

Sense-making in Embodied AI. Towards Autopoietic Chemical AI

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ABSTRACT

Experimental Epistemology (EE) – i.e., the branch of cybernetic epistemology founded by Warren McCulloch [1] to experimentally explore “embodiments of mind” – still has significant potential to be expressed in AI. This is the basic premise of our work, which recognizes in one of EE’s most interesting affiliations, namely Humberto Maturana and Francisco Varela’s [2] autopoietic approach to the description of the living organization, a framework useful to improve contemporary Embodied AI’s modeling of natural cognition. Our main goal is to incorporate the autopoietic theoretical model of the biological organization in EAI’s synthetic models of natural cognitive systems, in order to artificially generate forms of autonomy and sense-making similar to those of living systems. The core novelty of our research program relies on the hypothesis that, to be effective, this operation cannot be realized in software or hardware, and requires wetware modeling. We plan to use Synthetic Biology (SB)’s techniques to develop wetware models of minimal living-like systems, such as closed chemical reactions based on chemical organization theory and active inference (i.e., the free energy principle), to test whether they can implement sensory-motor loops arising from self-production and agent-environment interactions, and generating minimal forms of autonomous (chemically-)embodied cognition.

Keywords: Autopoiesis, organizational closure, sense-making, active inference, synthetic models, chemical networks.

1. THE SB-EAI RESEARCH PROGRAM

Embodied AI (EAI) emerged in the early 1990s to address the limitations of classical AI, emphasizing the role of the body in cognition. Unlike traditional AI, which relies on computer programs, EAI explores “embodied agents” – biologically inspired robots that learn about their environment and perform cognitive tasks through their physical bodies. This approach, grounded in insights from natural cognition, aims to create increasingly complex cognitive abilities in robots, starting from sensory-motor processes. The goal is to model the full spectrum of natural cognitive processes, capturing the functioning of the “embodied mind” [3].

Since the late 1990s, EAI has shown significant advancements in practical applications. However, pioneers of this approach questioned whether embodied agents can match the cognitive

abilities of living organisms. Rodney Brooks highlighted this challenge in 1997 [4], citing a lack of understanding of the principles of the organization of life, sparking an ongoing debate about the realizability of EAI’s modeling ambitions.

“Organismically-inspired robotics” [5] and “Enactive AI” [6] attempt to address EAI’s gaps by drawing on theoretical models of biological organization, such as the autopoietic model. Despite their theoretical significance, these programs have yet to develop concrete approaches in EAI that effectively model natural cognition by implementing the organizational principles of life.

We believe the limitations of classical robotics in modeling cognitive and mind-like properties stem from their development in a domain different from that of biological organisms. Advances in the “Brooksonian paradigm”, which emphasizes sensory-motor coupling with the environment and proprioception over abstract symbolic reasoning, are still under development. However, we argue that modeling natural cognition and related biological processes cannot be effectively achieved in classical hardware and software, as essential features of biological cognition cannot be transferred to hardware and software domains. For example, software systems can simulate some superficial aspects of biological cognition, but cannot associate a self-generated meaning to their own operations, as they merely manipulate purely syntactic, meaningless symbols (whose semantic content is defined, and recognized, by the software engineer only). Furthermore, physical constraints rarely affect the range of software functioning, as it resides within the virtual domain. Hardware systems (robot bodies), on the other hand, are strongly constrained by physics (e.g., a robot arm cannot freely rotate because of their physical hinges), but their parts cannot be easily converted, transformed, perturbed or made precarious in any manner, because of the high energy required for these transformations. More basic fundament to advance with wet models is that software and hardware approaches are limited in their ability to understand cognition because they are rooted in the Turing machine paradigm, which inherently cannot address the halting problem. The wet chemical approach, grounded in autopoiesis and metabolic closure, seeks to overcome this limitation. This is because the concept of living systems, as characterized by this approach, inherently involves cognitive processes capable of handling ambiguity. However, the challenge lies in the technical difficulty of implementing or replicating such biological organization in the laboratory. We believe that a viable way to model natural cognition is the chemical domain, which has the characteristics that allow the

authentic realization of a bioinspired AI. Properly designed reaction networks can emulate (not simulate) the processes occurring in biological organisms (in particular, the simplest ones – taken as prototypes of all forms of biological intelligence) because they can embody all theoretical requirements specified by the most relevant theories about agency, autonomy, and life.

Inspired by this thesis, programs like the “Synthetic Biology (SB) and Embodied AI” aim at approaching the problem of sense-making by looking for a convergence of the engineering problem of constructing intelligent devices with the scientific issue of understanding the origins of cognition and life [7-10]. These programs have two main goals: (i) developing wetware models of minimal, archetypical living and cognitive systems and (ii) transforming these models into useful engineering applications. Here, we expand on these research axes, emphasizing that synthetically modeling not just behaviors but the organizational features of biological cognitive systems is crucial for a deep chemical approach to EAI.

2. TOWARDS A SYNTHETIC BIOLOGY APPROACH TO SENSE-MAKING EMBODIED AI

Synthetic Biology can be widely defined as those bottom-up approaches to the construction (synthesis) of complex bio/chemical systems that share with biological organisms essential traits of their structural and/or dynamical organization. The SB we refer to, therefore, includes investigations on the origins of life, chemistry of complex dynamical systems (systems chemistry), wetware Artificial Life, bio-organic and chemo-enzymatic strategies, etc. These research areas have a common playground: the chemical domain, which we believe is indeed the right space for investigating various sort of organizational approaches to EAI, being quite different from the usual hardware/software ones.

Our main claim is that thanks to its chemical peculiarities, SB approaches can provide concepts and tools for an effective modeling of the biological organization, in particular with respect to life and cognition, overcoming the current limitations of hardware/software approaches to cognition and sense making. Effective models of bio-organizationally relevant cognitive processes have been not fruitful because the capacity of material transformations, which is a specific feature of the chemical domain, simply cannot be emulated by hardware systems, while software systems cannot even “perform” in the physical space – they just produce simulations of physical processes.

Chemical and biochemical networks, approached both experimentally and theoretically, are essential for understanding abiotic, prebiotic, and biotic systems due to the complex behaviors emerging from their dynamics and to the actual possibility of realizing the “organizational closure”, identified as the crucial property of life and cognition by Maturana and Varela [2] – see below. The diversity of chemical species in these networks generates varying topologies and dynamic stability. For instance, evolved enzymes exhibit strong substrate selectivity, whereas primitive catalysts were likely more promiscuous. Despite the mystery surrounding primitive chemical networks, it is generally accepted that several core carbon-based metabolic pathways were crucial for the origin of primitive cells, encapsulating primitive biogenesis [11]. These networks operate dynamically, producing and consuming their components in a cyclic organization. When such self-

maintaining systems can define themselves against their environment by producing a boundary, they are termed “autopoietic”.

Following Maturana and Varela’s concept of autopoiesis [2], autopoietic networks are seen as both living and cognitive systems. An autopoietic system continuously specifies its organization through the production of its components (metabolic closure/constraint closure, [12]). This involves compensating for environmental disturbances to remain organized. Maturana and Varela [2] viewed this as the fundamental cognitive process, described as “structural coupling” with the environment and “sense-making.” This is the generation of operational meanings for environmental perturbations, which are expressed in self-regulation schemes that ensure the system’s functional continuity amid perturbations and intertwine with self-production.

We believe this theoretical framework, focused on the dynamics of chemical networks, can offer new, promising approaches to EAI, especially when developed through cutting-edge wetware modeling methods from synthetic biology (SB). Current software and hardware EAI systems, while useful for solving cognitive tasks, lack true cognition in terms of structural coupling and sense-making because they do not exhibit metabolic-like self-production dynamics [13]. To create biologically-like AI, it is necessary to implement self-regulation processes of (bio)chemical self-production. In other words, the missing piece in EAI is the introduction of wetware chemical models, which are particularly suited for the artificial realization of biological organization — a wetware approach to organizational EAI.

Providing a roadmap for this modeling approach would help address questions about the continuity between life and cognition and clarify whether minimal synthetic biological systems can implement cognitive processes at the fundamental (bio)chemical level.

3. SENSE-MAKING EMBODIED AI THROUGH CHEMICAL ORGANIZATION THEORY (COT) AND FREE ENERGY PRINCIPLE (FEP).

To model cognitive processes within the SB-EAI framework, we propose combining Chemical Organization Theory (COT) [14] and active inference, a corollary of the Free Energy Principle (FEP) [15]. Our hypothesis is that a minimal self-maintaining metabolic system, which operates out-of-equilibrium, can arise from a set of primitive core metabolism-based chemical reactions through active inference. The implementation requires:

1. Identifying a small number of key chemical reactions capable of self-maintenance in COT terms (Fig. 1A).
2. Determining if some chemical reactions or products form the COT analysis can serve as internal and sensory-active states (Fig. 1B).
3. Allowing the system to interact with a fluctuating environment to assess if it maintains out-of-equilibrium dynamics via active inference, i.e., if the system self-maintains by inferring and responding to environmental fluctuations.

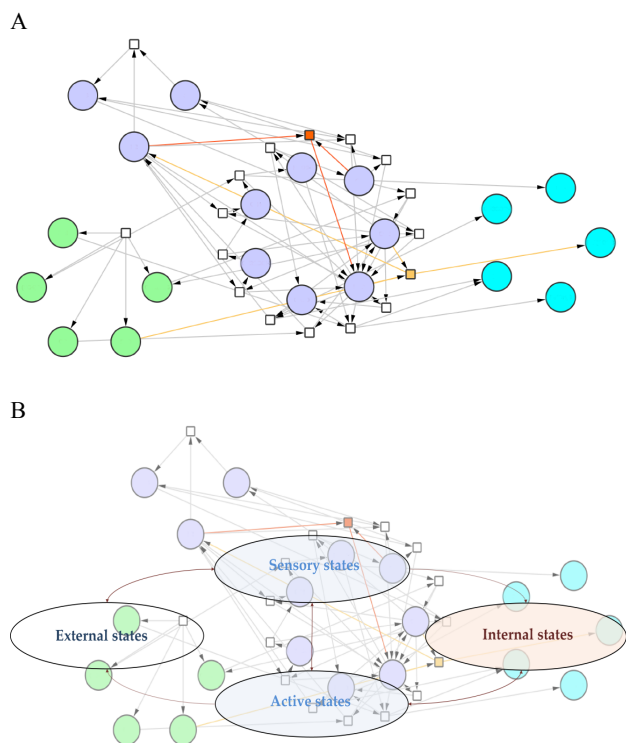


Figure 1. Minimal chemical reaction network capable of self-maintenance with partition states for active inference. A) The self-producing organization of living system depicted by COT involving the origin of life scenario. Circular nodes represent the component or chemical species (resources), while white square nodes represent the reactions. The yellow squares correspond to reactions associated with biotic activity, and the orange ones, with abiotic activity. Arrows go from reactants to products. Colors differentiate the dynamic properties of the resources. Green represents the inflow that is not self-maintained. Lilac represents the self-maintained chemical species that together with the inflow (lilac) form a sub-network that simulates operational closure. Cyan represents the waste chemical species. B) The self-producing organization of living system depicted by COT with an implementation of active inference, and thus the partition of the system with a Markov blanket.

These minimally chemically embodied cognition forms should be understood through sensory-active loops that selectively interact with environmental molecules, transforming them for the system's self-maintenance. Through active states, the system plans and selects environmental molecules to preserve its identity. In this sense, such an autopoietic-like chemical system would be capable of sense-making based on continuous chemical self-production.

This approach aligns with EAI's emphasis on sensorimotor coupling and embodied cognition. Reverse engineering can be applied to identify the key molecular components that are critical for the system's organizational stability. This determination could rely on the production rates of chemical components needed for self-maintenance in a fluctuating environment, where the assimilation rates for different elements are governed by the "blanket states" (a technical term defined within the FEP). It is crucial that the time dynamics of such an autopoietic-like chemical organization avoid dissipation within an analytically determined timescale.

4. A CALL FOR NOVEL EXPERIMENTAL PERSPECTIVES IN SYNTHETIC BIOLOGY AND SYSTEMS CHEMISTRY

Based on the above-mentioned proposal, it is evident that we call for a novel turn in experimental SB (and systems chemistry) that explicitly include the mechanisms underlying cognition and sense-making as derived from our analysis.

Current investigations on the so-called "synthetic cells" (SCs) are indeed advancing quite well, promoted by the significant efforts of a growing community. National and international consortia have proven to be effective in boosting SC research [16,17], which is often presented as one of the most innovative direction, not resembling anything existing in the past.

To date, studies on cell-like systems cover distinct interests, from the origin of life to the construction of SC with minimal complexity, from being used as synthetic models of cells, to possible applications as "smart" drug delivery systems (Fig. 2).

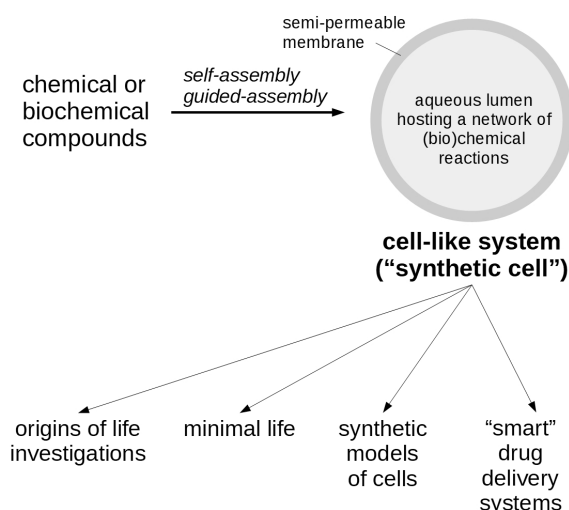


Figure 2. Synthetic Cells. The construction of cell-like systems (generally called Synthetic Cells, or SCs) is a flourishing branch in SB, origins of life investigation, systems chemistry, applied biotechnology. By means of the research project "Synthetic Biology and Embodied AI", we intend to extend the scientific interest toward fundamental questions as the emergence of autonomous systems, their capability of sense-making, and investigate in this manner novel approaches to embodied AI. The resulting perspective, which intrinsically requires collaboration from specialists of different disciplines, can be considered a modern version of the McCulloch's Experimental Epistemology.

For instance, systems made of allegedly primitive molecules are employed to model primitive cells. In this context, experimental targets are often focused on the self-replication or on the self-reproduction of the protocells, or of part of them. Using primitive (or anyway simple) molecules serves to demonstrate that some cell-like behavior are achievable in conditions that are far from modern biological ones. The search for minimal complexity, possibly using contemporary molecules (DNA, ribosomes, enzymes, etc.) is instead targeted to identify the irreducible core of those genetic-metabolic networks which generate a living system [18]. Such a direction attacks the problem of "minimal life" from the bottom-up, while other approaches are devoted to simplifying extant biological cells by removing unnecessary genes (top-down) [19]. The possibility of constructing a simplified version of cells helps to understand the dynamics of complex multi-molecular and often hierarchical

systems in absence of the complicated background present in biological cells. In this way, it is possible to study complex mechanisms from a privileged viewpoint. These three research directions pertain to basic science, i.e., they refer to fundamental questions in chemistry and biology. The fourth research area sees SC research applied angle, as these man-made structures can be used in nanomedicine. In this respect, there are already interesting reports that show how SCs could produce therapeutic proteins, acting in situ, near the damaged cell [20].

How SCs in nanomedicine scenarios actually elicit fundamental questions in communication, cognition and sense-making.

While SC research in the first three directions (see above) has been mainly carried out by focusing on what SCs do, irrespective of their environment (conceived, explicitly or implicitly, constant or buffered), just imagining the use of SC in a nanomedicine scenario immediately implies the need, for SCs, of understanding their environment, where they are, when the production or release of their therapeutic cargo should initiate. In other words, in this research area, the environment cannot be seen as a passive medium, but it co-determines the dynamics inside SCs. Such a perspective was very clear from the beginning, and indeed it stimulated our initial interest toward communication acts that SCs must implement in order to (re)cognize their environment [21]. It is certainly possible to model this scenario from the classical computational perspective, the one in which environmental signals are conceived as input, SC machinery as a computational unit, and the downstream production of molecules as output. This is a bio-engineering perspective that is usually adopted in the field of Molecular Communication, Molecular Computing, Molecular Robotics. In this perspective, the meaning of signals has been pre-established by the SC designer. For example, because the SC must activate an internal mechanism only when a certain molecule S is present in the environment, a receptor R for S is included in the SC, as well as a mechanism that transduces the S-to-R binding in order to activate a final effector (e.g., the production of a drug). The SC is a machine-like system that processes information (and it should be noted that in this context “information” is resembling “a thing”) and behaves in pre-programmed manner.

On the other hand, a more fundamental biological question is about how a chemical system (e.g., organized in a cell-like manner) can autonomously generate meanings of external cues, and understand this mechanism at different time scales (i.e. imminent or here-and-now, and evolutionary). It is in these context that SB becomes a powerful tool to explore these features – which, as mentioned, are nothing else than AI implemented in the chemical domain.

Exploring autopoiesis and cognition in SB and systems chemistry

Although it can be easily recognized that a decisive contribution to the birth of bottom-up minimal life and origin of life investigations based on the construction of synthetic cells actually comes from the autopoietic tradition (in particular from pioneer studies on “chemical autopoiesis” in the 1990s [22]) the central theme has been always focused on the material problem of realizing a self-bounded system capable of producing its own components. This is possibly due to the fact that early and current practitioners generally concentrate the attention on the chemical problem – which is far from being a trivial one.

On the other hand, autopoiesis and cognition are indissolubly bound to each other (“all knowing is doing and all doing is knowing” [2]). However, investigations that explicitly aim at considering the cognitive capability of minimal chemical systems are rather rare. Our research plan, the “Synthetic Biology and Embodied AI” aims at filling this gap, and therefore aims at identifying (by modeling and by constructing) chemical systems that will display (minimal) cognition.

At this aim, the first conceptual move is to depart from the information-as-a-thing idea, and conceive instead information as a process: the process of being in-formed. This critical consideration resonates well with early discussions on what information is (dating back to the first cybernetics), that involve primary figures of the Macy conferences such as Shannon, Bateson, MacKay, and others. As it is well known, and summarized in a recent review [23], the Shannon definition of information is not connected to its meaning [24]. For others, semantic aspects of information are relevant as well (e.g., the well-known Bateson definition “information is a difference that makes a difference” [25]). As remarked by Pask, the meaning of information was defined, by MacKay, as the selective function exerted by any event that can be detected by an organism or a machine upon the ensemble of transition probabilities that characterize their behavior [26]. This means that there are events capable of in-forming the system of interest, in the sense that can give it a new form (a new structure).

The process of in-formation, thus, requires that a system can change its structure, and therefore its detailed dynamics, to cope with events that act, evidently, as a perturbators of a pre-existing system dynamics (think, for example, to a chemical network with a certain set of relations between its elements; note that the relations are chemical interactions or chemical reactions. The set of relations should have the property of change qualitatively and quantitatively).

The capacity of a network of accommodating some perturbations, without losing its overall organization (e.g., its autopoiesis), becomes the target property for being implemented in novel SB and systems chemistry artifacts, in order to become cognitive and capable of sense-making. The innovative theoretical analyses mentioned in Section 3 (COT and FEP) would serve as a guide for developing those systems in the laboratory.

This move will represent surely a cultural shift, from conceiving autopoiesis just as the self-production of all system components – as it is currently done, to a richer theory that includes an adequate and self-determined structural plasticity with respect to certain environmental perturbations – those that have been selected by the system itself because of their compatibility with the ongoing dynamical organization. A useful starting point, for inspiring experimental research, would be the paper on autopoiesis with/without cognition written by Luisi, a pioneer of chemical autopoiesis [27], see examples in Fig. 3. Our plan for the “SB and Embodied AI” project, in addition to the above-mentioned theoretical understanding, foresees several possible modeling and experimental strategies.

Designing a proper noisy environment. While, in the natural evolution, environmental perturbations are evidently not bound to spatiotemporal constraints (the evolution and the ‘fate’ of species are de facto open-ended), in laboratory investigations it is plausible starting the approaches to minimal cognition from a pragmatic viewpoint and design systems (e.g., SCs) capable of here-and-now adaptation to given environmental perturbations. However, in order to exploit the selective capabilities of chemical dynamical systems, those perturbations need to have random spatiotemporal distributions,

or being random and recursive (aiming at observing minimal forms of learning), or randomly combined – to possibly trigger synergic (associative) pathways. As evidenced by Levin, many relatively simple genetic networks may unexpectedly display interesting behavioral patterns [28].

In other words, although the environment is still “designed”, it is designed to also presents uncertainty features (i.e., a form of noise). As mentioned, this will let the autonomous selections of “permitted” perturbations by the likewise stochastically built SCs (each SC, in a laboratory population, has a definite composition, which generally differ from the others). Due to the highly non-linear interactions in SCs, and the fact that at the molecular level interactions of any sort cannot be prevented [29], it is generally not possible to foresee which set of SC/environment combinations will work adaptively.

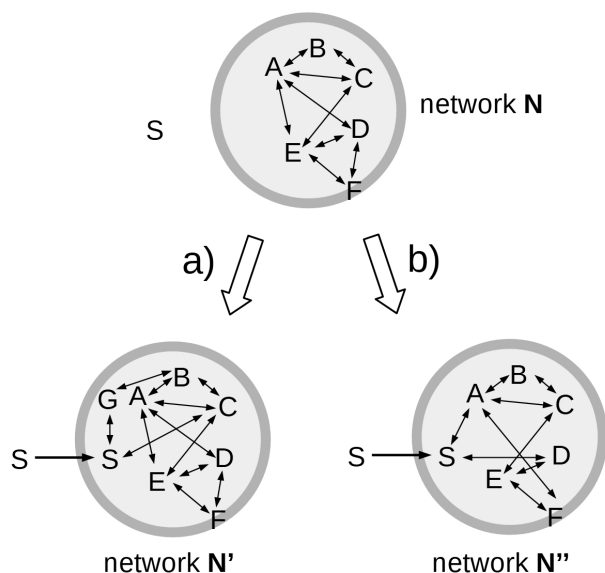


Figure 3. Possible interactions of an external event with a self-bounded chemical network. Inspired by the arguments presented in [27], the figure schematically represents some ways in which a self-bounded chemical network – supposed to be autopoietic (or autonomous) – accommodates the permeable compound S into its dynamics, with the requirement that there will be no modifications of the overall organization (autopoietic, or autonomous one). In a), S interacts with some of the system components (e.g., C), to generate new species (e.g. G), which in turn interacts with other components (e.g., B). In b), the presence of S leads to interactions (with A, with D) that directly or indirectly lead to the disappearance (or weakening) of some of the previously existing links (e.g. between A and D, between D and F), and the appearance of others (e.g. between A and F).

Autonomous chemical (sub)networks. The software modeling of a self-sustaining autopoietic system is always possible, but its concrete wetware realization is quite challenging. Despite the progress in SC research, there are still no report of artificial autopoietic systems. As mentioned in previous contributions [30], a pragmatic route to work on sense-making and minimal cognitive chemical systems could be the focus on autonomous systems instead of autopoietic ones. By autonomous system (actually, a sub-system) we mean a chemical network embodying a closed loop of causal entailments, possibly being supported by ancillary processes that do not necessarily form an autopoietic organization. The strategy here described is similar to a proposal referred hardware-software embodied AI (“Instead of building robots

that instantiate metabolic processes that self-organize to form autonomous networks, the strategy has been to build robots whose sensorimotor processes self-organize to form autonomous networks. [31]). Our approach, however, is conceived as propedeutic to a full-fledged realization of autopoiesis in wetware, while the same cannot be done in hardware-software domains.

Re-evaluating the early examples of chemical autopoiesis. During the years, the original design of chemical autopoietic systems, acutely devised by Luisi and Varela in their 1989 paper [32], has been firstly explored by means of several variations of implementations (reverse micelles, micelles, vesicles), and later it converged toward enzyme-containing vesicles because of some utilitarian reasons. Firstly, the use of enzymes allows the realization of complex transformation in mild conditions. Enzymes are amazing catalysts acting in chemo- regio- and stereospecific manner, but at the same time they can operate on substrates just similar to the natural ones. Their use is very convenient from the practical viewpoint. Second, the vesicle architecture is more cell-like than micelles and reverse micelles architectures. Moreover, vesicles made of fatty acids are also good models of primitive cells. Third, by exploiting the combination of transcription-translation mechanisms (DNA, mRNA, enzymes), it is rather straightforward to generate cell-like systems that summarize the most important processes of cell biology (the one associated to the so-called central dogma). It can be said that the evolution of research lead to a gradual transition from chemical autopoiesis to bottom-up synthetic biology [33].

However, this arrival point, which from a certain viewpoint is indeed very successful (as mentioned at the beginning of Section 4) have also some cons. In particular, the complexity associated to the transformation of biomacromolecules makes very difficult the achievement of autopoiesis. Indeed, in order to have all SC components produced and degraded according to the autopoietic need of a “network of processes of production (transformation and destruction) of components” [2], a very complex network must take place in SC, whose components are complex molecules, and processes are likewise complex. Indeed the minimal autopoietic cell would correspond, by and large, to the minimal top-down cell determined by Venter via the famous synthetic genome transplant experiments [19]. Even worst is the case in which some SC components are artificial molecules such as amphiphilic polymers, whose synthesis and degradation is out of reach in the conditions of SC existence.

Paradoxally, then, the very simple systems initially explored by Luisi in the early 1990s, that are made by a bunch of chemicals and very few transformation processes, seem to be a convenient prototype to start with, possibly enriched by the recent flourishing research on systems chemistry [34] on one hand, and by the above-mentioned COT and FEP formalisms on the other hand.

5. CONCLUDING REMARKS

The research program described in this paper – Synthetic Biology and Embodied AI – is still in an early development stage. We have highlighted the motivations behind its development and the goals of our proposal. It will represent a new form of bioinspired AI, more precisely of embodied AI, developed for the first time within the epistemologically fecund framework of autopoiesis. From a theoretical viewpoint our vision is alternative to the computational one, so that the scope and the questions that motivate us are not the construction of

programmable chemical robots, although some of the modeling/experimental tools might be the same or very similar ones.

As argued above, one of the major goals is the investigation of how sense-making emerge in certain chemical dynamical systems, those based on a specific form of dynamical organization, the autopoietic one. As mentioned, the processes we are interested in can be both in the short- and long-time range.

Research will be carried out by combining theory and experiments, conceptual and numerical models. We plan to investigate cognitive processes by combining COT and active inference, applied on minimal minimal self-maintaining metabolic systems operating out of equilibrium. Ideally, such a system would also be self-bounding, i.e., it will spontaneously self-confine and self-distinguish from the environment as biological cells do. From a practical viewpoint, the experimental approaches that seem more fruitful to this enterprise are those recognized as SB ones (including systems chemistry). SCs can be a well-suitable platform for these investigations.

Although our primary interest is facing fundamental questions about the origin of cognition in chemical systems with minimal complexity, we believe that our efforts can contribute to applied research too (including molecular robotics and the so-called chemical AI [gentili]), and in particular in all cases where the artificial agent (e.g., a SC) establishes communicative relations with other agents – think to biological cells in a nanomedicine scenario – a fascinating area of sure interest and development in next years.

6. ACKNOWLEDGEMENTS

The research on synthetic cells and minimal cognition based on autopoietic organization has been funded by the Italian MUR, within the PRIN2022 program (An Organizational Approach to the Synthetic Modeling of Cognition based on Synthetic Biology and Embodied AI; grant number 20222HHXAX).

7. REFERENCES

- [1] W. McCulloch, **Embodiments of Mind**. Boston: MIT Press, 1965.
- [2] H. R. Maturana, and F. J. Varela, **Autopoiesis and Cognition: The Realization of the Living**. Dordrecht: D. Reidel Publishing Company, 1980.
- [3] R. Pfeifer, and J. Bongard, **How the body shapes the way we think: a new view of intelligence**. Cambridge, MA: MIT press, 2006.
- [4] R. A. Brooks, “From earwigs to humans”, **Robotics and Autonomous Systems**, Vol. 20, No. 2, 1997, pp. 291-304.
- [5] E. A. Di Paolo, “Organismically-inspired robotics: homeostatic adaptation and teleology beyond the closed sensorimotor loop”, in: **Dynamical Systems Approach to Embodiment and Sociality**, K. Murase and T. Asakura (Eds.), Adelaide: Advanced Knowledge International, 2003, pp. 19-42.
- [6] T. Froese, and T. Ziemke, “Enactive artificial intelligence: Investigating the systemic organization of life and mind”, **Artificial Intelligence**, Vol. 173, No. 3, 2009, pp. 466-500.
- [7] L. Damiano, Y. Kuruma, and P. Stano, “What can Synthetic Biology offer to Artificial Intelligence (And Vice Versa)?”, **BioSystems**, Vol. 148, Supplement C, 2016, pp. 1-3.
- [8] L. Damiano, Y. Kuruma, and P. Stano, “Synthetic Biology and Artificial Intelligence: Towards Cross-fertilization”, **Complex Systems**, Vol. 27, No. 3, 2018, pp. i-vii.
- [9] L. Damiano, and P. Stano, “Synthetic Biology and Artificial Intelligence. Grounding a cross-disciplinary approach to the synthetic exploration of (embodied) cognition”, **Complex Systems**, Vol. 27, No. 3, 2018, pp. 199-228.
- [10] L. Damiano, and P. Stano, “Explorative Synthetic Biology in AI: Criteria of Relevance and a Taxonomy for Synthetic Models of Living and Cognitive Processes”, **Artificial Life**, vol. 29, 2023, pp.1-21.
- [11] H. J. Morowitz, **Beginnings of Cellular Life: Metabolism Recapitulates Biogenesis**. New Haven, CT: Yale University Press, 1992.
- [12] S. A. Kauffman, and A. Roli, “A third transition in science?”, **Interface Focus**, Vol. 13, 2023, 20220063.
- [13] S. Rubin, “Cartography of the multiple formal systems of molecular autopoiesis: from the biology of cognition and enaction to anticipation and active inference”, **BioSystems**, Vol. 230, 2023, 104955.
- [14] P. Dittrich, and P. Speroni Di Fenizio, “Chemical Organisation Theory”, in: **Systems Biology**, M. Al-Rubeai and M. Fussenegger (Eds.). Dordrecht: Springer, 2007, pp. 361-393.
- [15] K. Friston, “Life as we know it”, **J. Royal Society Interface**, Vol. 10, 2013, 20130475.
- [16] P. Schwille, J. Spatz, K. Landfester, E. Bodenschatz, S. Herminghaus, V. Sourjik, T. J. Erb, P. Bastiaens, R. Lipowsky, A. Hyman, P. Dabrock, J.-C. Baret, T. Vidakovic-Koch, P. Bieling, R. Dimova, H. Mutschler, T. Robinson, T. Y. D. Tang, S. Wegner, and K. Sundmacher, “MaxSynBio: Avenues Towards Creating Cells from the Bottom Up”, **Angewandte Chemie International Edition**, Vol. 57. No. 41, 2018, pp. 13382–13392.
- [17] C. Frischmon, C. Sorenson, M. Winikoff, and K. P. Adamala, “Build-a-Cell: Engineering a Synthetic Cell Community”. **Life**, Vol. 11, No. 11, 2021, 1176.
- [18] P. L. Luisi, T. Oberholzer, and A. Lazzano, “The Notion of a DNA Minimal Cell: A General Discourse and Some Guidelines for an Experimental Approach”. **Helvetica Chimica Acta**, Vol. 85, No. 6, 2002, pp. 1759–1777.
- [19] D. G. Gibson, J. I. Glass, C. Lartigue, V. N. Noskov, R.-Y. Chuang, M. A. Algire, G. A. Benders, M. G. Montague, L. Ma, M. M. Moodie, C. Merryman, S. Vashee, R. Krishnakumar, N. Assad-Garcia, C. Andrews-Pfannkoch, E. A. Denisova, L. Young, Z.-Q. Qi, T. H. Shapiro, C. H. Parmar, C. A. 3rd Hutchinson, H. O. Smith, and J. C. Venter, “Creation of a Bacterial Cell Controlled by a Chemically Synthesized Genome”, **Science**, Vol. 329, No. 5987, 2010, pp. 52-56.
- [20] N. Krinsky, M. Kaduri, A. Zinger, J. Shainsky-Roitman, M. Goldfeder, I. Benhar, D. Hershkovitz, and A. Schroeder, “Synthetic Cells Synthesize Therapeutic Proteins inside Tumors”. **Advanced Healthcare Materials**, Vol. 7, No. 9, 2018, e1701163.
- [21] P. Stano, G. Rampioni, P. Carrara, L. Damiano, L. Leoni, and P. L. Luisi, “Semi-Synthetic Minimal Cells as a Tool for Biochemical ICT”, **BioSystems**, Vol. 109, No. 1, 2012, pp. 24–34.
- [22] P. Stano, “The birth of liposome-based synthetic biology: A brief account”, in: **Liposomes: Historical, Clinical and Molecular Perspectives**, B. R. Pearson (Ed.). Hauppauge, NY: Nova Science Publishers, Inc., 2017, pp. 37-52.

- [23] R. K. Logan, “What Is Information?: Why Is It Relativistic and What Is Its Relationship to Materiality, Meaning and Organization”, **Information**, Vol. 3, No. 1, 2012, pp. 68-91.
- [24] C. E. Shannon, “A mathematical theory of communication”, **The Bell System Technical J.**, Vol. 27, 1948, pp. 379–423 and pp. 623–656.
- [25] G. Bateson, **Steps to an Ecology of Mind. Collected Essays in Anthropology, Psychiatry, Evolution, and Epistemology**. Chicago: University of Chicago Press, 1972.
- [26] G. Pask, **An Approach to Cybernetics**. London: Hutchinson and Co., 1961.
- [27] M. Bitbol, and P. L. Luisi, “Autopoiesis with or without Cognition: Defining Life at Its Edge”, **J. Royal Society Interface**, Vol. 1, No. 1, 2004, pp. 99-107.
- [28] C. I. Abramson, and M. Levin, “Behaviorist Approaches to Investigating Memory and Learning: A Primer for Synthetic Biology and Bioengineering”, **Communicative & Integrative Biology**, Vol. 14, No. 1, 2021, pp. 230-247.
- [29] P. Stano, “Chemical Systems for Wetware Artificial Life: Selected Perspectives in Synthetic Cell Research”, **International Journal of Molecular Sciences**, Vol. 24, No. 18, 2023, 14138.
- [30] L. Damiano, and P. Stano, “General Lines, Routes and Perspectives of Wetware Embodied AI. From its Organizational Bases to a Glimpse on Social Chemical Robotics”, in: **Artificial Life and Evolutionary Computation. 17th Italian Workshop, WIVACE 2023, Venice, Italy, September 6–8, 2023, Revised Selected Papers**. M. Villani, S. Cagnoni, R. Serra (Eds.). Cham: Springer. Communications in Computer and Information Science, Vol. 1977, 2024, pp. 111-122.
- [31] J. Kiverstein, M. D. Kirchhoff, and T. Froese, “The Problem of Meaning: The Free Energy Principle and Artificial Agency”, **Frontiers Neurobotics**, Vol. 16, 2022, 844773.
- [32] P. L. Luisi, and F. J. Varela, “Self-Replicating Micelles — A Chemical Version of a Minimal Autopoietic System”, **Origins Life Evol Biosphere**, Vol. 19. No. 6, 1989, pp. 633-643.
- [33] P. L. Luisi, F. Ferri, and P. Stano, “Approaches to Semi-Synthetic Minimal Cells: A Review”, **Die Naturwissenschaften**, Vol. 93, No. 1, 2006, pp. 1-13.
- [34] G. Ashkenasy, T. M. Hermans, S. Otto, and A. F. Taylor, “Systems Chemistry”, **Chemical Society Reviews**, Vol. 46, No. 9, 2017, pp. 2543–2554.