



Metabolism Instead of Machine: Towards an Ontology of Hybrids

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Abstract

The emerging field of synthetic biology aims to engineer novel biological entities. The envisioned future bio-based economy builds largely on “cell factories”: organisms that have been metabolically engineered to sustainably produce substances for human ends. In this paper, we argue that synthetic biology’s goal of creating efficient production vessels for industrial applications implies a set of ontological assumptions according to which living organisms are machines. Traditionally, a machine is understood as a technological, isolated and controllable production unit consisting of parts. But modified organisms, or hybrids, require us to think beyond the machine paradigm and its associated dichotomies between artificial and natural, organisms and artefacts. We ask: How may we conceptualise hybrids beyond limiting ontological categories? Our main claim is that the hybrids created by synthetic biology should be considered not as machines but as metabolic systems. We shall show how the philosophical account of metabolism can inform an ontology of hybrids that moves beyond what we call the “machine ontology”, considering that metabolism enables thinking beyond the dominant dichotomies and allows us to understand and design lifeforms in a bio-based economy. Thus, the aim of this paper is twofold: first, to develop the philosophical ontology of hybrids, and second, to move synthetic biology beyond the problematically limiting view of hybrids.

Keywords Synthetic biology · Metabolism · Hybrids · Bio-based economy · Ontology

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1 Introduction

Work within the field of synthetic biology generates novel entities, including engineered microbes, cultured meat or artificial cells. When they leave the laboratory, these entities enter society in a variety of applications, ranging from food, to drugs, to fuel. Their creation and deployment have disrupted practices in the agriculture, energy and chemical industries. Synthetic biological products are believed to offer sustainable solutions to industrial production problems, serving as the building blocks of a bio-based economy (Nielsen et al., 2014; Tsuge et al., 2016). In such an economy, renewable biological resources are used to sustainably produce food, energy and industrial goods.

Besides disrupting practices in multiple domains, synthetic biology also disrupts ontologies, concepts and values (Brey et al., 2019). Entities stemming from the field, which exhibit characteristics of both artificial creations and natural organisms, may be conceptualised as hybrids. They have been framed as artefactual organisms (Holm, 2012), synthetic organisms or living machines (Deplazes & Huppenbauer, 2009). Such hybrids blur traditional definitions that attempt to demarcate categories such as living beings, robots and machines (Bongard & Levin, 2021): they are neither purely natural nor purely artificial (Holy-Luczaj & Blok, 2021). The products of synthetic biology fit the criteria of technological artefacts only imperfectly, exhibiting qualities such as self-reproducibility that artefacts do not share (Schwyter, 2012). The supposedly fixed ontological categories deeply engrained in our thinking, such as “organism”, “machine”, “living being” and “artefact”, obscure the hybrid nature of synthetic biological entities and are put under pressure when we are confronted with them. The rapid proliferation of synthetic life forms brought forth by synthetic biology affects our thinking about each of these categories (Deplazes & Huppenbauer, 2009). Their advent raises the question: what implicit ontological assumptions does synthetic biology make about hybrids, and how may we transcend the challenged dichotomies? This paper’s philosophical reflection on the ontological assumptions implicit in synthetic biology contributes to the debate on hybrids to which that field has given rise. In addition to describing the machine-influenced thinking prevalent in the field, it will propose a way to move beyond it. This novel approach will enable a conceptualisation of hybrids beyond industrial production problems and foster a wider meditation on their role in a bio-based future.

In the next section of the paper, we shall explain why the ontology of hybrids calls for reflection. Because ontology refers to fundamental assumptions about the form and nature of reality, analysing ontological assumptions enables us to investigate the dominant perception and understanding latent within a field of enquiry. To avoid undue abstraction, this paper is informed empirically by its engagement with literature about synthetic biology, and our reflection is built around a concrete case of hybrids. In Sect. 3, we analyse the ontological assumptions about metabolic systems implicit in the literature about cell factories. Our analysis shows that the characterisation of these metabolically engineered organisms presupposes their ontological status to be of machines: controllable objects

consisting of parts, having the sole function of industrial production. In Sect. 4, we analyse the ontological assumptions about metabolic systems in the philosophy of biology. In Sect. 5, by contrasting two accounts of metabolism, we show how the philosophical account helps us to rethink the ontological status of hybrids and move beyond the ontology of machines. In addition to contributing to an understanding of hybrids that transcends one-sided dualistic categories and accurately represents their dual nature, the proposed ontology of hybrids as metabolic systems also helps to address challenges related with the machine framing ontology and to support synthetic biology in its endeavours.

2 Why and How to Think About the Ontology of Hybrids?

Before clarifying the method that will be employed here, it is important to justify the need for considering the ontology of hybrids.

First, the ontological novelties resulting from synthetic biology have normative implications. The field's proponents often characterise its outputs as nothing novel. According to this continuity argument (Christiansen, 2016), we have already been interfering with natural organisms for centuries. For instance, we have done so by practising agriculture, domesticating animals and cultivating crops. Therefore, that synthetic biology creates hybrids by technologically altering nature is nothing new. If the products of synthetic biology are no unique innovations discontinuous with the history of human civilisational practices, their ontological status presents no special philosophical challenge (Preston, 2013). However, advances in synthetic biology make possible a radically deeper level of manipulation and intensive control than traditional practices allow. For instance, advances in metabolic engineering, a synthetic biology technique, have radically increased the extent to which human intervention has shaped the metabolisms of microscopic organisms. Consider synthetic insulin. No naturally occurring bacteria can make insulin by themselves. However, thanks to metabolic engineering, genetically altered bacteria are now the major global producers of insulin (Baeshen et al., 2014). Here, a significant step has been taken: the organism has been transformed to become an artefact or a machine (K. Lee, 2012). Now, for instance, if we were to call this engineered organism a new form of life, that step would have important normative implications: the concept of life is already normative. Thinking of synthetic, insulin-producing bacteria as living organisms rules out a conceptualisation of them as having a purely instrumental use, since living organisms are typically ascribed intrinsic value. On the other hand, thinking of them as machines might impede their ethical treatment. Thus, hybrids' transgressive ontological character, or ontological messiness (Schwyter, 2012), might lead to ethical transgressions. It challenges us to revisit old moral concepts and to invent new ones to account for such nuances. For instance, some have argued that, as a hybrid, a cell factory has no mere instrumental value, nor full intrinsic value, but rather functional value (Holy-Luczaj and Blok, 2021). In any case, uncovering, explicating and challenging the ontological assumptions about hybrids are important because of the normative implications of these projects.

Second, while hybrids are crucially important to both the philosophy of technology and environmental philosophy, their transgressive nature puts them in a blind spot for both fields. While environmental philosophy need not engage with technology, hybrids' blurring of lines between technology and nature urges us to include them in environmental philosophy debates (Holy-Luczaj and Blok, 2021). Synthetic biology is projected as a means of realising a bio-based economy in response to the heightened awareness of global ecological challenges. The field facilitates the industrialisation of bio-based applications for multiple sectors by creating alternatives to fossil-fuel-based chemical synthesis and extraction methods (Clarke & Kitney, 2020). For instance, the European Union's €400 million research programme *Industrial Cell Factories and Sustainable Bioprocessing for Future Bioeconomy* (2020) celebrated how cell factories had the potential to mitigate global climate change. Such projections urgently demand that environmental philosophy reflect on how hybrids such as cell factories may contribute to addressing ecological challenges. In contrast, the philosophy of technology tends to exclude the environment from its analyses, being mainly concerned with artefacts (Lemmens et al., 2017). But the field must also consider the environment in which technologies are embedded. Since today's ecological challenges have mostly resulted from the process of industrialisation, thinking about technology cannot be detached from thinking about the environment. Hence, hybrids prompt debates in both philosophy of technology and environmental philosophy. They challenge our understanding of the relations between technology and biology, between artefacts and living beings, and between machines and organisms.

This paper addresses this gap in philosophical thought about hybrids. Investigations of hybrids, found for instance in the work of Holy-Luczaj and Blok (2021), have so far not uncovered the ontological assumptions implicit in the synthetic biology literature. While synthetic biology creates hybrids, scholars in that field do not espouse any clearly stated view of hybrids. This is because that field, focused on *making* hybrids—by designing, redesigning and building living organisms—has been less concerned with *understanding* them (Schwyter, 2013). However, as we shall argue in Sect. 3, implicit ontological assumptions already underpin these scientific practices. Therefore, in this paper, we shall conduct a qualitative analysis of scientific articles concerned with cell factories, a representative case of hybrids in synthetic biology. This analysis will help us, in Sect. 5, reflect on the implications of ontologies for the engineering aspirations of that field. Cell factories present a relevant case study: many synthetic biological hybrids entering society are cell factories, given that optimising metabolic pathways is considered a central aim in synthetic biology. These hybrids' importance is also emphasised by the promises attached to them. They are posited as having a crucial role in the development of sustainable solutions for the bio-based economy. Finally, as the products of cell factories cannot be found in nature, questions are raised about whether to label these products as “natural”.

Our analysis of cell factories will focus on the concept of metabolism, which is central to conceptualising these synthetic biological products. The most-cited article on cell factories, Nielsen and Keasling's “Engineering Cellular Metabolism” (2016) in the journal *Cell*, defines cell factories as microbes whose metabolism has been

genetically engineered to suit human needs. Or, as the leading journal *Microbial Cell Factories* states, “the Cell Factory concept stresses the relevance of host cell genetics and metabolism in the context of the production process, and focus on the physiological aspects of the productive event” (De Felice et al., 2008, p. 1). The term “cell factories” is taken to cover all microbes whose metabolism is modified to suit human production needs. Microbes naturally create metabolites, or substances that are the products of the organism’s metabolic reactions. They can be altered to create different metabolites than found in their unaltered state, including food, drugs, materials, fuel and other substances for human ends. Because the cell has a metabolism, it can be used as a factory. From yeast used for fermentation, animal cells used for cultured meat or algae used for biofuels, many synthetic biology solutions consist of modifying cellular metabolic systems to produce desired outputs.

Since its origin, the concept of the cell factory has been woven together with the concept of metabolism. In the past, the metaphor of the cell as a factory was popularised by the earliest discussions of cellular metabolism (Schwann, 1839). It has been in use at least since 1885, when Claude Bernard described cells as “the factories or the industrial establishments in an advanced society which provide the various members of this society with the means of clothing, heating, feeding, and lighting” (Bernard, 1885, p. 358). Such metaphors reflected the rise of industrial modernity and its effect on how production was viewed at the time (Reynolds, 2018).¹ The emergence of metabolic engineering allowed scientists to modify the cell’s metabolic pathways to enable talk of a “cell factory” (Bailey, 1991). While it would be unlikely for synthetic biologists to explicitly equate cells with factories, such metaphors reflect implicit ontological assumptions and influence the direction of the research and practice of synthetic biology.²

3 Uncovering Ontological Assumptions

What are the implicit ontological assumptions about metabolism in synthetic biology? Before turning to these assumptions, let us first briefly discuss why they remain underarticulated in this literature. This is because synthetic biology is a young field that has developed primarily as a kind of applied science or engineering. Its *raison d’être* is to design, modify and create things.³ As such, it is not primarily concerned

¹ This industrial logic is dominant not only in synthetic biology, but also in other domains with a paucity of critical ontological reflection.

² In Sect. 3, we take this metaphorical language seriously. Scrutinising scientists’ uses of metaphors offers a one way of disentangling their underlying ontological assumptions. Metaphors have a structuring effect on thought and have ontological significance (Bensaude-Vincent & Loeve, 2018; Boldt, 2018; Vaage, 2020). They imply a certain way of talking and thinking about concepts, engendering the risk of obscuring their status as metaphors, and, therefore, shaping our views on the concept at issue (Lakoff & Johnson, 2008).

³ While synthetic biologists generally define “design” in engineering terms, as a specification or process for the construction of a system (Ebrahimkhani & Levin, 2021), it is often unclear what they mean by the term (Rabinow & Bennett, 2008). A conceptual analysis of design in synthetic biology, perhaps based on the philosophy of information, is deeply necessary, although it is unfortunately beyond the scope of this paper (Floridi, 2019).

with ontology, or the nature of phenomena. However, being indifferent to ontology is not the same as being ontology-free. Although synthetic biology is heavily influenced by engineering language, it is not mere engineering. Multiple scholars have pointed out that the field is rather one of “tinkering” (Calvert, 2013) or “kludging” (O’Malley, 2009). Others have called synthetic biology a technoscience (Bensaude-Vincent & Loeve, 2018), neither pure science nor pure technology, but, rather, concerned with the interplay between enquiry and engineering. But engineers, too, must always make assumptions about the phenomena they work with. Certain theoretical assumptions are necessary even for designing: consider the mathematical models that form the basis of engineering practices (Knuutila & Loettgers, 2013).

Thus, ontological assumptions, even if unarticulated, are present in synthetic biology. In this section, we shall uncover these assumptions by analysing language. Definitions, conceptualisations, metaphors and the general use of language all structure our thinking about phenomena. This fact is presupposed by philosophers who have argued that synthetic biology is committed to certain ontological positions (Deplazes & Huppenbauer, 2009; Boudry & Pigliucci, 2013; Nicholson, 2014; Bensaude-Vincent & Loeve, 2018; Boldt, 2018; Vaage, 2020). Our qualitative analysis of the synthetic biology literature contributes to these debates. In particular, we may discern implicit ontological assumptions by identifying structural commonalities in references to metabolism in the literature on cell factories.⁴

Our study considered the five most-cited articles (2021) on cell factories indexed in Scopus and Web of Science, meeting our search criteria keywords “CELL FACTORIES”, “METABOLISM” and “SYNTHETIC BIOLOGY”. Since the beginnings of synthetic biology date to the early 2000s, the most-cited sources on cell factories are less than a decade old. On Scopus, the five most-cited sources are as follows:

Nielsen and Keasling (2016)
 J. W. Lee et al. (2012)
 Becker and Wittmann (2012)
 Wijffels et al. (2013)
 Poblete-Castro et al. (2012)

The five most-cited sources on Web of Science (2021) are as follows:

Nielsen and Keasling (2016)
 Calero and Nikel (2019)
 S.Y. Lee et al. (2019)
 Nikel and de Lorenzo (2018)
 Kwak and Jin (2017)

Since the only overlap between the two databases is the most-cited source in both—Nielsen and Keasling (2016)—an accurate analysis must include both

⁴ Our method resembles the method of critical hermeneutics developed by Timmermans and Blok (2021) and the method used by Korenhof et al. (2021).

databases. Although the literature about metabolism lacks a uniform description or conceptualisation of that phenomenon, we found these references to share a conceptual base. In the next three subsections, that base is described and interpreted as consisting of three ontological assumptions about metabolism: a production function (3.1), a composite and isolated nature (3.2) and the demand for control (3.3). In each subsection, we begin with references from the selected publications and proceed to elaborate on these references with supporting literature.

3.1 Production Function

In articles [1]–[9], the primary goal of engineering metabolic systems is described as achieving efficient and economically viable production. Metabolic engineering is said to aim at designing cell factories that can be commercially used [4] for industrial-scale production [9]. Engineered metabolic systems are called more efficient [3], producing a higher yield [9] than their natural counterparts. The literature also describes how microbes can become industrial microorganisms [4] and how modifying them amounts to, for instance, constructing a high-yield *E. coli* producer [6]. An engineered metabolism is claimed to offer a sustainable way of production, being simultaneously able to actually compete with oil-based counterparts [8].

These references indicate that the metabolism of cell factories is predominantly referred to as having a productive function. It is considered more efficient and economically viable than the metabolism of its natural counterparts, and its chemical transformation more sustainable than that of traditional production methods. The literature specifically aims to describe the process of turning cells into production vessels with industrial applications and high production value, as is already reflected by the language of “cell factories”. As mentioned, conceptualisations couched in the language of industrial production, associated with efficient and economically feasible production, are deeply rooted in modern cell biology. Our analysis attests to the continued relevance of such metaphors in synthetic biology. This literary framing of metabolism reflects the field’s conformity to the discourse of cell factories’ industrial promises and applications. Indeed, metabolic engineering has allowed synthetic biology to reach a level of technological advancement at which the metabolism’s production functions, like the functions of machines or factories, may be harnessed to efficiently and precisely cater to human needs.

The literature’s decisive focus on the production function of metabolic systems fits with what philosopher Albert Borgmann (1987) called the device paradigm. The observed reduction of the microbial metabolism to its production function resembles, in Borgmann’s terms, reducing it to a device. A traditional device produces one commodity: that commodity is what the device is *for*. Producing that commodity is its core function. In framing a cell’s metabolism as a device producing economic resources, we empty it of other functions that it may have. Because a device is a tool with a specific purpose, the user need not engage with the metabolism’s other functions. Thus, such functions are underemphasised in the literature, which is, instead, focused on questions of maximising production per cell. The metabolism of the cell factory is framed as a productive source or commodity.

3.2 Composite and Isolated

The second ontological assumption implicitly made in the literature results from framing the metabolic system as a composite phenomenon, built up of disparate and isolated parts, much as a traditional machine might be. Metabolism is discussed in terms of metabolic pathways [2], modular pathways [8] or metabolic machinery [8]. The literature further speaks of the compartmentalisation [9], standardisation [6] or assembly [3] of parts [8], devices [6] or genetic tools [8]. The host cell that is used to create cell factories is referred to as the chassis [1], serving as the host or frame for metabolic pathways that can be plugged-in/out [8], introduced, deleted or changed [4]. For instance, articles mention how to build a biological system from DNA parts and the production-relevant chassis [1] and describe designing entirely novel metabolic architectures that can be plugged-in to any bacterial chassis [6]. More generally, the practical goal of synthetic biology is described as the construction of living cells from individual parts, assembled to yield a functional entity [6]. Some scholars express doubts about this dominant discourse of composites and parts, suggesting an alternative systemic approach in metabolic engineering emerging from systems biology. Instead of manipulating individual pathways, this approach is interested in how the whole cell may be suitably modified [8]. Finally, the literature tends to contrast natural cells, which are not isolated from their environment, with cell factories, which operate as isolated entities. Certain scholars question whether this isolation is conducive to the field's efficiency goals, bemoaning how microbial metabolism has not evolved to suit the practical outcomes desired by humans, and when microbes are isolated from nature, this reduces their efficiency in producing desired substances [2].

Thus, we may conclude that there is a focus on metabolic systems as composites of separable parts or units. Scholars of the field also attest to the prevalence of this view, stating, for instance, that synthetic biology begins with the concept of modularity (Agapakis & Silver, 2009) and that one of the important goals of metabolic engineering is the design and construction of synthetic biological wholes out of standardised biological parts (Endy, 2005). The ontology of parts is also evidenced by the BioBrick assembly method widely used in synthetic biology (Kendig & Eckdahl, 2017). Based on this compositional view and the associated assumptions about the modular construction of the metabolism, cell factories are framed as technological, rather than living, matter. Synthetic biology's tendency to describe standardisable parts instead of living beings with distinctive features has been called organism agnosticism (Calvert & Szymanski, 2020). Its opponents emphasise that the so-called chassis or host cell, which is used to build the desired metabolic pathways, is, from the outset, not a technological machine-part, but a living cell.

In keeping with the composite view, the literature conceptualises systems as isolated input–output models. Metabolic engineering attempts to reduce a microbe's interactions with its environment, with the goal of making it more suitable for industrial purposes. As such, engineers reduce the complexity of hybrids to make them into exchangeable commodities, disentangled from various forms of specificity (MacKenzie, 2013). Although models of metabolic systems take into consideration how these systems interact with their environment, metabolic engineering aims to

make microbes more “industrial” by reducing “unintended” interactions (Knuutila & Loettgers, 2013). While the authors of the literature analysed above themselves question whether cell factories can be meaningfully isolated from the workings of their environmental context, the analysed literature predominantly focuses on isolated cells thought of as individual units of production.

3.3 Control

Like most design approaches, the design approaches mentioned in the selected literature aim at control. There are numerous references to controllable, stable or predictable [8] mechanisms. Increased efficiency demands that biologists engineer cell factory metabolism to become more controllable and predictable. For this, metabolic control theory provides the tool to predict the production of the metabolic pathway [4]. This goal is achieved by the creation of controlled conditions that prevail in the laboratory [6]. Furthermore, authors mention cutting off some of the cell’s own lines of control, thereby obviating the need to control each step of the metabolic pathway by putting the control in the hands of the cell [1]. In some situations, processes in the cell are crucially controlled by feedback loops. One author, effectively summarising the widespread language of control, describes how synthetic biology can dynamically control cell behaviour via feedback loops [8]. In this respect, methods such as rational design or rational engineering [3] are often mentioned.

Among synthetic biology’s central goals is the control of metabolic pathways for the purpose of increasing efficiency or, in other words, gaining predictive control over useful living machines for specific functions (Ebrahimkhani & Levin, 2021). The language of control is also echoed by calls for the products of synthetic biology to be regulated and controlled and to reliably execute operations in a predetermined way (Deplazes & Huppenbauer, 2009; Nicholson, 2019). The expectation is that simple control principles, such as positive and negative feedback loops, are the building blocks of biological functions. Environmental influences may hamper engineers’ capacity to design efficient and predictable machines, and their ability to control the metabolic behaviour of microbes. For these reasons, special laboratory conditions—in which disruptive environmental influences are reduced—are set up to control the cell’s operating conditions. Such concerns with control imply an orientation towards a metabolic system that, like a machine, should be controlled to optimise production.

The assumption of control is related to the compositional conception of metabolic systems. Standardised biological components are more reliable and exhibit more predictable behaviour than non-standardised ones. Although scholars recognise the metabolism’s complexity, the metabolism of cell factories is typically described as more controllable than its natural counterparts. Such control is further increased and facilitated by rational engineering or a rational design approach. Furthermore, novel discoveries about organisms can effectively translate into reliable technological methods for modifying and controlling behaviour.

3.4 Conclusion

The language used to describe metabolism in the synthetic biology literature indicates a certain set of notable assumptions, including a particular focus on the production function of metabolism and on its status as a composite of parts and as essentially isolated and controllable input–output systems. If these three assumptions capture how metabolism is conceptualised in synthetic biology, metabolism thus shares important ontological aspects with machines. Machines are, above all, functional objects, utilities or production units. Designing a traditional machine consists of assembling its parts to suit certain functions, such that the composite whole produces the desired outputs in a reliable and controllable way. The synthetic biology literature emphasises such machine-like aspects of engineered metabolic systems. Synthetic biologists often explicitly aim to produce biological technology that is more like a machine than like a natural organism (O'Malley, 2011). When a metabolic system exhibits few or no machine-like traits, synthetic biologists attempt to engineer such traits into it. The crucial goal, despite scholars' admission of the difficulty and complexity of the task, remains turning microbes into efficient, stable production vessels.

From this section's qualitative analysis, we may conclude that the synthetic biology literature on cell factories features a specific set of linguistic and ideological assumptions which we shall refer to as "the machine ontology". Of course, we cannot definitively judge whether synthetic biologists genuinely think of metabolic systems as machines: the reality is likely to be far more nuanced. In fact, Holm (2015) argues that synthetic biologists really do know that organisms are not machines. However, we argue that the language is not neutral, and that the patterns in figurative terminology such as those described in this section have implications for our thinking about a phenomenon. In this case, they provide evidence of the assumption of a machine ontology with regard to metabolic systems.

4 Metabolism in Philosophy

What are the ontological assumptions about metabolism in philosophy? Beyond merely analysing the machine ontology of engineered metabolic systems in the scientific literature, we also want to improve our understanding of metabolism. To this end, we now turn to how philosophers conceptualise metabolism, and what ontological claims they make about metabolising entities. Because metabolism is agreed to be a defining characteristic of living things, the concept of metabolism is central in the philosophy of biology (Jonas, 1966; Bedau, 2012; Dupré & O'Malley, 2013; Malaterre & Chartier, 2021). In this section, we discuss the ontological assumptions regarding metabolism, building on the work of philosophers such as Hans Jonas and Evan Thompson.

4.1 Self-assertion and Integration

In philosophy, metabolic systems are said to characteristically enable organisms to achieve two unique feats with respect to their environment: to stand apart from that environment, while simultaneously integrating into it. On the one hand, a metabolism enables an organism to self-assert or to self-generate (Thompson, 2007). Any living organism requires a metabolism to exchange matter, energy and information with the environment. By metabolising, the organism constitutes, organises, maintains and repairs itself. Despite continually transforming, the organism continues to exist as a stable whole. Put differently, an organism's metabolism enables it to emerge from the environment as a self, which it does by transforming that environment, distinguishing itself through self-assertion. In *The Phenomenon of Life* (1966), Hans Jonas calls an organism's act of asserting itself independently of its environment—this moment when life in its simplest form emerges—an ontological revolution. Jonas takes metabolism to be the process whereby an organism gains a degree of autonomy, the most basic form of freedom, as it facilitates the constitution of the self from within the environment. Recently, philosophers widely agree that metabolism enables the organism to gain agency and subjectivity (Godfrey-Smith, 2016) and lies at the root of minimal autonomous systems (Maturana & Varela, 1980).

At the same time, a metabolism enables an organism to become integrated in its environment. Depending on it for material, energy and information, any living being is necessarily embedded in its environment. Thus, perhaps paradoxically, metabolism enables an organism to both come into existence as an individual and, simultaneously, makes it inseparable from its environment. Organisms constantly interact, communicate and collaborate by means of their metabolism. Such interaction brings into stark relief the ecological dimension of metabolism (Dupré & O'Malley, 2013). It is not exhausted by the interactions between individual organisms and their environments. It also consists of the organism's responses and adaptations to environmental conditions. Instead of being a discrete "thing" or separate entity, a metabolic system is always active in an environment: it always changes its surroundings, and vice versa. Rather than a self-producing entity, metabolism is rather an activity through which an organism constitutes itself in interrelations with others and with an environment.

Thus, a metabolic system has a dual nature, being defined both by both activities of self-assertion and by integration.

4.2 Collaborative and Open System

Based on the activity of integration, philosophers such as John Dupré and Maureen O'Malley (2009) have argued against the autonomy of metabolic systems. Whereas much research in the philosophy of biology has been interested in individual organisms, recent insights from microbiology have extended the focus beyond individual cells to also include the collaborative interactions of cell colonies (Bich & Green, 2018; Dupré & O'Malley, 2013). In microbial communities, organisms influence each other by means of metabolic interdependencies, and metabolism enables robust

inter-organism communication through chemical signals (Guo et al., 2014). Within such richly cooperative communities, individual organisms are only relatively autonomous—but they are essentially open and collaboratively interactive with their cohorts. That life itself arises from such a cooperative mechanism featuring an organism and the environment makes it impossible to think about living beings as clearly demarcated units. Therefore, it is useful to reflect on metabolising systems not only as existing on their own, but also as functioning in integrated ecosystems with other living and non-living entities. They always co-exist with others in a community or collective. They are individual systems and simultaneously part of a larger system.

Metabolism's dual nature suggests a further important ontological assumption tied to metabolism: the metabolic system is an open system. As we have seen, an organism's dependence on the environment constitutes its independence and vice versa. This dependence endows all living beings with an openness, a constant receptivity to, interactivity with and responsiveness to the environment. Living beings and their environment are woven together in a complex system: the evolution of the organism and the evolution of the environment are inextricably coupled. A living entity and its surroundings form a dynamic context of exchange. As such, a metabolic system is better described as an open system, not a closed one (Luisi, 2016). Although the system is well-defined and discernible from its environment, it is simultaneously open to it. As material constantly flows into and out of the system, an open system evades being reduced to a fixed set of material components or parts. To successfully maintain a distinction between the inside and the outside of an organism, that organism must be integrated in the environment and embedded in the ecosystem. Metabolism is, in that sense, closely related to the membrane of the organism, serving not only as a container, but also as a mediator between the organism and the environment (Buehler, 2015). Instead of seeing a metabolic system as something composed of standardised parts independently of its environment, these features of the role of metabolism urge us to see the environment as integral to any metabolic system. The stability of an organism as a whole derives from the continuous regeneration of its parts. These parts are not standardisable, as the whole constantly dynamically interacts with the environment.

4.3 Evolvability

We have already mentioned another ontological assumption about metabolic systems: they are not only open but also evolving systems. Through metabolism, an organism grows, adapts, changes and responds to the environment. The openness of the system accounts for the evolution of living systems, according to increasing degrees of order, complexity and differentiation. Philosopher Peter Godfrey-Smith (2016) maintains that, if we could witness all the processes involved in a cell's metabolic system, we would observe “a storm of activity biased by charge and shape, generating partially random walks that, on average, tend in orderly directions” (Godfrey-Smith, 2016, p. 485). A machine designed for production, traditionally understood, exhibits certain unchanging properties, and its organisation and

operation may be completely accounted for by a description of its component parts and their interactions. The same is not true of a metabolic system. Philosophers Daniel Nicholson and John Dupré (2018) argue that metabolism represents one of the strongest motivations for rejecting an ontology of parts in favour of one of processes as the correct way to understand biology. Their starting point is the introduction of temporality: processes are extended in time. This process-based account of metabolism moves the focus away from biological individual entities composed of parts, suggesting instead that they be characterised in terms of how they emerge and the relationships they must satisfy to constitute a system (Baptiste & Dupré, 2013; Luisi, 2016; Nicholson & Dupré, 2018). Thus understood, a metabolism is not, properly speaking, a thing, as has been prevalent in thinking about metabolism so far (Landecker, 2017).

4.4 Conclusion

Philosophers discuss metabolism as a phenomenon with two distinct aspects: it enables both self-assertion and integration. This leads to dual ontological assumptions about metabolism: it is at once crucial to the emergence of individual biological entities and simultaneously accounts for their embeddedness in the environment or interrelationship with their community. Both these features are fundamental to the understanding of a metabolic system as a well-defined system, but also acknowledge its open and evolving character.

5 Towards an Ontology of Hybrids

How might a more complete understanding of metabolism inform an ontology of hybrids that moves beyond the assumptions of the machine ontology? In this section, we first contrast the implicit ontological assumptions about metabolic systems in synthetic biology literature on cell factories with ontological assumptions about metabolism in philosophy. Next, we show how the philosophical account of metabolism helps us to think differently about hybrids, informing an ontology of hybrids distinct from the machine ontology. Finally, we shall show that the proposed ontology of hybrids as metabolic systems might help to solve problems stemming from the machine ontology and support the endeavours of synthetic biology.

5.1 Contrasting the Two Accounts

Before undertaking the comparison that is this section's goal, we shall show why it is possible to contrast the divergent ontological accounts of a practical, synthetic biology, and a theoretical, philosophy, field. First, we must acknowledge that synthetic biology is more than mere practice, and is instead technoscientific practice (Bensaude-Vincent & Loeve, 2018). In this field, the practitioners' perspective necessarily presupposes certain ontological assumptions, producing a pragmatic understanding of phenomena (De Regt, 2017). From that perspective, it leads the field

Table 1 Contrasting the accounts of metabolism in synthetic biology (left) and the philosophy of (micro) biology (right)

Implicit ontological assumptions about metabolism of cell factories in synthetic biology literature	Ontological assumptions about metabolism in the philosophy of (micro)biology
Metabolism is primarily a function of production. A metabolic system is an input–output model whose yield and efficiency can be increased	Metabolism is two-sided: it serves both self-assertion and integration in the environment
Metabolism can be approached as a composite of standardisable components. The engineered metabolic system—the cell factory—is framed as an individual, isolated production unit	The metabolising organism cannot be reduced to a fixed set of components. Instead, it is an open system that, owing to its capacity to integrate, cannot be isolated from the environment and community that it inhabits
Metabolism is primarily an object of control. The predictability of its parts and processes can be enhanced to increase that control	Metabolic systems are characterised by complexity and differentiation, as well as by constant evolution, transformation and dynamism

to see these organisms as designable and engineerable. By consequence, designing them more or less successfully supports these views. The theoretical foundations of technoscience are ontological assumptions: they justify seeking the capacities of production, construction and control in the objects of metabolic engineering. Therefore, practice is inseparable from ontology. By contrasting an ontology connected firmly to practice with one without such a focus, we may become aware of how limiting such a perspective on phenomena is.⁵ Second, both synthetic biology and philosophy of biology are informed by biology. As a result, both construct ontologies around the same phenomena. Like traditional biology, the everyday practice of synthetic biology requires many pragmatic skills, such as using microscopes and other instruments. Thus, although the philosophy of biology may provide a perspective that is theoretical in the very general sense, it is nonetheless strongly influenced by practical considerations.

A summary of Table 1 will bring to the fore the relevant upshots of the contrast between the two accounts. In the first pair of implicit ontological assumptions, we see that the philosophical account, unlike the synthetic biology account, does not reduce metabolism to a one-dimensional entity solely for the purpose of production. In the second pair, the philosophical account is consistent with the hybrid as an individual composed of parts, but makes clear that these parts' dynamic nature should not be mistaken for the stability of machine parts: the account emphasises the openness of the metabolic system over its modularity. The third pair shows how, in the philosophical account, although consistent with certain metabolic processes being temporarily steered in a particular direction by genetic editing, controlling a metabolic system is unrealistic. Unlike a machine, a metabolic system is understood as a

⁵ Here, we build on recent scholarship, for example, Timmermans and Blok (2021), who discern between and analyse the ontological and axiological assumptions in the dominant paradigm of responsible innovation.

self-organising system that will adapt to its environment against humans' intentions to control it, thereby displaying unpredictable behaviour.

So, we may conclude that the philosophical account may serve as the basis for a novel interpretation of metabolism, offering an alternative to synthetic biology's prevalent machine ontology. That interpretation rejects the implicit assumptions that underlie the machine ontology: in place of the logic of mechanisms and industries, its point of departure is the consideration of lifeforms.

5.2 Thinking About Hybrids

Scholars have argued that a machine is a poor model for a metabolic system (Boden, 1999; Boldt, 2018; Godfrey-Smith, 2016; Jonas, 1966). As we shall now argue, thinking about *metabolic systems* instead of *machines* enables us to think more clearly about hybrids. In this section, we show why this different view on hybrids may inform the objectives of synthetic biology.

If we begin to think about cell factories in terms of metabolic systems rather than machines, we may rid ourselves of limiting categories. Often, hybrids are thought and spoken of in dichotomies, like natural–artificial, or clearly discrete ontological categories such as machine, factory or artefact. But a metabolic system may be a “natural” organism or a highly engineered one that nonetheless metabolises and proceeds from an organic origin. Living beings, be they engineered or not, always metabolise. Prevalent representations of hybrids as “living machines” or “cell factories” lead us to focus solely on the artificiality—juxtaposing it with naturalness. A “metabolic system” makes no such suggestion. A strict distinction between natural and artificial is unnecessary: metabolic systems are simply modified to a greater or lesser extent.

Moreover, thinking in terms of metabolic systems rather than machines prompts us to recognise hybrids' two complementary dimensions. Metabolism bridges the conceptual chasm between the *organism* and the *environment*, as it consists of the relationship between them that both constitutes the organism and enables it to shape the environment. An engineered metabolic system, likewise, cannot be simply some object detached from an environment. The notion of metabolism, being both an individual and a collaborative phenomenon, unites the *individual* and the *collective*. As such, it is constitutive of apparently contradictory concepts such as *autonomy* and *dependency*, or *freedom* and *necessity* (Luisi, 2016): by metabolising, an organism creates itself by building interdependencies. Furthermore, metabolism is both *stability* and *change*, as it is only from continuous transformation in response to dynamic environmental stimuli that an organism derives its stability. By reconciling seemingly opposing categories, the characterisation of the hybrid as a metabolic system shows these categories to be non-dichotomous, but, rather, constitutive for each other. Self-assertion and integration and individual and collective are not opposed to each other. On the contrary, they are fundamentally interrelated.

Last, this ontology is inclusive: beyond cell factories, it may accommodate a broad range of novel genetically modified organic hybrids. In this regard, the ontology of hybrids as metabolic systems is not flat, in the sense that it does not confer

the same ontological status on everything. Rather, it does not imply that “everything is technology”, “everything is nature”, “everything is materiality” or “everything is relations”. It distinguishes between metabolic and non-metabolic systems, leaving room for differences while recognising that (engineered) metabolic systems are embedded in the environment and not independent entities.

So, if we regard hybrids as metabolic systems, we may move beyond limiting categories, think about the two-sidedness of phenomena and create an inclusive ontology that does not ascribe the same ontological status to everything.

5.3 Implications for Synthetic Biology

Going beyond the machine ontology in synthetic biology is no mere ontological exercise: revising our thinking about hybrids produces favourable consequences in the field. Recall that synthetic biology’s main stated goals are to enhance our abilities to *understand* and *design* living things for a *bio-based economy*. Are these abilities enhanced or impeded by thinking of synthetic organisms as “living machines”? Does the machine language reveal the unique features of living beings, or facilitate our understanding of what engineering in biology means? As we shall now argue, based on some concrete examples, the machine ontology is unfavourable for synthetic biology’s engineering aspirations. It produces unfavourable implications for understanding, for design and control, and for realising the goals of a bio-based economy. In each case, we shall show how the ontology of hybrids as metabolic systems offers an alternative.

5.3.1 Understanding

The machine ontology has adverse epistemic implications. Of course, the ontology offers many useful contributions to the field, including helping to image the highly complex workings of organisms, creating novel hybrids with useful functions or aiding scientific communication (Nicholson, 2014). As such, we do not argue that the machine ontology should be rejected in its entirety. However, it is problematic to conflate metabolic systems with machines. At best, the machine perspective captures certain aspects of organisms, leaving certain of their qualities underappreciated or ignored. For instance, it inevitably underestimates the side effects that synthetically created organisms have on their environment (Boldt, 2018), perpetuates an overreliance on engineering and technological solutions and puts scientists at risk of missing opportunities for scientific understanding and discovery (Pigliucci & Boudry, 2011). In a concrete example of machine ontology’s steering of a research agenda, Víctor de Lorenzo et al. (2021) argue that the use of the term “chassis”—a clear instance of mechanistic language—may constrain the precise understanding of phenomena. Instead, the authors suggest the term “agent”, which is sensitive to hybrids’ more active features. The more general risk that research horizons may be restricted, rather than expanded, by machine metaphors has been discussed, for instance, by other authors in life sciences (Avise, 2001).

In Sect. 3, we showed how the synthetic biology literature primarily describes the construction of synthetic metabolic systems, without any special focus on further understanding them, despite certain allegations that gaining understanding is one of synthetic biology's goals (Knuuttila & Loettgers, 2013). The prevalent focus on creating more machine-like entities risks entirely decoupling synthetic biology's supposedly intertwined ends: building and understanding. In the pursuit of engineering, the science increasingly falls out of sight (Roosth, 2017). While synthetic biology is crucial to accurately understanding hybrids, they are being created on a massive and rapid scale by a field relying increasingly on automated processes and increasingly seeing the synthetic organism as a final product akin to an alienable commodity (Landecker, 2007). This is what Bruno Latour calls the black-boxing of technoscientific systems. When confronted with an efficiently running machine, engineers can focus on its inputs and outputs and need not engage extensively with its internal complexity (Latour, 1999). One may conclude that the machine ontology has a fundamental impact on understanding and the research practices of synthetic biology. In contrast, viewing hybrids as metabolic systems rather than mere machines cannot result in pure instrumental and reductionist thinking. It fosters understanding of them beyond their production function.⁶

5.3.2 Design

The machine-ontology obscures the uncontrollability and complexity of metabolic systems. This has implications for control-focused design. As an analogy, consider what systems biologists such as Pier Luigi Luisi (2016) and Víctor de Lorenzo (2015) call the dominant DNA paradigm or the gene-centric view. When we are focused on altering the DNA of an individual organism to make the organism function in a certain way, we tend to overlook that this organism reacts to and interacts with its environment. In response to what he considers the organism's relations with its environment and its exchange with other organisms, di Lorenzo (2015) calls for a view in which metabolism is more present. But the construction of a reliable machine demands restricting external factors that would influence its efficiency is by definition impossible for metabolising organisms. The view of organisms as machines has difficulty accounting for such interlevel interactions (Boldt, 2018).

Certain organisms may become more amenable to reconstruction, and certain metabolic pathways can be designed to function more efficiently for human purposes. However, even the proponents of synthetic biology admit that control remains an aspiration and not yet a reality. Insulating metabolic systems or protecting synthetic designs through change remains difficult (Elfrick & Endy, 2014). Metabolic systems are complex, being subject to oscillations, noise and other features that modular machines are not afflicted by. Synthetic biology, certain scholars have

⁶ Inversely, because hybrids blur the boundaries between machines and living agents, synthetic biologists argue that our conceptualisation of the machine must change as well. The outdated understanding of machine as mechanical, inflexible and driven entirely by external causes does not apply to hybrids (Bongard & Levin, 2021).

maintained, features a distinctively atemporal engineering logic, which ignores the necessarily temporal, fluctuating and changing nature of living beings (Calvert, 2014). Given that “metabolic engineering” literally means engineering something that is already self-organising, it should follow that a metabolic system is not simply a controllable object. Rather than passively bending to an externally imposed human will, the metabolism serves the organism’s interest. For instance, kill-switches inserted by humans can be eliminated by the microbe after a few generations—after all, such a switch does not suit the microbe’s own interest. Metabolic systems are not easily controllable because they are not closed: instead, metabolism implies the simultaneous, mutually determining and inseparable evolution of the organism and its environment.

5.3.3 Bio-based Future

A third implication of eschewing the machine ontology is that, by so doing, synthetic biology may more positively contribute to a bio-based future. Synthetic biology is oriented to designing bio-based industrial applications, hence its focus on engineering efficient solutions. However, these solutions are often framed in terms of technological drop-in replacement of commodities or substitutions for petrochemical equivalents (Ginsberg & Chieza, 2018; Karabin et al., 2021). This limits the envisioned bio-based future to the replacement of non-renewable chemical production sources with renewable ones. But proponents of the field argue that synthetic biology should have more ambitious goals. Rather, it “should not be about only being better at routing metabolic effort down a pathway in order to make compound B more efficiently. Nor must synthetic biology necessarily be restricted to producing products in bioreactor vats in order to achieve sustainable manufacture (Elfrick & Endy, 2014, p. 20). The focus on building industrial synthetic machines is consistent with the pursuit of quick wins for industrial applications, while keeping in place the entire machinery of traditional industrialised production. This approach to synthetic biology does not empower a fundamental transformation towards different means of production, merely reproducing and perpetuating the ideas and hopes of this unsustainable era, such as mass production. The machine view limits the scope for imaginative alternatives and inhibits the potential for a bio-based economy that offers a more fundamental answer to industrial production problems.

Constructing our thinking around the metabolism instead of the machine emphasises the ecological side of metabolic systems, in place of seeing modified organisms as isolated self-producers. Although metabolic engineering often takes into account the conditions in bioreactors and production facilities, this remains a narrow degree of engagement with the environment, especially since a rather controlled environment is also expected in a bioreactor. By stressing the hybrid’s metabolism, the field may extend to learning from or harnessing the responsive, adaptive qualities of organisms. This thinking is implicitly evoked by certain practices within synthetic

biology, such as metabolic engineering strategies using quorum sensing, which focus on the communicative aspects of modified organisms (Boo et al., 2021).⁷

In addition to these implications for understanding, design for control, and engineering for a bio-based economy, adopting the machine ontology for metabolic systems may have ethical and philosophical consequences, as mentioned in Sect. 2. From Table 1, we may conclude that the assumptions about metabolic systems that are widespread within synthetic biology imply those systems to have instrumental, economic and commercial value. On the other hand, the philosophical account implies their ecological, environmental and relational value. The first set of assumptions leads to an alienation of hybrids, as they are treated generally as artefacts. It implies that all of a metabolic system's values are eclipsed by engineers' technological mastery and control over it, and our general ability to exploit systems for production. Recognising the ecological value of metabolic systems is central to synthetic biology's aim of designing a bio-based economy. Finally, in Sect. 2, we suggested that environmental philosophy and the philosophy of technology alike must address how we ought to think about hybrids. In this paper, we have suggested a starting point for further philosophical research, drawing conclusions from prior work in the philosophy of technology and reflecting on how hybrids may contribute to a bio-based economy.

6 Conclusion

By uncovering the ontological assumptions implicit in the synthetic biology literature, we have reflected on the framing of engineered metabolic systems. By analysing the case of cell factories, which play an important role of an imagined bio-based future, we have shown how synthetic biology invokes limited ontological dichotomies, like the one between natural and artificial, and over-simplistic categories like “machine”, “factory” and “artefact”.

To transcend the limiting ontological framing of hybrids as machines, we have proposed thinking of them as metabolic systems. This is not a mere semantic shift in language. The framing of metabolic systems—engineered or not—as machines is not innocent terminology, bearing significant implications for the development of the field. Although synthetic biology is closely tied to engineering disciplines, it should not be led by thinking about living beings as being little different from machines. Such thinking obscures their innate differences.

A more thorough engagement with philosophical literature helps us to reconsider this limited framing. In the philosophy of (micro)biology, the metabolic system has been described as a two-dimensional phenomenon. Embracing this view enables us

⁷ Quorum sensing is a classic example of second-wave synthetic biology as it concerns bacterial communication (Stepney et al., 2018). Purnick and Weiss' (2009) first-wave of synthetic biology is said to be primarily concerned with parts, whereas the second-wave is marked by a systems approach. While the authors praise the non-trivial accomplishments of the first wave, they argue that it seriously limits the field. In line with our argument, they maintain that new perspectives for synthetic biology may be opened by shifting our attention to second-order problems and concepts.

to transcend the limiting, dualistic categories that underlie the prevalent machine ontology. It advances thinking about metabolism as neither thing-like nor machine-like, but, rather, life-like and process-based. It makes the natural–artificial dualism becomes redundant. As such, we contribute to the debate about hybrids. To date, that debate is often limited to binary oppositions. When we reject the machine ontology, we bridge these supposed oppositions, showing them to be interrelated. One may hope that becoming sensitive to the two-sidedness of metabolism will foster thinking beyond the logic of industrial production and towards an engagement with the unique biological features and ecological qualities of metabolic systems. Finally, we have shown how this thinking helps synthetic biology to achieve its own objectives of understanding and designing hybrids for a bio-based economy.

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