Causal Thinking in Physiology: A Search for Vertically Organizing Principles

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Abstract

Physiology has excelled at elucidating biological mechanisms at specific scales of organization, yet it lacks a robust framework for understanding causality across these scales. This paper argues for a paradigm shift, moving from a primary focus on scale-specific, or "horizontal," causality to a search for "vertically organizing" principles that are invariant across biological levels. Drawing inspiration from concepts in physics such as scaling laws, emergence, coarse-graining, and action principles, we explore the limitations of current causal thinking in physiology, particularly the prevailing genome-centric bias.

This paper is the first in a series exploring vertically organizing principles in biology. Here we establish the philosophical and theoretical foundation, examining existing frameworks and their limitations. We review information-theoretic approaches including the Free Energy Principle and dissipative adaptation, acknowledging both their insights and their challenges in achieving scale invariance. We introduce the concept of network-weighted action principles (minAction.net) as a promising candidate for scale-invariant organization that may complement these existing frameworks.

Building on Schrödinger's two secrets of life—heredity and self-organization—we argue that a third secret lies in the scale-invariant action principles that give rise to biological design itself. We present evidence from immunometabolism, developmental biology, complex systems physiology, and computational evolution studies supporting multi-scale, information-centric views of biological organization. Notably, recent computational evidence demonstrates that minimizing connection costs—a key component of action functionals—spontaneously generates the modular, evolvable architectures ubiquitous in biological systems. Finally, we posit that meaning—operationally defined as the successful reduction of uncertainty through predictive modeling and efficient action—can be conceptualized as a candidate for a high-level, vertically organizing principle that operates from the cellular to the cognitive level. This manuscript lays the conceptual foundation for a more unified and scalable science of life.

Keywords: emergence, complex systems, scale invariance, action principle, Free Energy Principle, phase transitions, network biology, systems physiology, modularity, evolvability

1 Introduction: The Search for Vertically Organizing Principles in Physiology

The success of modern physiology is rooted in its ability to deconstruct complex living systems and describe the mechanisms at play within specific scales of organization. We have developed sophisticated models of molecular dynamics, cellular signaling, tissue function, and integrated organ systems. This approach, focused on what could be termed "horizontal causality," has yielded profound insights and therapeutic advances. However, it has left a fundamental question largely unaddressed: what are the principles that govern the flow of information and causation across these scales? How do the rules governing a single cell scale up to dictate the behavior of an entire organism?

In 1944, Erwin Schrödinger presented biology with an unprecedented challenge in his monograph "What Is Life?" [1]. He identified two secrets of life: the passage of an encoded molecule from parents to offspring to explain heritable characteristics, and the spontaneous emergence of self-organized order. While biochemistry and biophysics have responded to the first challenge with stunning success, resulting in today's revolution in genetics and molecular biology, the second challenge—understanding emergent phenomena—remains largely unmet. As Macklem [2] emphasizes, if physiology fails to provide this deep understanding of life, it risks becoming a science secondary to biochemistry and biophysics.

Emergent phenomena, defined by Macklem as "the spontaneous development of self-organized order among ensembles that can neither be predicted nor explained by examining component parts in isolation," represent a fundamental challenge to reductionist approaches. This spontaneity and self-organization mean that no external agent is sculpting the organism: it sculpts itself through the interactions of its component parts. A key manifestation of this self-organization is modularity—the organization of biological systems into functional, sparsely connected subunits—which is ubiquitous across biological networks from gene regulation to neural architectures [56].

As Pearl [3] has emphasized in his work on causal inference, understanding causality requires more than correlation—it demands a theoretical framework that can distinguish genuine causal relationships from mere associations. In biology, this challenge is compounded by the need to understand causality not just within scales, but across them.

This paper argues that the next great frontier in physiology lies in the deliberate search for vertically organizing, or scale-invariant, principles (Figure 1). Drawing inspiration from physics, which has long relied on symmetry principles, conservation laws, and action principles that hold true from the quantum to the cosmic level, we propose a shift in mindset. Instead of viewing each biological scale as a distinct domain with its own emergent set of rules, we should seek the unifying principles that are conserved across all levels of biological organization.

The crisis in physics itself, as discussed by Hossenfelder [4] and Loeb [5], where mathematical beauty has sometimes led theory astray from empirical reality, offers important lessons. We must ensure that our search for unifying principles in biology remains firmly grounded in experimental observation while leveraging the power of theoretical frameworks.

A crucial insight guiding this work is that biological systems are fundamentally networks at every scale—from molecular interaction networks to neural networks to ecological webs. This network perspective suggests that principles governing optimal information flow and energy distribution through networks might provide the scale-invariant laws we seek. Recent computational evidence demonstrates that such network optimization principles spontaneously generate the modular architectures characteristic of biological systems [56].

This manuscript lays the conceptual groundwork for this approach and introduces a series of investigations into candidate organizing principles. We first explore the epistemological and practical challenges that have constrained our causal thinking. We then introduce concepts from physics—scaling, emergence, coarse-graining, phase transitions, and action principles—as essential tools for a multi-scale science. We examine existing information-theoretic frameworks, including the Active Inference framework, assessing both their contributions and limitations. We then propose that network-weighted action principles may provide a complementary mathematical and philosophical foundation for this endeavor, with computational evidence showing how such principles naturally generate modular, evolvable architectures. Finally, we conclude with the hypothesis that "meaning" itself can be understood as a primary, scale-invariant organizing principle of life.

2 The Challenge of Knowing: An Epistemological Stance

Before embarking on this search, we must adopt a stance of epistemological humility. The act of measurement in science is not a passive observation of reality, but an active interaction that captures only a limited projection of a system's true state. As Werner Heisenberg noted in the context of quantum physics, "What we observe is not nature itself, but nature exposed to our method of questioning." This is profoundly true in biology, a science of staggering complexity where our instruments and models inevitably filter and simplify the phenomena we study.

This epistemological challenge is further complicated by what Born [6] called the "natural philosophy of cause and chance"—the recognition that deterministic and stochastic processes are intertwined at every scale of biological organization. As Prigogine [7] argued in "The End of Certainty," complex systems force us to reconsider our notions of predictability and causation.

This is not a statement of futility, but a necessary caution. When we design an experiment, we must constantly ask whether we are truly capturing the phenomenon of interest or merely an artifact of our chosen scale and method of observation. The cognitive biases identified by Tversky and Kahneman [8] in human judgment under uncertainty apply equally to scientific observation—we tend to see patterns that confirm our theoretical expectations.

Acknowledging these limits is the first step toward building a more comprehensive framework that can integrate observations from multiple scales into a more cohesive whole. Furthermore, we must recognize that biological systems are simultaneously processing information and minimizing energetic costs—a duality that suggests any complete theory must account for both aspects. This energy-information duality will be a recurring theme as we explore candidate organizing principles.

3 Current Challenges in Physiological Causality

Our current approach to causality in physiology faces several key limitations that obscure the view of vertically organizing principles.

3.1 Practical Challenges in Quantitative Mapping

Physiology remains, in many areas, a qualitative science. While we can often describe that "A causes B," we frequently lack the quantitative, predictive models common in physics or chemistry. This makes it difficult to test whether a causal relationship observed at one scale holds true at another. The complex dynamics observed in physiological systems—from fractal heart rate variability [9,10,11] to synchronized oscillations [12]—suggest underlying organizing principles that we have yet to fully formalize.

3.2 Technological and Spatiotemporal Constraints

Our ability to observe biological processes is fundamentally limited by the resolution of our tools. We can either see great detail in a small area (e.g., electron microscopy) or a coarse overview of a large system (e.g., fMRI). Bridging this gap is a major technological challenge. While emerging technologies like wearables and high-throughput sequencing offer vast datasets, they also present new challenges in separating signal from noise and establishing causality. As Tavora [13] notes, insights from physics about explainability in deep learning may help us navigate these challenges.

3.3 Bias and Framework Limitations

Modern biology is dominated by a genome-centric framework. While the genome is undeniably crucial, its explanatory power is often overstated. We barely understand the combinatorial complexity of interactions within the genome itself, let alone how it deterministically maps to higher-order physiological and psychological phenomena. This reductionist bias often leads to the assumption that the lowest observable scale is the most "fundamental," a view that this paper directly challenges.

Recent work has revealed layers of non-genetic information storage and processing, from bioelectrical networks [14] to metabolic signaling [15], suggesting that the genome is just one component of a multi-scale information processing system. The remarkable examples of self-organization and self-replication in synthetic biological systems [16] further challenge our gene-centric assumptions.

As Macklem [2] points out, and Polanyi [17] before him argued, there is a third secret of life not mentioned by Schrödinger: the design of living organisms is not determined by physicochemical laws alone. Like a painting where the physical properties of paint determine what remains on canvas but not the meaning of the artwork, biological design transcends its material substrate.

4 A Framework from Physics: Scaling, Emergence, Coarse-Graining, Phase Transitions, and Action Principles

To overcome these challenges, we can turn to the conceptual toolkit of physics, which has centuries of experience in dealing with multi-scale systems.

4.1 Scaling and Invariant Causality

A core goal of physics is the identification of scaling laws—relationships that remain true when the scale of a system changes. The search for vertically organizing principles in biology is analogous: we are seeking the biological equivalent of conservation laws, principles that are invariant to the scale of observation. West and colleagues [18] have demonstrated the power of this approach in understanding allometric scaling laws in biology.

4.2 Emergence and Coarse-Graining

Physics recognizes that complex systems exhibit emergence, where novel properties and behaviors arise at higher levels of organization that are not explicitly present in the lower-level components. As Anderson [19] famously stated, "More is Different"—each level of organization brings genuinely new properties that cannot be predicted from lower levels alone.

This notion of emergence has been extensively debated in the philosophy of science, particularly regarding the distinction between weak emergence (novel properties that are in principle derivable from lower-level descriptions) and strong emergence (properties that are fundamentally irreducible). Our search for vertically organizing principles represents a distinct approach to this debate. Rather than focusing on constitutive mechanistic relationships between levels, as advocated by philosophers like Carl Craver [57], we seek invariant principles that operate across all scales. This is not to dismiss mechanistic explanation—which has proven invaluable for understanding specific biological phenomena—but rather to complement it with a search for scale-invariant laws that constrain the space of possible mechanisms. As Kim [58] has argued in his work on supervenience, there may be lawlike regularities that connect different levels of organization without reducing to simple bottom-up causation.

Macklem [2] defines emergent phenomena as involving "the spontaneous development of self-organized order among ensembles that can neither be predicted nor explained by examining component parts in isolation." To study these emergent properties, physicists use coarse-graining—a technique of simplifying a model by averaging over fine-grained details. This allows for the creation of effective theories that are predictive at a specific scale. The philosophical implications are profound: each level of biological organization may require its own effective theory, yet these theories can be unified by common organizing principles that transcend specific scales.

In causal thinking, we must embrace this approach in biology. To understand organ function, it should not be necessary to model every single molecular interaction. A coarse-grained model of cellular populations can be more powerful and predictive, allowing us to identify principles that are obscured by excessive detail. The success of complexity analysis in clinical medicine [20], where fractal dynamics and variability measures predict health outcomes better than traditional biomarkers, demonstrates the power of scale-appropriate models.

4.3 Phase Transitions and the Edge of Chaos

A critical insight from complex systems theory, articulated clearly by Macklem [2], is that life exists in a narrow phase transition between order and chaos (Figure 1B). As energy consumption increases, systems move from crystalline order through a phase transition into deterministic chaos. Life occupies this critical transition zone—what Kauffman [21,22] calls “the edge of chaos.”

This positioning is not accidental but necessary. Crystals are stable and ordered but cannot adapt or evolve. Weather-like chaotic systems evolve but are unstable and cannot survive. Only in the phase transition can systems be both ordered and adaptable, stable yet able to evolve. This is where Darwinian selection operates, allowing both survival and evolution.

The narrow range of energy consumption over which this phase transition occurs has profound implications. Global and local changes in metabolic rate might have dramatic consequences in both health and disease. In myocardial ischemia, decreased local metabolic rate correlates with decreased heart rate fluctuations and poor outcomes [23,24]. Conversely, in asthma, increased local metabolic rate associates with increased variability of respiratory impedance [25,26].

The modular structures that emerge from minimizing connection costs [56] may themselves contribute to maintaining systems at the edge of chaos. Modular organization allows for both stability within modules and flexibility between modules, providing the architectural foundation for systems to balance order and adaptability. This suggests that the action principle (see Section 4.5) not only drives systems toward the phase transition zone energetically but also structurally, through the emergence of modular architectures.

4.4 Quantum Effects in Biology

Schrödinger’s [1] prescient question “What is Life?” anticipated the role of quantum mechanics in biological systems. Recent discoveries of quantum coherence in photosynthesis [27] and quantum effects in protein dynamics [28] suggest that biological systems exploit physical principles across an even wider range of scales than previously imagined. These findings underscore the need for theoretical frameworks that can bridge quantum to classical scales in living systems.

4.5 The Action Principle: A Universal Organizing Framework

Perhaps the most profound organizing principle in physics is the principle of least action. From Maupertuis to Hamilton to Feynman [29], physicists have recognized that nature seems to find optimal paths through the space of possibilities. Classical mechanics, quantum mechanics, electromagnetism, and general relativity can all be formulated in terms of action principles [30]. The power of this approach lies in its universality: the same mathematical framework applies whether describing the trajectory of a planet or the path of a photon.

The action principle states that physical systems evolve along paths that extremize (usually minimize) a quantity called the action, typically the integral of energy over time. What makes this principle so powerful is its scale invariance—it applies equally to microscopic and macroscopic systems. Furthermore, it naturally incorporates constraints and boundary conditions, making it ideal for describing systems that must satisfy multiple requirements simultaneously.

At the quantum level, action principles become even more fundamental—Feynman's path integral formulation shows that quantum mechanics itself is entirely based on summing over all possible paths weighted by their action, with classical mechanics emerging in the limit where action is large compared to Planck's constant. This quantum foundation demonstrates that action principles truly are scale-invariant, operating from the Planck scale to biological and cosmic scales.

Biology has been resistant to action formulations for several reasons: the apparent complexity of living systems, their non-equilibrium nature, and the difficulty in defining appropriate action functionals for biological processes. However, recent advances in network theory [31] and non-equilibrium thermodynamics suggest that these obstacles may not be insurmountable. If biological systems are fundamentally networks operating under energetic and informational constraints, then a network-weighted action principle might provide the unifying framework we seek (Figure 1).

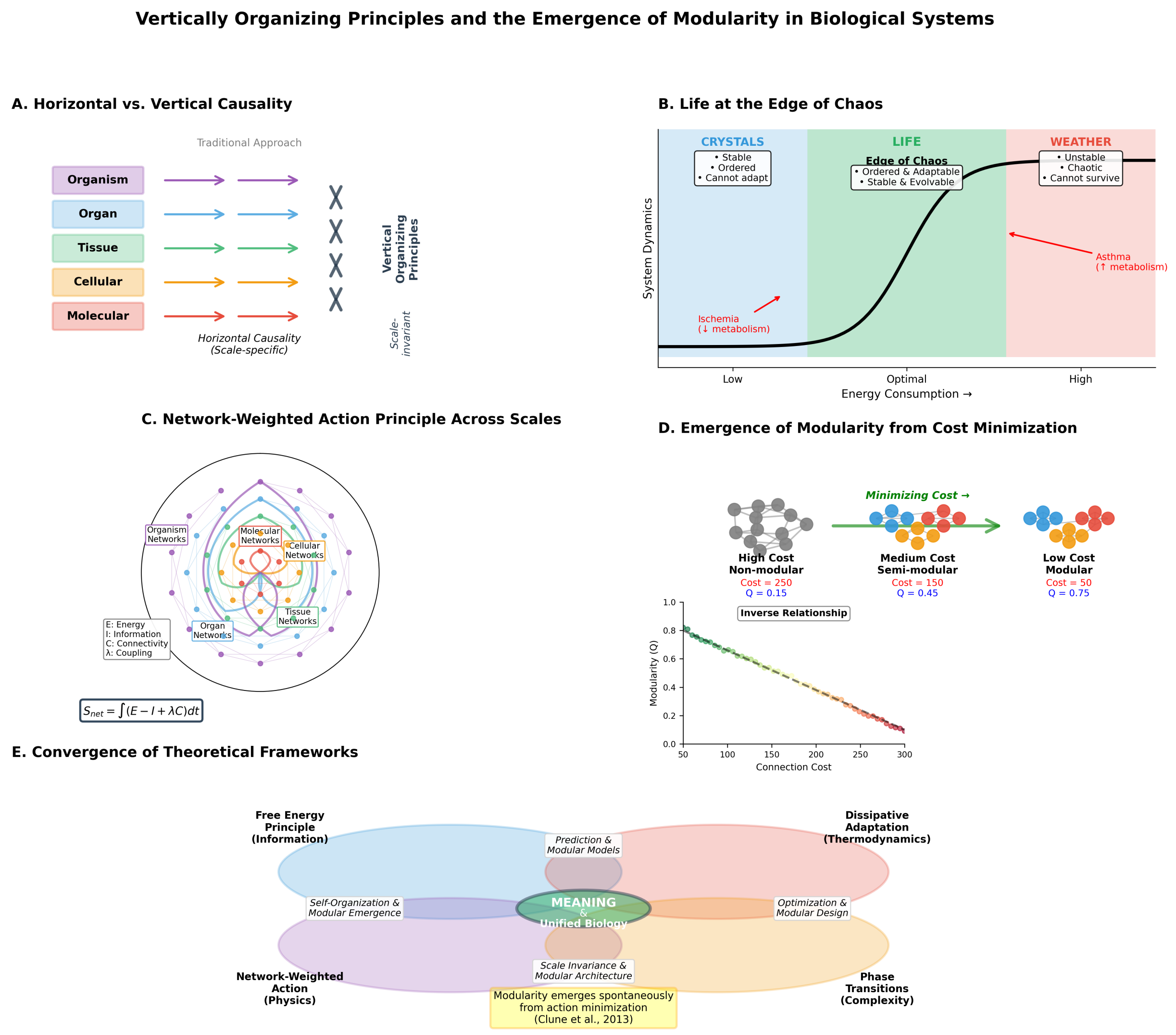

Figure 1. Integration of physical, informational, and thermodynamic principles demonstrating how modularity emerges from action minimization.

Figure 1: **Vertically Organizing Principles and the Emergence of Modularity in Biological Systems.** **(A)** The shift from horizontal (scale-specific) to vertical (scale-invariant) approaches. Traditional physiology focuses on mechanisms within scales, while vertically organizing principles seek laws governing information and energy flow across all scales. **(B)** Life at the edge of chaos. Systems exist in a narrow phase transition zone providing optimal balance between stability and adaptability. Disease states represent deviations from this critical zone. **(C)** Network-weighted action principle (minAction.net) incorporating energy (E), information (I), and connectivity (C) constraints. The principle operates across all biological scales, with network structures modulating the action functional. **(D)** Emergence of modularity from connection cost minimization. Computational evidence [56] demonstrates that minimizing connection costs—a key component of action—spontaneously generates modular networks. The inverse relationship between cost and modularity validates action principles as drivers of biological organization. **(E)** Convergence of theoretical frameworks. The Free Energy Principle, Dissipative Adaptation, Network-Weighted Action, and Phase Transitions intersect at "meaning"—operationally defined as successful uncertainty reduction through efficient action. Modularity provides the architectural substrate for this convergence.

5 Toward Unifying Theories: Information-Theoretic Approaches, Thermodynamics, and Their Limitations

While biology lacks a unified theoretical framework comparable to physics, recent advances in information theory and non-equilibrium thermodynamics offer promising directions. These approaches provide valuable insights into biological organization, though each faces challenges in scaling across biological levels and making quantitative predictions.

5.1 Non-Equilibrium Thermodynamics and Open Systems

As Prigogine [32] demonstrated in his Nobel Prize-winning work, the importation and dissipation of energy into chemical systems can reverse the inexorable disintegration into disorder predicted by the second law of thermodynamics. The second law only applies to closed systems with no exchange of energy or entropy with the environment. Life, as an open thermodynamic system, imports energy as food and oxygen, utilizes it through metabolism, and exports entropy as waste products. As entropy decreases internally, order must increase.

This thermodynamic perspective is fundamental: the imported energy creates the spontaneous development of self-organized, emergent phenomena. This is how both eons of Darwinian evolution and the much shorter gestational times for fetal development create the stunning order of life. As Macklem [2] emphasizes, it is only when we die and stop importing energy that we obey the second law, with its inevitable decay into thermodynamic equilibrium.

5.2 The Free Energy Principle and Active Inference

The concept of entropy has emerged as a potential unifying concept. All living systems must resist the second law of thermodynamics by actively maintaining a state of low entropy, or order.

The Active Inference framework, developed by Karl Friston and colleagues [33,34,35], provides a formal, mathematical description of how systems achieve this. It posits that all living systems, from a single cell to a human brain, are fundamentally predictive systems. They maintain a model of their world and act to minimize the error between their predictions and their sensory inputs (a quantity known as "free energy").

The framework has been particularly successful in explaining how stress and uncertainty lead to disease [36], and how neural systems encode and process uncertainty [37]. Active Inference is inherently multi-scale in aspiration. The principles of prediction, inference, and action apply equally to a cell maintaining metabolic homeostasis and an organism navigating a complex environment.

5.3 Dissipative Adaptation and Self-Organization

England's work on dissipative adaptation [38] offers a complementary perspective, suggesting that matter self-organizes to maximize entropy production under certain conditions. This framework has successfully predicted emergent behaviors in driven systems, including self-organized novelty detection in spin glasses [39].

Kauffman's [21,22] work on autocatalytic sets demonstrates how, in an ensemble of peptides, as diversity increases, the probability of catalytic cycles becomes a virtual certainty. Eventually, "a giant catalyzed reaction web forms" where the original peptides reproduce themselves spontaneously. Such autocatalytic sets have now been created in the laboratory [40].

5.4 Homeokinesis: Beyond Homeostasis

A crucial insight is that biological systems are not static but dynamic. As Yates [41] proposed, "homeokinesis" may be a better term than homeostasis, defined as "the ability of an organism to utilize external energy sources to maintain a highly organized internal environment fluctuating within acceptable limits in a far from [thermodynamic] equilibrium state" [26]. This fluctuating stability in the phase transition between order and chaos is essential for both adaptability and survival.

5.5 Challenges and Limitations

Despite these strengths, information-theoretic and thermodynamic approaches face several challenges:

1. **Scale-dependency of formulations**: While the concepts are universal, the mathematical formulations often require scale-specific definitions of states, boundaries, and Markov blankets [34].
2. **Difficulty in quantitative predictions**: These frameworks excel at post-hoc explanations but struggle to make precise, testable predictions about biological behavior across scales.
3. **The action gap**: Information-theoretic approaches often lack a direct connection to the fundamental physical principle of action, which has proven so powerful in physics.
4. **Energy constraints**: As Pontzer [42] demonstrates, biological systems operate under strict energy constraints that shape their evolution and function. Current frameworks don't always adequately account for these energetic limitations.
5. **The design problem**: As Macklem [2] notes, building on Polanyi's [17] insight, the design of living organisms is not determined by physicochemical laws alone. Who is the artist? We sculpt ourselves, but our survival depends on Darwinian selection.

These limitations suggest the need for complementary approaches that can bridge the gap between abstract information-theoretic principles and concrete physical laws.

5.6 Network-Weighted Action: A Complementary Principle

The principle of least action, fundamental to physics, suggests that nature finds optimal paths through possibility space. We propose that biological systems implement a network-weighted version of this principle (minAction.net), where the 'action' is modulated by the network structure of interactions at each scale. In this foundational paper, we present this as a conceptual proposal—a theoretical framework whose mathematical formalization and rigorous testing will be the subjects of the subsequent papers in this series. Here, we establish the conceptual foundations and present supporting evidence that such a principle could serve as a vertically organizing force in biology. This framework naturally accommodates both the information-processing aspects emphasized by Active Inference and the thermodynamic constraints highlighted by dissipative adaptation theories.

Recent computational evidence strongly supports this network-weighted action framework. Clune et al. [56] demonstrated that direct selection to minimize connection costs in networks causes the emergence of modular structures, without requiring selection for evolvability. Their experiments showed an inverse correlation between connection costs and modularity, with the lowest-cost, highest-performing networks being inherently modular. This finding validates our hypothesis that biological networks implementing a network-weighted action principle will naturally evolve modular architectures as an emergent property of minimizing action functionals.

In this view, biological networks—from gene regulatory networks to neural networks to ecological networks—evolve to minimize a weighted action functional that incorporates:

- Energy expenditure (classical action)
- Information processing costs (entropy production)
- Network connectivity constraints (structural limitations)
- Environmental uncertainty (predictive demands)
- Metabolic rate constraints (phase transition requirements)

This network-weighted action principle offers several advantages:

1. It is inherently scale-invariant, as action principles are in physics
2. It naturally incorporates both energetic and informational constraints
3. It provides a mathematical framework for making quantitative predictions
4. It connects biological organization to fundamental physical laws
5. It accommodates the phase transition dynamics essential for life
6. It spontaneously generates modular, evolvable architectures [56]

The convergence of these theoretical frameworks (Figure 1E) suggests that diverse approaches are complementary aspects of a deeper, unified principle governing life across scales. The empirical validation that connection cost minimization produces modularity [56] provides a crucial bridge between abstract principles and observable biological architecture.

6 Application and Evidence

This theoretical perspective is not merely a philosophical exercise; it has concrete applications that support the multi-scale, organizing principles we seek.

6.1 Emergent Phenomena in Simple Systems: Slime Molds

Macklem [2] provides an instructive example of emergence through slime mold aggregation. This system demonstrates the minimum requirements for emergent biological phenomena:

1. An open thermodynamic system of ensembles
2. A positive feedback loop causing non-linear dynamic behavior
3. Interconnections between component parts

When starved amoebae aggregate, one randomly sends out a chemotactic signal, inducing others to do the same, creating a feedforward loop that acts at progressively greater distances. The intracellular pressure measurements by Yanai et al. [43] reveal how food molecules trigger actin polymerization, increasing wall tension and internal pressure, followed by local depolymerization that converts potential to kinetic energy, creating pseudopods.

6.2 Immunometabolism

The discovery that immune cells repurpose metabolites from core energy pathways as signaling molecules [15] demonstrates a deep, informational link between metabolism and immunity. Recent work on the vagal regulation of immunometabolic homeostasis in the developing fetus [44] reveals how this coupling operates across multiple scales—from cellular metabolism to autonomic nervous system control.

From an action principle perspective, this represents an optimization of resource allocation across multiple time scales—immediate metabolic needs versus future immune challenges. The phase transition framework suggests that immune activation shifts local metabolic rates, moving the system along the order-chaos continuum.

6.3 Developmental Origins of Health and Disease (DOHaD)

The DOHaD model [45] shows that early-life environmental information shapes an organism's physiological trajectory for life. This can be framed as an adaptive, predictive process: the fetus uses early sensory data to calibrate its metabolic and stress-response systems in anticipation of the postnatal world.

Our research has demonstrated multiple facets of this programming:

- Fetal microglial cells carry "memory" of inflammatory exposure [46]

- Early-life stress creates lasting changes in neuro-immunometabolic coupling that may contribute to autism spectrum disorders [47,48]
- Microglial control extends to adult neurodegeneration [49]
- The fetal brain actively responds to inflammatory signals through cholinergic pathways [50]

These findings reveal that mismatches between predicted and actual environments can lead to disease—a form of catastrophic prediction error. From the perspective of network-weighted action, these disruptions represent forced deviations from optimal developmental trajectories.

6.4 Heart Rate Variability and System Health

Our work on fetal heart rate variability [51,52,53] demonstrates how multi-scale dynamics encode information about system health. The intrinsic variability of the fetal heart, independent of autonomic input [53], suggests that healthy complexity emerges from the optimization of information processing at multiple scales simultaneously.

The loss of fractal dynamics in disease states [11] can be understood as a collapse of the multi-scale optimization that characterizes healthy systems—a shift away from the edge of chaos either toward excessive order (rigidity) or excessive disorder (instability). As Goldberger [10] and others have shown, healthy physiological systems exhibit 1/f-like scaling and complex variability patterns that are lost in disease.

6.5 Cellular Dynamics and Phase Transitions

Recent work has shown that individual cells exist in a phase transition between solid and liquid states [54,55]. When activated, cells "fluidize" as their effective temperature increases, with important consequences for their behavior. This cellular-level phase transition mirrors the organism-level positioning at the edge of chaos, suggesting a fractal organization of criticality across scales.

6.6 Neural Development and Architecture

The developing nervous system provides perhaps the clearest example of multi-scale optimization. Neural networks must simultaneously minimize wiring length (energy cost), maximize information processing capacity, and maintain robustness to perturbations. Recent work applying the minAction.net principle to neural architecture search [59] demonstrates that biological neural architectures closely approximate the solutions found by minimizing a network-weighted action functional.

6.7 Computational Evidence for Action-Driven Modularity

The network-weighted action principle finds strong support in computational evolution experiments. Clune et al. [56] evolved networks to solve pattern recognition and Boolean logic tasks while minimizing connection costs—a key component of our action functional. Their results demonstrate that:

- Networks evolved with pressure to minimize connection costs (analogous to minimizing action) spontaneously develop modular architectures
- These modular networks are significantly more evolvable, adapting to new environments in 3-65 generations versus 65-290 generations for non-modular networks
- The relationship between cost and modularity is inverse: high-performing, low-cost networks are inherently modular
- This principle generalizes across different problem domains and network types

These findings provide computational validation that minimizing action functionals naturally produces the modular organization observed throughout biology, from gene regulatory networks to neural architectures. Importantly, this modularity emerges without explicit selection for evolvability, supporting our thesis that action principles serve as fundamental organizing forces that bootstrap the very properties (like evolvability) that ensure biological success.

The concept of modularity as a “spandrel”—a byproduct of selection for other traits [56]—aligns perfectly with our framework where meaning and organization emerge from the optimization of action. Just as architectural spandrels became spaces for artistic expression, the modularity emerging from action minimization becomes the substrate for biological innovation and adaptation.

7 Future Directions: Meaning as a Scale-Invariant Organizing Principle

The framework established in this paper invites a bold hypothesis. We propose that meaning itself can be understood as a high-level, vertically organizing principle in biology. Within both the Active Inference framework and the action principle perspective, the imperative to minimize prediction error and find efficient paths through state space is functionally equivalent to making sense of the world.

We acknowledge that this step—positing “meaning” as a fundamental organizing principle—is the most speculative aspect of our framework. The term “meaning” carries significant philosophical weight and has traditionally resided outside the domain of empirical science. However, by providing an operational definition grounded in measurable quantities (uncertainty reduction, action optimization, modular organization), we aim to establish a scientific foothold into this traditionally philosophical concept. This should be understood as a guiding hypothesis for our research program—a horizon toward which we aim—rather than a firm conclusion of this specific paper. The value of this hypothesis will ultimately be determined by its ability to generate testable predictions and unify observations across biological scales.

The modular structures that emerge from action minimization [56] may be fundamental to the construction of meaning at each scale. Modules provide semi-independent units of function that can be recombined and refined, allowing systems to build increasingly sophisticated models of their environment. This modular ‘vocabulary’ of functional units, emerging naturally from action principles, provides the substrate upon which meaning-making processes operate.

This is not a purely metaphorical claim. We propose that this “sense-making” is a scale-invariant process that can be operationally defined and measured:

At the molecular level, meaning manifests as autocatalytic sets finding self-sustaining reaction networks, creating order from molecular chaos through the optimization of chemical pathways. The modular organization of metabolic networks reflects this optimization.

At the cellular level, meaning manifests as maintaining metabolic and structural integrity in the face of environmental perturbations—finding efficient paths through biochemical state space while remaining in the critical phase transition zone. The modular compartmentalization of cellular functions enables robust adaptation.

At the tissue level, meaning emerges in the coordinated behavior of cell populations, as seen in bioelectrical pattern memories that guide regeneration [14] and the self-organizing properties of biological materials [16]. Modular tissue architectures allow for both local specialization and global coordination.

At the organismal level, it involves navigating the physical and social world to find sustenance and avoid threats—optimizing trajectories through behavioral space while managing energy constraints [42] and maintaining the delicate balance at the edge of chaos. The modular organization of neural circuits and behavioral repertoires enables flexible adaptation to changing environments.

At the cognitive level, it manifests as the conscious perception of purpose, the construction of narratives, and the drive to understand the world—minimizing action through conceptual space while managing uncertainty [36,37]. The modular structure of cognitive representations allows for compositional thought and creative problem-solving.

This operational definition of meaning—as the successful reduction of uncertainty through efficient action while maintaining criticality and modular organization—provides a framework that can be formalized mathematically. In subsequent work, as begun in [59], we will show how this maps directly to the Emin/Imax formalism developed for neural architecture search, where systems simultaneously minimize energy expenditure (Emin) while maximizing information processing capacity (Imax).

By framing meaning as emerging from the optimization of network-weighted action within phase transition constraints, with modularity as its architectural foundation, we can begin to bridge the gap between the physical processes of life and the subjective nature of existence. This is not merely philosophical speculation but a testable hypothesis: systems that better minimize their network-weighted action while maintaining criticality should demonstrate greater adaptive capacity, robustness, modular organization, and what we might recognize as “understanding” of their environment.

8 Conclusion

To advance physiology, we must supplement our investigation of horizontal, scale-specific mechanisms with a dedicated search for vertically organizing principles. This requires a paradigm shift: an embrace of theoretical frameworks from physics and information theory, a focus on the flow of information and energy through biological networks, recognition of the critical importance of phase transitions and modular organization, and the courage to ask bigger questions about the fundamental nature of life.

As Macklem [2] warns, physiology must meet Schrödinger's challenge of understanding emergent phenomena or risk becoming secondary to biochemistry and biophysics. We believe the next biological revolution lies in understanding life's design principles—how we sculpt ourselves through the interplay of thermodynamics, information, and evolution, with modularity emerging as a fundamental architectural principle from the optimization of action.

This paper has laid the philosophical and theoretical foundation for this endeavor. We have:

1. Identified the limitations of current approaches to biological causality
2. Introduced tools from physics essential for multi-scale thinking
3. Examined existing information-theoretic and thermodynamic frameworks
4. Highlighted the critical importance of phase transitions and the edge of chaos
5. Proposed network-weighted action principles as a promising candidate for scale-invariant organization
6. Demonstrated that action minimization (via connection cost reduction) spontaneously generates modular, evolvable networks [56]
7. Suggested an operational definition of meaning that spans biological scales
8. Provided concrete evidence supporting these theoretical perspectives

The subsequent papers in this series will build on this foundation:

- Paper 2 will demonstrate the application of minAction.net principles to neural architecture search, showing how biological design principles emerge from action minimization [59]
- Paper 3 will present a framework for automated discovery of physical laws using these principles
- Paper 4 will provide a comprehensive mathematical framework linking physical constants to biological complexity

Together, these works aim to establish a new theoretical biology—one that is predictive, quantitative, and unified across scales. By seeking the fundamental principles that govern life at all levels, from the thermodynamic imperatives that create order from chaos to the design principles that transcend physicochemical laws, we can move toward a more comprehensive and ultimately more profound understanding of the living world.

The computational validation that connection cost minimization produces the modular architectures ubiquitous in biology [56] provides a crucial empirical foundation for this theoretical framework. It demonstrates that the abstract principle of action minimization has concrete, observable consequences that shape biological organization at every scale. This finding transforms modularity from a puzzling feature requiring explanation to a natural consequence of fundamental physical principles, bridging the gap between theoretical physics and empirical biology.

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