Loopomics: A possible breakthrough in the understanding and control of life

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Abstract: *Life sciences face challenges in developing theoretical frameworks for operating on biological systems. This is evident when considering disappointing results in biomedicine, as many diseases remain poorly understood despite decades of intensive efforts. The complexity of living systems is often cited as the reason for these shortcomings. To address these challenges, I have proposed a new definition of life, which I call Loopomics. According to this new paradigm, life is defined as any natural entity consisting of agents that produce physical changes, interconnected through chains of interactions that form closed loops. These loops create nonlinear systems whose dynamics are known to be characterized by single equilibrium points or transitions between different equilibrium points. The number of equilibrium points is determined by the kind of loop but is modified by bifurcation parameters, whose variation over time can significantly alter the behavior of the system. Thus, bifurcation parameters are key targets for interventions aimed at acquiring control of these systems. Biological loops give rise to ordered and predictable accumulations of materials that realize epiphenomena, including subcellular organelles, cells, tissues, organs, and organisms. These epiphenomena do not help in conceptualizing life and can be only used to identify, map, and manipulate the loop systems. The verification of the Loopomics hypothesis can be carried out by developing loop models of pathogenesis, identifying bifurcation parameters, and addressing them as therapeutic targets. If this approach is successful, it would provide positive validation for the hypothesis and could chart a new direction for biomedical research and applied biology.*

Key words: *Bifurcation parameters, Biodiversity, Biouniformity, Closed loops, Nonlinear dynamical systems, Life complexity, Unsolved diseases.*

Introduction

Complexity is a term frequently used in scientific literature related to life sciences. Unsurprisingly, the book by Nobel laureate Erwin Schrödinger, *What Is Life* (Schrödinger, 1944), is considered a precursor to complexity theory (Portugali, 2023). One of the key concepts analyzed in the book is delayed entropy, which refers to a living organism's ability to postpone thermodynamic equilibrium, i.e. death, through its metabolism. In this paper, I present a new perspective on life, which reveals that Schrödinger's viewpoint is fundamentally misleading. However, this is not a flaw specific to Schrödinger himself but rather reflects a widely held belief among scientists. The specific mistake I highlight in the concept of delayed entropy, and concomitantly in the interpretation of life itself, is a confusion between the process of life and the products that it produces. These products give rise to epiphenomena, such as an organism and its lifetime, while life is an underlying phenomenon that transcends these epiphenomena. Within life, entropy is neither delayed nor abolished, it is simply present, just as it is in all other physical processes. The most critical point to address when analyzing life is how it achieves a self-sustaining process that continues indefinitely, as long as boundary conditions permit. My analysis clarifies this essential characteristic of life by providing a precise definition and exploring its implications.

Life is undeniably complex. Living beings are highly diversified, both among themselves and within their own structures (Campbell, 2003). This complexity is why modeling life is so challenging, particularly when using mathematical tools (Vittadello & Stumpf, 2022). It is also likely why our ability to interact with and engineer living systems is far more limited compared to inorganic objects. Despite the development of genetic engineering and biotechnology, the ability to control biological systems, even at the level of single cells, remains considerably lower compared to the achievements in physics and chemistry. These latter fields have given rise to technological advancements such as electronics, photonics, chemical synthesis, and materials science. In contrast, progress in the engineering ability of life sciences has been dramatically slow, as evidenced by the challenges faced in biomedicine. Despite decades of intense global efforts, backed by substantial financial investment, the results have been disappointingly limited. The rise of high-throughput analyses in the form of bio-omics, along with the concurrent development of systems biology, has not yet resulted in a significant acceleration in this area (Naylor & Chen, 2010). A staggering number of diseases still lack models for pathogenesis and the identification of effective therapeutic targets, while at the same time, biomedicine continues to seek an appropriate scientific approach to adopt (Rocca & Anjum, 2020).

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The debate on the problems of biomedicine seems inextricably linked to the complexity of biological systems, and therefore, complexity weighs as some sort of original sin for this area. Hence, overcoming such difficulty could imply the removal of complexity in the conceptualization of these systems. I have proposed an approach to the analysis of living systems that reaches this goal by starting from a definition of life that is totally non-conformist (Burlando, 2017).

Defining life is challenging

Despite the extreme diversification of living beings, the notion has long been established that these entities represent a unified phenomenon with a common origin, also known as the Last Universal Common Ancestor, or LUCA (Jheeta, 2017). However, as mentioned above, life is complex, and this is reflected in the various attempts by different authors to define the phenomenon (Benner, 2010; Cleland, 2019; Dhar & Giuliani, 2010). The definitions that have been proposed lack conciseness and are scarcely effective on an operational level, the one where they should enable the solving of practical problems. So, the core issue we face is determining whether it is possible to eliminate complexity in defining life.

I have proposed that the definition of life, or, in other words, its fundamental conceptual modeling, should focus on the interactions observed in the phenomenon, rather than on the elements that interact with each other and are ultimately produced through these interactions. The chemistry of life is extraordinarily diverse, with thousands of different compounds being present within a single cell (Naylor & Chen, 2010). The combination of some of these substances into insoluble aggregates (membranes, cytoskeleton, chromosomes, etc.) creates an astonishing variety of objects at subcellular (organelles), cellular (cell types), extracellular (matrix), and supracellular levels (tissues). Eventually, whole organisms are formed (bacteria, fungi, algae, plants, animals, etc.) whose individuality (worms, spiders, dogs, etc.) or coloniality (corals, superorganism plants, fungal mycelia, etc.) varies in prominence.

According to my proposal, all theoretical and practical problems faced by life sciences stem from prioritizing objects over processes. In contrast, I categorize life into two levels: one pertaining to interactions and the other to the epiphenomena produced by these interactions. Focusing on epiphenomena inevitably entangles us with the vast complexity of life, whereas focusing on interactions can eliminate the burden of complexity. An analogy can help clarify the problem. Flocks of birds form striking shapes in the sky, sometimes resembling familiar objects. These shapes are connected to bird flight through cause-effect relationships. However, if we attempted to study bird flight by analyzing these shapes, we would gain no

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useful information. While these shapes are highly diverse, they are always rooted in the same mechanical activity of individual birds. It is this dynamic activity that we should focus on to understand bird flight rather than the epiphenomena that emerge from it. In my opinion, a similar drawback affects our understanding of life as a natural process, leading to negative consequences across all applied fields of the life sciences, including the management of human health.

The Nobel laureate Richard Feynman stated that it is not possible to define anything precisely (Feynman *et al.*, 1963). This is quite correct, as any definition of a physical entity is affected by vagueness, and therefore, we can have various definitions for a specific physical entity. However, this does not mean that all possible definitions are equivalent. We can distinguish between good definitions and poor definitions, with the former allowing to acquire control of physical processes with higher efficiency than the latter. In physics and chemistry, it has been possible to formulate good definitions of physical entities, enabling various technological developments. Conversely, the current definitions of life are unsatisfactory, not because of their vagueness, but rather because they do not allow for operating on life processes with high efficiency, thus leaving many problems unsolved.

Loopomics: a new definition of life

The definition of life that I have proposed is characterized by the attempt to eliminate any element that could introduce complication or require additional distinctions. Therefore, my definition avoids referencing any physical or chemical feature of life, aiming to capture the essential traits that distinguish this natural phenomenon (Burlando, 2017). I started from the evidence that living systems are characterized by entities able to produce physical changes, which I will term agents. A typical example is provided by enzymes, which promote and sustain the intense chemical activity of living systems, known as metabolism. Another well assessed notion is the establishing of series of interactions among agents, or chains. To distinguish living from non-living entities, I hypothesize that any biological agent controls the activity of other agents and is reciprocally controlled by the same or different agents. Therefore, given an obvious non-infinity of agents, it follows that all chains are closed, i.e. they have the shape of closed loops. Branched chains are also present, but they are hypothesized to be part of closed loops too. Hence, a living being is defined as any entity where the above conditions are satisfied, irrespective of its physical nature. I have termed this kind of arrangement Loopomics (Burlando, 2017), where the suffix "-omics" emphasizes the global nature of the loop arrangement. However, unlike other omics, it does not signify multiplicity but rather, as we will see, uniformity.

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My definition of life is very concise compared to those we generally find in the literature (Gómez-Márquez, 2021). However, it explains various basic features of biological systems and provides distinct operational guidelines for design-based manipulation and control of these systems. The interactions between biological agents are generally nonlinear, i.e., the relationship between the input and output is not described by a straight line. In most cases, such interactions can be suitably modeled by Hill functions, as demonstrated by extensive data spanning from ligand-to-receptor binding (Gesztelyi *et al.*, 2012), to interneuron modulatory activities (Silver, 2010).

Nonlinear dynamical systems arranged as closed loops have been extensively studied in Systems and Control Theory. Given a series of agents mutually interacting in a closed chain, we have a negative loop if there is an odd number of inhibitory steps, or a positive loop if this number is even or zero (Blanchini *et al.*, 2014). Negative loops give rise to dynamical systems characterized by single equilibrium points or limit cycles, i.e., producing hoemostasis or confined oscillations. In contrast, positive loops can be multistationary, i.e. with multiple equilibrium points, allowing the possibility of switching from one equilibrium point to another upon suitable stimuli (Domijan & Pécou, 2012) (Fig. 1).

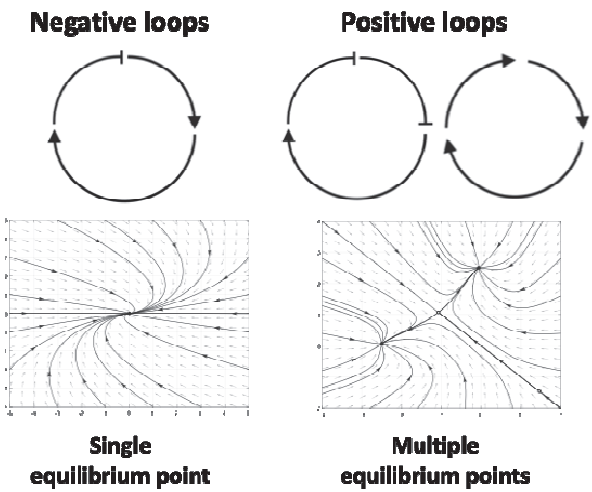

Figure 1. Different loop systems (above) and their dynamics depicted in phase space diagrams (below). Negative loops consist of closed series of interactions with an odd number of inhibitory steps (T-bar lines) and admit single equilibrium points. Positive loops have no inhibitory steps or an even number of them and admit multiple equilibrium points. Created in Matlab, version R2024b, MathWorks, Natick, MS, USA, https://it.mathworks.com/matlabcentral/fileexchange/110785-phase-portrait-plotter-on-2d-phase-plane, Copyright (c) 2022, Yu Zhang, Copyright (c) 2021, Erik A. Johnson.

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My definition of life involves a completely new perspective that simplifies the complexity of biodiversity into biouniformity. Within this framework, biodiversity is understood as a vast collection of epiphenomena resulting from the ordered accumulation of materials and their ongoing transformation (Fig. 2). These objects are considered ancillary when it comes to understanding the principles governing the phenomenon of life. On the other hand, the complex interactions among biological agents are viewed as nonlinear systems arranged topologically as closed loops, adhering to a very limited set of rules that constrain the behaviors of positive and negative loops.

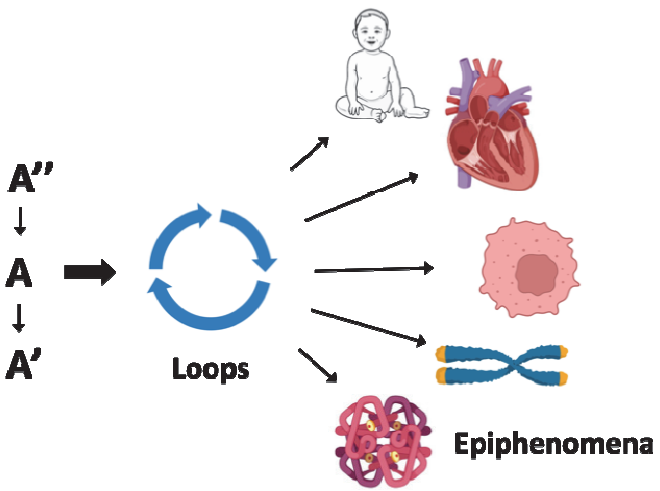

Figure 2. Schematic representation of a hypothetical definition of life. Life consists of agents (A) capable of producing physical changes, each of which interacts upstream with at least one other agent and downstream with at least one other agent. As a result, agents form closed loops of interactions. These loops are the essential phenomena of life, while the observable entities – such as macromolecules, supramolecular structures, cells, organs, organisms, etc. – are epiphenomena arising from the activity of loops. Created in Biorender.com, https://app.biorender.com (last visited 01-21-2025).

Limitations and advantages of Loopomics

Loopomics is currently a theoretical hypothesis awaiting experimental evaluation. However, it could offer several advantages. First, by adhering to the Loopomics conceptualization, life becomes fully analyzable on a mathematical basis. Thus, Loopomics could fulfill the prediction made by Uri Alon, one of the pioneers of systems biology, that biology has the potential to become a truly quantitative science through the application of mathematical tools (Alon, 2019). Such a revolution-

ary shift in biological research could potentially lay the groundwork for designing operational interventions with the same precision and efficacy as those based on the principles of physics and chemistry, potentially ushering in a new era for the control and engineering of biological systems and addressing inherent challenges, such as diseases.

Second, Loopomics provides an explanation for an apparently paradoxical feature of life: the exact predictability of its epiphenomena. Based on the relatively precise estimate of the number of cells in the human body (Bianconi *et al.*, 2013), and the number of chemical reactions per second occurring in a single cell (Hołyst *et al.*, 2024), a rough estimate suggests at least 10^{25} (ten trillions of trillions) chemical reactions take place during human prenatal life. Even so, while a mother might feel anxious that anything proceeds well, once she has assumed that everything will go well, she is never concerned about the result of her pregnancy. She is absolutely confident that a baby with all the expected features of a newborn human will be born. Of course, a mother is generally unaware of biological mechanisms and places her confidence in the overwhelming case history of human births. However, and most surprisingly, even qualified neonatologists are quite certain that no butterfly effect, i.e., chaotic behavior (Lorenz, 1993), will occur during the baby's development. Yet, cellular processes are subject to thermal fluctuations and are inherently chaotic. Despite such thermodynamic constraints, an astonishing number of chemical reactions proceeds in perfect coordination, leading to cell division and differentiation. Furthermore, billions of cells carry out these activities under perfect harmony, allowing for tissue and organ development (Hołyst *et al.*, 2024). Many experts will seek answers in the human genome, but although genes direct the development, it is like a dog chasing its own tail because the genome and its metabolism are not external to the aforementioned thermodynamics. Conversely, on the Loopomics ground, everything seems quite reasonable. Loop systems allow for equilibrium points which represent poles of attraction for their dynamics (Luenberger, 1979). Then, if we assume that everything happening in a living being results from the activity of this kind of systems, then each biological event represents the attainment of some equilibrium point. In other words, only events corresponding to equilibrium points can occur, and therefore, given a specific starting point, the dynamics will proceed from one equilibrium point to another in a strictly predictable manner. This is why, without exception, a child develops from a fertilized human egg, or a wheat plant grows from the germination of a grain seed.

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Proving the Loopomics hypothesis

Nonlinear dynamical systems with loop arrangements have been identified in a wide range of biological processes (Angeli *et al.*, 2004; El-Samad, 2021), but a comprehensive theory in this sense has yet to be developed. Additionally, it is not yet understood that these systems represent the essence of life processes and that their analysis is the only way to comprehend the meaning of life processes and determine the most effective ways to manipulate them. The Loopomics hypothesis asserts these ideas but, as said above, it still requires experimental validation before being eventually acknowledged as a scientific theory.

By searching for a way to prove the hypothesis on an experimental basis, we could, for example, attempt to demonstrate that following its principles makes it possible to manipulate a biological system with an efficiency level not yet achieved. The wide array of diseases that affect the human body offers many opportunities in this regard. Several diseases remain problematic due to a lack of knowledge about their pathogenesis, pathophysiology, and therapeutic targets. This challenging category includes not only idiopathic and rare diseases but also a long list of common disorders, such as autoimmune, neurodegenerative, infectious, malignant, neurological, psychiatric, and metabolic diseases. Many of these diseases have been studied for decades with limited progress in developing cures, as evidenced by numerous examples: rheumatoid arthritis (Watanabe *et al.*, 2022), Alzheimer's disease (Anderson *et al.*, 2017), amyotrophic lateral sclerosis (Petrov *et al.*, 2017), and chronic pain (Maiarú *et al.*, 2023), among others. Therefore, the search for effective treatments for these challenging diseases could represent a testing ground for Loopomics.

Together with a group of co-authors, I have developed pathogenesis models for some challenging diseases based on loop systems of interacting biological agents. These pathogenesis models include fibromyalgia (Demori *et al.*, 2022), Alzheimer's disease (Burlando *et al.*, 2022), amyotrophic lateral sclerosis (Burlando *et al.*, 2020), and mal de debarquement syndrome (Burlando *et al.*, 2020). Like their inspiring Loopomics hypothesis, these results remain theoretical but nonetheless provide innovative insights. They demonstrate that it is possible to approach the triggering events of widely different pathological conditions using essentially the same kind of model. Moreover, these theoretical models are consistent with a range of data related to the corresponding pathological conditions. The case study of fibromyalgia is emblematic because it has been possible to extend the pathogenesis model through theoretical analysis up to the formulation of a potential treatment based on neurosteroid drugs (Burlando & Demori, 2024; Demori *et al.*, 2024).

The seminal idea of this kind of analysis is the obvious consideration that the

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development of any disease must involve some change in an organism's functioning. As mentioned earlier, the Loopomics hypothesis proposes that any phenomenon occurring in a living being reflects the nonlinear dynamics of loop systems. Specifically, the occurrence of changes is attributed to multistationary positive loops that undergo transitions from one equilibrium point to another under the action of certain stimuli (Rombouts & Gelens, 2021). The possibility of undergoing transitions depends on the variation of specific factors known as bifurcation parameters. As these parameters vary, the system's behavior changes abruptly in correspondence of bifurcation points, for example shifting from monostable to bistable or vice versa (Tsumoto *et al.*, 2012). Additionally, if multiple equilibrium points exist, their importance can vary depending on changes in the extension of their basins of attraction in the system's phase space, i.e. the space representing all possible functional states. Under the Loopomics framework, bifurcation parameters are viewed as the control buttons that offer the potential to gain influence over a specific biological process.

The fibromyalgia model mentioned above is based on a thalamocortical loop in which GABAergic transmission functions as a bifurcation parameter (Demori *et al.*, 2022). When GABAergic strength decreases, the system changes from monostable to bistable, acquiring a new pathogenic equilibrium point whose basin of attraction expands as GABA weakens further. As a result, the system becomes increasingly prone to settle on the pathogenic equilibrium point upon the action of stimuli such as signals from the spinothalamic tract. This model explains why gabapentinoids rate among the most effective pharmacological treatments for fibromyalgia. Gabapentinoids reduce the release of excitatory neurotransmitters, notably glutamate, thus potentially offsetting the weakening of GABAergic transmission. Additionally, the model is consistent with the poor efficacy of benzodiazepines, despite their role as positive modulators of specific GABA receptor subtypes. Conversely, it suggests that other positive modulators of GABA receptors, such as neurosteroids, which have never been considered for this disorder, could be an excellent therapeutic option (Burlando & Demori, 2024).

A unifying model for pathogenesis processes

Various studies have attempted to model diseases by using loop systems (Glass, 2015). However, these investigations have been always conducted on a case-by-case basis, without any effort to establish a unifying theoretical framework. The Loopomics hypothesis offers such unifying principles. If all changes in biological systems result from the dynamics of positive loops, and if diseases represent changes in the functioning of specific biological systems, then at the root of any

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disease there must be a multistationary positive loop that transitions between different equilibrium points (Burlando, 2022). Thus, Loopomics provides a unifying model for understanding the pathogenesis of the extraordinarily diverse range of human diseases, effectively transforming complexity into uniformity.

These ideas lead to the consideration of all diseases as essentially a single type of event, which is observed as a multitude of different conditions due to the diversification of biological epiphenomena. This perspective is highly unconventional respect to current opinions in biomedicine and clinical practice. More significantly, it is apparently in contrast with the innovative precision medicine, which views each patient as a unique case based on genetic traits, lifestyle, and environmental factors, thus aiming at tailored treatments on which great hopes are being placed (Evans W. *et al.*, 2024). However, this contrast is only superficial and, once again, arises from the confusion between fundamental life processes and their epiphenomena.

To understand the effective contribution Loopomics can bring to the medical field, it is helpful to divide health sciences into two classes of activities, viz. patient management and disease management. By patient management, I mean a set of activities including patient intake, diagnostic tests, prescriptions, hospitalization, surgery, psychological and nutritional help, and any other interaction between the patient and medical or paramedical staff. This complex system of operations requires significant effort and financial resources but offers satisfaction and rewards as it continuously evolves and incorporates technological innovations. On the other hand, by disease management I mean assuming control of a biological system that has switched between different functioning regimes, thus leading to an epiphenomenon generally referred to as a pathological condition. Secondary events, such as symptom proliferation, tissue degeneration, and interpersonal variations, generally create confusion in disease management. Instead, the focus should be on the primary event that marks the transition from physiological to pathological condition. Unlike patient management, disease management is a slowly advancing field of research. Furthermore, its progress remains relatively uncoupled from technological advancements, which, in my view, is the clearest evidence of the underlying conceptual limitations.

Loopomics is a genuine biological field that does not directly contribute to patient management. This latter addresses epiphenomena, ranging from anatomical details to whole organisms, including their essence as human emotional beings and social identities. By contrast, Loopomics could provide crucial support to disease management, as this field needs to address the biological events underlying pathogenic processes with an appropriate conceptual framework.

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Conclusions

In summary, this study argues that the current conceptualization and modeling of life are insufficient, offering limited opportunities to effectively manage biological processes. This shortcoming is evident in the challenges biomedicine faces when studying a wide range of diseases. To overcome this stagnation, I have previously proposed the Loopomics hypothesis. This hypothesis suggests that observable life is a collection of diverse epiphenomena generated by the activity of loop systems, which can be conceptually unified within a single framework. As such, Loopomics provides a pathway to navigate the complexity of life, by focusing on abstract constructs, such as interaction patterns, rather than on physical objects. These patterns are then represented through mathematical models as loop systems with nonlinear dynamics, ultimately identifying equilibrium points and bifurcation parameters. The physical counterparts of bifurcation parameters can then be targeted to gain control over biological processes. Loopomics offers insights into fundamental questions about life, such as the paradox between the vast array of life events and their precise predictability in the absence of butterfly effects. Although still theoretical, this framework could be validated through experimental evidence. If Loopomics successfully addresses biomedicine's current struggles to resolve health challenges, the hypothesis would be confirmed. Therefore, experimentally validating this hypothesis represents a worthwhile pursuit.

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