Modeling the Cell as a Network of Parallel Processes—a New Approach

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Abstract

This study addresses the problem of combining insights from artificial life, artificial intelligence, and biology in an efficient way to form a holistic unified view of life and living systems. Today, the study of biological life has a common *root object* – the cell – although lacking a formal definition of it. The theory of artificial life and artificial intelligence lacks this type of a root object. Here, we present a generalized model of the real biological cell in terms of a framework that is derived from theoretical studies of life. The framework is conceptualized generally as the MIC framework (Metabolism, Information, Compartment). The result is an autopoietic model with generic systemic properties and a network structure that can be examined further from a formal system-theoretic perspective. This study introduces a new way of describing the cell, providing new kind of access to existing biological knowledge of life. It may provide new tools for more efficient utilization of biological data and knowledge in the design and study of artificial life.

Introduction

It is widely acknowledged that the study of Artificial life (ALife) is not only about mimicking the design principles of biological life. The science of ALife is already moving in many new directions fully in its own right. Many of the new approaches are not directly tied to the basic principles, constraints, or to the material realm of biological objects. Research has proceeded well also in the absence of a formal definition or a basic concept that would link the applied field of ALife directly to biology and thereby to the natural foundation of all organismic life on earth.

However, as the result of the latest technological and computational advances, ALife is entering a new era. There is significant current interest for developing new kinds of life-like, physical machines that can interact intelligently and adaptively not only with humans, but also with many other kinds of biological life-forms. There is real need for new kind of understanding of biological life from an engineering perspective. This should preferably involve a formal integration of the wider perspective of living systems to the general picture in such a way that it can cover all instances (biological and artificial).

There is today no universal way of studying life using general formal approaches or models that would capture the essence of what a living system is. There is no general way of describing life by using a general methodology based on systems theory or mathematical methods that could offer a common perspective for scientists with different backgrounds. A general model should be applicable at least in the natural sciences and engineering. Abstracting biological behavior as computational behavior (Regev & Shapiro, 2002), reverse engineering of biological systems (Villaverde & Banga, 2014) or using principles of theoretical physics (Grenfell et al., 2006) have been suggested as possible ways forward.

A major theoretical problem is linked to the fact, that the biological sciences do not have a consistent formalism for describing the life of living cells or organisms in an abstract way. This is not a major problem among most biologists, but it hinders the possibility of using the full potential of currently existing biological knowledge in ALife research.

Theories of life

Many different theories and definitions try to capture the essence of life from a scientific perspective (for reviews see Cornish-Bowden & Cárdenas, 2020; Letelier et al., 2011). Explanations may derive from chemistry, mathematical study of life as abstract systems of organization and relations, cybernetics, molecular biology and more recently systems biology. Several of the theories focus on the circularity of metabolism and how it leads to metabolic closure at whole-system level. Notably, these theories have been developed independently, but there are similarities between them. Especially three of them attracted our attention and inspired us to conduct this study. The theory of *autopoiesis* (Maturana & Varela, 1980) Focuses on the ability of the living system to synthesize the components of which it consists of, while setting aside the question about the precise nature of the realizing mechanisms. Instead, it does highlight the importance of a physical separation of the system from its environment and how the living system can influence the properties of the environment (known as structural coupling). The *Chemoton* model was introduced by Tibor Gánti as an abstract model of a minimal chemical system that can be considered to be alive

(Gánti, 1975, 2003). It features three interconnected, cyclic processes that support metabolism, membrane synthesis and information processing. These are according to Gánti the three main properties that all living cells have in common. The *metabolism-repair (M,R)* systems approach was developed by Robert Rosen. It belongs to a field of biomathematics that is known as *relational biology,* established by Nicolas Rashevsky (Rashevsky, 1954). Rosen developed his theories over several decades, during which some of his views also changed as reflected in books that he wrote about life (Rosen 1985, 1991, 2012; reviewed in Pattee, 2007). The focus was on examining how a living system, that consists of components that have limited lifespans, needs to be internally organized in order for it to be able to (re)produce copies of all kinds of components that it consists of, thereby managing to repair and maintain itself against detrimental forces that would otherwise lead to the death and decay of the organismic entity.

Rosen emphasized the purely formal nature of his approach and did not connect it to any real-life examples. (*M,R*) systems have been contrasted against autopoietic systems and they are considered to form a more general class of systems that includes autopoietic systems as a subset (Letelier et al., 2003). Another study (Cornish-Bowden, 2015) has compared them against the Chemoton model. It ended with a general plea for the scientific community to form a holistic general synthesis of as many living systems theories as possible.

A new approach

In this study, we have tackled the problem of modeling life and living organisms conceptually by formulating a description of the real biological cell from a general systems perspective. We took as our starting point the one thing for which there seems to be a wide consensus—that *the biological cell is the basic unit of natural life*. We focused specifically on the question of how to describe the cell in a generic manner so that broad classes are included, taking advantage of existing theoretical views to life (reviewed above). This resulted in a general model of cellular biomolecular organization that is presented in the form a tailored network formalism. Our model provides an orderly foundation for the development of more rigorous mathematical formalism and understanding of the cell's biomolecular-level system-organizing properties, while remaining connected to the biological reality.

Overview of the MIC Framework

In the study of Alife and minimal modeling of living cells, there exists a certain general consensus, that for a cell or a cell-like system to be considered alive it must at least exhibit the following properties: *metabolism, information and compartmentalization* (e.g., Banzhaf & Yamamoto, 2015; Fellermann et al., 2007; Gánti, 1975; Rasmussen et al., 2016; Solé, 2009; Solé et al., 2007). We conceptualized these properties collectively for practical modeling purposes of this study as the *MIC properties of life*.

We used this conceptualization as a framework for considering what are the most relevant aspects of cell biology to be focused on. These topics form the main body of textbook literature on molecular cell biology and many details are known at the atomic scale of resolution (e.g., Alberts et al., 2014; Stryer, 1988). The outcome of this survey was, that despite the many differences that exist between the three main types of biological cells (archaeal, eubacterial, eukaryotic), one may postulate that there is a universal biomolecular foundation on which the cellular realization of the MIC properties is based on:

(1) Compartmentalization is provided by a cell membrane that separates the cell from the outside environment. The two main types of components found in all biological cell membranes are phospholipids and membrane-bound proteins. Structural assembly of the lipid fraction of the cell membrane depends universally on the physical behavior of phospholipid molecules in liquid water environment. Signal recognition particle (SRP) mediated mechanisms attach cell membrane proteins to the lipid fraction of the membrane. These mechanisms have an ancient basis and include protein and RNA components that are universal for all cells (Nagai et al., 2003).

(2) Cellular metabolism produces complex chemical compounds from simple raw materials. In all modern cells this is predominantly based on chemical reaction pathways and networks that are catalyzed by protein enzymes. All cellular protein strands are produced by the translation step of gene expression, involving ribosomes (complexes of rRNA molecules and ribosomal proteins), mRNA molecules that provide the genetic message to the site of protein chain synthesis, and tRNA molecules that carry amino acids to the site of protein chain synthesis.

(3) Chromosomal double-stranded DNA molecules are the universal physical carriers of genetic information in all living cells. Cells synthesize new DNA predominantly through the well-characterized mechanisms of semi-conservative DNA replication.

We set out to model this system from a holistic self-production perspective. The MIC conceptualization of life was included by considering these properties in a theoretical way as abstract components of a modeling space, in terms of which the most relevant aspects of cell biology for realizing these universal properties of cellular life could be described in a generic way. We divided this system-conceptual modeling space into thematic *partitions*, as described in table 1. Note, that the table lists four partitions. We extended the MIC paradigm by adding a partition named *Embodiment* to the bigger picture for practical modeling purposes. It accommodates the description of the main events of cell membrane assembly that all living cells have in common.

Furthermore, we adopted guidelines from the autopoietic theory of life (Maturana, 2002; Maturana and Varela, 1980) and set out to organize the model from the perspective of cellular material production pathways. The autopoietic theory describes living systems as self-producing entities that use simple raw materials that they acquire from the outside environment to synthesize the complex components from which they consist of. It recognizes the biomolecules of the cellular MIC properties as the main material foundation of living cells (Maturana, 1980). While the autopoietic theory is well recognized in ALife research (e.g., Beer, 2004, 2015; Ikegami and Suzuki, 2008; Masumori et al., 2020; Suzuki and Ikegami,

2009), it is not part of the current description paradigm of molecular cell biology in the biological literature.

Results

Our model, shown in figure 1, provides a general way of describing the biological cell from a holistic living systems perspective. The model refers to general aspects of molecular cell biology that all living cells have in common. It provides a visual representation of the type of system-level network connectivity that organizes the production of the material components on which the cellular MIC properties are based on.

The layout of the network is a particularly important aspect of our model and clarity of the visual representation was of specific interest to us (Polančič and Cegnar, 2017). We have arranged the model so that it is organized as a process flowchart. This gives it an appearance that is structurally very consistent even though the biochemistry that it describes is very complex. The network contains substance nodes (rounded) and process nodes (rectangular) that are connected by directed arrows. The nodes were defined and organized relative to each other so that there is a regular alternation of the two types. Solid arrows indicate a formal direction of process flow from the perspective of complexity increase of the material products.

Going through the network in the direction of the arrows, increasingly more complex organizational states of matter occur. Each type of product is formed from components that were produced by the events of the previous process step(s) of the network. The type of products that are formed have functional roles in the network. They are needed as components of the machineries through which the process node events are operated in real cells. Based on this, the model includes dotted directed arrows that describe how the core types of components that are formed by cells (blue nodes) effectively form a system-wide control network organization via the type of products that they form. Connection to real biology is maintained by labeling nodes using biological or biochemical terminology. Nodes are also numbered to enable easy referencing of specific parts of the model.

The abstract modeling space, which is divided into four system-conceptual partitions, is an important constituent part of our model. It makes it possible to assign higher-level system-related attributes to the characterization of the type of material components of cell biology that form the network. Each network components has a location in the system space relative to the partitions that provide system-level coordinates for how the components are distributed across the abstract system-space that represents the MIC properties of life. For example, the cell membrane (node 22) is formally localized to the C-partition as the main type of substance of molecular cell biology that provides a physical barrier between the cell and its environment. At the same time we know, however, that the membrane also has many channels (formed by protein molecules) and these are needed for the membrane to be able to realize its system-level function of providing raw materials from the environment to the living cell (node 2). In the model, node 2 is also a higher-level connecting element that joins the C and M-partitions together. In a similar manner, the 20 different kinds of natural amino acids are referred to by one substance node (node 7). On one hand, the node represents

Thematic partition	**Heuristic description**
Metabolism (M)	The biochemical reactions that distribute energy and matter in the cell, producing biomolecular chemical substances.
Information management (I)	The material components that contain the genetic hereditary information of the cell, and the cellular components and events that process it for cellular usage and storage.
Compartment (C)	A compartment defines the cell as an object in space, establishing a barrier between the cell and its physical environment, influencing the flow of energy and matter into and out of the cell.
Embodiment (E)	The mechanisms through which the cell's biomolecular components come to share a system-wide interface, that connects them to the external environment and gives them a holistic existence as an integrated cell-level entity.

Table 1: Theoretical partitioning of molecular cell biology into operating units, that together provide the kind of organization for the cell that formally (in the light of the autopoietic theory and the MIC properties of life) makes it a living system entity.

products that are formed by cellular metabolic reaction events (node 4) and that are used by the cell to synthesize protein strands (node 10). On the other hand, node 7 has a systemic role in our theoretical abstraction of the cell. It is an important connecting element at the description level of the abstract partitions, with a specific location in the intermediate system space between the M and the I-partition of the cell model.

Our model also clearly shows, that real molecular cell biology of the I-partition is organized as an autocatalytic subset of network functions and process events: DNA is used as the molecular template both for the synthesis of DNA during DNA replication and for the synthesis of RNA strands during gene expression; RNA molecules participate in DNA synthesis as so-called primers and in protein synthesis as mRNA, tRNA and rRNA molecules; Proteins are needed as components of the biomolecular complexes that form the cellular machinery for the synthesis of new DNA, RNA, and protein strands. These functional connections, formally operating within the theoretical I-partition of the model, are visualized by directed dotted arrows. Autocatalytic sets (Kauffman, 1993) are an important theory for the modeling of gene regulatory networks and chemical-level reaction networks of cell metabolism. This interesting network motif emerges here at a high level of abstraction. It is a real organizational property of molecular cell biology that can be clearly seen in our model where chemical reaction events and many intermediate steps are abstracted away.

It is possible to also consider other kinds of ways of describing our network model. Figure 2a shows a version of the model where the system-wide network organization, including the

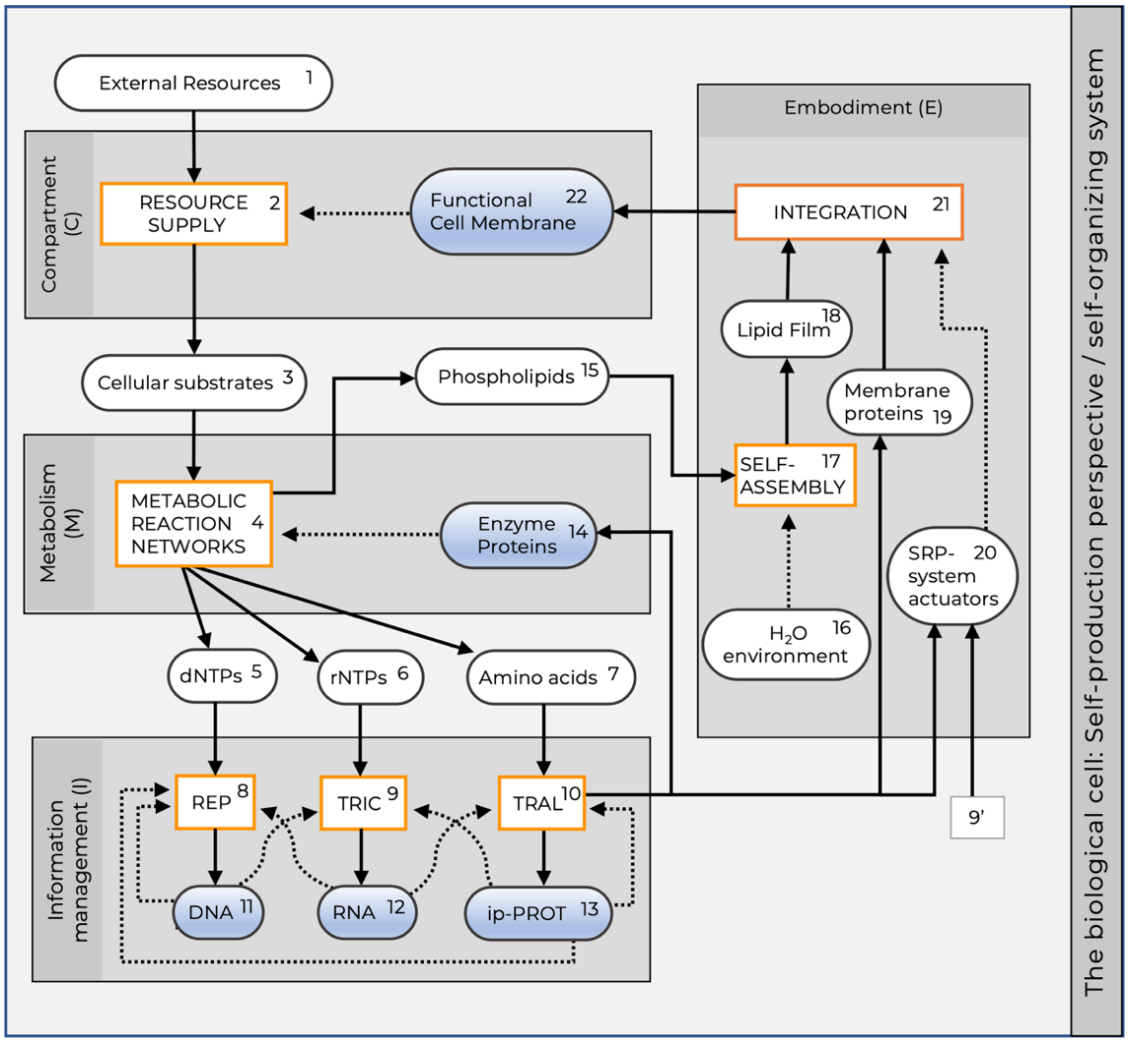

Figure 1: Diagrammatic model of the cell that describes it from a holistic perspective as a network of parallel processes. The description is given from an unconventional material production perspective, motivated by the autopoietic systems view that living cells produce the complex biological material components from which they consist of. The grey areas in the background describe an abstract modeling space and its system-theoretic partitioning into four parts (see table 1). The network describes knowledge that can be found in current textbooks of molecular cell biology. It features key aspects of molecular cell biology that all living cells have in common regarding the production of the main types of material components on which the cell's physical existence formally as a MIC (Metabolism, Information, Compartment) system entity is based on. The model is given in the form of a process flowchart with regularly alternating substance nodes (rounded) and process nodes (rectangular). Blue nodes indicate the main types of complex biomaterial products. Additional network elements are solid arrows that show the direction of process flow and how the different types of products and their system-wide distribution across the abstract modeling space of the thematic partitions. Dotted arrows indicate functional contribution coming from the type of material components that are formed for the execution of the target node events. Nodes are connected to the biological reality by the labeling. Numbering (1-22) enables easy referencing of specific parts of the model. dNTPs = the four types of deoxyribonucleotides, the monomeric substrates for DNA strand synthesis. rNTPs = the four types of deoxyribonucleotides that are the monomeric substrates of RNA strand synthesis. Node 7 refers to the 20 natural amino acids. REP = the process of semiconservative DNA replication. TRIC = the process of RNA synthesis during transcription step of gene expression. TRAL = the process of ribosomal protein synthesis during the translation step of gene expression. ip-PROT = **i**nformation **p**artition proteins, the set of proteins that are involved in the molecular mechanisms of the process node events of the I-partition. 9' is a duplicate of node 9 (replacing a solid arrow to enhance visual clarity of the diagram). The network components of the I-partition (nodes 8-13) form an autocatalytic subset in real biological cells. The dotted link 12→10 covers the contribution of mRNA, tRNA as well as rRNA molecules to the mechanisms of cellular protein synthesis. SRP = signal recognition particle dependent system for attaching cell membrane proteins to the lipid fraction of the membrane (see Nagai et al. 2003 for additional information). H_2O = reference to liquid water as the universal medium in which cells exist as physical entities, and as the main driving force behind biological self-assembly of lipid films.

self-referential aspects, can be seen more clearly. Figure 2b provides another kind of version of the model, where only the system-wide network connectivity that emerges at the highest possible description level of the MIC partitions is shown.

Discussion

Our model describes general knowledge of molecular cell biology in a new way by reorganizing it according to existing theoretical viewpoints to life and living systems. The conventional way of describing the cell from a holistic perspective is by using images that reflect the visual appearance that the cells have under the microscope as concrete physical objects. There is currently no universal model in general scientific use, that would describe the cell in a generic way. Thus, our model is a significant attempt to change this situation and provide new kind of access to biological knowledge about the system-level aspects of the natural biomolecular organization of the cell—the basic unit and (using our terminology) the formal *root object* of natural life.

An important design principle of graphical network representations is to keep the number of network components (especially the links) as low as possible (Polančič and Cegnar 2017). This provided a modeling constraint that influenced the selection of appropriate levels of abstraction and the choice of terminology that was used for labeling the nodes especially in those parts of the system where the amount of detailed biochemical knowledge is particularly high. Each node in our model captures a level of description that is at the same time sufficiently detailed as well and as general enough for the modeling purposis of this study (judged by the overall purpose to form a holistic, yet reasonably simple general model for the description of natural biomolecular organization of living cells from the MIC system perspective).

Our model integrates several viewpoints that exist for the theoretical study and modeling of life and living organisms. It describes the cell as an autopoietic system (that can synthesize the complex components from which it consists of), organized as a MIC system entity (a reflection of the Chemoton theory), and one part of the model is organized as an autocatalytic set. The (*M,R*) system formalism is another framework that is of interest to ALife research.

The model that we have provided features interactions and parallel mappings of process events and the resulting network has a system-level functional role in connecting distinct parts of the abstract cell-system modeling space (the partitions shown in Figure 1). These properties connect it to the theoretical domain defined by the (*M,R*) systems and relational biology. (*M,R*) systems focus on the functional relationships of components and products that together form a living system that can (re)produce the type of components that it consists of. Based on Letelier et al. (2003), (*M,R*) systems in deal with concepts such as *input* materials, that are transformed into *output* materials, that include *catalysts* that operate process events of material production, *components that select* for the synthesis of (biologically) *meaningful products*, and an agent that is referred to as the *efficient material cause* because it

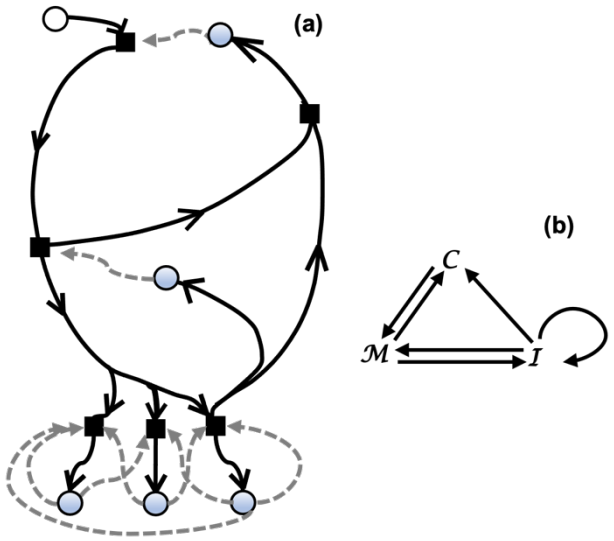

Figure 2: Two variations of our system-theoretic holistic cell model (see figure 1 for the full description). (a) A short-hand version of the model that highlights the system-level process flow aspects for the synthesis of the complex material products from which the cell consists of. Circles represent substance nodes and squares represent process nodes. The blue nodes correspond to the blue nodes of figure 1. The autocatalytic set of the information management (I-partition) components forms the bottom part of the graph. (b) Description of system-level network closure that arises at the abstraction level of the systemic cell partitions (see table 1). C, M, I = Compartment, Metabolism, Information management. This is an ultimate reduction of the model into a form that can be analyzed, for instance, in the light of network motifs of complex networks (Milo et al. 2002). The diagram shows how the three partitions support each other, in addition to which the information management partition also produces the types of material components from which it consists of (shown by the self-referential link I→I).

defines what products are meaningful for the organism. Two specific problems have been identified regarding the modeling of cells from the (*M,R*) systems perspective: (1) (*M,R*) systems do not account for the cell membrane, yet it is unrealistic to imagine real cells that have no cell membrane and (2) (*M,R*) systems seem to lack the ability to capture information processing aspects of living cells (Cornish-Bowden, 2015). However, Rosen has described an outline for dealing with properties of cellular information. He defined three categories of information—genomic, phenotypic and environmental—that are not equivalent which has consequences for the possibility of extrapolating results from formal models into the concrete realm of physical realizations (Rosen, 1986).

Based on our model, we divide the problem of applying the (*M,R*) system formalism to the modeling of living cells into two parts. *First* we focus only on the information management part of the model (the I-partition) and consider how (*M,R*) system viewpoints can be connected to the knowledge of molecular components and process dynamics of molecular cell biology

that are associated with this part of the network. For modeling purposes, the rest of the cell can then be viewed relative to I-partition as byproducts. The result is a bipartite view of cellular organization. *Then* attention is shifted to the whole-cell level and to the reciprocal mutual inter-dependences that exist both between as well as within these two theoretical parts of cellular system organization (the I-partition versus the rest of the cell, see figures 1 and 2a). This is an even higher-level systemic view to the organization of the living cell than the one provided by the four partitions (figure 1). It assigns a certain kind of asymmetry to the biological organization of the living cell, where the rest of the cell can be considered to constitute an acquired environment for the components and processes of the I-partition.

But all four parts (compartment, metabolism, information management and embodiment) are needed to form a real living cell. Each of them depends on the other parts for the supply of input materials as well components of the molecular machinery that is needed for realizing the process node events assigned to them. They support themselves by supporting each other, and all this together supports the life and survival of the cell as a holistic, autopoietic MIC system entity.

Our modeling formalism combines theoretical viewpoints and descriptions of reality in a way that may allow expanding the use of formal methods of systems biology (Machado et al., 2011; Szallasi et al., 2006) to the whole-cell level. The (*M,R*) systems theory has already been brought to the attention of systems biologists (Gatherer & Galpin, 2013). By examining from the holistic perspective of living systems theories what is already known about natural cells and molecular cell biology, important general systemic properties of higher-level organizational aspects of living systems may be discovered and properly characterized.

A particularly interesting topic for future study is to conduct a system-theoretic analysis of the higher-level structural and dynamic properties of the material components and interaction mechanisms that form the autocatalytic set of the I-partition in real cells. This is a nonconventional way of studying the mechanism and events of cell biology that form the foundation for the cell's information related properties and genetic inheritance.

Our model contains feedforward and feedback loops and the general structure that we have presented in this study resembles the network structures of communication networks and control systems (Machado et al., 2011; Milo et al., 2002). These aspects can be studied further from the perspective of complex networks (see, e.g., Basler et al., 2016; Liu & Barabási, 2016). The system dynamics of this network in the concrete physical realm are influenced by the recycling and repurposing of the type of materials that are formed. A related issue is to find good ways of presenting energetic and thermodynamic aspects of real cellular life in relation to our model. We aim to extend our modeling approach with a method(ology) for including systems biological knowledge of gene regulatory networks and metabolic pathways. An eco-evolutionary framework needs to be developed for studying evolution of life from the living systems perspective using our model as a connecting element between theory and reality of life's complexity evolution—After all, living cells are evolutionary adaptive entities and can only fully be understood in relation to their living environment. We also need a way to describe cellular reproduction as a key operation that the components perform together as an organismic whole. We continue our search for practical ways of linking further living systems viewpoints, such as symbiosis (King, 1977), cooperation (Stewart 2019) and hypercycles (Eigen & Schuster, 1977, 1978a, 1978b), to our model.

Conclusion

The MIC model describes parallel processes and flows in a generic cell. It combines several existing theories of life. It is possible to extend the model to a broad class of biological and life-like systems.

Acknowledgements

We are grateful to Kimmo Kaski, Wolfgang Banzhaf, Robin Dunbar and Juan Carlos Letelier for their influential scientific discussions with MS that encouraged her to take on this modeling task, to Sinikka Segerståhl for sharing her knowledge of the complexity of language and its usage and to Katarina Segerståhl for many discussions on the complexity of human organizations. JCL made important comments to an early version of figure 1 and suggested adding a distinct fourth part to the description of the abstract modeling space to accommodate the process events of cellular self-encapsulation through cell membrane assembly. KS designed the visual details of figure 1.

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