Understanding, virtually: How does the synthetic cell matter?

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Abstract

This paper examines how scientific understanding is enhanced by virtual entities, focusing on the case of the synthetic cell. Comparing it to other virtual entities and environments in science, we argue that the synthetic cell has a virtual dimension, in that it is functionally similar to living cells, though it does not mimic any particular naturally evolved cell (nor is it constructed to do so). In being cell-*like* at most, the synthetic cell is akin to many other virtual objects as it is selective and only partially implemented. However, there is one important difference: it is constructed by using the same materials and, to some extent, the same kind of processes as its natural counterparts. In contrast to virtual reality, especially to that of digital entities and environments, the details of its implementation is what matters for the scientific understanding generated by the synthetic cell. We conclude by arguing for the close connection between the virtual and the artifactual.

1. Introduction

Scientific endeavors are rife with virtual entities and environments. The notion of virtuality occurs across scientific disciplines, ranging from virtual particles and virtual oscillators in theoretical physics to virtual cells in biology and virtual reality in social psychology and science education. Many of these virtualities originate in and date back to practices that are not related to digital technologies or to the various related artifacts (computers, headsets, data gloves, etc.) that provide the usual context for our contemporary discussion of virtuality.[1] The difficulty of finding a common denominator for virtual objects and environments of scientific research reflects the different ways in which the notion of virtual itself has been defined.

To capture the elusiveness of the virtual, it has been likened or contrasted to various other notions and qualifiers such as fiction, ideal, actual, potential, possible, and concrete (e.g., Shields 2003). Perhaps the most fundamental contrast is to that of reality, the prefix "virtual" pointing to a deviation from reality, illusion, or make-believe, or at the very least to a difference in kind between the virtual and the real. Virtual objects, or virtual phenomena, have a different ontological status, or character, than the objects and phenomena of our physical reality. Where do these differences lie, and can such a clear-cut line between virtual and real objects and phenomena be drawn? What is the rationale for employing virtual entities and environments in science, given that science is engaged in producing knowledge of the real?

In this paper, we will examine the understanding brought by virtual entities and virtuality in science by studying a specific case in synthetic biology: the construction of a synthetic cell. At the outset, a synthetic cell does not seem to

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[1] Wilson's contribution to this volume deals with the introduction of the notion of virtuality in post-WW2 computer science.

involve any virtuality: it is constructed from biological components in contrast to, for instance, a virtual cell software environment[2] that enables the modeling and simulation of living organisms. The ambitious aim of building a synthetic cell is that of creating a living cell, a biological entity that would at least partially be on par with other biological entities. Although the synthetic cell is not explicitly characterized as virtual by scientists themselves, we will argue that it features aspects of virtuality. While being a biological entity, the synthetic cell is also artificial through and through, idealized, fictional, and doomed to remain in the modal limbo between realizable features, and unactualized, and perhaps unactualizable, functions. What makes it virtual, we submit, is that while it is an entity that is not, to date, even close to the complexity of any naturally evolved biological cell, and will likely remain "something that looks sort of alive" (Powell 2018, p. 75), it nevertheless is expected to possess some of the effectiveness of naturally evolved cells. Such effectiveness is crucial for the scientific understanding of the living cells that it delivers.

We will first discuss the relationship between the real and the virtual, distinguishing virtuality that is associated to *effectiveness* from virtuality that is due to *appearances* (Section 2). In Section 3, we discuss a research project that aims at building a synthetic cell (BaSyC) and show that conceiving of the

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[2] https://vcell.org

synthetic cell as a virtual entity helps to understand its epistemic fruitfulness and scientists' reasons for constructing it. The virtual character of the synthetic cell sheds light on how the aim of BaSyC – achieving scientific understanding of life in general and cellular life in particular – is sought for. In Section 4, we compare the virtuality of the synthetic cell to virtual entities and environments in physics and social psychology. Despite the differences between these disciplines, especially regarding their material media and representational tools, some unexpected parallels lead us to consider the epistemic roles and value of virtuality *and* artifactuality in scientific understanding. Virtual entities and environments in science and elsewhere are like other artifacts in that they are constructed to satisfy scientific and other human aims, thereby affording some uses, but not others.

2. Virtuality and Reality, and Virtual Reality

In an oft-quoted definition, virtual is characterized as "not actually, but as if" (Heim 1994, p. 60). Shields, in another book-length philosophical study of virtuality defines it as "that which is so in essence but not actually so" (Shields 2003, p. 3). Both definitions accommodate the common-sense understanding of the words 'virtually' and 'virtual' as something that is 'almost so', both in the sense of something being nearly the case as well as in the sense of contrasting the virtual to the actual. Nonetheless, there seems to be a difference between the two definitions, in that Heim picks up the fictional qualities of the virtual in underlining its as-if nature. Shields, in turn, emphasizes the particular kind of reality of the virtual. It resides in our thoughts and imagination and the intangible aspects of our cultural products, becoming later associated with digital renderings and creations of a new kind of reality, whose physical basis is in information structures and their computational realizations.

The notion of virtual has a long lineage in Western culture, assuming through its history different meanings and connotations, all the way from its appearance in medieval religious discourse to its arrival in contemporary discussions characterizing nearly any aspect of human involvement with computers and digital environments as virtual. For our purposes, we distinguish between two recurring senses of the virtual (cf. Skagestad 1993). On the one hand, the virtual has been understood in terms of its *effectiveness*, and on the other, it has been approached through its *appearances*. The relationship between the virtual and the real is different in these two cases: while the effectiveness of the virtual emphasizes its functional similarity with the real, the focus on appearances latches onto the phenomenal likeness between the virtual and the real.

The effectiveness of the virtual is succinctly captured by C.S. Peirce's classic definition: "A virtual X is something, not an X, which has the efficiency of an X"

(Peirce 1902, p. 763).[3] Peirce's notion of the virtual has its roots in the scholastic tradition and relates to the meaning of the Latin term *virtus*, which referred to human powers and potentiality, and later to human "virtues". The virtual X in Peirce's definition is a stand-in or a surrogate that serves the function or purpose of the actual thing. There is an intimate link between Peirce's notion of the virtual and his semiotics. A "sign" for Peirce was anything that in some respect is capable of standing for something else to somebody, and he considered both meaning and mind as something virtual. Since signs presume a sign-vehicle and Peirce also appreciated the importance of external sign-vehicles for thinking, it is clear that he envisioned material artifacts as embodiments and mediators of the virtual.

In modern-day digital environments, one comes across many applications and entities that are functionally similar to offline environments, such as meeting rooms, classrooms, some features of games, and e-books, for example. What makes them virtual, is that these activities and contents have been detached from their earlier physical media while serving the same function. Though invoking the idea of sameness is also somewhat misleading here, as the new media creates new affordances even for old practices such as writing.

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[3] See Steinle's discussion in this volume of Peirce's definition.

The virtual embedded in the similarity of appearances is a theme that also has run through the centuries. Shields (2003) finds precursors for contemporary digital virtualities in “historical virtualities” such as *trompe-l’oeil* decorations, mirrors to extend rooms, panoramas, stereoscopes, movies, and other artificial immersive environments. Once again, these artifacts and environments do not necessarily aim to reproduce the external reality, but rather to create something akin to it, an almost-like reality. It is the feeling of reality that is important, even if virtual reality uncannily diverges from it. Such excursions into the virtual tend to take on a life of their own, creating liminal spaces for imagination, where one is neither “in” nor “out”, and the “rules of quotidian face-to-face life are suspended” (Shields 2003, p. 12).

The phenomenal and functional similarities between the virtual and the real come together in present-day virtual realities in various modalities (visual, auditory, and even sensorial), both immersively as well as interactively. Such environments were already characterized as virtual by their early architects and visionaries:

> “The central concern of interactive system design is what I call a system’s *virtuality*. This is intended as a quite general term, extending into all fields where mind, effects and illusions are proper issues. […] A “virtuality”, then, is a structure of seeming – the conceptual feel of what is created. What conceptual

environment are you in? It is this environment, and its response qualities and feel, that matter – not the irrelevant "reality" of implementation details" (Theodore Nelson, quoted in Rheingold 1991, p. 177).

Should we then conclude that the virtual reality Nelson anticipated does not have the same ontological status as physical reality? Chalmers argues that this is not the case (e.g. Chalmers 2017, 2019). According to him, virtual objects are digital objects that are grounded in data structures that in turn can have different physical realizations. Once realized, the virtual objects have causal powers (and this of course holds for all cultural objects, which Peirce viewed as bearing the virtual, and for which Popper set up a world of their own, World 3). While the offline world is realized by physical and biological processes, the digital world is realized by concrete computational systems in a particular computer. Such realizations can consist of an array of marks or of voltages realizing the symbols, or even DNA and proteins to perform computations (Garfinkel 2000).

Furthermore, what should we make of the intuition that the very fact that virtual reality is differently realized than our physical, biological, and social realities brings it closer to fiction? Juul (2019) argues that virtual reality is "fictional all the way down" drawing inspiration from the work on fictional worlds (Pavel 1989). He argues that a full-blown virtual world would be exponentially more complex than the present-day virtual worlds, as they would require vastly more computational power than what is conceivable given our current technology. Juul calls virtual reality both fictional and half-real. Virtual reality is fictional because it is selective, which makes the fictional world more readable and predictable. Such limited implementation makes some actions possible, but not others: a virtual reality or a virtual object is "designed for particular limited set of interactions" (Juul 2019, p. 337). Juul maintains that due to their selectiveness, virtual objects are also half-real precisely because in fictional worlds only some aspects of, for instance, fictional characters are specified (we do not e.g. know most of their physical features). In contrast, reality proper would be maximally specific which implies, moreover, a continuity between virtual and real objects as the virtual objects gain in reality by becoming more specific. However, such virtual reality is simultaneously a qualitatively different kind of real as it corresponds "more cleanly to human concepts" and is as such more easily understood (Juul 2019, p. 340).

In view of the aforementioned discussion of virtuality, and in anticipation of our discussion of the BaSyC project below, we suggest that the virtuality of the synthetic cell is mainly due to its efficiency. As such it fits Peirce's definition of the virtual: it is virtual in that it is not supposed to replicate any naturally evolved cell in its full complexity, yet it is supposed to have (some of) the efficiency of real cells. In being "a lousy mimic of what already exists" (Powell 2018, p. 175), i.e. naturally evolved cells, a synthetic cell is fictional and only half-real. Like many virtual objects, it is selective, and only partially implemented. However, there is one important difference: it is implemented by using the same materials and, to some extent, the same kind of processes as its natural “counterparts”. In contrast to virtual reality, it is these details of implementation that *matter* for the understanding generated by the synthetic cell.

3. Building a Synthetic Cell: BaSyC

Synthetic biology is a field that applies engineering approaches to cellular systems. Although the origins of its cultural and experimental traditions can be traced back to at least the 1960s, it was not until the 2000s that the field began to come into its own (Cameron, Bashor and Collins 2014). Since then, synthetic biology has functioned as an umbrella term, covering practices that range from the construction of genetic circuits from well-defined parts to the pursuit of fundamental insight by constructing synthetic cells (O’Malley et al. 2007). Synthetic cells can be constructed in two ways: *top-down* and *bottom-up.* The minimal genome construction represents the former approach that starts from an existing cell aiming to reduce its genome to the minimum number of genes needed to maintain cellular life. The synthetic cells JCVI-syn1.0 and JCVI-syn3.0 (Hutchison et al. 2016) built by the J. Craig Venter Institute, situated at campuses in Maryland and California[4], have been the milestones of this line of research. The JCVI-syn 1.0 was celebrated as “the first self-replicating synthetic bacterial cell” since although it was based on the (reduced and altered) genomic sequence of the *M. mycoides* cell, it was designed on a computer, synthetized in a laboratory, and then transplanted into another bacterium, producing a self-replicating cell (American Association for the Advancement of Science 2016).

Monumental as the success of the creation of JCVI-syn1.0 and JCVI-syn3.0 was, a minimal cell derived by a top-down selective removal process does not reveal how its remaining components co-construct a living whole nor how, for example, metabolism, compartmentalization and DNA are linked. The aspiration to instead start from the building blocks and construct something in which life-like properties emerge is what drives the pursuit to construct synthetic cells from the *bottom-up* (e.g., Schwille et al. 2018; Sikkema et al. 2019).

The BaSyC research project began in 2017, aiming to attain understanding of molecular life by building a synthetic cell using a bottom-up approach. The main epistemic goal is to unravel how the individual parts of cells, which are already well-understood, interact and create life; to gain basic mechanistic insight into the principles of cellular life. The fundamental question addressed is: how do lifeless subsystems create a whole larger than the sum of their parts, that is, a living

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[4] www.jcvi.org

whole? (Abil and Danelon 2020). In order to answer this fundamental question BaSyC seeks to build a “cell-like, growing and dividing system” (Powell 2018, p. 173). The project consortium involves six Dutch research institutions and expertise in chemistry, physics, and biology[5]. The seven work packages are: (1) modeling; (2) cell fueling; (3) DNA processing; (4) cell division; (5) spatio-temporal integration; (6) autonomy; (7) philosophical reflection, ethical impact, and societal awareness. The last work package enabled one of the authors to attend BaSyC meetings and converse with researchers since its inception.

To construct life in the lab, one first needs to understand what is required for minimal life. To begin with, a cell cycle – composed of DNA replication, DNA segregation, cell growth and cell division – is needed. As proteins control these processes, a cell also requires a transcription-translation machinery. Furthermore, these processes need to occur somewhere: inside a compartment. Finally, the cell requires fuel to conduct biosynthesis and therefore should have a metabolism. BaSyC has addressed all these necessary minimal components of life.

Now at its halfway mark, it has become clearer what is and what is not feasible to accomplish within BaSyC’s ten-year duration. For instance, the cell-fueling work package has succeeded in *in vitro* construction of a pathway that produces ATP (the main source of energy for a cell) which could function as a sustained

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[5] https://www.basyc.nl

metabolism (Pols et al. 2019). However, it is acknowledged that “the first forms of synthetic life *will not make every building block for polymers de novo* according to complex pathways, rather they will be fed with amino acids, fatty acids and nucleotides” (Sikkema et al. 2019, p. 2581, emphasis added). Specifically, the metabolism that has been constructed is “a molecular system integrated into a cell-like container with control of solute fluxes and tunable supply of energy to fuel ATP-requiring processes” (Pols et al. 2019, p. 2). This system is not identical to the metabolism of any unicellular organism in nature, but it is functionally similar – it fulfills the same role: providing the energy that a cell requires.

Consequently, the need to control the external environment has been emphasized, e.g., ‘feeding’ the synthetic cell the building blocks it will need. This, however, does not impede the autonomy of the synthetic cell, as it is argued that all organisms require specific environmental conditions to survive (Deshpande and Dekker 2019). Having an inflow of required nutrients is part of the definition of an autonomous system: “Hence, a system would be considered autonomous if it is able to maintain its far-from-equilibrium state by means of intrinsically governed building of its components and operation of vital processes, provided there is an inflow of necessary substrates and outflow of byproducts (Abil and Danelon 2020, p. 2).

Another challenge has been the ribosome – the *de novo* construction of which is an immense challenge. It has not yet been possible to express all parts of a ribosome from DNA in a liposome – which would incorporate about 50 proteins, parts of rRNA and the enzymes required to process them, and other chaperone proteins required to construct a ribosome in the right order. Therefore, the PURE (Protein synthesis Using Recombinant Elements) system is a practical *in vitro* alternative for a ribosome and a solution to the problem of protein synthesis. The most important components of PURE are the T7 RNA polymerase for transcription, the *E. coli* ribosome, tRNAs, translation factors and translation initiation, elongation, and release factors. At this moment it is still a challenge to make the PURE system self-regenerate (Doerr et al. 2021), yet it remains one of the prime candidates for achieving transcription and translation in a synthetic cell. In terms of virtuality, we can see that a ribosome is a necessary part of a natural cell; however, reconstituting a ribosome *de novo* has not yet been achieved. One would either need to wait with building a synthetic cell until this milestone is reached or find a functionally similar way for transcription and translation to occur. This shows how something can simultaneously qualify as ‘not a cell’ – because cells have their own ribosomes - while still retaining the efficiency of a cell.

So far, we have seen that scientists needed workaround solutions to the energy supply and the transcription and translation machinery of a synthetic cell. What about the container and the cell cycle? Cooperating between work packages, BaSyC participants addressed DNA replication, DNA segregation, cell growth and division (Olivi et al. 2021). For DNA replication, it has proven difficult to rebuild the *E. coli* replication machinery *in vitro*. The authors note that "a promising, simpler alternative to achieve replication in synthetic cells is the single-protein DNA polymerase (DNAP) of bacteriophages" (Olivi et al. 2021, p. 2), especially the ϕ29 system. If this system were used in the synthetic cell, it would entail adjusting the composition of PURE as well as selecting a linear genome. Most bacteria have a circular genome in nature, so another viral replicase system that does work well with circular chromosomes may also be selected. Moreover, the ϕ29 system's processivity is not sufficient for replication at this point - although employing laboratory evolution to improve its processivity is an option. Finally, viral replicative systems lack regulation, which is an essential feature of life and should be included in a synthetic cell. Despite all these bottlenecks, for now the ϕ29 system does appear to be the prime candidate for DNA replication in a synthetic cell.

Where DNA segregation is concerned, scientists have considered both biological and physical approaches. The biological approach focuses on well-known natural modules that drive segregation such as the mitotic spindle apparatus and the Par system. Yet the DNA segregation module should accomplish three main tasks: 1) break symmetry and initiate disaggregation; 2) achieve complete spatial segregation and 3) ensure correct partitioning over the daughter cells. If these tasks could be accomplished in a manner that is fully controllable and is, moreover, much simpler, then that minimal mechanism would be the prime candidate over such natural modules. This brings us to the physical approach: entropy-driven segregation. Despite being based on an in-silico prediction and thus, only supported by indirect evidence (Jun and Mulder 2006; Gogou, Japaridze and Dekker 2021), entropy-driven segregation is considered worthwhile for two reasons: 1) the biological mechanisms inevitably cause too much complexity; 2) the physical route's success relies on a general physical principle rather than on 'precisely tuned biochemistry' (Olivi et al. 2021). It is the less complex and more robust route.

Similar concerns emerge concerning the pros and cons of synthetic containers. The candidates are: 1) water-in-oil droplets: easy to produce, great at encapsulation, difficult to deform, and hard to penetrate; 2) coacervates: easy to penetrate, difficult to keep from fusing; and 3) liposomes: provide an excellent minimal model for a container of a synthetic cell, but their boundaries are hard to penetrate for most molecules. Then why should liposomes nevertheless be considered the best option? For one, liposomes are simply the most well-studied of the three. For another, their lipid bilayer mimics natural cell membranes and could be equipped with molecular machinery that enables deformation and division as well as channels that enable the influx of building blocks. For example, DNA origami membrane pores have been constructed in liposomes (Fragasso et al. 2021). As such, liposomes enable researchers to ‘equip’ the synthetic cell so that it is functionally similar to a natural cell.

Accomplishing the third aspect of the cellcycle, cell division, is a tall order. Again, many different alternatives are still being considered, both well-studied natural division mechanisms as well as physical ones. For a cell to divide, its symmetry must be broken first, which can be achieved through reaction-diffusion at the membrane. The Min system of rod-shaped bacteria has been most thoroughly researched and has the additional benefit of functioning in liposomes. Entropy-driven segregation also occurs most commonly in rod-shaped bacteria, which speaks in favor of the Min system. After symmetry has been broken, the cell has to deform, which has been achieved *in vitro* by applying osmotic pressure across the membrane. This has already resulted in dumbbell-shaped liposomes *in vitro.* However, symmetric abscission – the eventual splitting of the cell into two viable daughter cells of similar size – has not yet been achieved *in vitro*. For now, therefore, the solution will be to use a microfluidic trap – a non-natural solution that will be discussed in greater detail below, and which will have to be replaced with dedicated division machinery if the synthetic cell is to become autonomous. To this end, FtsZ might be used to deform the membrane, and the bacterial dynamin system that it is related to could accomplish abscission.

The final aspect of the cell cycle, the growth of the cell, depends on other selected modules. Cell growth must be coupled to replication and cell division. However, this coupling of processes differs greatly between organisms and its mechanisms have not yet been satisfactorily understood. Rather than work with complicated and opaque mechanisms, “simplified synthetic solutions based on the accumulation of an initiator protein up to a threshold level could be considered for implementation in a synthetic cell” (Olivi et al. 2021, p. 8).

Overall, every choice made within any one work package has prerequisites and consequences attached to it that impact other work packages, sparking strategic discussions at the end of 2021, when the project reached its midpoint. The decision was made to move beyond the explorative phase that characterized the first five years of BaSyC, and progress towards the engineering phase. One of the biggest problems that remains is how to achieve cell division (abscission). Therefore, the current engineering goal is to build a microfluidic lifecycle on a chip, which not only offers a mechanical way to achieve cell division but also several additional advantages for the purpose of engineering a synthetic cell (Deshpande and Dekker 2019). Aside from enabling an efficient division of liposomes, microfluidics offers additional ways to manipulate synthetic cells and “achieve a step-by-step bottom-up assembly” (Deshpande and Dekker 2019, p. 564). To list but a few of such advantages, they can be: kept locked in place, continuously observed, and deformed, and the external environment can be controlled. Microfluidics thus enables control over the building, maintenance and manipulation of synthetic cells. This, however, does somewhat lessen the autonomy of the synthetic cell as some of the temporal control will not be internal to the synthetic cell, but rather externally imposed. Moving forwards, the goal would be to increase complexity and autonomy and to reduce external aid.

Returning to the topic of virtuality in science, the virtual nature of a synthetic cell is clear: it is not a cell, but rather cell-like, yet it does have (some of) the efficiency of a cell. But what does it mean to have the efficiency of a cell? The synthetic cell is expected to be functionally similar to naturally evolved cells. The synthetic cell being built within the BaSyC research consortium employs modules that are functionally similar, though far from identical to their counterparts in natural cells. The BaSyCcell will not be a recreation of any one cell that is the product of natural evolution. It has been emphasized that the goal is not to rebuild, for example, *E. coli*. Instead, the synthetic cell is inspired by and composed of natural parts, as well as some non-natural modules. As mentioned, the replication machinery will for instance be based on a virus, while the PUREsystem is based on a bacterium.

Finally, it is important to draw attention to the reason why scientists choose one functionally similar module over another. The strategy appears to be to select those modules that fit best with the others and to prefer simpler systems over more complex ones. The alternative, to construct it from badly understood parts, is unlikely to result in much mechanistic insight into the workings of a cell. As Deshpande and Dekker (2019, p. 559) write in the introduction of their article on synthetic life on a microfluidic chip device: "[…] it is very hard to get a hang of how millions of biomolecules self-organize to form autonomous self-sustaining systems. Systematically working on simplified minimal systems may help to disentangle some of the enormous complexity."

4. Virtuality as a Route to Understanding Reality

The attempt to build a synthetic cell is motivated by the desire to understand a real, living cell, and how life emerges from lifeless biological parts. Although the synthetic cell is not explicitly called virtual, it does exhibit virtuality in not aiming to reproduce any actual cell, but instead possessing some appearances and effectiveness of naturally evolved cells. The appearances are due to the biological parts the synthetic cell is built with, but as we have argued earlier, the recreation of the effectiveness of actual cells is the overriding goal when appearances and effectiveness clash. In terms of Peirce's definition of a virtual X, the synthetic cell is "not an X (living cell), which has the efficiency of an X (living cell)."

If scientists aim to understand real, living cells, why would they prefer to make a detour via building a synthetic cell? Why would building a synthetic or virtual X promote understanding of the real X? Such surrogate entities allow scientists to gain *epistemic access* to (aspects of) reality that are otherwise closed off, or difficult to access directly. Often the real X may be far too complex (as a whole) to be understood directly, or it may be too far away, or too small in scale. Another reason may be that a surrogate X allows for types of experimental manipulation that are – e.g. for practical or ethical reasons – inapplicable to the real X. A closer look at various scientific disciplines reveals a multitude of entities and environments with virtual features that are used to achieve epistemic access and understanding. Below, we discuss some of them and compare them to the synthetic cell.

The notion of virtuality has had many uses in physics, of which we will discuss two.[6] First, it was employed by Bohr, Kramers, and Slater (1924) in their quantum theory of radiation, which was a final attempt to rescue a classical space-time description of atomic structure. This theory featured a so-called virtual radiation field, represented as a set of virtual oscillators, that transmits probabilities for transitions in other atoms in a non-causal way. The field was called virtual because it is not observable and does not carry momentum or energy (see De Regt 2017, pp. 234-235). According to Heilbron (1994), the practice of using virtual oscillators – albeit not explicitly referred to as such – can be traced back to the late nineteenth century, in physicists' attempts to model the luminiferous ether.

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[6] Cf. Borrelli's, Blum and Jähnert's, and Martinez' discussions in this volume.

Having abandoned the hope of constructing a mechanical model of the ether, they still needed it as a medium in which electromagnetic waves propagate. Therefore, they modeled the ether as a collection of harmonic oscillators transmitting these waves, even though they knew such oscillators could not be real. This started a practice of using virtual oscillators, of which the most famous example is Planck's introduction of quantized oscillators in his 1900 theory of black-body radiation, which initiated the quantum revolution in physics (Heilbron 1994, p. 181-182). For Planck, the oscillators were only surrogates (*Ersatz* models) to be replaced by a better treatment in classical terms. In the ensuing transition from classical to quantum physics, virtuality played a central role. The virtual entities employed by physicists in the early days of quantum theory acted as surrogates for (still) inaccessible real entities. Although different from the synthetic cell in not being material, they are also artificial constructs designed for understanding the real by indirectly accessing it. They are virtual because they are functionally similar to the target system, but only partially so. Their epistemic power is enhanced by their selectiveness: virtual entities highlight the significant features of reality.

Second, in contemporary physics, virtual entities occur in the form of 'virtual particles' in quantum field theory (QFT). This theory was developed during the 1930s and 1940s to describe the interaction between particles and radiation. Virtual particles played a role in various stages of this development (see Ehberger

2020). They became especially prominent in 1948 when Feynman introduced his diagrammatic method for calculation and problem-solving (see Kaiser 2005). Feynman's diagrams include virtual quanta that account for interaction processes (such as exchange of energy and momentum) between real particles (e.g. electrons). In contrast to real particles, virtual particles cannot be detected; They appear only during the very short time of the interaction. A prolonged existence would violate the principle of conservation of energy. There is an ongoing debate in the philosophy of physics about their ontological status. Most philosophers (and physicists) regard virtual particles as 'fictions' and accordingly unreal (Fox 2008; Arthur 2012; Passon 2019), but some argue that they are as real as ordinary particles (Jaeger 2019). We will not enter the debate about the reality of virtual particles, but instead, accept the majority view that they do not exist in the way ordinary (real) particles exist. Indeed, this is precisely why they are called virtual (and why advocates of their reality object to the term 'virtual'). For us the key question is: What is their purpose and function? Again, it appears that the functional similarity of the virtual to the real, i.e. the effectiveness, is essential: virtual particles provide epistemic access to real interaction processes, and thereby allow for understanding reality.

Social-psychological research provides an example of making scientific use of state-of-the-art digitally-created immersive environments, i.e. virtual reality (VR). In the research of human behavior, it is difficult to collect valid data, a problem that can be ameliorated with virtual reality. Blascovich et al. (2002) discuss two methodological problems that could be reduced by using ‘immersive virtual environment technology’ (IVET). The first is the trade-off between having experimental control and facilitating ‘mundane realism’, i.e. how well an experiment corresponds to real-life situations. In real-life settings, increasing mundane realism often leads to a loss of experimental control. Increasing experimental control, on the other hand, will make the results less generalizable. The second problem that IVET could fix is the lack of replicability, as it is nearly impossible for another team of researchers to perfectly copy the circumstances of an original real-world experiment (e.g. clothes, furniture, décor). Yaremych and Persky’s 2019 review of the methods used for behavioral tracing in VR vindicates the earlier predictions by Blascovich et al. (2002). First, the trade-off between experimental control and ecological validity (mundane realism) has indeed been reduced by VR. In fact, experimental control is considerably enhanced in VR, because of the ability to manipulate any variable. Second, VR allows for replicability, as the virtual environment can be easily shared. Finally, VR is an improvement on real-life experiments in that it allows the measurement of the behavior of the user in great detail as the VR system automatically collects data on e.g., posture, allowing for continuous tracing of physical behavior.

VR provides, then, more reliable *epistemic access* to the social processes than normal experiments because of the complexity and variation that the actual social world inherently has. Since virtual reality is expected to be ‘functionally similar’ to the reality that social psychologists are interested in, but evades the methodological problems of real-life experiments, the results derived from VR experiments are more reliable and better generalizable. In this sense, VRresearch has improved the scientific understanding of human behavior beyond what a study of real-life situations can achieve. Synthetic cell construction, in comparison, also aims for reliability and generalizability. In replacing some particular natural parts of the cell with artificial parts that can perform the same function, i.e., biological parts derived from other contexts, or mechanical parts, the researchers seek to find a reliably performing engineering solution. Also, the generic nature of the synthetic cell deserves a mention: it does not aim to replicate any given cell, but rather is put together from parts and functions that are thought to be general to all cells.

In the above examples, as well as in the synthetic cell case described in Section 3, scientists seek to understand some phenomena by fashioning (physically, digitally, or conceptually) synthetic or virtual surrogates, because of the limited or unreliable access to the phenomenon of interest. Epistemic access is a precondition for understanding. Therefore, epistemic tools and strategies like idealization, abstraction, and selection are crucial for achieving understanding, even though they may seem to warp the phenomenon of interest. Such tools and strategies can be used to exemplify particular features of the natural and social world, and they afford, as Elgin has put it, “epistemic access to aspects of their target[s] that are otherwise overshadowed or underemphasized” (Elgin 2017, p. 2). But what exactly constitutes scientific understanding? For Elgin, understanding is “having a suitable grasp of or take on a topic” (Elgin 2017, p. 38), involving “an adeptness in using the information one has, not merely an appreciation that things are so” (Elgin 2017, p. 46). Merely possessing information does not suffice, it also has to be usable. Thus, complexity may hinder epistemic access and thereby prevent understanding. As observed in relation to understanding the cell:

> “Information is a necessary, but unfortunately by no means sufficient, requirement for understanding, and the vast amount of data we are now producing may help understand the details but obscure our vision of the cell as a whole. Living systems are inherently complex; […] unfortunately, the tolerable level of complexity in a connection of thoughts that our brain accepts as an “understanding” is usually rather low, and the most powerful scientific insights, derived by abstraction, have been formulated on the basis of only a few parameters” (Schwille 2015, p. 687).

The idea that understanding involves the ability to *use* the available knowledge, and accordingly involves (human) cognitive skills, is a key element of the contextual theory of scientific understanding developed by De Regt (2017). In this account, intelligibility (of scientific theories and models) is crucial to understanding phenomena scientifically. Intelligibility is a pragmatic value that is associated with scientists' skills. Whether or not a theory is true or a model is representationally accurate is less important than whether it is intelligible. The use of virtuality – be it in social psychology, synthetic biology or quantum physics – is a perfect example of this: it provides access to complex reality by reducing complexity and enhancing intelligibility, also offering possibilities for intervention by representational, experimental and technological means. Wherever reality cannot be experimentally investigated or controlled to the extent that scientists would like to, either in terms of variables (social psychology, synthetic biology) or in terms of scale (quantum theory, synthetic biology), virtuality may offer insight by moving away from complexity through selective attention within virtual entities and environments that are tuned towards human understanding and epistemic goals.

Although similar appearances – or corresponding features to be more exact – certainly play a role, functional similarities are prioritized, especially in the case of synthetic cells and VR in social psychology. Then how to address their representational inaccuracy? In Section 2 we referred to the representational inaccuracy of virtual entities and environments as their half-reality or fictionality that is conspicuous in the cases of VR and synthetic cells precisely because of their aim of reproducing some features of reality (in contrast to the examples from physics we discussed). A VR environment is a highly selective and artificial version of actual social reality, much like the synthetic cell, though in the latter case, for the cell to approximate life, the scientists are not so free to choose what to include and how. While from the representational perspective such divergences from reality certainly seem defective, we wish to underline that they do provide *reliable* access in the first place. For example, experiments conducted with the aid of virtual and synthetic entities allow scientists to extrapolate to the real entities they are interested in, and also to engage in modal questions concerning how, e.g., life could *possibly* work. By programming and building novel entities and environments, new insights can be gained, old beliefs confirmed, and unactualized, yet actualizable possibilities can be examined. In other words: a possibility space can be explored.

To better appreciate how virtual entities and environments give scientific understanding, a change from a representational to an artifactual perspective is needed. The artifactual approach focuses on how the construction of diverse epistemic objects enables scientists to tackle the questions they are interested in (Knuuttila 2021). Among such virtual entities are models, which from the artifactual perspective are, "epistemic tools, concrete artifacts, which are built by various representational means, and are constrained by their design in such a way that they enable the study of certain scientific questions and learning through constructing and manipulating them” (Knuuttila 2011, p. 267). The understanding delivered by models is thus largely based on their specific construction and concrete manipulability, allowed by the representational tools and media with which they are rendered.

Models seem prime examples of virtual entities attesting both to the appearances and effectiveness of the virtual. The representational approach to models has tended to concentrate on the former, while the artifactual approach underlines the epistemic importance of efficiency. Though being an experimental system, the synthetic cell can also be considered a model of a cell even though it does not seek to mimic any of the appearances of some particular cells (Fanalista, et al. 2019). Instead, as we have claimed, it aims to replicate the effectiveness of cells, in general. VR exhibits some of the effectiveness and appearances of reality as well, but it rather functions as an experimental design, i.e. a controlled research environment. In contrast to virtual environments, models typically have a hypothetical character: they address specific empirical and theoretical problems and are constructed in light of their anticipated results. Though models are tailored with particular uses in mind, they also are amenable to improvements and repurposing, like any other human-made or altered objects.

In our view, it is illuminating to look at scientific objects and environments through the lens of virtuality – which is not too burdened by the epistemological and historical baggage of representationalism – concentrating instead on the artifactual detours, translations, and replacements immanent in our scientific practices. Our claim is that virtual entities and environments in science and elsewhere follow an artifactual logic: they are motivated by scientific and other human aims to which their design is tailored, thereby affording some uses, but not others. As such, they can be viewed as entities and environments into which human purposes are already built in, as being relativized to the human perspective.

From the artifactual viewpoint, any entities rendered with various representational and other tools, and involving a variety of material media, are endowed, in the spirit of Peircean semiosis, with virtuality. Consequently, the virtual entities and environments scientists engage with are diverse and numerous, as are their uses. We have suggested, however, that when it comes to scientific understanding, one predominant reason for constructing various kinds of artifacts with a virtual dimension is to provide epistemic access to reality. Another important motivation is reliability: the human-made or altered entities and environments afford more possibilities for control and systematic experimentation with and generation of data.

The focus on representational tools and media reveals what is special about the synthetic cell vis-à-vis many other entities more readily called virtual: it is mainly constructed from biological parts. That the synthetic cell largely makes use of the same media as the naturally evolved cells it has been constructed to study, means that in contrast to digital entities and environments, the processes it simulates are not causally detached from their “natural media”. The epistemic functioning of the synthetic cell is then due to its distinct mixture of sharing the same materiality with natural cells alongside its artificial features. As such a synthetic cell can then be characterized as a “concrete fiction” (Knuuttila and Koskinen 2021) that draws it closer to other “virtual” entities.

5. A Concluding Remark

Virtually no scientific discipline is without artificiality; and, we would like to add, perhaps there is no virtuality without human artifice. Therefore, it is curious that artifactuality is rarely mentioned in the discussions of virtuality, although the notions of fiction, ideal, actual, potential, and possible are frequently referred to. Consequently, the virtual is often understood as something intangible, to be contrasted to the material and the real. But emphasizing the unreal or nonmaterial quality of the virtual is oblivious to how the virtual makes itself felt in the effects and appearances created by human artifactual practices. We have studied the synthetic cell, arguing why it qualifies as a virtual entity and how it compares to other examples of virtuality in science, despite its patently material nature. Such considerations enabled us to elucidate how scientific understanding is inextricably bound to the ever more sophisticated technologies and artifacts developed in scientific practices.

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