Hypothesis

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

Cheng Wang *

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

Cheng Wang

School of Pharmacy, Changzhou University, Changzhou 213164, Jiangsu Province, China;
wangc90@cczu.edu.cn

Abstract

The Central Dogma has provided a foundational framework for understanding biological information flow, yet it does not fully explain how living systems maintain 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 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-based boundary systems occupy a near-irreplaceable physical position in implementing this central homeostatic constraint in aqueous cellular life, not as exclusive causal authorship, but as the dominant substrate of feasibility control. To render the theory scientifically actionable, the manuscript provides a formal articulation of CHP, a three-tier realization model, operational corollaries, and a rule typology distinguishing strong and weak 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-centered regulation; state-dependent reprogramming

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 orchestrated countless scientific triumphs, from CRISPR gene editing to targeted therapeutics, cementing its indelible contribution to modern biology.

However, brilliance does not equate to completeness. As we advance from the question of "how genes encode proteins" to the more fundamental inquiry of "how cells maintain their identity amidst

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complex physical perturbations," the limitations of the classic dogma become increasingly glaring. As Francis Crick himself implied when proposing the dogma in 1958, it was merely a hypothesis regarding the directionality of information flow, not a comprehensive physical theory of how living systems operate.

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 breakthrough wet-lab studies has exposed the boundaries of the Central Dogma in explaining complex phenotypes. These diverse phenomena point to a unified reality: the linear flow of genetic information is often insufficient to independently lock in high-order cellular phenotypes. Instead, factors ranging from the topological folding of microscopic molecules to the macroscopic physical and mechanical states of the cell exert a profound "veto power" over the execution pathways of underlying genetic programs.

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

Recent evidence reveals that even at the core level of sequence decoding, information does not simply "linearly dictate" phenotype. For instance, synonymous mutations on the cucumber ACS2 gene—classically presumed to be transcriptionally "silent"—were found to dictate macroscopic traits such as fruit length [1]. These mutations leave the amino acid sequence entirely unaltered, yet they precisely modulate translational efficiency by altering epitranscriptomic m^6A modification sites and RNA secondary structure. This discovery, akin to uncovering the "dark matter" of the genome, strongly implies that the "readability" of genetic information is fundamentally governed by the microscopic physical structural features of the molecules housing it. The effective flow of information must first be permitted by physical conformations.

1.2.2. Topological and Mechanical Boundaries Forcing Reprogramming

Scaling up to the cellular level, mechanical forces exhibit a profound capacity to directly reshape and lock in cell fate. Under pure mechanical confinement, melanoma cells can transmit external force signals directly to the nucleus by forming an acetylated microtubule "corset," driving dedifferentiation into an invasive state and acquiring targeted therapy resistance—completely bypassing the need for novel genetic mutations [2].

Furthermore, cells can retain a long-term memory of past mechanical environments. Stem cells cultured on stiff substrates and subsequently transferred to soft substrates maintain long-term nuclear YAP/TAZ activation, irreversibly locking in their differentiation fate [3]. Extended exposure to such stiff microenvironments leads to persistent chromatin remodeling, including irreversible alterations in histone acetylation [4]. Similarly, epithelial cells "primed" by past matrix stiffness retain nuclear YAP and maintain accelerated collective migration even after transitioning to soft substrates [5]. Collectively, these empirical findings indicate that macroscopic geometric and mechanical boundary conditions not only guide immediate phenotypes but can lock them in across temporal scales. Physical constraints thus act as a "reprogramming engine" that supersedes transient biochemical signaling, with underlying epigenetic remodeling serving as a passive recording of these upstream macroscopic constraints.

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

Even the initiation of gene expression is exquisitely contingent upon the global fluidic phase state of the cell. Super-enhancer regions drive robust gene expression by forming high-concentration transcription factor droplets via liquid-liquid phase separation (LLPS) [6]. Yet, the stability of these coactivator condensates is highly sensitive to global intra-nuclear physical parameters, such as osmotic stress [7,8]. Phase-separated nuclear condensates can also repress gene transcription by physically sequestering transcription factors [9].

 doi:10.20944/preprints202603.0083.v1

Moreover, upon encountering severe stress such as starvation, the cytoplasm of yeast and bacteria undergoes a physical "liquid-to-solid" phase transition (vitrification). During this glass-like state, macromolecular diffusion essentially halts, abruptly freezing all translational and metabolic activities [10,11]. These observations suggest that the global physical phase state serves as the ultimate switch for biological activities: when systemic physical parameters cross critical thresholds, localized molecular expression networks face forced dormancy or resetting at the physical level.

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

The existence of 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 instance, are strictly constrained by cell membrane tension and the mechanical properties of the microenvironment; cells must overcome physical resistance to complete division [12].

Additionally, large-scale single-cell phenotyping and classic biochemical network models emphasize that complex biochemical networks possess extraordinary robustness [13,14]. Through the self-adjustment of system dynamics, these networks can largely compensate for the haploinsufficiency of essential genes. It appears that living systems continuously and dynamically "solve" against their physical hardware and network resistance. The "state buffer" formed by metabolic networks tends to pull the system back to a homeostatic attractor, effectively smoothing out partial genetic defects at the macroscopic level and underscoring the necessity of a system-level state constraint.

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

The aforementioned phenomena collectively point to a profound underlying question: How do living systems maintain a "stable yet plastic" phenotypic state amidst relentless molecular noise and environmental perturbations?

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

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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

The CHP is not pure philosophical speculation. Recent breakthrough studies, while focusing on disparate molecular mechanisms, converge from multiple physical dimensions—mechanics, electrophysiology, topology, and thermodynamics—on a singular conclusion: a system-level state constraint unequivocally exists within the cell. These findings provide a robust empirical foundation for the CHP framework.

1.5.1. The Mechanical Dimension: Physical Baselines and Gating Limits

Traditional molecular models rarely account for the global impact of membrane physical states. However, recent quantitative studies confirm that membrane tension acts as an independent physical parameter; elevated tension significantly inhibits the assembly and clustering of curvature-generating proteins (such as the N-BAR family) on the membrane [15]. Concurrently, cryo-EM visualization and electrophysiological analyses have demonstrated that alterations in membrane tension directly supply the driving energy for the conformational transition of mechanosensitive channels like MscS and K2P [16,17]. Under the CHP framework, resting plasma membrane tension functions systemically as a "substrate constraint layer," proactively setting critical physical energy barriers or activation thresholds for the functional execution layer.

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

While classical electrophysiology has long viewed membrane potential as the exclusive domain of excitable cells, recent consensus reveals that non-excitable cells possess equally complex electrical topologies. The membrane potential of epithelial or stem cells exhibits spatial heterogeneity, highly coupled with the polarized distribution of specific anionic lipids (such as PIP3) [18]. Upon sensing external mechanical pressure, this "lipid-potential" network relays signals at millisecond speeds to modulate cell morphology and downstream kinase networks [19]. Because this conduction velocity vastly exceeds the diffusion limits of conventional biochemical molecules, it strongly suggests a reliance on a physical network based on "lipid-potential" coupling to achieve rapid signal integration. This physical constraint layer is a vital mechanism for preventing local mechanical perturbations from causing systemic dysregulation.

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

Membrane systems also establish intricate topological connections internally. Mechanobiology research has confirmed that external strain applied to the plasma membrane (PM) is directly relayed to the endoplasmic reticulum (ER) via PM-ER contact sites, resulting in adaptive alterations in ER tension [20]. Such ER disruption can further stimulate nuclear membrane mechanotransduction, regulating chromatin architecture [21]. These findings indicate that an internal cross-scale physical transduction network, constructed by the lipid continuum, facilitates the rapid inward propagation of localized physical perturbations. This provides plausible mechanistic support for a direct "physical state broadcast" that relays macroscopic boundary conditions directly to the underlying genetic material.

 doi:10.20944/preprints202603.0083.v1

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

The three-dimensional liquid-liquid phase separation (3D LLPS) of proteins is highly dependent on its microenvironment. Studies explicitly demonstrate that 2D membrane phase separation drives the responsive assembly of B cell and T cell receptor signaling domains. The lipid membrane reduces the dimensionality of freely diffusing proteins to a 2D plane, significantly lowering the critical concentration required for phase separation. Simultaneously, microscopic phase transitions of the lipid state can trigger the reorganization of membrane-associated protein networks [22]. Thus, the 3D execution programs of proteins do not occur in complete independence but are highly reliant on the templating effects provided by the 2D biophysical state of lipids, reinforcing the core hypothesis that digital biochemical execution programs are nested within an analog physical state space.

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 is sustained by tens of billions of molecular machines operating concurrently amidst intense thermal fluctuations and environmental noise. If life relied solely on the linear instructions of genetic sequences and the localized, stochastic collisions of proteins in the cytoplasm, the system would inevitably collapse under combinatorial explosion and homeostatic failure. Therefore, derived from the first principles of complex systems, life inherently requires a "Global Homeostatic Constraint Layer" spanning the nanoscale to the microscale. Acting as a top-down physical dome, this layer absorbs microscopic molecular noise, synchronizes localized biochemical reactions, and delineates a coherent "feasible state space" for the execution of all underlying molecular programs.

Given that this global constraint layer is a physical prerequisite for maintaining macroscopic phenotypic stability, a critical scientific inquiry emerges: Among the known material systems constituting life, which class of macromolecules is logically best positioned to bear the core function of this overarching constraint? This cannot be answered by merely cataloging the basic functions of molecules; it requires a rigorous deduction from "what the system necessitates" to "what the material must be." To this end, I propose a strict, four-stage deductive chain: systemic prerequisites → functional imperatives → material constraints → categorical screening.

2.1. Stage One: Deriving Functional Imperatives from Systemic Prerequisites

To sustain itself amidst continuous thermodynamic dissipation and perturbations, an open, non-equilibrium living system must simultaneously resolve four fundamental challenges. First, it requires boundary insulation to strictly separate the internal from the external environment, thereby maintaining the transmembrane electrochemical asymmetry that drives life. Second, it demands state tunability, enabling the continuous and reversible modulation of its own physical properties to buffer microenvironmental noise. Third, it needs cross-scale organization to establish a coherent network from nanoscale microdomains to the whole-cell microscale, ensuring global consistency. Finally, it must possess systemic coupling capabilities to instantaneously translate macroscopic physical boundary alterations into chemical signals responsive by internal molecular networks. These four imperatives are not independent tasks to be delegated to disparate molecules; rather, they constitute a "strong coupling requirement" for maintaining central homeostasis and must be concurrently resolved by a singular material system.

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

The aforementioned macroscopic systemic demands impose exceptionally stringent, joint physical and chemical constraints on any candidate substrate. The substrate must be capable of spontaneously assembling into closed structures in an aqueous phase while exhibiting extremely low ion permeability. Its macroscopic physical properties (e.g., fluidity, curvature, phase behavior) must

 doi:10.20944/preprints202603.0083.v1

be continuously modulable. It must form continuous mechanical and electrical networks across scales, and directly couple topologically and physically with protein machines and ion gradients. Any material lacking even one of these attributes is fundamentally incapable of bearing the systemic function of the "central homeostatic constraint layer."

2.3. Stage Three: Exclusionary Screening of the Four Major Biological Macromolecules

Having established these joint necessary conditions, I execute an exclusionary screening across the four fundamental biological macromolecules: While nucleic acids (DNA/RNA)—highly water-soluble, one-dimensional linear polymers—serve as life's "informational blueprints," they cannot spontaneously form insulating closed boundaries in an aqueous phase and lack cross-scale physical continuity. Similarly, polysaccharides, despite forming macroscopic peripheral boundaries like animal glycocalyces or plant/bacterial cell walls, are essentially highly permeable hydrogels or rigid lattices. They cannot sequester charges to maintain transmembrane electrochemical gradients and are thus entirely excluded from the thermodynamic constraint layer, functioning merely as mechanical buffers. Proteins, functioning as discrete 3D folding machines, execute highly specific "digital logic." Although some can assemble into rigid capsids (e.g., viral envelopes), such porous structures based on precise geometric assembly cannot spontaneously and seamlessly self-seal without energy expenditure once ruptured, lacking the autonomy to generate continuous fluid boundaries.

Through rigorous categorical exhaustion, lipids—specifically amphiphilic lipids driven purely by the thermodynamic hydrophobic effect—emerge as the only candidates capable of spontaneously assembling into 2D fluid bilayers with exceedingly low ion permeability and inherent self-sealing capacity. The supramolecular phase state of lipids constitutes the only viable physical container for life. This does not diminish the importance of nucleic acids or proteins; rather, it clarifies that the realization of their functions is always strictly nested within the "physical feasibility space" provided by lipid organization.

2.4. Stage Four: From Joint Fulfillment to Near-Irreplaceable Physical Privilege

Beyond satisfying the basic criteria, the lipid system firmly establishes its hegemony as the central homeostatic controller through physical privileges in four key dimensions. First, lipid membranes act as a "continuous analog parameter buffer." If cells were merely constructed of discrete, all-or-none protein switches, minor noise would trigger systemic avalanches. Instead, continuous modulations in lipid lateral fluidity, phase behavior, and spontaneous curvature directly set the activation thresholds for protein machines, as evidenced by the tension-gated opening of mechanosensitive channels (e.g., Piezo1) and the clustering of receptor kinases (e.g., EGFR) within physical raft constraints. Second, unlike protein or small-molecule messengers whose 3D diffusion suffers from significant spatiotemporal delays, lipids form continuous physical networks spanning the entire cell via membrane contact sites (MCS). This creates high-speed topological highways for the instantaneous transduction of membrane tension, allowing local deformations to orchestrate global state remodeling at speeds far exceeding molecular diffusion. Third, while 3D liquid-liquid phase separation (LLPS) of proteins forms membraneless organelles, these permeable "sponges" cannot maintain electrochemical gradients and are highly dependent on global pH and ionic strength—parameters maintained by the lipid bilayer. The lipid membrane reduces the dimensionality of protein diffusion to a 2D plane, with its own 2D phase behavior acting as a templating interface (2D templating) that translates macroscopic physical alterations into micro-functional clustering. Finally, this physical privilege is corroborated by evolutionary consensus: although archaeal lipids differ fundamentally in chemical structure from those of eubacteria, convergent evolution has driven both to form hydrophobic 2D fluid barriers with functionally equivalent macroscopic biophysical properties. This proves that while natural selection may innovate chemically, the underlying homeostatic architecture—a 2D continuous physical phase state formed by amphiphilic self-assembly—is an inescapable physical imperative for living systems.

 doi:10.20944/preprints202603.0083.v1

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. Lipid organizational structures—by establishing boundaries, compartmentalization, and tunable physical boundary conditions—constitute the critical (and likely core) biophysical substrate of this homeostasis, thereby enabling and shaping downstream molecular processes.

The CHP is a system-level constraint principle. It does not posit that lipids alone dictate all biological outcomes, nor does it deny the central role of genes in the causal chain. Its core assertion is that molecular information and protein execution operate strictly within a physical feasibility space defined by a homeostatic state, with lipid organization holding a privileged position in establishing and modulating this 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 Organization). Responsible for boundary formation, selective exchange, physical modulation, compartmentalization, and topological network organization, this layer forms the indispensable material foundation for maintaining the non-equilibrium state.

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 the membrane microenvironment.

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

3.3. Operational Corollaries

The relationship between state and molecular programs is recursively coupled, yet fundamentally asymmetric: the physical state dictates which molecular programs can be stably actualized, while those executed programs, in turn, iteratively reshape the state. This refines the simplified "genes dictate phenotype" paradigm into a more rigorous systemic view: genes encode a "repertoire of possibilities," whereas the homeostatic state determines which possibilities are activated, stabilized, suppressed, or reversed.

3.4. A Necessary Clarification: The Typology of CHP Rules

A profound skepticism often accompanies the CHP: how exactly does the physical state of lipids achieve such intricate biological regulation without resorting to the vague concept of "emergence"? Our response is that the CHP posits a set of identifiable, measurable, and testable state constraint rules. To this end, I delineate five core rules: boundary priority, state restriction, threshold regulation, global coupling, and recovery dynamics.

Briefly, boundary priority dictates that all intracellular molecular processes depend on the physical space defined by closed lipid bilayers. State restriction posits that a cell's phenotypic identity is constrained by the global physical state of its membrane system, where a single genome can support multiple stable phenotypes corresponding to distinct attractors in the membrane state space. Threshold regulation emphasizes that protein functional output is gated by local membrane physical parameters. Global coupling indicates that local physical perturbations can instantly remodel the global state via lipid mechanical transduction. Finally, recovery dynamics asserts that a cell's ability

 doi:10.20944/preprints202603.0083.v1

to return to homeostasis post-perturbation is governed by the physical recovery properties of the lipid system, the decline of which is a fundamental hallmark of aging and chronic diseases.

Rather than acting independently, these rules map collectively onto a set of testable hypotheses. Fate transitions, pathological state migrations, and cellular reprogramming are not linear responses but occur within a dynamic space constrained by these boundary conditions, threshold gates, and multiscale couplings.

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

If the CHP merely offered a retrospective explanation for known phenomena, it would be reduced to theoretical rebranding. A vital scientific principle must generate specific, daring, and falsifiable predictions. By applying the CHP framework, I propose five cross-dimensional hypotheses. These not only serve as pressure tests for the principle's causal logic but also outline a grand roadmap for transitioning disease intervention from "molecular targeting" to "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 alterations in membrane biophysical metrics (such as global fluidity, local curvature stress, or phase separation thresholds) must chronologically precede the irreversible commitment of master regulators. To rigorously test this, researchers could employ subcellular-resolution physical probes coupled with single-cell multi-omics to track fate trajectories. The null hypothesis would posit that lipid changes are merely downstream consequences of gene expression, appearing only after master regulators have established commitment. Support for the CHP requires demonstrating that physical boundary resets stably occur prior to transcriptional network leaps, and that artificially perturbing these physical states systematically shifts the temporal location and reversibility of the commitment point.

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., targeted therapy-sensitive versus "persister" resistant subpopulations) are strictly anchored by disparities in their underlying lipid homeostatic states. To empirically challenge this, one could utilize persister tumor cells lacking resistance mutations. By exclusively modifying their lipid assembly phase and physical microdomains (e.g., using lipid nanoparticles with defined phase transition characteristics) without introducing exogenous nucleic acids, one could attempt to forcefully pull the cells out of the resistant attractor and stabilize them back in a drug-sensitive state. The null hypothesis would assume that resistance is entirely dictated by epigenetic modifications or localized microenvironmental signals, making lipid state remodeling inconsequential 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 focus from static molecular damage (e.g., telomere attrition), the CHP emphasizes dynamic resilience. I hypothesize that the fundamental commonality underlying systemic aging and localized chronic diseases (such as fibrosis or degenerative disorders) is the systemic prolongation of the "time constant" required for lipid networks to return to baseline physiological homeostasis following thermodynamic or biochemical perturbations. As this recovery dynamic attenuates, cells

 doi:10.20944/preprints202603.0083.v1

fail to overcome energy barriers and become permanently trapped in sub-optimal pathological attractors. This can be tested in vitro by subjecting young and senescent cell models to uniform transient stresses (e.g., osmotic shocks) and continuously monitoring the recovery curves of membrane phase separation or tension. A key indicator of CHP validity would be proving that a prolonged "recovery lag phase" serves as a quantitative biomarker for irreversible pathological decline, which can potentially be reversed to a youthful baseline via lipid homeostasis remodeling.

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 absolute limit, I propose two hypotheses of escalating intensity. The weak form (currently testable) posits that in classic iPSC reprogramming, lipid state remodeling can partially substitute for exogenous transcription factors. Specifically, inducing a pluripotency-characteristic membrane state via lipid physical intervention while expressing only a subset of Yamanaka factors (e.g., Oct4/Sox2) should significantly elevate reprogramming efficiency. The strong form (ultimate deduction) proposes that cell fate can be reprogrammed into pluripotency via sequenced lipid physical perturbations alone, completely independent of exogenous transcription factors or small molecules. This would represent the ultimate evidence of "topological forcing": by coercing the physical boundary state into a pluripotent profile, the underlying transcriptional network, left with "no alternative space to inhabit," is passively reconfigured and spontaneously falls into a new attractor.

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

From a deep evolutionary perspective, the CHP predicts that during the transition from non-living chemical systems to protocells, the physical homeostasis (e.g., the balance of deformation resistance and selective permeability) acquired by closed compartments of amphiphilic molecules was an absolute prerequisite. This physical stability was essential for the subsequent complexification of internal nucleic acid networks and their retention by natural selection. Experimental models utilizing tunable vesicle systems loaded with simple catalytic networks could verify how boundary physical characteristics dictate the persistence, thermal dissipation resistance, and fidelity limits of primitive metabolic cycles, challenging the null hypothesis that informational complexity can evolve independently of defining boundary properties.

5. Translational Corollary: The Homeostatic Restoration Hypothesis

5.1. Theoretical Foundation and Formal Articulation

Rooted in the CHP's core logic, I formally articulate the Homeostatic Restoration Hypothesis: By targeted interventions that partially restore the core biophysical homeostasis mediated by lipids, it is possible to drive cells or tissues to stably migrate from a pathological phenotypic attractor back to a physiological, functional attractor. Crucially, this state migration can occur and be maintained even if the upstream genetic defects or protein toxicities driving the pathology are not entirely eradicated.

This hypothesis provides, for the first time, a systemic theoretical foundation for lipid-state reprogramming as a paradigm-shifting intervention strategy. "Homeostatic restoration" here does not mean reverting to a fixed lipid molecular profile, but rather restoring a set of core functional boundary conditions and dynamic state features—including membrane phase behavior, cross-scale organizational capacity, and resilience to perturbations.

5.2. Core Scientific and Clinical Value

This hypothesis breaks through the foundational limitations of current molecular-targeting paradigms, which rigidly adhere to a "correct the upstream cause → reverse the pathological

 doi:10.20944/preprints202603.0083.v1

phenotype" logic. Such linear strategies often falter against chronic pathologies driven by polygenic factors or self-sustaining positive feedback loops. By proposing an intervention logic that resets physical homeostatic boundaries rather than directly attacking upstream causes, this hypothesis offers novel therapeutic avenues.

Furthermore, it unifies experimental anomalies that have long eluded adequate theoretical explanation. Notably, the biological effects generated by engineered lipid systems (including lipid nanoparticles and liposomes) often vastly exceed their narrow expectations as mere "drug delivery vehicles." Numerous studies demonstrate that empty LNPs devoid of nucleic acids can trigger systemic immune reprogramming [23,24], while liposomes presenting specific phospholipids can directly reverse macrophage polarization [25]. Traditionally dismissed as "adjuvant effects" or "off-target toxicities," these phenomena represent direct empirical evidence under the CHP framework: exogenous lipids forcibly embed into and alter the cell's global physical constraint state, thereby rewriting the underlying gene transcription programs top-down.

5.3. Strict Applicability Boundaries

To prevent unwarranted extrapolation, this hypothesis is bound by strict prerequisites. It is applicable only when the pathological state retains phenotypic plasticity with accessible functional attractors, is maintained by self-sustaining feedback loops rather than irreversible structural damage, and possesses a core lipid membrane system that has not undergone catastrophic destruction. Conversely, the hypothesis is explicitly inapplicable in scenarios characterized by irreversible loss of core functional units, complete exhaustion of regenerative capacity, or overwhelming, continuous exogenous toxic drivers.

5.4. Core Testable Criteria

The hypothesis holds clear falsifiability. Its core validation criterion requires demonstrating that, after rigorously excluding confounding factors such as biochemical signaling effects of lipid molecules, non-specific anti-inflammatory responses, or altered drug delivery efficiencies, the specific modulation of lipid biophysical homeostasis alone is sufficient to achieve stable migration from a pathological to a functional phenotype.

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

For the CHP to stand as a rigorous scientific framework, its physical and biological boundaries of falsification must be unambiguously defined. Depending on the destructiveness of the evidence, I categorize potential falsification scenarios into three stringent tiers.

Tier I: Fundamental Invalidation of CHP Core Principles

The central tenets of the CHP would be completely overturned if independent cross-system experiments proved the stripping of biophysical centrality—that is, if specifically modulating the biophysical state of lipids while keeping their biochemical composition constant failed to induce any stable fate changes, proving that lipids act solely as classic biochemical ligands. Furthermore, a rupture of asymmetric causality would be demonstrated if, within a living cell system where the lipid biophysical state is artificially and completely "frozen" (via chemical cross-linking or eliminating cytoskeletal dynamics), the cell could still flawlessly execute full-spectrum phenotypic transitions unconstrained by physical feasibility spaces. Finally, the principle would be invalidated by the discovery of complete structural substitutability, wherein a modern biological module achieves equivalent non-equilibrium state control and cross-scale compartmentalization utilizing only nucleic acid and protein networks, entirely devoid of lipid-like self-assembling amphiphilic phase structures.

 doi:10.20944/preprints202603.0083.v1

Tier II: Significant Attenuation of CHP Core Assertions and Universality

The theoretical scope of the CHP would be severely restricted if a reversal of the temporal dimension were proven. If state-of-the-art live-cell tracking at subcellular spatiotemporal resolution definitively showed that the "fate commitment point" at the transcriptomic or proteomic level consistently occurs before any global biophysical remodeling of the membrane system (strictly excluding transient microdomain fluctuations), it would suggest lipids are merely passive, lagging indicators. Additionally, a complete decoupling of spatial scales—where highly localized receptor activations complete fate reprogramming without triggering any cross-scale physical boundary remodeling, and where distinct membrane organelles operate completely independently—would shatter the assumption of global physical consistency.

Tier III: Invalidation of Translational Corollaries

The failure of the translational path (the Homeostatic Restoration Hypothesis) would not necessarily undermine the foundational biology of the CHP, but it would invalidate its clinical applicability. This would occur if false positives at the translational level were proven: if, in highly plastic pathological models, specific interventions targeting lipid biophysical homeostasis consistently failed to produce sustained functional improvement or state topological correction, after strictly excluding confounding toxic or biochemical effects.

7. Conclusion and Perspectives

This manuscript proposes the Central Homeostatic Principle (CHP) of life: cellular identity and fate are governed upstream by a holistic homeostatic state, with lipid organization acting as the critical, and likely core, biophysical substrate. This framework elevates the problem of phenotype from a mere "question of molecular composition" to a "question of state architecture"—investigating under what boundary conditions and non-equilibrium operating ranges molecular programs are actualized, stabilized, and transformed.

The primary value of the CHP lies in its predictive power. It urges researchers to ask not only "which molecules changed," but imperatively, "which state variables shifted first, which boundary conditions were reset, and which system recovery dynamics were altered." In this sense, the CHP is not merely an explanatory framework, but a new methodology for organizing scientific inquiry.

Should the CHP garner further experimental support, its implications will drive the biomedical intervention paradigm beyond pure molecular targeting toward State Engineering. This encompasses the design of lipid formulations, membrane state modulators, compartmental remodeling, and therapeutic strategies centered on lipid-state reprogramming. Whether the CHP is ultimately proven to possess sweeping universality or is refined to specific classes of cellular state problems, subjecting it to rigorous systemic testing will inevitably bring us closer to answering a fundamental biological question: life is not merely about how information is encoded, but profoundly about how the physical conditions are maintained to allow information to "become life."

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