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The Central Homeostatic Principle: A Lipid-Centered Constraint Framework for Biological Organization, Robustness, and State Transitions

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Abstract

The Central Dogma has provided a foundational framework for biological information flow, yet it does not fully explain how living systems preserve stable identity, functional robustness, and recoverability under continuous molecular noise and environmental perturbation. Here, I propose the Central Homeostatic Principle (CHP) as a complementary first-principle framework that shifts the explanatory center from information execution alone to the physical constraint architecture that makes biological execution possible. The CHP posits that, in living cells, a central homeostatic state functions as a system-level coordinating layer that defines the feasible state space within which genetic and biochemical programs can operate. This framework is motivated by convergent evidence across mechanical confinement, electrophysiological coupling, membrane contact-site transduction, phase-state regulation, and non-genetic phenotypic heterogeneity, all of which indicate that global physical states can gate, reshape, or buffer molecular outcomes. Building from systemic prerequisites and material constraints, I further argue through an exclusionary first-principle analysis that lipid-organized boundary systems occupy a near-irreplaceable physical position in implementing this central homeostatic constraint in aqueous cellular life-not as exclusive causal authors, but as the dominant substrate of feasibility control. To render the theory scientifically actionable, this manuscript provides a formal articulation of CHP, a three-tier realization model, operational corollaries, and a rule typology that distinguishes stronger and weaker forms. It then derives a set of falsifiable hypotheses spanning temporal commitment dynamics, non-genetic resistance, aging-related resilience loss, state-engineering-based reprogramming, and evolutionary primacy in prebiotic systems. By reframing life as a problem of constrained state maintainability rather than information flow alone, the CHP offers a testable theoretical scaffold for integrating molecular biology, biophysics, systems biology, and translational state engineering.

Keywords: Central Homeostatic Principle (CHP); biophysical constraints; lipid-organized boundary systems; state-dependent reprogramming

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1. From "Information Flow" to "State Constraint": The Crisis of the Central Dogma and a First-Principle Breakthrough

1.1. Introduction: The Triumphs and Hidden Boundaries of the Central Dogma

In the mid-twentieth century, the Central Dogma of molecular biology (DNA- RNA - protein) established a formidable foundation for understanding the storage and transmission of genetic information. Over the past half-century, this framework has enabled countless scientific triumphs, from CRISPR gene editing to targeted therapeutics, and remains one of the most powerful organizing principles in modern biology.

However, brilliance does not equate to completeness. As the field advances from the question of 'how genes encode proteins' to the deeper question of 'how cells preserve identity under complex physical perturbations,' the boundaries of the classical dogma become increasingly visible. As Francis

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Crick himself emphasized when proposing the dogma in 1958, it was a statement about the directionality of information transfer, not a comprehensive physical theory of how living systems maintain organization.

1.2. The Absolute Explanatory Boundaries of the Central Dogma: From Information Conundrums to Physical Dimensionality Reduction

Over the past decade, a critical mass of wet-lab breakthroughs has exposed the explanatory boundaries of the Central Dogma for complex phenotypes. These diverse findings converge on a common point: the linear flow of genetic information is often insufficient, by itself, to lock in higher-order cellular phenotypes. Instead, factors spanning molecular topology, mesoscale organization, and whole-cell physical and mechanical states exert substantial "veto power" over how genetic programs are executed.

1.2.1. The "Dark Matter" of Genetic Instructions and Physical Interpretation

Recent evidence shows that even at the core level of sequence decoding, information does not simply linearly dictate phenotype. For instance, synonymous mutations in the cucumber ACS2 gene-classically presumed to be transcriptionally 'silent'-were shown to shape macroscopic traits such as fruit length [1]. Although these mutations leave the amino acid sequence unchanged, they modulate translational efficiency by altering epitranscriptomic m^6A sites and RNA secondary structure. This finding strongly implies that the effective readability of genetic information is conditioned by the microscopic physical structure of the molecules that carry it: information flow must first be physically permitted.

1.2.2. Topological and Mechanical Boundaries Forcing Reprogramming

Scaling up to the cellular level, mechanical forces can directly reshape and lock in cell fate. Under pure mechanical confinement, melanoma cells relay external force signals to the nucleus through formation of an acetylated microtubule 'corset,' driving dedifferentiation into an invasive state and acquisition of targeted-therapy resistance without requiring new genetic mutations [2].

Cells can also retain a long-term memory of prior mechanical environments. Stem cells cultured on stiff substrates and then transferred to soft substrates maintain persistent nuclear YAP/TAZ activation, effectively locking in differentiation trajectories [3]. Extended exposure to stiffness induces durable chromatin remodeling, including persistent histone acetylation changes [4]. Likewise, epithelial cells primed by matrix stiffness retain nuclear YAP and sustain accelerated collective migration after transfer to soft matrices [5]. Collectively, these observations indicate that macroscopic geometric and mechanical boundary conditions do more than bias immediate phenotypes-they can lock phenotypes across time. In this sense, physical constraints act as a reprogramming engine, while downstream epigenetic remodeling records these upstream constraints.

1.2.3. The Gating Role of Global Physical Phase States on Core Transcriptional Processes

Even the initiation of gene expression is contingent on the global fluidic phase state of the cell. Super-enhancer regions drive strong transcription through high-concentration coactivator condensates formed by liquid-liquid phase separation (LLPS) [6]. Yet the stability of these condensates is highly sensitive to global intranuclear physical parameters, including osmotic stress [7, 8]. Phase-separated nuclear condensates can also repress transcription by physically sequestering transcription factors [9].

Moreover, under severe stress such as starvation, the cytoplasm of yeast and bacteria can undergo a liquid-to-solid-like transition (vitrification), during which macromolecular diffusion is drastically reduced and translation and metabolism are effectively arrested [10, 11]. These observations suggest that global physical phase state can function as an ultimate switch for biological activity: once systemic physical parameters cross critical thresholds, localized molecular programs are forced into dormancy or reset at the physical level.

1.2.4. Physical Solving" of Macroscopic Cellular Traits and Metabolic Network Buffering

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Stable phenotypic heterogeneity within isogenic populations further implies that higher-order traits are not strictly hard-coded by individual genes. Cell-cycle progression and cell-volume regulation, for example, are strongly constrained by membrane tension and by the mechanical properties of the microenvironment; cells must overcome physical resistance to complete division [12].

In parallel, large-scale single-cell phenotyping and classical biochemical network models emphasize that complex biochemical networks exhibit extraordinary robustness [13, 14]. Through dynamic self-adjustment, these networks can compensate for haploinsufficiency in many essential genes. Living systems therefore appear to continuously solve against both physical hardware constraints and network resistance. The state buffer generated by metabolic and regulatory networks tends to pull the system back toward a homeostatic attractor, smoothing partial genetic defects at the macroscopic level and underscoring the need for a system-level state constraint.

1.3. First-Principle Inquiry: How Is a Living System Possible?

Taken together, the foregoing phenomena point to a deeper question: how do living systems preserve a stable-yet-plastic phenotypic state amid relentless molecular noise and environmental perturbation?

Let us return to first principles. A living cell is an open, non-equilibrium dissipative system—it continuously dissipates energy, exchanges matter with its environment, and endures perturbations. To sustain viability, life must simultaneously satisfy two seemingly contradictory mandates: it must maintain ordered internal structures to prevent the thermodynamically driven slide toward equilibrium (death), while retaining the plasticity to adapt to environmental fluctuations rather than rigidly adhering to a singular state.

This implies that life cannot rely solely on the instantaneous success of localized molecular reactions. The expression of a single gene can easily be drowned out by thermal noise. There must exist a higher-order state constraint mechanism designed to stabilize the global operating range, thereby delineating a "physical feasibility space" within which molecular programs can be securely executed.

Therefore, what the living system requires is not merely dispersed local homeostases, but a constraint layer capable of maintaining global consistency across multiscale coupling. Absent this layer, the cell would be highly susceptible to internal conflicts: certain reactions might be locally optimal yet disrupt overall gradients, or localized metabolic adaptations might enhance regional flux but compromise the system's resilience for recovery.

1.4. Introducing the CHP: The Central Homeostatic Principle as a More Complete Explanatory Framework

Against this backdrop, I propose the Central Homeostatic Principle (CHP) of life: Cellular phenotype and fate are not determined solely by molecular components, but are governed upstream by a holistic homeostatic state that serves a central coordinating function.

The CHP does not seek to invalidate the Central Dogma's explanatory power regarding molecular information flow. Rather, its core assertion is that molecular information and protein execution invariably operate within a physical feasibility space defined by a homeostatic state. This space dictates "which molecular programs can be stably actualized," "which phenotypic states can be sustainably maintained," and "which fate transitions are permitted by the system." If the Central Dogma answers "how information flows," the CHP answers "under what physical conditions information can successfully become life."

1.5. Empirical Integration: Reverse Validation of the CHP Constraint Framework by Frontier Research

These four dimensions of evidence-mechanics, electrophysiology, topology, and thermodynamics-converge on a single conclusion: a system-level state constraint exists within cells. They do not, by themselves, prove the CHP, but they provide a strong empirical foundation for proposing and testing it.

1.5.1. The Mechanical Dimension: Physical Baselines and Gating Limits

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Conventional molecular models rarely treat membrane physical state as an independent control variable. Yet quantitative studies now show that membrane tension acts as a distinct physical parameter: elevated tension significantly inhibits the assembly and clustering of curvature-generating proteins such as N-BAR family members [15]. Cryo-EM and electrophysiological analyses further demonstrate that changes in membrane tension directly supply the driving energy for conformational transitions of mechanosensitive channels including MscS and K2P [16, 17]. Within the CHP framework, resting membrane tension functions as part of a system-level substrate constraint, setting physical energy barriers and activation thresholds for the downstream execution layer.

1.5.2. The Electrophysiological Dimension: Rapid Coupling of Membrane Potential and Lipid Polarity

Classical electrophysiology long framed membrane potential as the domain of excitable cells, yet non-excitable cells also maintain complex electrical topologies. The membrane potential of epithelial and stem cells exhibits spatial heterogeneity and is tightly coupled to the polarized distribution of anionic lipids such as PIP3 [18]. Upon mechanical stimulation, this lipid-potential network can relay signals on millisecond timescales to reshape cell morphology and downstream kinase signaling [19]. Because this speed far exceeds diffusion-limited molecular signaling alone, it supports the existence of a rapid physical integration network built on coupled membrane state variables.

1.5.3. The Spatial Topological Dimension: Physical Transduction Networks Mediated by Membrane Contact Sites

Membrane systems also establish intricate internal topologies. Mechanobiology studies show that external strain applied to the plasma membrane is relayed to the endoplasmic reticulum through PM-ER contact sites, producing adaptive changes in ER tension [20]. ER disruption can in turn stimulate nuclear membrane mechanotransduction and alter chromatin architecture [21]. These findings support the plausibility of an internal cross-scale physical transduction network, organized around membrane-connected boundary states, through which localized perturbations can be propagated inward as a form of physical state broadcast.

1.5.4. The Thermodynamic Phase Dimension: 2D Lipid Phase Behavior as a Dimensionality-Reduction Template

Protein LLPS in three dimensions is strongly dependent on local physical context. Studies show that two-dimensional membrane phase separation drives responsive assembly of B-cell and T-cell receptor signaling domains: the membrane effectively reduces the dimensionality of diffusing proteins to a 2D plane, thereby lowering the critical concentration for phase separation [22]. At the same time, microscopic lipid-state transitions reorganize membrane-associated protein networks. Thus, protein execution programs do not operate in isolation; they are templated and gated by the biophysical state of membrane-organized lipid systems.

2. Deductive Reasoning of Substrate Privilege: A Four-Stage Exclusionary Argument for the Central Homeostatic Constraint

As a highly complex, non-equilibrium dissipative system, life cannot be fully explained by information flow and local molecular execution alone. A system-level physical constraint architecture is also required to stabilize feasible operating states across scales.

I therefore introduce the GHCL as a molecule-neutral systems requirement and analyze candidate substrates through a four-stage deduction: systemic prerequisites, functional imperatives, material constraints, and categorical screening. This ordering is intended to reduce candidate leakage and avoid circular reasoning.

2.1. Stage One: Deriving Functional Imperatives from Systemic Prerequisites

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An open living system must maintain selective boundary isolation with controlled permeability and gradient maintenance, a tunable yet stably maintainable physical feasible state space, cross-scale functional continuity for perturbation propagation and integration, and bidirectional coupling with protein, ionic, and metabolic networks under non-equilibrium flux. These are joint engineering requirements for a central homeostatic constraint substrate.

2.2. Stage Two: Mapping Functional Imperatives to Physical Material Constraints

A viable GHCL substrate must form persistent self-bounded interfaces in water, support selective permeability and electrochemical asymmetry, allow reversible in situ tuning of supramolecular physical state, support cross-scale coupling, directly interface with protein machines and ion gradients, and exhibit measurable perturbation recovery dynamics. A substrate lacking any one of these dimensions cannot bear the full systemic function proposed here.

2.3. Stage Three: Exclusionary Screening of the Major Biological Macromolecular Classes

Applying these criteria in molecule-neutral terms indicates that nucleic acids, polysaccharides, and proteins remain indispensable but are systematically insufficient as the dominant interfacial carrier of the full requirement set. Nucleic acids mainly provide information and regulation, polysaccharides mainly provide support and buffering, and proteins mainly provide execution and local control rather than a ubiquitous self-sealing interfacial substrate with continuous state tunability across cellular scales.

2.4. Stage Four: Categorical Convergence and the Current Best Solution in Aqueous Cellular Life

Under these constraints, lipid-organized amphiphilic boundary systems emerge as the strongest current solution for implementing the core physical function of the GHCL in modern aqueous cellular life. This conclusion follows from exclusionary comparison rather than prior lipid primacy and supports a narrower claim of substrate privilege: lipid-organized boundary states act as the dominant substrate of feasibility control in modern cells.

[Section 2.4 detailed examples condensed in this revision for logical neutrality and to avoid candidate leakage.]

3. The Central Homeostatic Principle (CHP): Formal Articulation and Conceptual Architecture

3.1. Formal Articulation

The phenotypic identity and fate of a cell are governed upstream by its holistic homeostatic state. In modern aqueous cellular systems, lipid-organized boundary systems-by establishing selective boundaries, compartmentalization, and tunable physical boundary conditions-constitute the dominant (and likely core) biophysical substrate for implementing this homeostatic constraint, thereby enabling and shaping downstream molecular processes.

The CHP is a system-level constraint principle. It does not claim that lipids alone determine all biological outcomes, nor does it deny the central role of genes in causal chains. Its core assertion is that molecular information and protein execution operate within a physical feasibility space defined by homeostatic state variables, with lipid-organized boundary states holding a privileged position in establishing and modulating that space.

3.2. The Three-Tier Model (Minimal Realization)

For operational clarity, I propose a three-tier architectural model:

Tier 1: The Biophysical State Substrate Layer (Lipid-Organized Boundary Systems). Responsible for selective boundary formation, regulated exchange, physical state modulation, compartmentalization, and topological network organization, this layer provides the primary material foundation for maintaining a non-equilibrium operating state.

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Tier 2: The Functional Execution Layer (Protein Networks). Responsible for catalysis, transport, signaling, mechanics, and repair, whose behaviors are exquisitely dependent on localization, clustering, assembly state, and membrane-organized microenvironments.

Tier 3: The Information and Memory Layer (Nucleic Acid System). Provides component templates, regulatory logic, and genetic memory, while its accessibility and expression remain substantially constrained and reshaped by the prevailing state substrate layer.

3.3. Operational Corollaries

The relationship between state and molecular programs is recursively coupled yet functionally asymmetric: the physical state constrains which molecular programs can be stably actualized, while executed molecular programs iteratively remodel that state. This refines the simplified 'genes dictate phenotype' paradigm into a systems view in which genes encode a repertoire of possibilities, whereas homeostatic state determines which possibilities are activated, stabilized, suppressed, or reversed.

3.4. A Necessary Clarification: The Typology of CHP Rules

A common skepticism toward the CHP is that it appears to invoke 'emergence' too broadly: how can lipid-organized physical states produce specific biological regulation without dissolving into vagueness? The CHP responds by positing identifiable, measurable, and testable state-constraint rules. I therefore delineate five core rule classes: boundary priority, state restriction, threshold regulation, global coupling, and recovery dynamics.

Briefly, boundary priority states that intracellular molecular processes depend on the physical space established by closed boundary systems. State restriction posits that cellular phenotype is constrained by the global physical state of lipid-organized boundary systems, such that a single genome can support multiple stable phenotypes corresponding to distinct attractors in state space. Threshold regulation emphasizes that protein output is gated by local physical parameters. Global coupling indicates that local perturbations can remodel broader system states through multiscale physical transduction. Recovery dynamics asserts that the ability to return to homeostasis after perturbation is governed by physical recovery properties of the boundary system, and that attenuation of these properties is a fundamental hallmark of aging and chronic disease.

These rule classes are not independent slogans; taken together, they map onto a set of testable hypotheses. In this framework, fate transitions, pathological state migrations, and reprogramming are not linear molecular responses, but transitions within a dynamic state space constrained by boundary conditions, thresholds, and multiscale couplings.

4. Translational Corollaries and Testable Hypotheses: State Engineering Under the CHP Framework

If the CHP only retroactively explained known phenomena, it would amount to theoretical rebranding. A useful scientific principle must generate specific, risky, and falsifiable predictions. Applying the CHP framework, I therefore propose five cross-dimensional hypotheses that serve both as pressure tests of the principle's causal logic and as a roadmap for shifting intervention from molecular targeting alone toward state engineering.

4.1. Hypothesis I (Temporal Dynamics): State Variables Precede Irreversible Molecular Commitment

Classical models view phenotypic transitions primarily as the exclusive output of transcriptional programs.

The CHP predicts that during cell-fate transitions (e.g., somatic reprogramming or stem-cell differentiation), systemic or threshold changes in membrane biophysical metrics-such as global fluidity, local curvature stress, or phase-separation thresholds-must chronologically precede irreversible commitment by master regulators. A stringent test would combine subcellular-resolution physical probes with single-cell multi-omics to track fate trajectories. The null hypothesis is that lipid-state changes are merely downstream consequences of gene expression and appear only after commitment has been established. Support for the CHP would require showing that physical

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boundary resets stably precede transcriptional-network leaps, and that targeted perturbation of those physical states systematically shifts the timing and reversibility of commitment.

4.2. Hypothesis II (Pathological Attractors): Non-Genetic Resistance is Intrinsically a Migration of Lipid Physical Homeostasis

The CHP predicts that, in the absence of driving mutations, distinct pathological phenotypes (e.g., therapy-sensitive versus persister-resistant subpopulations) are anchored by differences in underlying lipid homeostatic state. To challenge this claim empirically, one could use persister tumor cells lacking resistance mutations and attempt to force migration out of the resistant attractor by selectively remodeling lipid assembly phase and physical microdomains (for example, using lipid nanoparticles with defined phase-transition characteristics) without introducing exogenous nucleic acids. The null hypothesis is that resistance is entirely dictated by epigenetic remodeling or localized microenvironmental cues, rendering lipid-state remodeling irrelevant to the stability of the resistant phenotype.

4.3. Hypothesis III (Loss of Homeostatic Resilience): Aging and Chronic Diseases Stem from the Attenuation of Physical Recovery Dynamics

Shifting attention away from static molecular damage alone (e.g., telomere attrition), the CHP emphasizes dynamic resilience. I hypothesize that the shared core of systemic aging and many chronic diseases (including fibrosis and degenerative disorders) is attenuation of the physical recovery dynamics by which lipid-organized boundary systems return to baseline homeostasis after thermodynamic or biochemical perturbation. As recovery dynamics slow, cells fail to cross energy barriers back into physiological attractors and become trapped in suboptimal pathological states. This can be tested in vitro by subjecting young and senescent cell models to standardized transient stresses (e.g., osmotic shock) and continuously measuring recovery curves of membrane phase behavior or tension. A key indicator supporting CHP would be that prolonged recovery lag quantitatively predicts irreversible pathological decline and can be shortened by interventions that remodel lipid-organized homeostasis.

4.4. Hypothesis IV (Limit Deduction of State Engineering): Pure Lipid-Driven Cell Fate Reprogramming

Pushing the CHP logic-that physical boundary conditions define the feasibility space of molecular programs-to its strongest deductive form, I propose two nested hypotheses. The weak form (currently testable) posits that lipid-state remodeling can partially substitute for exogenous transcription factors in classical induced Pluripotent Stem Cells (iPSC) reprogramming: inducing a pluripotency-compatible boundary state while expressing only a subset of Yamanaka factors (e.g., Oct4/Sox2) should significantly improve reprogramming efficiency. The strong form (ultimate deduction) proposes that cell fate can be reprogrammed to pluripotency through sequenced lipid-physical perturbations alone, entirely without exogenous transcription factors or small molecules. This would constitute the strongest evidence for topological forcing: by coercing the physical boundary state toward a pluripotent profile, the underlying transcriptional network is left with no stable alternative state and passively falls into a new attractor.

4.5. Hypothesis V (Evolutionary Primacy): Boundary Homeostasis Precedes Informational Complexity in Prebiotic Systems

From an evolutionary perspective, the CHP predicts that during the transition from non-living chemistry to protocells, physical homeostasis of closed amphiphilic compartments (including deformation resistance balanced with selective permeability) was a prerequisite for the later complexification and selective retention of internal nucleic-acid networks. Tunable vesicle models loaded with simple catalytic networks could test how boundary physical characteristics determine persistence, thermal dissipation resistance, and fidelity limits of primitive metabolic cycles, against the null hypothesis that informational complexity can evolve independently of defining boundary properties.

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5. Translational Corollary: The Homeostatic Restoration Hypothesis

5.1. Theoretical Foundation and Formal Articulation

Rooted in the core logic of CHP, I formalize the Homeostatic Restoration Hypothesis as follows: by targeted intervention that partially restores lipid-mediated biophysical homeostasis, cells or tissues can be driven to migrate stably from a pathological phenotypic attractor toward a physiological functional attractor. Crucially, this state migration may occur and remain stable even when the upstream genetic defects or protein toxicities that initiate pathology are not fully eliminated.

This hypothesis provides a systems-level theoretical foundation for lipid-state reprogramming as an intervention strategy. Here, 'homeostatic restoration' does not mean reverting to a fixed lipid composition; it means restoring a set of core functional boundary conditions and dynamic state features-including membrane phase behavior, cross-scale organizational capacity, and resilience to perturbation.

5.2. Core Scientific and Clinical Value

This hypothesis directly addresses a major limitation of current molecular-targeting paradigms, which often assume a linear sequence-correct the upstream cause, then reverse the phenotype. Such strategies frequently fail in chronic pathologies driven by polygenic factors, distributed damage, or self-sustaining feedback loops. By proposing interventions that reset physical homeostatic boundary conditions rather than exclusively attacking upstream causes, the hypothesis opens an alternative therapeutic logic.

It also provides a unifying explanation for experimental anomalies that remain poorly integrated conceptually. In particular, engineered lipid systems-including lipid nanoparticles and liposomes-often produce biological effects far beyond their narrow designation as drug-delivery vehicles. Under the CHP framework, such observations are not accidental side effects but expected consequences of perturbing or reconfiguring state variables within the central homeostatic constraint substrate.

5.3. Strict Applicability Boundaries

This translational corollary has strict boundaries. It does not imply that all diseases are reducible to lipid dysfunction, nor that lipid-state intervention can override irreversible structural destruction, terminal genetic collapse, or complete loss of viable tissue architecture. The claim is narrower: in pathologies with sufficient state plasticity, restoring key boundary-state variables may be sufficient to re-enter a more functional attractor even without complete removal of upstream causes.

5.4. Core Testable Criteria

A rigorous test of the Homeostatic Restoration Hypothesis must satisfy three criteria simultaneously: (i) selective modulation of lipid-organized biophysical state variables, (ii) exclusion of confounding toxicity and classical biochemical-ligand effects, and (iii) demonstration of sustained functional recovery or durable state-topology correction after intervention withdrawal. Without all three, apparent efficacy cannot be interpreted as evidence for homeostatic restoration.

6. Falsifiability: What Evidence Would Weaken or Overturn the CHP?

Because the CHP makes strong claims about explanatory priority, constraint topology, and translational implications, it must be openly vulnerable to refutation. To make this explicit, I categorize possible falsification scenarios into three increasingly stringent tiers.

6.1. Tier I: Fundamental Invalidation of CHP Core Principles

The CHP would be fundamentally overturned if independent cross-system experiments eliminated biophysical centrality. This would occur if specific modulation of lipid biophysical state-while biochemical composition is held constant-failed to induce any stable fate change, thereby showing that lipids function only as classical biochemical ligands. It would also occur if asymmetric causality were broken: for example, if cells with an artificially frozen lipid biophysical state (e.g., via

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extensive cross-linking or elimination of essential cytoskeletal dynamics) could still execute full-spectrum phenotypic transitions entirely unconstrained by physical feasibility space. Finally, the principle would be invalidated by complete structural substitutability-if a modern biological module achieved equivalent non-equilibrium state control and cross-scale compartmentalization using only nucleic-acid and protein networks, without lipid-like self-assembling amphiphilic phase structures.

6.2. Tier II: Significant Attenuation of CHP Core Assertions and Universality

The scope of CHP would be substantially narrowed if the temporal directionality central to the framework were reversed. If state-of-the-art live-cell tracking at subcellular spatiotemporal resolution showed that transcriptomic or proteomic fate commitment consistently precedes any global membrane-system biophysical remodeling (strictly excluding transient microdomain fluctuations), lipid state would be better interpreted as a lagging indicator than an upstream constraint. Likewise, a demonstrated complete decoupling of spatial scales-such that highly localized receptor activation can produce stable fate reprogramming without any cross-scale boundary remodeling, and membrane organelles operate as physically independent modules-would severely weaken the assumption of global physical consistency.

6.3. Tier III: Invalidation of Translational Corollaries

Failure of the translational path (the Homeostatic Restoration Hypothesis) would not necessarily overturn the biological core of CHP, but it would invalidate its clinical corollary. This would be established if, in sufficiently plastic pathological models, interventions specifically targeting lipid biophysical homeostasis repeatedly failed to produce sustained functional improvement or durable state-topology correction after confounding toxic and biochemical effects were rigorously excluded.

7. Conclusions and Perspectives

This manuscript proposes the Central Homeostatic Principle (CHP): cellular identity and fate are governed upstream by a holistic homeostatic state, with lipid-organized boundary systems acting as the critical-and likely core-biophysical substrate in modern aqueous cellular life. The framework shifts the phenotype question from molecular composition alone to state architecture: under which boundary conditions and non-equilibrium operating ranges are molecular programs actualized, stabilized, and transformed?

The primary value of CHP lies in its predictive discipline. It urges researchers to ask not only which molecules changed, but which state variables shifted first, which boundary conditions were reset, and which recovery dynamics were altered. In this sense, CHP is not merely an explanatory framework; it is a methodological program for organizing inquiry.

If CHP gains stronger experimental support, its implications would extend biomedical intervention beyond molecular targeting toward state engineering-including lipid formulations, membrane-state modulators, compartmental remodeling, and therapeutic strategies centered on lipid-state reprogramming. Whether CHP ultimately proves broadly general or is refined to a narrower class of cellular state problems, rigorous testing of its claims should bring us closer to a deeper biological question: life is not only about how information is encoded, but also about how physical conditions are maintained so that information can become living function.

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