Explorative Synthetic Biology in AI: Criteria of Relevance and a Taxonomy for Synthetic Models of Living and Cognitive Processes

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Abstract This article tackles the topic of the special issue "Biology in AI: New Frontiers in Hardware, Software and Wetware Modeling of Cognition" in two ways. It addresses the problem of the relevance of hardware, software, and wetware models for the scientific understanding of biological cognition, and it clarifies the contributions that synthetic biology, construed as the synthetic exploration of cognition, can offer to artificial intelligence (AI). The research work proposed in this article is based on the idea that the relevance of hardware, software, and wetware models of biological and cognitive processes—that is, the concrete contribution that these models can make to the scientific understanding of life and cognition—is still unclear, mainly because of the lack of explicit criteria to assess in what ways synthetic models can support the experimental exploration of biological and cognitive phenomena. Our article draws on elements from cybernetic and autopoietic epistemology to define a framework of reference, for the synthetic study of life and cognition, capable of generating a set of assessment criteria and a classification of forms of relevance, for synthetic models, able to overcome the sterile, traditional polarization of their evaluation between *mere imitation* and *full reproduction* of the target processes. On the basis of these tools, we tentatively map the forms of relevance characterizing wetware models of living and cognitive processes that synthetic biology can produce and outline a programmatic direction for the development of "organizationally relevant approaches" applying synthetic biology techniques to the investigative field of (embodied) AI.

Keywords
Artificial intelligence, synthetic biology, epistemology of synthetic models, taxonomy of synthetic models, synthetic method, criteria of relevance

1 Explorative Synthetic Biology and AI

Within the context of experimental research in biology, the development of synthetic biology (SB) (Chiarabelli et al., 2009; Endy, 2005; Morange, 2009; Schwille & Diez, 2009) represents one of the most relevant novelties. The interest of this emerging sci-tech area relies on its hybrid nature. SB arose at the beginning of the new millennium, based on the interbreeding of biology and engineering, primarily to design and build biological parts or systems not existing in nature to achieve practical goals (biosynthesis of fine chemicals, biofuels, pharmaceutics, etc.). However, increasingly

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often, SB overcomes merely applicative purposes and contributes in a new way to addressing the scientific exploration of life. Current frontier techniques of (bio)chemical synthesis, assembly, and molecular and supramolecular manipulation allow SB not only to modify effectively extant biological cells but also to construct from scratch synthetic (or artificial) cells (SCs/ACs) (Buddingh' & van Hest, 2017; Gaut & Adamala, 2021; Guindani et al., 2022; Luisi, 2002; Luisi et al., 2006; Mansy & Szostak, 2009; Salehi-Reyhani et al., 2017), which enables SB to fully express an original explorative vein. The latter inquiring approach can be recognized as a variant of what Christopher Langton (1989), while defining Artificial Life (AL), called the "synthetic approach to biology." Indeed, SCs can be built as means to model primitive cells, simplified (minimal) cells, or even alternative cellular forms and thus to study at an experimental level the fundamental features of life by "put[ting] living systems together" from scratch—that is, from (bio)chemical molecules—"rather than taking [them] apart" (Langton, 1989, p. 40; Liu & Fletcher, 2009). On the basis of the rapid growth of related research directions, contemporary SB is now overcoming the mere status of a branch of engineering and is defining itself as a science: a *synthetic science of life*, aiming at deepening the scientific understanding of life through the construction and the experimental exploration of molecular models of biological systems and processes.

However, this is not the only potential that the synthetic approach to life can provide. As we have shown in detail previously (Damiano & Stano, 2018a, 2021a, 2021b), the synthetic exploration of biological processes allows SB to produce scientific contributions of interest outside the traditional perimeter of biology and, specifically, within the domain of the cognitive sciences. Following the emergence of the embodied approach (e.g., Clark, 1997; Varela et al., 1991), the cognitive sciences are increasingly recognizing, as well as focusing on, the biological dimensions of cognitive processes and developing synergies with the sciences of life. As we have argued (Damiano & Stano, 2018a), in the context of this general process of transdisciplinary interconnection, explorative SB appears as an artificial science of life capable of involving AI—in particular, embodied AI—in a process of cross-fertilization, favored by methodological and experimental preconditions that are already set.

From the methodological point of view, as it happens in AL, explorative SB implements, in its specific research context, and, in this sense, in a specific way, the method of inquiry characterizing the lines of AI engaged in studying natural cognitive systems and processes. This is the so-called synthetic method, which AI inherited from cybernetics and its precursor—"proto-cybernetic"—research lines (Cordeschi, 2002) and has been applied, since the 1950s, to the study of natural cognition through the construction of *software* and *hardware* models. Often, starting from the late 1990s, the synthetic method is designated within AI by the slogan "understanding-by-building" (Pfeifer & Scheier, 1999) and presented to the scientific community as the method characterizing investigations that intend to contribute to the scientific understanding of natural processes through forms of "artificial" or "synthetic" modeling—in other words, the creation and the experimental study of artifacts that reproduce target natural processes on the basis of scientific hypotheses and thus can be considered "material models" of these processes, namely, functioning physical artifacts allowing science to test these hypotheses experimentally. In their scientific literature, specialists in explorative SB explicitly indicate the understanding-by-building approach as their methodological framework of reference and define the chemical artifacts produced based on its implementation as "chemical models" of the target biological processes. On these grounds, philosophical analyses conceptualize these models, frequently defined "wetware models" (e.g., Bedau, 2003), as a third type of model that, together with software and hardware models, contemporary science produces through the synthetic method (Damiano & Stano, 2018a, 2018b).

Such a methodological convergence prepares cross-disciplinary collaboration between SB and AI and, specifically, embodied AI (EAI), that is, the form of AI closest to the sciences of life.

From the experimental point of view, in SB, the implementation of the understanding-by-building approach can generate concrete research scenarios to study, at an empirical level, processes of emergence of minimal living organisms through the synthesis of artificial chemical systems. As we have discussed in the series of works mentioned earlier, on the basis of these scenarios, SB can pave the way to the synthetic study of biological adaptive dynamics through chemical models of minimal biological systems and processes—in other words, a form of synthetic investigation of minimal expressions of natural cognition that will be based not on software or hardware but on *wetware* models. The related programmatic idea conceptualizes it as a new "chemical explorative AI" directed to support EAI in advancing the scientific understanding of the biological dimensions of cognitive processes.

Indeed, at present, the transition of SB to the status of a full-fledged synthetic science of life and cognition still appears as a programmatic project whose complete accomplishment appears uncertain. As we discuss later, the bottom-up construction of complex-enough molecular systems presents several challenges. However, technical issues are just one side of the coin. SB's ability to produce effective contributions to the scientific understanding of target biological and cognitive processes does not depend only on the soundness of technical solutions. It depends also, and primarily, on the possibility for SB to effectually address the epistemological critical questions that today affect the synthetic modeling of life and cognition, which, if left unanswered, threaten the effective acceptance of this approach among the methodological strategies that the pertinent scientific communities recognize as capable of producing valid insights. Among such epistemological issues, a critical one concerns the *relevance* of synthetic models of biological and cognitive processes, understood as the contribution(s) that they can make to the scientific description of the target processes (Stano & Damiano, 2023). Can systems endowed with artificial "embodiments" and "embedments" be considered effective models of natural living and cognitive processes? In what conditions and in what sense can exploring synthetic models of biological and cognitive phenomena provide significant advancements in biological and cognitive sciences?

The issue of relevance is not limited to wetware models but also affects software and hardware models. Typically, the literature of the artificial disciplines engaged in investigating natural processes, including SB, defines the synthetic systems produced for exploratory purposes as models of the target systems but does not support this definition through epistemological inquiries on the relationship between these models and the target processes, nor on concrete ways in which synthetic models can contribute to understanding their target processes. The problem is particularly critical because, as we discuss, synthetic models often appear to have a merely "imitative" value whose contribution to advancing scientific knowledge of the target processes is unclear. Furthermore, the current evaluation of synthetic models is often polarized in the rigid, sterile alternative between, on one side, the mere behavioral imitation and, on the other side, the full reproduction of target processes: a clear-cut opposition between the simple reproduction of the target processes, based on biologically implausible mechanisms, and the perfect re-creation of the "real thing"—whose relevance, as we will argue, is not less problematic (and often coincident with idle technical virtuosity).

We believe that effectively addressing the problem of the relevance of synthetic models, and transforming the aforementioned binary alternative into a productive space for the synthetic exploration of life and cognition, is a precondition for the development of SB from an ancillary discipline to a (synthetic) science of life and cognition. To support the fulfillment of this preliminary requirement, we present in this article an epistemological inquiry into the relevance of synthetic models. The main goal is to generate a conceptual framework to determine and assess the different forms of relevance that (hardware, software, and wetware) models can have for the scientific understanding of life and cognition, in order to clarify the contributions that SB can offer to AI construed as the synthetic exploration of cognition and, on these grounds, pave the way to the development of research approaches in SB able to productively investigate the territory of EAI.

The present article is organized as follows. In section 2, we show the limits of the alternative "mere imitation/complete reproduction" for evaluating the relevance of synthetic models and the need for assessment criteria that overcome the imitation paradigm. In the third section, we pave the way to an alternative paradigm of assessment by defining an epistemological framework of reference for the synthetic study of life and cognition, grounded in autopoietic cognitive biology and proposing a related set of criteria to evaluate the relevance of synthetic models. In the fourth section, we use these criteria to define a range of different forms of relevance for synthetic models, and we tentatively map SB models based on them. In the fifth and concluding section, we draw a programmatic direction for "organizationally relevant" SB–AI approaches and finish by briefly recapitulating our path and prospecting future work.

2 Mere Imitation and Complete Reproduction: From an Alternative to a Workspace

The alternative "mere imitation/complete reproduction" has historical significance with respect to the issue of evaluating the relevance of synthetic models. Indeed, its thematization is at the heart of the cybernetic literature on the synthetic approach and, in particular, of the three groundbreaking works dated 1943 that are usually recognized as having laid the epistemological foundations of the synthetic modeling of life and cognition: "Behavior, Purpose and Teleology" by Rosenblueth and colleagues (1943), "A Logical Calculus of the Ideas Immanent in Nervous Activity" by McCulloch and Pitts (1943), and *The Nature of Explanation* by Craik (1943). Their epistemological coverages of the sciences of the artificial converge in questioning the approach to the assessment of synthetic models introduced by "proto-cybernetics," that is, by the scientists and engineers who, between the first and the third decades of the last century, began to develop the synthetic method (e.g., Cordeschi, 2008). Actually, to evaluate their models of living and cognitive processes, these precursors of cybernetics set up a "proof of sufficiency" approach, which, for the purpose of the scientific explanation of a target natural process, proposes to consider relevant synthetic models all artificial systems capable of reproducing the target process, independently of their biological plausibility. According to this approach, the empirical demonstration that a human-made mechanism can produce behaviors typical of an organism is enough to ensure the possibility of providing for them a mechanistic—and, in this sense, a scientific—explanation. The founders of cybernetics' unanimous criticism of this approach was directed to elevating the ambitions of the synthetic exploration of life and cognition. The core idea was that, when artificial systems do not incorporate scientific hypotheses on what functional organization—that is, on what specific mechanisms—generates the target behaviors in nature, they are of no use with respect to the scientific explanation of such behaviors. In other words, to be considered relevant models of a target natural process, artificial systems have to reenact this process based on the operationalization of scientific hypotheses of how it is generated in natural systems.

In Rosenblueth et al. (1943), this position is presented in connection with two compelling remarks, both central to the purposes of the present article. The first suggests that chemical artificial systems (i.e., wetware systems), having a physical realization similar to that of biological systems, may be better candidates than electromechanical systems (i.e., hardware systems) for a successful artificial modeling of natural cognitive processes:

> If an engineer were to design a robot, roughly similar in behavior to an animal organism, he would not attempt at present to make it out of proteins and other colloids. He would probably build it out of metallic parts, some dielectrics and many vacuum tubes. The movement of the robot could readily be much faster and more powerful than those of the original organism. Learning and memory, however, would be quite rudimentary. In future years, as the knowledge of colloids and protein increases, future engineers may attempt the design of robots not only with a behavior, but also with a structure similar to that of a mammal. (p. 23)

The development of hardware models is recognized by Rosenblueth et al. (1943) as useful to express aspects of the behavior of natural systems, but not to instantiate and explore the underlying mechanisms, for which it is considered a better option to build wetware models. This view was shared by other protagonists of early cybernetics, such as Donald M. MacKay (1951), who proposed that, to generate deep models of cognitive processes, "one would have to go in for mechanisms in protoplasm instead of mechanisms in copper" (p. 221).

The second remark associates the introduction of this visionary perspective to a cautionary comment related to the limits of such a realistic approach. Rosenblueth et al. (1943) present it through a joke, famously stating that "the ultimate model of a cat is of course another cat, whether it is born of still another cat or synthetized in a laboratory" (p. 23). From an epistemological point of view, this appears as a warning targeting "over-realist" strategies of implementation for the synthetic method. If merely imitative, or "underdetermined," models have no utility for the scientific explanation of target behaviors, the same can be said for models that would fully reproduce the target systems. Indeed, these would be "overdetermined" models, whose level of detail, instead of clarifying principles and mechanisms underlying life and cognition, would hide them. As Roberto Cordeschi (2008), condensing the related debate, points out,

> while, at one extreme, models based on simple functional equivalence turn out to be underdetermined, models that would go, say, down to the level of the most detailed physicochemical characteristics … [of the target systems] might turn out to be "overdetermined," as Stevan Harnad has effectively put it, in the sense that, in order to be as realistic as possible, the models would end up including physical and functional properties that might be irrelevant or nonessential to the researcher's understanding of the phenomenon under consideration: in this case the models would end up obscuring those principles or assumptions that they are called upon to elucidate. Restrictions do indeed increase the chance that the model will tell us something about the real phenomenon by approximating it (perhaps by forward motion), but we cannot delude ourselves that the rule is always and only: the more restrictions, the better. Unless we have to conclude, with Norbert Wiener's quip, that the best model of the cat is the cat itself. (p. 188)

It is beyond the scope of this article to take up the entire debate on this topic, for which we refer the reader to the relevant scientific literature (e.g., Boccignone & Cordeschi, 2007; Harnad, 1994; Webb, 2006). For the aims of this article, it is sufficient to bring into focus the central message of this debate: In a nutshell, with regard to the purpose of the scientific description of target natural processes, a synthetic model is significant if it lies between the extremes of mere imitation and full reproduction of those processes.

This epistemological insight, although diffused in the debate since its cybernetic origins, has been mostly neglected in the work of specialists engaged in modeling biological and cognitive processes synthetically. Since the 1950s, the community of the sciences of the artificial, to evaluate its models, refers to the Turing test, which focuses the assessment on their ability to imitate the target system's manifest behavior. Introduced by Alan Turing (1950) in "Computing Machinery and Intelligence" for other purposes, on the basis of the "imitation game," this test proposes that an artifact is ascribed the property of intelligence—construed as the ability to think like a human—when it is impossible for a human observer to distinguish such a machine from another human agent based on the answers it and that agent give to the human's questions. Despite multiple critiques and related reformulations, for which we refer to the extensive related literature (Copeland, 2000; French, 1990, 2000; Hernandez-Orallo, 2000), this test still constitutes a paradigmatic reference for assessing the relevance of synthetic models. Currently, not only is it still at the center of the debate in AI but it is acquiring a central role in the other sciences of the artificial. Recently, in the field of explorative SB, the Turing test has been at the basis of one of the first attempts of assessing the life-likeness of synthetic cells (Cronin et al., 2006). A recent investigation explicitly refers to the Turing test for SCs while discussing the result of a bidirectional chemical communication (via the exchange of signaling molecules and the corresponding activation of genes) between SCs and bacteria (Lentini et al., 2017). In particular, experimental data were employed to (cautiously) define the life-likeness of the SCs employed in the study, at approximately 40% (for a commentary, see Damiano & Stano, 2020).

Among the most severe criticisms of the Turing test, questioning its paradigmatic role as a tool for assessing the relevance of synthetic models of cognitive processes, is the Chinese Room argument presented by John Searle in his 1980 article “Minds, Brains, and Programs.” This argument, based on a thought experiment that reenacts key features of the Turing test, points out the limitations of its assessment approach and, at the same time, suggests that, when a form of AI focuses on imitation exclusively, it turns out incapable of reproducing deep, essential features of natural cognition. Searle delineates this view by discussing specifically the case of classical or computationalist AI, whose synthetic models of human cognition, he argues, are able to simulate, but not to re-create, its most distinctive aspect, that is, understanding—more in general, its semantic dimension. In his 1980 article, Searle traces this impossibility to classical AI’s tendency to synthetically model manifest aspects of cognitive behaviors and not their physical realization nor related underlying mechanisms. These are the grounds on which Searle denounces classical AI for being affected by the traditional mind–body dualism and offered theoretical and epistemological bases for developing EAI, that is, the biologically inspired form of AI that arose in the late 1980s, bringing forth a positive emphasis on the role the biological body plays in cognitive processes (e.g., Pfeifer & Bongard, 2006). However, Searle’s attack on classical AI, beyond Searle’s intentions, and despite his critique of the imitation paradigm, has been favoring a further polarization of the debate on the relevance of synthetic models, around the duality “mere simulation–complete reproduction” of the target cognitive processes. Indeed, in his 1980 article, Searle grounds his position in the conceptual alternative “weak AI/strong AI,” which, to this day, remains a paradigmatic reference point for assessing the relevance of synthetic models in terms of the alternative mere simulation–complete reproduction of the target natural processes. In fact, several EAI lines, such as android science (Ishiguro, 2016), use in this polarizing way Searle’s distinction in the context of research work producing frameworks to assess the relevance of synthetic models (Damiano & Dumouchel, 2020; Kahn et al., 2007).

As we mentioned earlier, one of the main goals of this article is to provide the scientific community with epistemological tools useful to overcome the mere simulation–complete reproduction alternative in assessing synthetic models. The ambition is to help make operational, within the synthetic modeling practice, the central message of the cybernetic and subsequent debate on the relevance of synthetic models. In view of a positive contribution of synthetic modeling to the scientific understanding of life and cognition, “imitation” and “full reproduction” of the target processes can be more fruitful if construed not as terms of a choice but as limits of a wide and plural field of exploration. In the next section, to support the operationalization of this epistemological perspective into synthetic modeling practice, we propose research work dedicated to generating assessment criteria, for synthetic models, allowing us to distinguish for them a variety of different forms of relevance (which include, but are not limited to, mere imitation and complete reproduction of target processes) and related forms of usefulness in the context of the synthetic exploration of life and cognition.

3 Two Criteria of Relevance for Synthetic Models

The research work presented in this section takes as its general frame of reference the autopoietic epistemology developed by Humberto Maturana and Francisco Varela (1973). This choice stems from the recognition of the strong connection between the synthetic approach and autopoietic cognitive biology, relying on the fact that the latter, besides proposing a systemic theory of life and cognition effectively inspiring the production of synthetic models for 50 years, also provides an explicit theory of scientific knowledge that defines the synthetic approach as the proper method to investigate biological and cognitive processes both at the theoretical and the experimental levels (Damiano, 2009). On these grounds, we consider that the notions and principles in which the autopoietic thematization of the synthetic approach is expressed can be seen as useful elements to provide a shared epistemological framework to the synthetic study of life and cognition (Damiano et al., 2011).

Coherently with this view, to elaborate criteria of relevance for synthetic models to be proposed to the whole synthetic modeling community, we extracted from autopoiesis two epistemological principles. In what follows, we propose a schematic description of them and of the way we ground in them the two criteria of relevance for synthetic models that we intend to propose to innovate the assessment approach of the synthetic modeling of life and cognition.[1]

3.1 Explaining as Constructing

The first principle we extracted from the autopoietic epistemology introduces an operational definition of the scientific explanation, which claims that explaining a phenomenon amounts to proposing a mechanism able to produce it (cf. Maturana & Varela, 1987, chap. 1). The epistemological ambition is redefining the traditional view of the scientific explanation, more specifically, shifting from the classical "explaining = predicting" perspective to an operational approach, which, by proposing the "explaining = constructing" notion of the scientific explanation, can be applied to systems exceeding the predictive ability of science. Asking for models that are able not to predict but to generate the natural target processes, the "explaining = constructing" principle focuses the scientific explanation not on actual but on possible behaviors of the systems explored. In this way, it defines a form of scientific explanation that is characterized by two main advantages. On one side, it is particularly suitable for biological and cognitive processes, as it cannot be affected by their unpredictability; on the other, it is able to ground a "general" science of life and cognition—as Christopher Langton (1989) would put it, a science of life and cognition as they are and could be (see also Damiano, 2009; Damiano et al., 2011).

Through its operational definition of the scientific explanation, the autopoietic cognitive biology generates the epistemological structure underlying the synthetic modeling of life and cognition. Schematically, target of the inquiry = natural phenomena untreatable through the classical predictive modeling; general approach = to scientifically understand means to build the target process; heuristic strategy = elaborating operational descriptions of the target natural processes; procedure = definition of (a set of) mechanisms able to generate the target natural phenomenology, and experimental exploration of the phenomenology they produce.

Also in Maturana and Varela's (1987) literature, this kind of scientific endeavor is articulated around the notion "synthetic." Indeed, the notion of synthesis defines explicitly the entire autopoietic biology's methodological orientation. On the basis of their principle of scientific explanation, Maturana and Varela target a new definition of life that, instead of listing the main features of biological systems, specifies a mechanism apt at producing the whole biological phenomenology (Damiano, 2009; Damiano & Luisi, 2010). They distinguish this form of definition from the traditional "analytic" definitions of life, consisting of lists of properties, by characterizing it as "synthetic" and by assigning it a condition to satisfy to be considered an appropriate operational explanation of life. The mechanism that the synthetic definition proposes has to manifest the ability to create, from a set of elemental components, the entire biological domain as we know it. In other words, the synthetic definition of life has to be able to generate, through the dynamical coordination of a set of elements, a minimal form of life—a minimal cellular system—and its characteristic phenomenology. Maturana and Varela (1987) include in this phenomenology not only self-production, but, on this basis, also reproduction and evolution, which, in principle, make the minimal living unit able to generate a differentiated living domain, as complex and populated as the terrestrial one.

This kind of scientific description captures the main traits of the synthetic modeling of life and, in particular, the traits of one of its most interesting expressions. We refer to Langton's (1989) program of AL, which intends to implement this approach in the form of an experimental construction: the synthesis of "any and all biological phenomena, from viral self-assembly to the evolution of the entire biosphere" (p. 53), without restriction to carbon-chain chemistry. Along with Maturana and Varela (1987), Langton (1989) associates the synthetic approach to a constructive and universal biology. His program meets autopoietic biology not only in the operational principle of the scientific

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[1] A partial, preliminary version of the research work presented in this paragraph can be found in Damiano et al. (2011).

explanation but also in a related "principle of universalization" of biology, according to which "life is . . . a result of organization of matter, rather than something that inheres in the matter itself" (p. 53).

3.2 Organization and Structure

The second autopoietic principle we consider relevant for the epistemological grounding of the synthetic approach is a theoretical element endowed with a significant epistemological value: the distinction between the notion of organization and the notion of structure. A simplification of Maturana and Varela's (1987, chap. 2) theoretical definition of this distinction puts it as follows: The organization of a biological system is its relational frame, that is, the network of relations defining the system as a unity of components; the structure of a biological system is its materialization, constituted of the actual components and the interconnections between them of which, in every instant, the system is made.

This theoretical distinction, far from being a theoretical novelty by Maturana and Varela (1987), was introduced by Jean Piaget (1967, chap. 4), who defined it as the theoretical key to understanding the specificity of the dynamic of biological systems. According to Piaget, indeed, while the organization is the invariant aspect of living systems, the structure is their variant aspect, because in these systems, all the elementary components permanently change, while the systems as wholes—that is, as relational unities of components—remain. As Piaget pointed out, this can be affirmed at both the ontogenetic and the phylogenetic levels. The relational unity keeps unchanged not only in the metabolic flux of physical-chemical components characterizing biological organisms but also during the ontogenetic changes making the living system unrecognizable from one observation to the next. Furthermore, the relational unity is what is transmitted through reproduction and stays unchanged through different generations. Being in this sense the invariant of the biological dynamics, the relational unity is the lowest common denominator of living systems. Hence operating the theoretical distinction of this invariant relational frame from the changeable materializations of living systems, and realizing its scientific description, means to define the common element of the whole class of biological systems—in other words, to define life itself.

The epistemological relevance of the distinction between organization and structure relies here and is at least twofold. First, this distinction allows one to characterize the mechanism underlying the biological dynamics in terms of a mechanism creating organizational invariance through permanent structural variation, which opens the possibility of providing an operational explanation of life in line with the autopoietic principle of the scientific explanation. Second, this distinction provides insights about the relevance of the synthetic approach for the study of natural living and cognitive processes, as it implies that (a) in principle, the material realization (structure) of living systems can be manifold and that (b) artificial systems displaying the same organization as living systems, and materializing it in different structures, belong to the class of living systems.

In this sense, by reproposing the Piagetian distinction between organization and structure of biological systems, the autopoietic cognitive biology offers theoretical grounds to the thesis—"the big claim"—through which Langton (1989) expresses the ambition of the synthetic approach to biology:

> A properly organized set of artificial primitives carrying out the same functional roles as the bio-molecules in natural living systems will support a process that will be "alive" in the same way that natural organisms are alive. Artificial Life will therefore be genuine life—it will simply be made of different stuff than the life that has evolved here on Earth. (p. 69)

3.3 Autopoiesis and the Extension of the Synthetic Approach to the Domain of Cognition

In line with the Piagetian approach, which treats the problem of cognition and the problem of life jointly, Maturana and Varela (1987) have emphasized that the process of metabolic self-production (i.e., autopoiesis) characterizing biological systems corresponds to a permanent dynamics of interaction with the environment and other systems, which they called "structural coupling" and conceptualized as a symmetric relationship made of reciprocal dynamics of perturbations triggering endogenous self-regulations. The thematization of this process as a cognitive process is at the basis of the cognitive biology that Maturana and Varela have developed as an integral part of their theory of life, paving the way to radical approaches to embodied cognitive science (e.g., Clark, 1999). Based on this view, the phenomenology that has to be produced by the autopoietic synthetic definition of life, to provide a scientific explanation of the living, includes not only all the biological but also all the cognitive phenomenology—*lato sensu* (Maturana & Varela, 1987). Hence the autopoietic operational principle of the scientific explanation and the autopoietic distinction between organization and structure, considered together, offer a grounding framework for both the synthetic study of life and the synthetic study of cognition.

3.4 Two Criteria of Relevance for the Synthetic Approach

The two autopoietic principles presented in the preceding pages generate two criteria useful for evaluating the relevance of synthetic models for the scientific exploration of life and cognition.

3.4.1 C1: Phenomenological Relevance

From the autopoietic operational principle of the scientific explanation (P1: *To explain scientifically is to provide a mechanism able to produce the phenomenology to be explained*) can be derived a criterion of *phenomenological relevance* for synthetic models of living and cognitive phenomena, according to which (C1) *A synthetic model is relevant at a phenomenological level if it provides a mechanism that produces (according to explicit parameters) the same phenomenology as the target living and/or cognitive phenomenology*.

We use the expression "phenomenological relevance" to emphasize that this criterion requires only a relation of identity, defined by explicit parameters, between the phenomenology generated synthetically and the target natural phenomenology. In other words, C1 does not impose any constraints on the biological plausibility of the synthetic mechanism used to reproduce the target phenomenology. Hence, in case C1 is not integrated with a criterion requiring the biological plausibility of synthetic models, and defining this plausibility, then C1 is not able to warrant that synthetic models express a biologically plausible operational explanation. In this sense, by itself, C1 assesses the capability of a model to imitate the target natural phenomenology without referring to a biologically plausible generative mechanism.

However, the autopoietic theory of the scientific explanation helps in addressing this limit by proposing a tool to distinguish between different phenomenologically—or imitatively—relevant models based on their operational explanatory power. This epistemological tool is a principle introduced by Maturana and Varela to orient the choice between different models describing the same phenomenological domain (cf. Maturana, 1988; Maturana & Varela, 1987, chap. 1). According to this principle, a better scientific explanation specifies a mechanism able to generate not only the target phenomenology but also other phenomena belonging to the same domain that were not considered in the context of the definition of the mechanism. In this way, this principle associates the operational explanatory power of a model to what we can call its "progressive" character—its capability of producing supplementary relevant phenomena. On the basis of this principle, we distinguish two basic kinds of phenomenologically relevant models: (a) *basic phenomenological models*, which produce only the target phenomenology, and in this sense have a basic operational explanatory power, and (b) *progressive phenomenological models*, which produce, together with the target phenomenology, other phenomena belonging to the same domain. The latter are characterized by an operational explanatory power proportional to the supplementary phenomena that they produce.

Importantly, the evolution toward higher-level progressive phenomenological models generates models endowed with a higher operational explanatory power but that are not necessarily plausible from a biological point of view. Indeed, although a greater operational explanatory power can be considered a clue of greater biological plausibility, the latter remains uncertain in the absence of a criterion defining this form of plausibility.

As we emphasize in the next section, the lack of full-fledged biological plausibility does not imply that basic and progressive phenomenological—or imitative—models are not useful tools for the scientific investigation of life and cognition. When the exploration of the target processes does not yet have consolidated and detailed theories of reference, attracting at least a partial consensus within the scientific community, these models can be precious sources of inspiration for the production of hypotheses about the mechanisms underlying the target phenomenology. In particular, when a synthetic model does not produce the target phenomenology, not only will the “failure” indirectly guide the research to more productive directions but also can help understanding “how not” and “why not” questions related to the mechanisms under inquiry.

3.4.2 C2: Organizational Relevance

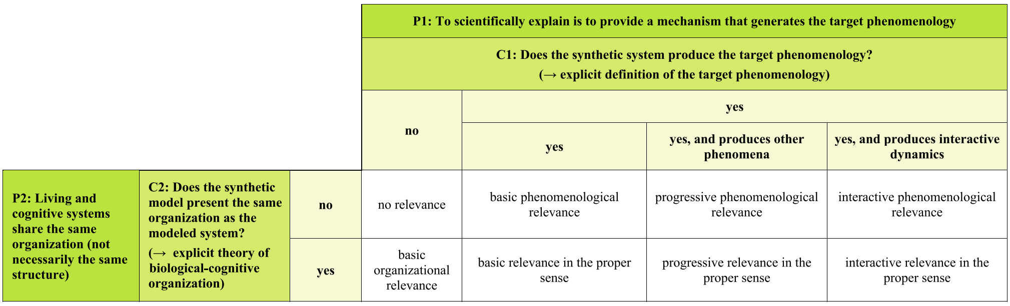
As mentioned in section 3.2, the autopoietic distinction between organization and structure implies that (a) all living systems share the same organization, but not necessarily the same structure, and thus that (b) synthetic systems displaying a different structure but the same organization as living systems have to be considered as belonging to the class of living systems. On these grounds, the organization–structure distinction produces a strong criterion of relevance for synthetic models. Indeed, according to (b), when synthetic models share the organization of living systems, they can be considered deep models of them, because they constitute specimens of the class of living systems. We can refer to this criterion as a criterion of *organizational relevance*, which warrants the biological plausibility of synthetic models. Considering the continuity between life and cognition advanced by the theory of autopoiesis, this criterion can be formulated as follows: (C2) *Synthetic models are organizationally relevant if they display (according to an explicit theory of the living-cognitive organization that is coherent with the distinction between organization and structure) the same organization as living-cognitive systems.*

To be met, this criterion requires the scientific community to engage in attempts of implementing, in artificial models, theories of the biological-cognitive organization, which represents an undertaking at the limits of realizability. Indeed, these attempts involve a series of difficulties that, far from being limited to technical problems, include critical epistemological obstacles, such as the irreducible multiplicity of the possible interpretations of a target theory, the different levels of abstraction at which each interpretation can be realized synthetically, and the related constraints limiting the possibilities of these implementations.

Although schematic, this overview of the challenges involved in meeting C2 is enough to emphasize that “relevance in the proper sense” cannot correspond to a “complete reproduction” of the target processes, which, to be attained, would require the availability of a definitive, exhaustive, univocally interpretable and perfectly implementable theory of the biological-cognitive organization. However, in this impossibility lies the interest of C2. As we show in the next pages, C2 encourages the adoption of a pluralist approach to the synthetic modeling of life and cognition, which, at the scientific level, appears more generative than a (over-)realist approach aiming at the complete reproduction of the target natural systems and processes–as Rosenblueth et al. (1943) suggested through their quip about modeling a cat (cf. section 2 of this article). A pluralist approach (Stano & Damiano, 2023) would indeed multiply the possibilities of generating interesting insights by engaging the sciences of the artificial not only in implementing a variety of theories of biological-cognitive organization, but also in exploring, with regard to each of them, a variety of different ways of implementation, based on diverse interpretations of the theory of reference and multiple options related to the choice of the level of abstraction defining the synthetic realization.

4 A Taxonomy for Synthetic Models: Forms of Relevance and Uses in Scientific Research

The criteria we introduced present two main advantages. First, they can be applied to hardware, software, and wetware models and thus provide the community of the synthetic modeling with a framework of assessment able to extend across the contributions generated by all the sciences of the artificial. Second, these criteria allow an evaluation of the relevance of synthetic models that, while overcoming the classical focus on their capability of imitating the target processes, avoids



			P1: To scientifically explain is to provide a mechanism that generates the target phenomenology			
			C1: Does the synthetic system produce the target phenomenology? (→ explicit definition of the target phenomenology)			
			no	yes		
				yes	yes, and produces other phenomena	yes, and produces interactive dynamics
P2: Living and cognitive systems share the same organization (not necessarily the same structure)	C2: Does the synthetic model present the same organization as the modeled system? (→ explicit theory of biological-cognitive organization)	no	no relevance	basic phenomenological relevance	progressive phenomenological relevance	interactive phenomenological relevance
		yes	basic organizational relevance	basic relevance in the proper sense	progressive relevance in the proper sense	interactive relevance in the proper sense

Figure 1. A taxonomy for synthetic models: forms of phenomenological and/or organizational relevance.

falling into the traditional pure imitation/authentic reproduction polarization. Indeed, the two criteria we propose generate a taxonomy of synthetic models that accounts for a variety of forms of phenomenological and organizational relevance, as well as their combinations (Figure 1).

Indeed, within the assessment space opened by C1 and C2, the polarization between "weak" and "strong" AI mentioned earlier, which is typically used to discuss the relevance of synthetic models within and beyond the field of AI, reflects a simplifying approach that recognizes only two extreme cases. Weak AI deals with purely phenomenologically relevant models, whereas strong AI targets models that are perfectly organizationally relevant and that, as a consequence, are considered phenomenologically relevant as well. Here the implicit hypothesis is that organizational relevance necessarily brings about phenomenological relevance, implying a hierarchy between the two poles of this classic opposition. On the contrary, including all the combinations of phenomenological and organizational relevance involves other, more articulated and interesting relations between them than a simple hierarchy and proposes to the synthetic modeling of life and cognition a wide and diversified map of possible development paths.

In this section, we explore this space—which, as we said, is inherently accessible to hardware, software, and wetware synthetic explorations of life and cognition—by focusing on wetware models, to clarify the concrete contributions that SB can offer to the synthetic modeling and show a map of potential paths for developing explorative SB by means of a synergic growth in basic and applied sciences.

4.1 Forms of Phenomenological Relevance

As mentioned, the criterion of phenomenological relevance C1 states that a synthetic model is phenomenologically relevant if it exhibits, coherently with well-defined parameters, the same phenomenology as displayed by the target system, independently of the plausibility of the particular mechanism used to achieve this. The focal point is the ability of a synthetic system to reproduce the behavior of a natural system, regardless of how that behavior is generated. In this sense, models that satisfy C1 are only imitative or "superficial" models of the target phenomena (Breazeal, 2003). They offer evidence of the sufficiency of the mechanisms implemented for the generation of the target processes, but in general, they say nothing about how these processes are generated in nature.

When theories of reference are missing, or paradigms are uncertain, these models and their implemented mechanisms can function as a drive to further investigate by trial and error the generative mechanisms of the phenomenology under inquiry. However, it is sometimes difficult to spot, without deeper knowledge of the finest details of the mechanism of the imitative models and the one of the biological targets, whether or not there is a partial correspondence between them.

In the context of explorative SB, several attempts to generate cell-like particles can be counted in the class of phenomenologically relevant models, satisfying C1 only. Reports on the generation of "sulphobes," coacervates, membrane-less droplets, "jeevanu," proteinoid microspheres, and so on (for a review, see Hanczyc, 2009) fill the annals of science. Usually these cell-like particles, which form spontaneously under certain conditions, serve the aim of investigating the structure and, occasionally, some rudimentary behavioral aspects of "primitive cells," as well as their spontaneous formation from very simple chemicals. These approaches succeed in reconstituting the phenomenology of micrometric cell-like structures, their physical stability, capability of solute retention, semipermeability, and generation by molecular self-assembly. On these bases, they embody the concept of self-distinction from the surrounding environment but generally fail to capture the topological structure of cells. This explains the superior relevance of lipid vesicles as modern-cell models, even if they are characterized by other limitations. In case the target phenomenology refers to primitive cells, the question of identifying suitable models is much more open; in this domain, a very partial phenomenological relevance (e.g., failure to produce stable-enough particles or generation of particles unable to grow and divide) can anyway help to progress the field and gain knowledge in an etiological sense, for example, Why this and not that (Bolli et al., 1997; Luisi, 2011)? In general, these purely imitative approaches to the generation of cell-like particles are viable as "biomimetic" systems and have a long tradition in experimental contexts. Quite often, experiments with these cell-like systems are carried out without claiming that the model provides an explanation about a target biological phenomenology (i.e., the origin of early cells). In most cases, the explicit intention refers to their employment as novel materials, exploiting novel chemistries and exploring novel reactivities for very diverse purposes, including those of applied science.

Another very interesting aspect of phenomenologically relevant models concerns the possibility of using them to investigate interactions between the target processes, which they imitatively reproduce, and the environment of reference. From the point of view of scientific research, this investigative function of basic imitative models can have particularly effective applications when the environment of reference, in which the models are situated for exploratory purposes, includes natural systems of interest for the ongoing inquiry. In this case, the possibility exists that the models, through their imitation of the target behaviors, engage natural systems in interactive dynamics that are of scientific interest for the investigation in progress. In these circumstances, the models constitute, for the scientific research on life and cognition, synthetic tools useful to explore and manipulate experimentally, in the natural systems with which they interact, dynamics of interest.

The significant value of this kind of model makes it worth distinguishing their specific form of phenomenological relevance, which we call *interactive phenomenological relevance*. Accordingly, we define artificial systems as *interactive phenomenological models* when they are able to synthetically produce the phenomenology under inquiry and, through the production of this phenomenology, engage natural biological-cognitive systems in interactive dynamics that (according to some explicit parameter) are germane to the scientific exploration of the target processes conducted through these models.

This form of phenomenological relevance finds an example in chemical cells ("chells"; Gardner et al., 2009) interacting with natural cells. Chells have been built by encapsulating some chemical components that generate the so-called formose reaction inside lipid vesicles. As a result of the reaction, a set of sugar-like molecules is produced; one of them, once released in the medium and transformed by another additional reaction, becomes a "signal molecule"—like species that can elicit a biological response in a nearby population of bacteria. Phenomenologically, the entire process looks like the biological process of (unidirectional) signaling between cells, but the sender cells (the chells) are artificial, and indeed they are just superficial analogs of biological cells, both in structure and in function. In particular, while the signaling event has a meaning for the bacteria, it makes no sense for the chells. Nevertheless, chells participate in the signal transmission event in a functional way, generating a behavior in the receiving biological cells that is similar to what happens in biology (chemiluminescence activation).

A third kind of imitative model are those characterized by the *progressive form of phenomenological relevance* introduced in section 3.4. *Progressive phenomenological models* are artificial systems that, besides reproducing the target phenomena, exhibit unexpected behaviors pertinent to the inquiry on the target processes.

An example can be found in a series of reports that describe the formation of solute-rich liposomes intended as primitive cell models (Luisi et al., 2010; Pereira de Souza et al., 2009). In this case, the target phenomenology was referred to modeling primitive cells that host nontrivial, network-like reactions in their lumen, generating liposomes in aqueous solutions where the solutes of interest were present—without any special interventions. The phenomenological relevance of this model is progressive because of some additional unexpected observations. In particular, the model not only showed that liposomes could host the target complex reaction successfully but also revealed that such an event occurred in demanding conditions too. In particular, the successful outcome was demonstrated either when liposomes were extremely small or when the chemicals were diluted—two conditions wherein, a priori, it should not have happened for the adverse statistics. This synthetic model of primitive cells, in addition to reproducing the target phenomenology, generates another phenomenology (the co-encapsulation of chemicals inside liposomes in adverse conditions), contributing to the development of investigations about the onset of conditions to support protometabolism thanks to the local concentration enhancement that can occur in some primitive cells.

A further type of phenomenological relevance combines the last two forms considered—that is, interactive and progressive phenomenological relevance. It refers to artificial systems that exhibit unexpected interactive behaviors relevant to the investigation within which they are used as models. An example in SB is given by SCs that were designed to send a chemical message to bacteria (Rampioni et al., 2018). In addition to the reproduction of the target (interactive) phenomenology, the model generated a phenomenology with progressive relevance as it resulted in an unexpected predator behavior (bacteria attacked and destroyed SCs, probably due to an unintended but very effective chemotactic signaling). In terms of explanatory power, the progressive aspect of this model converges with currently accepted views by showing, in a rather dramatic manner, why the de novo spontaneous generation of simple "defenseless" cells can occur only in natural scenarios where life is not preexisting.

Not intended to be exhaustive, the examples from SB proposed in this section show that the forms of phenomenological relevance defined by our taxonomy have concrete expressions in the current synthetic modeling research in the wetware domain. Further examples could have been made based on an epistemological analysis of already published studies about software and hardware models of biological-cognitive processes. This is not the case for the forms of (full-fledged) organizational relevance we are about to introduce, for which we believe contemporary research cannot provide concrete examples.

4.2 Forms of Organizational Relevance

As mentioned, the criterion of organizational relevance C2 states that a synthetic model is organizationally relevant if its organization reproduces the target system's organization, according to a pertinent scientific theory. This second criterion shifts the focus from phenomenology to organization, that is, from the target natural systems' behavior to their underlying mechanisms. Schematically, a synthetic model is *phenomenologically relevant* if it reproduces the behavior observable in the target systems, and it is *organizationally relevant* if it reproduces the target systems' organization and, in this sense, the organizational mechanisms that underlie that behavior.

Concerning organizationally relevant models, our taxonomy introduces a possibility that is typically excluded by the *pure imitation/authentic reproduction* polarization and hence by Searle's dichotomy of *weak versus strong AI*. This option covers the case of synthetic models that are organizationally relevant but not phenomenologically relevant, in other words, models whose reproduction of the target organizational mechanisms gives rise to new behaviors, different from those of the target natural systems. By taking into account this case, our taxonomy leaves open the possibility that the synthetic modeling may lead to *human-made variants* of natural systems that manifest different behaviors. This possibility, which we define through the label of *basic organizational relevance*, corresponds to the synthetic creation of new forms of life and biological cognition. Models characterized by this type of relevance would represent the most basic case of what Christopher Langton (1989), in the "big claim" about AL's ambition (see section 3.2 above), proposes, that is, Artificial Life as "genuine life . . . made of different stuff than the life that has evolved here on Earth" (p. 69) and, we add, displaying different behaviors.

An example that could express this possibility can be found in the programmatic design of an artificial system dubbed Los Alamos Bug, a protocellular model studied extensively but not yet fully realized experimentally (DeClue et al., 2009; Maurer et al., 2011). It is interesting to note that its design was focused on the thermodynamic coupling between the three functional structures (container, metabolism, and genes), which are themselves defined in an alternative way—when compared with usual biological models. An artificial peptide-nucleic-acid (PNA) genetic component was selected for an easier physical binding with the hydrophobic container, which in turn was a small, nonhollow structure (e.g., a micelle) and thus hosting reactions on its surface. An organic photosensitizer anchored to the template (or template precursor) is introduced to harvest the light energy and generate a redox-based proto-metabolism (Rasmussen et al., 2003).

The second form of organizational relevance generated by the criteria we proposed refers to models that satisfy both C2 and C1, that is, basic phenomenologically relevant models that are also organizationally relevant. We can define their form of relevance as *basic relevance in the proper sense*, as these models, at the same time, would reproduce the behavior observable in the target systems and the organization underlying that behavior. In this sense, they would correspond to artificial re-creations of living-cognitive systems, but not necessarily to those synthetic re-creations that Rosenblueth and colleagues, in their 1943 article, defined as “ultimate” models in their quip on the cat—“born of still another cat or synthetized in a laboratory”—quoted earlier. As argued, within the context of the synthetic modeling, reproducing living-cognitive systems’ organization means to attempt to embody theories of biological-cognitive organization in artificial systems. Related modeling procedures, far from enduring spans of time compatible with those characterizing the evolution of life and cognition on Earth, would be those typical of our biological lab procedures, which plausibly excludes the possibility of generating the kind of biological-cognitive structures that evolutionary processes of adaptation (and exaptation) could produce. In this perspective, a synthetic model endowed with both organizational and phenomenological relevance would probably be a much simpler system than the “real thing”—its target living-cognitive system.

This is the reason for the high scientific importance of models that, although organized according to the same principles that we found in known biological systems, express their behaviors via similar generative mechanisms, but at a lower or minimal level of complexity. It is generally supposed that part of living beings’ complexity comes from adaptation mechanisms and actually represents a map of the evolutive history of the organism. It is probable that in stable and controlled environments, the same organizational principles can be realized in a simplified manner.

A third form of organizational relevance refers to organizationally relevant artificial systems that are characterized by an interactive form of phenomenological relevance and thus can engage natural systems in dynamics that are germane for the study in which they are used as models. This form of relevance, which we define as *interactive relevance in the proper sense*, would characterize synthetic models that could be used as tools to explore interaction dynamics between natural living-cognitive systems and their human-made reproductions. This kind of investigation could be particularly interesting when these artificial systems, as suggested earlier, would express simplified versions of the target natural systems.

A fourth form of organizational relevance covered by the taxonomy that we are proposing reflects the possibility of organizationally relevant artificial systems that are characterized by a progressive form of phenomenological relevance. This option introduces the case of synthetic models that, while reproducing the organization of their target systems, would generate unexpected phenomena, supplementary with regard to those observed in the target systems. Hence the possibility of *progressive relevance in the proper sense* refers to synthetic models that would bring into evidence aspects of the target natural living-cognitive systems that are still unknown or genuinely new living-cognitive phenomena belonging to these artificial systems exclusively. In this second case, models that would be progressively relevant in the proper sense, as basic organizationally relevant models, would open to science the possibility of exploring “life as it could be,” as well as “cognition as it could be,” according to the ambition that Langton (1989) ascribed to the synthetic approach.

As mentioned at the end of section 4.1, models with phenomenological relevance can be found in current research based on software and hardware systems (not discussed in this article). On the other hand, it is a question whether organizational relevance can characterize software and hardware models–an issue that currently is debated in various ways. We believe, in line with the intuitions from early cybernetics (see section 2), that synthetic models endowed with organizational relevance can be built only within the wetware domain. Indeed, the biological-cognitive organization and phenomenology, which express autopoiesis as the distinctive property of living-cognitive systems, are based on a continuous production and transformation of their components that cannot take place in software or hardware systems. Chemical networks dynamically embody the set of relations of reciprocal production and transformation that characterizes autopoietic systems and their responses to environmental perturbations.

4.3 Partial Forms of Phenomenological and Organizational Relevance

We can also consider the case of partial ways of meeting the proposed criteria and thus of partial forms of relevance characterizing synthetic models. *Partial phenomenological relevance* refers to synthetic models that partially reproduce, according to well-defined parameters, the phenomenology under inquiry. These kinds of models can be particularly interesting, from the scientific point of view, to study complex interactions between the target processes and their environment of reference, because they allow the exploration of specific aspects of these interactions. *Partial organizational relevance* instead expresses the capability of a synthetic model to reproduce part of the organization of the target living-cognitive system. A particularly interesting case, from the point of view of scientific research, would be that of *partial organizational relevance in the proper sense*, in which the part of the target system's organization, incorporated in the artificial system, would correspond to the underlying mechanisms of the phenomenology that the model reproduces. In this case, the synthetic system would not be fully plausible from the biological point of view but would generate the target phenomenology through organizationally relevant mechanisms. This kind of artificial model, offering a partially realistic implementation of the target phenomenology, could be useful in the context of progressive approaches to constructing organizationally relevant models in the proper sense.

We believe that these categories cover the large majority of contemporary experimental wetware approaches, which pragmatically face the complexity of biological systems by generating models intended as milestones for a stepwise approximation of the full phenomenological or organizational targets. For example, the early reports on chemical autopoiesis, owing to Pier Luigi Luisi and his group in the 1990s (e.g., autopoietic reverse micelles, micelles, and vesicles, made by a handful of simple chemical compounds; Bachmann et al., 1990, 1991; Luisi & Varela, 1989; Walde et al., 1994), evidence partial forms of phenomenological and organizational relevance. These models were able to capture both aspects of the phenomenon of the growth and division of cell-like particles (whose structure was also relevant) and aspects of the corresponding generative mechanism (production of compounds of the structure by internal reactions). In another known example, production and consumption processes were balanced to achieve a phenomenological and organizational relevant, yet rudimentary, form of chemical homeostasis (Zepik et al., 2001). It is not surprising, then, that these pioneer efforts inspired, in renovated forms, attempts based on nucleic acids and proteins (Luisi et al., 2002, 2006; Oberholzer et al., 1999; Yu et al., 2001), which later flowed into contemporary SB research.

4.4 Between Underdetermination and Overdetermination

The criteria and taxonomy of forms of relevance here proposed articulate the space between the traditional poles of pure imitation and complete reproduction in a wide multiplicity of different forms of relevance for synthetic models, related to a variety of different research purposes, paths, and uses for the scientific research on life and cognition. On these bases, the approach we are proposing can be seen as an epistemological tool to make operational the warning through which

Rosenblueth et al. (1943) suggested the scientific community adopt the synthetic approach to avoid the unproductive shift from the problem of *underdetermined models*, whose explanatory power and production of insights are limited by their imitative value, to the problem of *overdetermined models*, whose proximity to the "real thing" itself would obscure, instead of clarifying, the principles at the basis of life and cognition that this community intends to explore.

The approach we are advancing, on one side, provides the synthetic modeling with a broad, concrete workspace between underdetermination and overdetermination and, on the other side, proposes to make it generative based on the pluralist operative hypothesis according to which there are many different ways to model the living-cognitive organization and, in this sense, to create artificial systems grounded in the same principles of life and cognition as the living-cognitive systems populating Earth.

In our view, it is in this space that exploratory SB can define new frontiers for EAI. Hence we refer to this workspace to organize a research program to ground, in SB techniques, a minimal EAI capable of overcoming the paradigm of imitation in the synthetic modeling of life and cognition.

5 Perspectives for Future Research and Concluding Remarks

How to advance SB research by designing and fabricating wetware systems characterized by forms of basic, interactive, or progressive organizational relevance? The position we put forward in this article is that a wide range of possibilities exists, lying between the extremes of pure imitation and complete reproduction of biological and cognitive processes.

We have insisted on how the theory of autopoiesis provides a valid epistemological and operational framework for designing synthetic systems that have chances of being relevant models of living-cognitive systems. However, as we argued in previous works, autopoietic mechanisms are very complex and thus highly difficult to re-create artificially. Natural autopoietic—that is, living-cognitive—systems have been shaped by evolution and, in their ontogenesis, are immersed in a process of permanent coconstitution and codefinition (through the terms of the autopoietic theory: "structural coupling") with their environment, which means that they originated and constantly emerge from a coevolutionary path. Synthetic models, on the other hand, are generated by a designer (the experimenter) who is bound to create for them internal mechanisms that, owing to the scientific need to work within the experimental reach, represent simplified—often oversimplified—versions of the target system (or of specific aspects of it) even when largely inspired by autopoietic cognitive biology. Typically, the limits imposed by the experimental reach lead to the search of minimal levels of complexity, either in the system's parts or in its organization.

As a consequence, synthetic models currently produced can cope only with a narrow range of environmental variations—imposed by the designer too. In other words, artificial systems have no mechanisms and no time to evolve—or better, to coevolve—with an environment, also because, in most cases, the environment itself is under the experimenter's control. Synthetic systems are born with prepacked instructions that are embodied not only in their structure but also in their rules of functioning (e.g., the chemical reaction network in the case of wetware models), valid for a specific (over-)simplified environment only. This constraint implies an obvious but rarely mentioned aspect of explorative SB research, namely, that the designer actually does not fabricate only a synthetic model (an agent) but a "supersystem" composed by the synthetic model situated in a certain environment—that is, a "synthetic ecology." In this sense, what "makes sense" to wetware synthetic models, and what does not, has actually been decided in advance. Within this experimentally accessible scenario, the "cognitive domain" of such synthetic models is also predefined at the time of their design and construction. Only unexpected adaptations can broaden the horizon of what the synthetic models can perceive and react to.

On the basis of these considerations, we would like to highlight one possible perspective for future research concerning wetware SB models of cells (SCs and systems alike). Side by side with the constantly reported advancements in the number of reconstituted functions, which ultimately serve to approach a lifelike behavior typically identified with a self-reproduction by growth division, a productive direction for targeting organizationally relevant models could focus on exploring processes potentially able to generate autonomous adaptive systems, characterized by a high level of plasticity. This, in our view (Damiano & Stano, 2018a, 2018b), means concentrating the synthetic modeling on mechanisms of self-regulation supporting self-maintenance, as these mechanisms, from an autopoietic point of view, are at the basis of sensemaking—biological cognition.

One of the most productive tendencies in current SB modeling approaches makes use of highly evolved elements, such as DNA and proteins, to build synthetic models of cells. These elements are conveniently used for their high performance in terms of specificity and reliability, because of the significant constraints they generate on the system dynamics. The other side of the coin is that the resulting system is significantly stiff, in the sense that it is made of specialized elements—a feature that is certainly a plus for a bioengineering perspective that aims at artificial systems that perform accurately predetermined operations; indeed, synthetic biologists refer to this aspect as the "programmability" of artificial systems (Fu, 2006; Kobayashi et al., 2004). A possible strategy for introducing regulation mechanisms would be based on recruiting a sensorial layer, for example, by implementing chemical neural networks in SCs (Gentili & Stano, 2022). This layer, however, needs to be designed properly to evidence context-dependent responses and a form of adaptivity or even plasticity. And it is an open question whether these goals can be achieved by employing molecular devices like two-component signaling systems (Hellingwerf et al., 1995), possibly coupled with self-referential gene expression.

However, other implementations can perhaps meet the organizational relevance criterion C2 differently, and should be explored too. For example, chemical networks and chemical systems with autopoietic traits (e.g., even simple ones, as the possible revisitation of the aforementioned example of micelles; Bachmann et al., 1990, 1991) could have the potential to respond to nonpredefined environmental perturbations in a systemic, adaptive way—specific investigations must be devised for exploring these new scenarios. As mentioned, experimenters need to learn to interpret network behavior according to a wholeness perspective. Here the long tradition of AL research can strongly contribute, providing conceptual and technical tools that would enrich SB approaches. Frontier fields of chemistry, such as the so-called systems chemistry (Ashkenasy et al., 2017; Ludlow & Otto, 2007; Ruiz-Mirazo et al., 2014; Szostak, 2009), can further contribute to this vision with new strategies.

Taking into consideration the vast field of experimental possibilities and the increasing interest that wetware synthetic models are attracting per se, we plan future investigations on these (and related) subjects. In particular, by relying on the proposed criteria (C1 and C2), and on the taxonomy that they generate (Figure 1), we intend to offer a first classification of the forms of relevance characterizing the variegate existing models, and from this starting point, we plan to move forward to define a research program to advance the field (Damiano & Stano, 2018a, 2021a, 2021b).

We believe that identifying the (forms/degrees of) phenomenological and organizational relevance is in itself a tool that helps to define new systems and modeling projects of interest. We expect that elaborating a set of theoretical models based on selected theories of the biological organization, and realistic ways of material implementation, is the next critical step for advancing research and related scientific discoveries in the field of explorative SB applied to AI. This will also limit the risks of stumbling on issues already met in the sciences of the artificial operating in other domains. Wetware synthetic models can indeed leak into the discussion on diffused analogy dyads, such as machine–organism, computer–mind, and similar concepts, by providing insights that uniquely stem from the very nature of chemical systems, whereby the distinction between operations and operands tends to vanish and circular casualties can often be recognized—especially in networks.

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