact concerning all known life on Earth. We have argued that minimal cells

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[14] In the present-day scientific discussion of minimal cells, one line of research concerns the Last Universal Common Ancestor (LUCA), the supposed ancestor of all the life forms on Earth.

and alternative genetic systems are both concrete and fictional in that they are (partial) realizations of unactualized but possible biological systems (see also Koskinen 2019a).

In order to analyze the concrete, yet fictional, character, of synthetic constructs we reviewed some, in our view, promising discussions of fictions in science. Two different approaches were discerned: the more contemporary theorizing focusing on imagination as mental activity (e.g. Godfrey-Smith 2006; Frigg 2010; Frigg and Nguyen 2016), and the earlier Vaihingerian account of fiction as a deviation from reality (Vaihinger 1924; Mäki 1980; Fine 1993). Of the former accounts, the DEKI account (e.g. Frigg and Nguyen 2016, 2018) has the advantage of analyzing both the cases of nonconcrete and concrete models, imagination playing partially different role in them. That the DEKI account does not, in our view, accommodate the most pertinent features of synthetic fictions is due to, first, the fact that it is not dynamic,[15] and so not designed to address the changing fictional-cum-concrete status of synthetic models. Second, the DEKI account is an account of representation and as such unduly convoluted to study synthetic fictions, since they do not primarily function as representations. Synthetic constructs can rather be viewed as biological research objects in their own right, whose epistemic functioning can be better accommodated from the artefactual than representational perspective.

The artefactual account of models (Knuuttila 2011, 2017) attributes the epistemic value of models, first, to the scientific questions that they are designed to probe, and, second, to the representational modes and material media used in model construction. Both of these aspects of the artefactual account are crucial for the practice of synthetic modeling. Through turning fictional ideas into concrete entities, scientists study *modal questions* concerning whether specific biological materials, principles and organizational features are necessary for some biological function, or might they be contingent, and if so, how else could the function in question be realized. That synthetic systems are constructed from biological material, according to particular design choices, is crucial for answering these questions, underlining the epistemic importance of the representational modes and media used. Apart from synthetic systems, the practice of synthetic biology combines many other kinds of models (i.e. mathematical, diagrammatic and digital). Such models tend to remain merely hypothetical, however, as they do not allow scientists to judge whether the mechanisms studied could in fact be realized, or realized by different biochemical materials.

The artefactual understanding of models can be aligned with the Vaihingerian account of fictions as "artificial deviations" from reality intended "to overcome difficulties of thought" (see above Sect. 2.1.). Synthetic constructs can be conceived as Vaihingerian semi-fictions since they do not contradict, at the outset, the existing scientific knowledge, and so amount to the exploration of unactualized biological possibilia. We proposed that one central strategy that synthetic biologists employ in studying the realizability of biological semi-fictions can be characterized as semifactual. We then interpreted such semifactual strategy through its utilization of multiple realizability, that is, keeping some higher level biological function fixed and studying experimentally its possible realizations.

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[15] We thank the anonymous reviewer for urging us to make this point explicit.

The notion of fiction, we suggest, is valuable for even such a material practice as synthetic biology, if only because not all prima facie possibilities will turn out to be genuine biological possibilities. Viewing synthetic constructs as concrete fictions addresses also the important question of how to understand those synthetic systems which wind up being only partially realizable (in view of their intended functions). These systems might prove to be eventually impossible, or, even more likely, doomed to occupy the "modal in-between". What synthetic biology teaches us, is that fictions do not wear their justification on their sleeves and so we should not take unaided human imagination for a very good guide on what is genuinely possible. Indeed, before their realizations neither minimal cells nor alternative genetic systems were any well-defined imagined-objects, they were rather preliminary sketches largely based on general criteria derived from known features of actual cells and genetic systems. Attempts at realizing them gave more content and coherence to these imaginings. It is no wonder, then, that such fictional systems start multiplying when technological possibilities for their realization are emerging.

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Compliance with ethical standards

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