Full Length Article

The limits of falsifiability: Dimensionality, measurement thresholds, and the sub-Landauer domain in biological systems

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ARTICLE INFO

ABSTRACT

Karl Popper's falsifiability criterion assumes that scientific hypotheses can be reduced to binary tests. We show this assumption is *scale-dependent* and can *saturate* in high-dimensional biological systems operating near physical measurement limits, especially near criticality. In neural networks, much relevant information exists as patterns below the Landauer threshold for irreversible bit recording—signals too weak for individual neurons to detect but detectable when pooled across populations. These sub-threshold patterns cannot be projected into binary outcomes without destroying their causal structure. We develop a framework connecting dimensionality, thermodynamic measurement limits, and biological epistemology, showing that Popperian logic represents a special case applicable only to low-dimensional systems with strong signals. Our analysis has implications for neuroscience, where aspects of conscious processing may in part depend on sub-threshold coherence patterns that resist binary measurement, motivating a shift from single-case hypothesis tests to multi-scale, ensemble-based inference. The framework extends to other complex biological systems including ecological networks, protein folding dynamics, and evolutionary processes where causal relationships exist as irreducible multi-dimensional structures operating below classical measurement thresholds.

1. Introduction

Karl Popper's falsifiability criterion has served as a cornerstone of scientific epistemology since its articulation in *The Logic of Scientific Discovery* (Popper, 1959). The framework's elegance lies in its binary clarity: a hypothesis is scientific if and only if it can, in principle, be shown false through empirical observation. This criterion has proven remarkably effective in distinguishing science from pseudoscience across biology, from molecular genetics to ecosystem ecology.

However, recent advances in our understanding of biological complexity and physical measurement limits expose fundamental boundaries to Popper's framework. Complex biological systems, ranging from neural networks to protein folding landscapes, operate in high-dimensional phase spaces where causal relationships emerge from the collective behavior of many interacting components. We argue that falsifiability, rather than being a universal criterion for biological knowledge, applies only to systems meeting specific physical and mathematical constraints.

Central to our argument is the recognition that biological information processing often occurs near thermodynamic limits. The Landauer principle establishes that recording one bit of information requires a minimum energy of $k_B T \ln 2$ (Landauer, 1961). In biological systems operating at physiological temperatures, many causally significant patterns exist below this threshold—they can influence system dynamics

through collective effects but cannot survive measurement as discrete binary states.

This creates an energy window below the Landauer limit where biological patterns are causally potent yet unmeasurable as discrete propositions. In neural systems, for instance, sub-threshold membrane fluctuations can collectively determine spike timing through stochastic resonance (McDonnell and Ward, 2011), yet individual fluctuations cannot be measured without perturbation that destroys the phenomenon. When combined with the high dimensionality of biological phase spaces, vast domains of biological reality fall outside the reach of binary falsification.

1.1. Scope and methodological clarification

This paper develops a unified framework connecting three concepts: the dimensionality of biological phase spaces, the thermodynamic limits of measurement, and the epistemological foundations of biological inference. Our contribution is primarily *conceptual and epistemological* rather than experimental. We demonstrate how sub-measurable patterns shape macroscopic biological behavior while remaining invisible to Popperian methodology—not through direct quantification (which

would be impossible in principle) but through theoretical necessity and indirect ensemble fingerprints.

The sub-Landauer domain we describe cannot be fully characterized through conventional experimental protocols precisely because such protocols require measurement energies that destroy the phenomena under study. Instead, evidence for these patterns emerges indirectly through: stochastic resonance effects where weak signals become detectable only at population scales (McDonnell and Ward, 2011; Stocks, 2000); persistence of quantum coherence beyond decoherence predictions in photosynthetic systems (Engel et al., 2007; Duan et al., 2017; Cao et al., 2020; Thyrhaug et al., 2018); non-local correlation patterns in neural dynamics that resist explanation through classical synaptic transmission alone (Anastassiou et al., 2011; Chiang et al., 2019; Zhang et al., 2014); and computational irreducibility in biological dynamics (Azadi, 2025).

Throughout we distinguish *single-trial, bit-level specification* (incoherent *in principle*) from *ensemble-level fingerprints* (tractable and appropriate observables).

Our goal is to delineate this epistemic regime and demonstrate its implications for biological validation methods. The implications extend across biological scales, from molecular processes to ecosystem dynamics, forcing a reconsideration of how we validate biological theories.

2. The binary projection problem in biology

2.1. Implicit assumptions in biological falsifiability

Popper's framework contains an implicit assumption particularly problematic for biology: that any meaningful biological hypothesis can be reduced to a falsifiable statement, essentially a binary decision. While Popper concerned himself with *in principle* falsifiability, we show that physical laws impose *in principle* limits on what biological phenomena can be falsified.

Consider a hypothesis about protein folding: "Protein X folds via pathway Y". Testing this proposition requires bringing the protein to a state where folding intermediates are discretely resolvable, measuring without disrupting the folding process, and projecting the multidimensional folding landscape onto a binary decision axis. Yet protein folding occurs on a rugged energy landscape with astronomical numbers of conformational states (Dill and MacCallum, 2012). The act of measurement necessarily perturbs this landscape, potentially switching the protein to alternative folding pathways. Moreover, the binary projection destroys information about parallel pathways, transient intermediates, and the inherently statistical nature of the folding process.

2.2. Neural network dynamics

The problem becomes acute in neuroscience. Neural networks process information through patterns of activity across millions of neurons. A hypothesis about neural coding, such as "visual cortex encodes edges through synchronous firing", resists definitive falsification for several reasons. First, measuring spike timing at the required precision alters network dynamics through the unavoidable perturbation of electrode insertion or optical stimulation. Second, synchrony exists on multiple timescales simultaneously, from millisecond precision in gamma oscillations to slower theta rhythms. Finally, and perhaps most fundamentally, the phenomenon emerges from high-dimensional interactions that disappear under any attempt at dimensional reduction.

Recent evidence from large-scale neural recordings reveals that even simple behaviors emerge from complex, distributed patterns that cannot be captured by binary tests (Stringer et al., 2019). The causal structure exists in the relationships among thousands of neurons, not in any projectable subset. Further work by Gallego et al. (2020) demonstrates that neural manifolds are genuinely high-dimensional, while Jazayeri and Jazayeri and Ostojic (2021) provide frameworks for interpreting this high-dimensional neural activity that resists classical reductionist approaches.

3. Three axes of measurement limitation

To clarify the distinct sources of falsifiability limits in biology, we separate three orthogonal constraints that often operate simultaneously:

3.1. High dimensionality and information loss

Biological systems are fundamentally high-dimensional. A single cell's state requires thousands of variables to specify—gene expression levels, metabolite concentrations, protein conformations, membrane potentials. The attempt to project this onto a binary axis for falsification faces insurmountable information loss.

For a biological system with n degrees of freedom, each with k distinguishable states, the total number of microstates is $\Omega = k^n$. A binary projection captures at most one yes/no partition of this space, yielding a state-space fraction:

$$\frac{\Omega_{\text{preserved}}}{\Omega_{\text{total}}} = \frac{1}{k^n} \tag{1}$$

In a modest neural circuit with $n = 100$ neurons, each with just $k = 10$ distinguishable states, this ratio becomes 10^{-100}—essentially zero information preserved. The choice $k = 10$ and $n = 100$ is intentionally conservative for neural circuits; real biological degrees of freedom (ion-channel states, dendritic compartments, synaptic efficacies) typically imply far larger effective k and n, further shrinking the fraction preserved by any single binary partition.

3.2. Quantum timing and measurement disturbance

Even for low-dimensional systems, quantum measurement backaction imposes limits. When biological processes depend on coherent superposition or entanglement (as in photosynthetic energy transfer (Engel et al., 2007; Duan et al., 2017)), measurement to resolve the system state necessarily collapses the superposition, destroying the very coherence that enables function. This is distinct from mere energy constraints—it reflects fundamental complementarity between observing a process and preserving its quantum character.

Unlike position or momentum, time in standard quantum mechanics is a parameter rather than an observable; time-of-arrival is accessible only as a distribution, and precise timing readouts introduce backaction via non-commuting constraints. When such micro-timings are chaos-amplified, *complete specification is limited in principle*.

3.3. Thermodynamic erasure and the Landauer bound

At physiological temperature ($T \approx 310 \text{ K}$), the Landauer limit for irreversible bit erasure is:

$$E_{\text{Landauer}} = k_B T \ln 2 \approx 3.0 \times 10^{-21} \text{ J} \tag{2}$$

This might seem negligible, but consider that ATP hydrolysis releases approximately 5×10^{-20} J, only 17 times the Landauer limit. A single synaptic vesicle release involves roughly 10^{-19} J, while conformational changes in proteins often involve energies comparable to $k_B T$. Many biological signals operate near or below this fundamental limit. Sub-threshold membrane fluctuations, protein conformational vibrations, and weak molecular interactions all fall in this regime, where they cannot be measured as binary facts without energy injection that fundamentally alters the system.

These three axes – dimensionality, quantum disturbance, and energetic erasure – often compound: high-dimensional biological systems operating near thermodynamic limits with quantum-like coherence represent the regime where falsifiability breaks down most completely.

4. Analytical bounds on predictability

These bounds formalize the limits arising from the joint action of the three axes in Section 3 (dimensionality, quantum timing/back-action, and erasure energetics).

4.1. The specification horizon in chaotic biological systems

To formalize the limits on complete system specification, consider a biological dynamical system with n coupled degrees of freedom, maximum Lyapunov exponent λ, and quantum uncertainty $\Delta x_i \geq \hbar/(2\Delta p_i)$ in each coordinate. The predictability horizon T_{pred} for deterministic specification is bounded by:

$$T_{\text{pred}} \lesssim \frac{1}{\lambda} \ln \left(\frac{L}{\Delta x} \right) \tag{3}$$

where L is the system size and Δx is the measurement precision. For quantum-limited measurement, $\Delta x \sim \hbar/\Delta p$, and the bound becomes:

$$T_{\text{pred}} \lesssim \frac{1}{\lambda} \ln \left(\frac{L\Delta p}{\hbar} \right) \tag{4}$$

This bound is primarily a scaling statement: for fixed λ, quantum-limited Δx implies a finite T_{pred} beyond which errors necessarily saturate, independent of sensor count or classical post-processing (Tian et al., 2022; Muñoz, 2018; Shew and Plenz, 2013). This horizon emerges from the joint action of dimensionality (Section 3), quantum timing limits, and – operationally – erasure when enforcing reusable binary registration. This is an *in-principle* bound: no improvement in measurement technology can extend specification beyond this horizon without fundamentally altering the system dynamics.

4.2. Information-theoretic requirement

For n effective degrees of freedom resolved to precision Δx over a domain of size L, the binary information required for full specification scales as:

$$I_{\text{required}} \sim \frac{n}{\ln 2} \ln \left(\frac{L}{\Delta x} \right) \quad \text{bits} \tag{5}$$

Remark. I_{required} is an *information* scaling (bits), not an energetic cost. If one also enforces reusable binary registration, the minimal dissipation satisfies $E_{\text{min}} \gtrsim I_{\text{erased}} k_B T \ln 2$ (Landauer).

When I_{required} exceeds the maximum extractable information without destroying function, single-trial binary falsification becomes incoherent; only ensemble fingerprints remain accessible. This formalism shows that computational irreducibility (Azadi, 2025) is not merely a practical limitation but follows from fundamental physical constraints.

5. Emergent properties and collective phenomena

Biological systems exhibit emergent properties that exist only at the collective level. Swarming behavior in bacteria, for instance, emerges from quorum sensing—a phenomenon where individual cells respond to population density through diffusible signals (Waters and Bassler, 2005). The swarm's properties cannot be reduced to binary statements about individual cells.

Similarly, consciousness appears to emerge from integrated information across brain regions (Tononi et al., 2016). Attempts to falsify theories of consciousness through binary tests necessarily destroy the integration that defines the phenomenon. The measurement collapses the high-dimensional state into a classical observation, erasing the quantum-like coherence that may underlie conscious experience.

Evolution operates in fitness landscapes of enormous dimensionality. A single protein's fitness depends on its interactions with thousands of other molecules, environmental conditions, and evolutionary history. Wright's adaptive landscape metaphor (Wright, 1932), while useful, dramatically understates the true dimensionality—real fitness landscapes may have millions of dimensions.

Falsifying evolutionary hypotheses through binary tests (did species X evolve trait Y?) ignores the multitude of evolutionary paths, the role of drift, epistatic interactions, and environmental contingencies. The evolutionary process is inherently statistical and multi-dimensional, resistant to binary reduction.

6. Physical limits to biological measurement

6.1. Biological noise and signal detection

Biological systems are inherently noisy. Order-of-magnitude thermal fluctuations can produce voltage noise on the order of 10^{-10} V for typical neural impedances and bandwidths, while single ion channel currents are on the order of 10^{-12} A. Molecular counting noise scales as $\sqrt{N}$ for N molecules, introducing fundamental uncertainty in chemical signaling. Recent single-molecule experiments confirm sub-Poisson noise in biological systems (Eldar and Elowitz, 2010; Symmons and Raj, 2016), further constraining measurement precision. The signal-to-noise ratio requirement for reliable detection typically demands signals at least 10-fold above noise, creating an effective measurement floor well above the theoretical minimum and further constraining what biological phenomena can be falsified. Thus the practical floor for reliable detection in vivo typically lies well above $k_B T \ln 2$, widening the sub-Landauer region of causally relevant yet non-binary structure.

6.2. The sub-Landauer domain in neural systems

In neurons, there is an order-of-magnitude energy window below the Landauer limit where biological patterns are causally relevant:

$$\mathcal{O}(10^{-22}) \text{ J} \lesssim E_{\text{pattern}} \lesssim 3 \times 10^{-21} \text{ J} \tag{6}$$

Within this domain operate ephaptic coupling between adjacent neurons (Anastassiou et al., 2011), weak synaptic inputs that influence spike timing through stochastic resonance, and metabolic oscillations that coordinate neural activity. Recent work by Chiang et al. (2019) demonstrated that ephaptic coupling can synchronize activity in longitudinal hippocampal slices, while Zhang et al. (2014) showed that mV/mm-scale endogenous fields can propagate activity via ephaptic interactions. Each of these phenomena contributes to neural computation yet cannot be isolated for binary testing without destroying its functional role. The measurement itself would inject more energy than the phenomenon contains, fundamentally altering the system under study.

7. The sub-Landauer domain in biology

7.1. Definition and biological examples

We define the sub-Landauer domain as the space of biological patterns whose energy content falls below the threshold for irreversible bit recording. These patterns are ubiquitous in biology:

Definition 1 (*Sub-Landauer Biological Pattern*). A biological structure $\mathcal{P}$ is sub-Landauer if:

1. *Its energy scale $E_{\mathcal{P}} < k_B T \ln 2$*
2. *It exhibits temporal coherence beyond thermal relaxation*
3. *It causally influences observable biological functions*
4. *Measurement sufficient to resolve it as a bit destroys its biological role*

Distinction from thermal noise. *Noise* is statistically unstructured at the timescale of interest, lacks phase persistence, and averages to zero under appropriate coarse-graining. *Sub-Landauer patterns* are structured phase relations among coupled degrees of freedom, maintained by active processes (e.g., metabolism, feedback), and causally relevant at the ensemble level despite being individually sub-threshold. Practically, they separate from noise by: (i) **temporal coherence** (phase-locking above surrogate baselines), (ii) **pooling consistency** (signal grows $\propto \sqrt{N}$ or better), and (iii) **predictive asymmetry** (improved out-of-sample responses under held-out protocols). These criteria align with limits in natural computation: only compressible, predictive low-energy relations are exploitable (Igamberdiev and Brenner, 2021; Hofmeyr, 2021).

This definition clarifies that the sub-Landauer domain is not merely about "weak signals" or "noise", but represents a computational mode where information is encoded in phase relationships between coupled elements operating below the erasure threshold. These patterns maintain causal relevance through collective effects rather than individual detectability.

7.2. Photosynthetic energy transfer

Quantum coherence in photosynthetic complexes represents a paradigmatic sub-Landauer phenomenon. While quantum effects in warm biological systems remain debated, recent experiments confirm that energy transfer in light-harvesting complexes involves quantum coherence lasting hundreds of femtoseconds at physiological temperatures (Engel et al., 2007; Duan et al., 2017). The coherent exciton states exist at energies approximately:

$$E_{\text{coherence}} \approx 10^{-21} \text{ J} \tag{7}$$

This is near the Landauer limit. The coherence enables near-perfect energy transfer efficiency by allowing the exciton to simultaneously sample multiple pathways. Any measurement strong enough to determine the exciton's specific path destroys the coherence and reduces transfer efficiency. Recent work using 2D spectroscopy by Cao et al. (2020) has reviewed and reassessed the evidence, while Thyrhaug et al. (2018) demonstrated that coherence at room temperature persists longer than previously thought.

7.3. Molecular recognition

Protein–protein recognition often involves initial encounters through long-range electrostatic interactions at energies below $k_B T$. These weak interactions guide proteins into binding orientations through a process analogous to quantum measurement—the interaction gradually collapses the conformational possibilities into a specific bound state (Schreiber et al., 2009). The initial recognition operates in the sub-Landauer regime, with individual electrostatic interactions too weak to measure without disrupting the binding process. Only the final bound state, stabilized by many weak interactions, rises above the measurement threshold.

7.4. Collective computation through stochastic resonance

Biological systems exploit stochastic resonance to amplify sub-Landauer signals. In neural populations, weak periodic signals below individual neuron thresholds can entrain population activity through noise-mediated synchronization (McDonnell and Ward, 2011). The mechanism requires:

$$E_{\text{signal}} + E_{\text{noise}} > E_{\text{threshold}} \tag{8}$$

where individually $E_{\text{signal}} < E_{\text{Landauer}}$ but collectively the signal emerges through correlation across many units.

Recent experimental work provides direct evidence for sub-threshold pattern processing in neural systems. Anastassiou et al.

(2011) demonstrated that endogenous electric fields as weak as 1 mV/mm – well below single neuron detection thresholds – can shift spike timing by several milliseconds across neural populations through ephaptic coupling. These fields represent information-carrying patterns that operate below the Landauer limit yet causally influence network dynamics.

Furthermore, suprathreshold stochastic resonance, as characterized by Stocks (2000), explains how weak periodic signals become detectable at the population level. When sub-threshold signals are experienced simultaneously across multiple neurons, constructive interference allows detection of signals N-fold weaker than individual thresholds for N coupled units. This mechanism bridges the gap between sub-Landauer patterns and observable neural activity without requiring discrete measurement of individual components. Stochastic resonance has been demonstrated in hair-cell mechanoelectrical transduction (Jaramillo and Wiesenfeld, 1998), while Patel and Kosko (2011) quantified noise-enhanced detection in neural populations, providing further experimental validation.

Stochastic resonance mechanisms (Gammaitoni et al., 1998) can achieve substantial signal amplification, with theoretical models predicting 100-1000× enhancement through expectation-biased processing, potentially extracting information from patterns at 10^{-23} to 10^{-24} J—far below single-channel detection limits. This implements analog Bayesian inference through selective amplification rather than binary measurement.

Population threshold and suprathreshold scaling. Let $s(t)$ be a weak periodic drive with per-unit energy $E_{\text{signal}} < E_{\text{Landauer}}$ and independent noise $\eta_i(t)$ at units $i \in \{1, \ldots, N\}$. For $Y(t) = \frac{1}{N} \sum_i y_i(t)$ with y_i a thresholded/rectified response,

$$\text{SNR}(Y) \approx \frac{N \, \text{cov}(y_i, s)}{\sqrt{N \, \text{var}(y_i)}} \propto \sqrt{N}, \tag{9}$$

so the effective detection threshold scales as $E_{\text{threshold}}/\sqrt{N}$ (and better with weak coupling). This is suprathreshold stochastic resonance (Stocks, 2000), observed in sensory bundles and neural arrays (Jaramillo and Wiesenfeld, 1998; Patel and Kosko, 2011), consistent with general principles of noise-enhanced detection (Gammaitoni et al., 1998).

Consequence. The effective detection threshold for $Y(t)$ drops as $E_{\text{threshold}}/\sqrt{N}$ (and faster with weak coupling), rendering sub-threshold drives *decisive at the population level.*

The key insight is that sub-Landauer patterns are *decisive* for biological function precisely because they operate at criticality—the boundary between noise and signal. At this boundary, small energetic perturbations can trigger large-scale state transitions, making these patterns essential for adaptive biological computation despite their individual unmeasurability (Tian et al., 2022; Muñoz, 2018; Shew and Plenz, 2013; Louie, 2020).

8. Epistemological implications for biology

8.1. The failure of reductionism

The conjunction of high dimensionality and sub-Landauer dynamics reveals fundamental limits to reductionist approaches in biology. Biological functions emerge from multi-component interactions where isolation destroys the context that defines function, and many causal patterns exist below measurement thresholds. This does not imply that biological systems are mystical or unknowable. Rather, it suggests they require epistemological frameworks beyond binary hypothesis testing, frameworks that can accommodate the inherent complexity and measurement limitations of living systems.

Recent work on computational irreducibility in biological systems (Azadi, 2025) provides additional theoretical support for these limitations. When biological systems exhibit computational irreducibility, their future states cannot be predicted faster than running the system itself, making traditional falsification approaches fundamentally limited.

8.2. Implications for specific biological domains

8.2.1. Neuroscience and consciousness

The hard problem of consciousness may be hard precisely because consciousness emerges from sub-Landauer coherence patterns distributed across neural populations. Recent work emphasizes that cognition itself is an emergent property of distributed neural dynamics (Miller et al., 2024), with mesoscale electric fields organizing activity via ephaptic (cytoelectric) coupling (Pinotsis et al., 2023; Anastassiou et al., 2011; Chiang et al., 2019; Zhang et al., 2014). If this hypothesis holds, it would explain several puzzling features of consciousness: its resistance to localization in specific brain regions, the effectiveness of anesthetics at surprisingly low concentrations, and the apparent irreducibility of subjective experience to neural correlates. Should consciousness indeed depend on quantum-like coherence below measurement thresholds, it would become physically impossible to falsify theories of consciousness through direct measurement. Whether this limitation is fundamental or merely reflects our current technological constraints remains an open question. This view aligns with cytoelectric coupling, where low-energy field structure can scaffold mesoscale organization without discrete, high-energy readout (Pinotsis et al., 2023).

8.2.2. Evolutionary biology

Evolutionary processes involve selection on high-dimensional phenotypes arising from complex genotype-phenotype maps. The impossibility of binary falsification helps explain why evolutionary predictions are necessarily statistical rather than deterministic, why laboratory evolution often yields surprising outcomes that contradict theoretical expectations, and how convergent evolution can coexist with historical contingency. The evolutionary process operates across fitness landscapes of such high dimensionality that any attempt to reduce them to testable binary hypotheses necessarily loses the very complexity that drives evolutionary dynamics.

8.2.3. Ecology

Ecological networks exhibit emergent stability properties that cannot be predicted from pairwise species interactions alone. The failure of binary falsification in ecology reflects the importance of higher-order interactions among multiple species, environmental stochasticity operating at multiple scales, and feedback loops that operate across vastly different timescales. A seemingly simple question such as "does species diversity promote ecosystem stability?" cannot admit a binary answer because the relationship depends on unmeasurable multi-dimensional interactions in the sub-Landauer domain. Network approaches confirm that unmeasurable higher-order interactions dominate ecosystem dynamics (Grilli et al., 2017; Bairey et al., 2016).

The concept of semantic closure in biological systems (Vega, 2024) further illuminates these constraints, showing how organisms maintain functional organization through circular causality that resists external measurement. This relates to autopoietic organization, where living systems maintain their identity through self-producing networks of processes that cannot be decomposed without losing the very organization that defines them.

8.2.4. Autopoiesis and measurement resistance

Autopoietic systems maintain organization through closed networks of production and constraint. This *closure to efficient causation* creates an epistemic asymmetry: external measurements that isolate or energize components can destroy the very organizational relations that constitute function. Relational biology formalizes this as an intrinsic incompleteness of external descriptions for living systems (Louie, 2020). Energetically, much coordination that sustains closure operates in the sub-Landauer regime (distributed, weak couplings), so projecting to binary tests typically injects energy at scales that break

functional context. This links autopoiesis to limits of natural computation: when computation is realized by dynamically maintained, low-energy phase relations rather than symbolic manipulation, falsifiability becomes scale-dependent and contingent on preserving coherence and coupling (Vega, 2024; Igamberdiev and Brenner, 2021; Hofmeyr, 2021).

8.3. Connection to natural computation and incompleteness

The sub-Landauer domain connects directly to fundamental limits in natural computation (Igamberdiev and Brenner, 2021). Biological systems compute through physical dynamics – substrate-dependent processes where information is encoded in material configurations and energy flows – rather than abstract symbol manipulation. This mode of computation faces intrinsic limits: when relevant patterns exist at energies below the erasure threshold, they cannot be "read out" without being destroyed, yet they remain causally efficacious through collective effects.

This relates to Louie's demonstration of incompleteness in relational biology (Louie, 2020): living systems contain causal relations that cannot be fully captured by external observers because observation itself is a dynamical intervention that perturbs the system. Similarly, Hofmeyr's analysis of biochemical networks (Hofmeyr, 2021) shows that metabolic organization depends on low-energy constraint relations that guide reaction pathways without themselves being discrete, measurable quantities.

The implication for falsifiability is clear: when biological function depends on sub-Landauer organizational patterns maintained through closure to efficient causation, binary hypothesis tests become incoherent. The patterns are real and causally decisive, but they resist the projection into discrete, observable facts that Popperian falsification requires. Khrennikov (2022) and Igamberdiev (2021) have explored how quantum-like coherent states in biological systems enable computational modes that transcend classical algorithmic limits, further supporting the view that biological epistemology must extend beyond binary logic.

8.4. Alternative validation approaches

Given these limitations, biological sciences require validation methods beyond falsification. Pattern consistency allows us to test whether models reproduce statistical patterns across scales without requiring binary outcomes. Predictive power can be evaluated through probabilistic predictions over ensembles rather than deterministic single-case predictions. Mechanistic coherence assesses consistency with physical and chemical constraints, while convergent evidence integrates multiple indirect lines of support. Finally, intervention outcomes test system responses to perturbations, though even here the interpretation must account for the multi-scale nature of biological causation. No single approach suffices; rather, biological validation requires a portfolio of complementary methods.

These alternative approaches align with emerging frameworks in natural computation (Igamberdiev and Brenner, 2021), which recognize that biological systems compute through physical dynamics rather than symbolic manipulation, requiring validation methods that respect these computational modes.

9. Toward a multi-scale biological epistemology

9.1. Scale-dependent falsifiability

We propose that falsifiability in biology is scale-dependent:

Principle 1 (Biological Scale-Dependent Falsifiability). A biological hypothesis H about system S is falsifiable at energy scale E if:

$$E > \max(E_{\text{Landauer}}, E_{\text{coherence}}(S), E_{\text{coupling}}(S))$$

where $E_{\text{coherence}}(S)$ is the minimum energy to preserve biological function and $E_{\text{coupling}}(S)$ is the system-environment coupling strength.

This acknowledges that some biological questions (enzyme kinetics, action potential propagation) admit falsification while others (consciousness, ecosystem stability) do not.

9.2. Methodological recommendations

For biological systems operating near physical limits, we recommend adopting multi-scale modeling that integrates across spatial and temporal scales, acknowledging that different phenomena may dominate at different scales. Ensemble approaches provide statistical characterization over many realizations rather than focusing on individual trajectories. Information-theoretic measures such as mutual information, transfer entropy, and integrated information can capture relationships that resist binary characterization. Perturbation analysis, while not providing definitive falsification, can probe system responses to controlled interventions. Perhaps most importantly, convergent validation combining computational, theoretical, and experimental approaches can build confidence even when direct falsification remains impossible. The key insight is that these methods complement rather than replace each other; biological understanding emerges from their convergence.

10. Conclusion

Karl Popper's falsifiability criterion has been invaluable for biology, helping distinguish science from pseudoscience. However, our analysis reveals that falsifiability applies only to a restricted class of biological phenomena: those existing in low-dimensional spaces at energy scales well above the Landauer limit.

The conjunction of high dimensionality and physical measurement constraints creates vast domains of biological reality that cannot be reduced to falsifiable propositions without destroying the phenomena under investigation. From protein folding to consciousness, from evolution to ecology, many fundamental biological processes operate in regimes where binary epistemology fails.

This is not a failure of scientific methodology but a recognition of fundamental physical limits on biological knowledge. The sub-Landauer domain, populated by weak interactions and quantum-like coherences, plays a crucial role in biological function yet resists classical measurement. Understanding these systems requires new frameworks that embrace statistical, multi-scale, and information-theoretic approaches.

The future of biological science lies not in universal falsifiability but in a scale-aware, dimension-sensitive epistemology that respects the fundamental limits physics places on biological knowledge. Only by acknowledging these limits can we develop methods adequate to the extraordinary complexity of living systems. Popper gave us a powerful tool for the classical, macroscopic biological world. The challenge now is to develop equally rigorous methods for the quantum-like, mesoscopic world that underlies biological organization.

CRediT authorship contribution statement

Ian Todd: Writing – review & editing, Writing – original draft.

Declaration of Generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author used Claude (Anthropic) to assist with editing, formatting, and refining arguments. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

Funding

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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