Hypothesis

The Central Homeorhetic Principle: Lipid-Organized Boundary Systems as Constraints on Cellular State Realization

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Posted Date: 15 May 2026

doi: 10.20944/preprints202603.0083.v3

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 doi:10.20944/preprints202603.0083.v3

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The Central Homeorhetic Principle: Lipid-Organized Boundary Systems as Constraints on Cellular State Realization

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Abstract

Sequence information can specify molecular components, but specification is not equivalent to cellular state realization. A gene product contributes to living function only when the cell occupies a physical state in which gradients persist, compartments remain intact, diffusion and phase organization remain compatible with execution, and perturbations can be recovered without loss of viability. This gap defines a state-realization problem: what physical architecture constrains the feasible state space within which molecular programs can be executed, stabilized, reversed, or transformed? From this problem, I derive a set of substrate requirements: self-bounded aqueous interfaces, selective permeability, electrochemical asymmetry, tunable continuous physical variables, cross-scale coupling, recursive interaction with protein and information-memory systems, and measurable recovery dynamics. Lipid-organized boundary systems satisfy these requirements in an exceptionally integrated way in modern aqueous cellular life. I therefore propose the Central Homeorhetic Principle (CHP): cellular identity, robustness, and fate transitions are constrained by a distributed homeorhetic state architecture, with lipid-organized boundary systems occupying a privileged but nonexclusive substrate position. CHP is not a rejection of the Central Dogma, nor a claim that lipids alone determine phenotype. It is a complementary constraint framework that asks how molecular information becomes physically executable and dynamically sustainable. The proposed mechanism is a distributed constraint-sensing-enactment loop in which boundary-state variables are sensed, evaluated through thresholds, converted into regulatory responses, and recursively remodeled by execution and memory systems. The framework yields testable predictions concerning temporal precedence of boundary-state shifts, threshold-like fate transitions, recovery kinetics, state degeneracy, protocell persistence, and state-trajectory restoration. It is falsifiable if boundary-state variables consistently follow rather than precede commitment, fail to alter fate thresholds under controlled perturbation, or add no predictive power beyond molecular profiles.

Keywords: Central Homeorhetic Principle (CHP); homeorhesis; lipid-organized boundary systems; state realization; biophysical constraints; recovery dynamics

1. The State-Realization Problem

1.1. Sequence Transfer is Not Cellular State Realization

In its strict Crickian formulation, the Central Dogma is not identical to the popular shorthand that DNA makes RNA and RNA makes protein. It concerns the directionality of residue-by-residue sequence-information transfer, especially the restriction that sequence information cannot be transferred from protein back to nucleic acids or to protein sequence (F. Crick, 1970; F. H. Crick). This distinction matters because it separates a rule about sequence-information transfer from the broader problem of how molecular information becomes living organization (Nurse, 2008).

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A rule about sequence-information transfer is not, by itself, a theory of cellular state realization. It does not specify the boundary conditions under which a sequence-derived molecular program becomes physically executable, reversible, buffered, pathological, or irreversibly committed (F. Crick, 1970; Ferrell, 2012; Kitano, 2004).

A gene may encode a component, and that component may participate in a pathway. Yet the success of that pathway depends on whether the cell is in a permissive state (Barabasi & Oltvai, 2004): whether gradients persist (Gurdon & Bourillot, 2001), compartments remain intact (Mellman & Warren, 2000), macromolecular diffusion is possible (Verkman, 2002), membrane tension and curvature lie within executable ranges (McMahon & Gallop, 2005), phase-separated assemblies are stable or dissolved (Brangwynne et al., 2009), and recovery mechanisms can restore the system after perturbation (Kitano, 2004). The residual problem is therefore not the storage or transfer of biological information, but the physical feasibility of its living execution.

This leads to the central state-realization question: what kind of physical architecture defines the feasible state space within which molecular programs can be executed, stabilized, reversed, or transformed?

1.2. Why Living Execution Requires a Feasible State Space

A living cell is an open, non-equilibrium dissipative system—it continuously dissipates energy, exchanges matter with its environment, and endures perturbations (Fang & Wang, 2020). Such a system cannot be explained solely by the existence of molecular instructions or by the instantaneous success of local reactions (Hartwell, Hopfield, Leibler, & Murray, 1999; Nurse, 2008). A molecular program becomes living function only if at least four classes of conditions are satisfied. First, the program must be physically executable: the required molecules must be localized, accessible, mobile, folded, assembled, or separated in ways that permit action (Hartl, Bracher, & Hayer-Hartl, 2011; Pawson & Nash, 2003). Second, the program must be dynamically sustainable: gradients, compartments, and energy flux must persist long enough for the program to matter (Fang & Wang, 2020; Goldbeter, 2018). Third, the program must be recoverable: perturbations must not destroy the state architecture needed for renewed execution (Chovatiya & Medzhitov, 2014; Kitano, 2004). Fourth, the program must be phenotypically integrated: its local effect must not destabilize the global viability of the cell (Barabasi & Oltvai, 2004; Hartwell et al., 1999).

These requirements imply that cells operate within a feasible state space (Huang, Eichler, Bar-Yam, & Ingber, 2005). This space is not merely a list of expressed genes or present molecules. It is the subset of possible molecular configurations that can remain far from equilibrium while sustaining boundary integrity (Fang & Wang, 2020; Van Meer, Voelker, & Feigenson, 2008), electrochemical asymmetry (Mitchell, 1966), compartmental topology (Mellman & Warren, 2000), mechanical coherence (Fletcher & Mullins, 2010), phase compatibility (Banani, Lee, Hyman, & Rosen, 2017), and recovery after disturbance (Kitano, 2004). The problem is therefore one of constrained state maintainability rather than sequence transfer alone.

In statistical-physical terms, the cell must restrict an enormous configurational space to a smaller set of viable attractor regions (Huang et al., 2005). Boundary conditions do not encode specific fates as digital messages; they reshape the probability landscape over which molecular programs can be actualized (J. Wang, Zhang, Xu, & Wang, 2011). The same sequence-derived program can therefore have different actualization probabilities, reversibility, or pathological stability under different physical state architectures (Raj & Van Oudenaarden, 2008).

1.3. Existing Answers and the Remaining Material Gap

If living execution requires a feasible state space, the next question is whether this problem has already been solved by existing post-gene-centric frameworks. Several traditions answer important parts of the problem and should be treated as conceptual prerequisites rather than opponents.

Epigenetics and chromatin dynamics show that genomic output depends on accessibility, nuclear organization, RNA processing, and regulatory memory (Allis & Jenuwein, 2016; Misteli,

 doi:10.20944/preprints202603.0083.v3

2007). Conversely, the genome is not a passive upstream script: protein complexes continuously repair, remodel, recombine, transpose, edit, splice, and chemically modify DNA and RNA, providing well-defined routes through which proteomic activity feeds back onto genomic and transcriptomic states (Shapiro, 2009).This explains why sequence output is context-dependent, but it does not by itself identify the physical boundary architecture that makes a cellular program executable, reversible, buffered, or recoverable (Fang & Wang, 2020; Kitano, 2004).

Systems biology and biological relativity have established that cellular function arises from multilevel networks, feedback, robustness and circular causation, with no single privileged causal level(Barabasi & Oltvai, 2004; Noble, 2012). This view is essential. However, the present framework shifts the emphasis from boundary conditions as contextual constraints on network dynamics to physical boundary state as a candidate material substrate that helps determine which network states are dynamically accessible, sustainable, reversible or pathologically stabilized (Fang & Wang, 2020; J. Wang et al., 2011).

Developmental systems theory and the extended evolutionary synthesis show that phenotypes arise through organism-environment-development interactions rather than genetic instruction alone. Allostasis, homeorhesis, and highly optimized tolerance clarify that stability is achieved through changing trajectories, tolerance ranges, and adaptive load rather than fixed set points (Csete & Doyle, 2002; Laland et al., 2015; McEwen & Wingfield, 2003; West-Eberhard, 2005). These frameworks explain why state trajectories matter, but they do not specify the cellular material architecture that implements trajectory maintainability.

Cellular agency, basal cognition, bioelectricity, and constructal or biogenic-principle accounts add sensing, memory, problem solving, flow access, and reciprocal information exchange (Levin, 2025; McMillen & Levin, 2024; Miller Jr et al., 2025). They help explain why cells and tissues are active, adaptive systems. Yet they leave open a narrower substrate question: through what physical boundary architecture are sensing, thresholding, memory, flow, and recovery made executable in an aqueous cell?

Thus, the residual problem is no longer whether biology exceeds linear gene-centric explanation; that point is already well established. The remaining question is more specific: what material architecture implements the feasible state space required for living execution? Answering this requires deriving substrate requirements rather than listing more examples of state-level regulation.

2. Deriving the Substrate Requirements for State Feasibility

2.1. Necessary Properties of a State-Feasibility Substrate

If feasible state space is a real biological constraint rather than a metaphor, it must be implemented by material structures with specific properties. The relevant substrate must satisfy several joint requirements. First, it must generate a semi-permeable, self-bounded organization that distinguishes an internal state from its environment. Without such a boundary, there is no persistent internal state to maintain (Gánti, 1975; Ruiz-Mirazo, Peretó, & Moreno, 2004; Varela, Maturana, & Uribe, 1974). Second, it must support selective exchange and electrochemical asymmetry. Without regulated permeability and gradients, the cell cannot remain far from equilibrium (Mitchell, 1966; Ruiz-Mirazo et al., 2004). Third, it must provide tunable continuous physical variables, because living systems require graded adjustment rather than only discrete molecular switches (Montévil & Mossio, 2015; Prigogine, 1978). Fourth, it must couple local perturbations to global organization, otherwise local stress cannot be integrated into cellular state change (Kitano, 2004; Montévil & Mossio, 2015). Fifth, it must be recursively remodelable by the metabolic, boundary-forming, regulatory, and informational processes that it helps sustain (Gánti, 1975; Ruiz-Mirazo et al., 2004; Varela et al., 1974). Sixth, it must exhibit measurable recovery dynamics, because resilience is not a static composition but a trajectory after perturbation (Csete & Doyle, 2002; Kitano, 2004).

These requirements are restrictive. A candidate substrate that stores information but cannot maintain boundaries is insufficient. A substrate that catalyzes reactions but cannot provide

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continuous compartmental state is insufficient. A substrate that provides mechanical support but cannot maintain electrochemical gradients is insufficient. The substrate problem therefore requires categorical comparison among biological molecular systems.

2.2. Screening Biological Molecular Systems

Nucleic acids are indispensable for sequence memory, regulatory templates, and inheritance, but they do not spontaneously form closed, ion-insulating, self-sealing boundaries in aqueous environments. Proteins provide catalytic, structural, transport, signaling, and repair functions, but discrete folded proteins alone do not generate a continuous deformable cellular interface capable of maintaining global gradients. Polysaccharides and extracellular matrices contribute mechanical support, hydration, protection, and extracellular organization, but porous gels or rigid wall-like structures cannot by themselves sustain the electrochemical asymmetry and dynamic compartmentalization required for cellular nonequilibrium (Mitchell, 1966; Ruiz-Mirazo et al., 2004; Szostak, Bartel, & Luisi, 2001; Theocharis, Skandalis, Gialeli, & Karamanos, 2016).

Amphiphilic lipids, however, are especially well suited among canonical biomolecular classes to satisfy these exact systemic mandates (Tanford, 1978). Through hydrophobic self-assembly, they generate bilayers, vesicles, and membrane networks with low ion permeability, self-sealing capacity, lateral fluidity, curvature responsiveness, phase tunability, and compatibility with embedded or associated protein machines. Lipid systems therefore do not merely surround cellular processes. They establish a deformable, tunable, and recoverable boundary-state architecture within which other molecular systems can operate (Budin & Szostak, 2011; Israelachvili, Mitchell, & Ninham, 1976; Phillips, Ursell, Wiggins, & Sens, 2009; Veatch & Keller, 2005).

2.3. Why Lipid-Organized Boundary Systems Are Privileged But Not Exclusive

The argument is not that lipids alone determine phenotype. Such a claim would be biologically untenable. Genes, proteins, metabolites, ions, cytoskeleton, extracellular matrix, tissue mechanics, and ecological context all participate in causation. The narrower claim is that lipid-organized boundary systems occupy a privileged substrate position because they combine boundary formation, selective permeability, electrochemical gradient support, continuous mechanical variables, phase behavior, compartmental topology, and recovery dynamics in a single material architecture.

This privilege is functional rather than absolute. It means that in modern aqueous cellular life, lipid-organized boundaries are the best-supported candidate for implementing the physical feasibility constraints that make molecular execution possible. Protein and nucleic-acid systems can remodel, read, and stabilize this architecture; they do not eliminate the need for an architecture that establishes compartments, gradients, and recoverable interfaces in the first place.

The evolutionary record is consistent with this interpretation. Bacterial and archaeal membranes differ profoundly in lipid chemistry, including hydrocarbon chain type, linkage chemistry and glycerol-phosphate stereochemistry, yet both lineages implement cellular boundaries based on amphiphilic phospholipid architectures(Koga, Kyuragi, Nishihara, & Sone, 1998; Lombard, López-García, & Moreira, 2012). Despite this chemical divergence, both solve the same architectural problem: construction of hydrophobic, self-bounded, selectively permeable and gradient-supporting interfaces in water (Lombard et al., 2012; Mitchell, 1966; Ruiz-Mirazo et al., 2004). This convergence does not prove lipid primacy in every possible form of life, but it strengthens the inference that boundary-state architecture is a recurrent physical requirement for persistent aqueous cellular systems.

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3. The Central Homeorhetic Principle

3.1. Formal Statement Derived from the Substrate Argument

The Central Homeorhetic Principle (CHP) states that cellular identity, robustness, and fate transitions are constrained by a distributed homeorhetic state architecture that defines the feasible state space within which genetic, protein, metabolic, and bioelectrical programs can be stably executed. In modern aqueous cellular life, lipid-organized boundary systems constitute a privileged biophysical substrate for this architecture because they establish selective boundaries, compartmental topology, electrochemical asymmetry, membrane mechanics, phase behavior, cross-scale coupling, and recovery dynamics.

The term homeorhetic is used deliberately. The relevant problem is not return to a single fixed set point. It is trajectory maintainability: the capacity of a living system to preserve viable state paths, recover after perturbation, and move between attractor basins without losing nonequilibrium organization. Local homeostasis is one component of this process, but the system-level problem is broader than static homeostasis.

CHP therefore does not replace the Central Dogma, epigenetics, systems biology, allostasis, cellular agency, or evolutionary theory. It occupies a different explanatory position. It asks how the physical state architecture of the cell constrains which molecular programs can become executable, sustainable, reversible, or pathological.

3.2. Boundaries of the Claim

CHP is intentionally bounded. It does not claim that physical constraints alone explain standing biological diversity, body plans, or the historical path of evolution. Physical constraints define a viability envelope; evolutionary contingency, natural selection, drift, developmental bias, ecological interaction, niche construction, and genetic innovation determine which regions of that envelope are actually explored and stabilized.

If the tape of life were replayed, CHP would not predict the recurrence of identical genes, pathways, or organisms. It would predict recurrence of architectural requirements for persistent aqueous cellular life: bounded compartments, selective permeability, gradient maintenance, tunable interfaces, perturbation recovery, and mechanisms that restrict otherwise enormous configurational possibilities.

CHP also does not require a strong philosophical claim that cells possess consciousness or sentience. Agency-like regulation can be treated operationally: a cellular system senses constraints, converts them into thresholds, enacts responses, and preserves or revises state trajectories. This operational view is compatible with cellular agency frameworks without making sentience a premise of the theory.

Nor should CHP be read as maintaining one narrow tolerance band. It is compatible with highly optimized tolerance and nested tolerance architectures, in which local homeostatic ranges, broader homeorhetic trajectories, allostatic load, and evolutionary shifts in viable optima can coexist.

3.3. Three-Layer Architecture and Recursive Coupling

The substrate argument establishes why lipid-organized boundary systems occupy a privileged position, but it does not imply that cellular state is controlled by boundary physics alone. A living cell is sustained by a layered architecture in which boundary state, molecular execution, and information-bearing memory are recursively coupled.

The first layer is the lipid-organized boundary-state layer. It includes cellular and organellar membranes, membrane contact sites, lipid domains, electrochemical gradients, membrane tension, curvature, phase behavior, compartmental topology, and recovery dynamics. Its role is not to encode biological instructions in a sequence-like manner. Rather, it defines the physical feasibility envelope within which molecular programs can become executable. Through selective boundary formation,

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compartmental topology, electrochemical asymmetry, membrane mechanics, phase behavior, cross-scale coupling, and recovery dynamics, this layer constrains which downstream processes can be sustained.

The second layer is the protein-metabolic execution layer. Channels, transporters, receptors, enzymes, cytoskeletal systems, signaling networks, metabolic fluxes, trafficking machinery, repair systems, and biomolecular condensates perform the active work of the cell. Their localization, assembly, activity, and reversibility are shaped by boundary-state conditions. At the same time, they remodel those conditions through lipid synthesis, membrane trafficking, cytoskeletal force, ion flux, metabolic feedback, and repair.

The third layer is the genomic and epigenetic information-memory layer. DNA sequence, RNA processing, chromatin accessibility, transcriptional networks, histone modification, and epigenetic memory provide molecular possibilities and stabilize durable cellular identities. However, these possibilities are not actualized by sequence alone. Their execution depends on the physical and metabolic context generated by the boundary-state and execution layers.

The three layers therefore form a recursive state architecture rather than a one-way hierarchy. Boundary-state variables constrain molecular execution and information accessibility; execution networks remodel boundary conditions; and information-memory systems bias future responses by altering the components and regulatory programs available to the cell. Through this coupling, a cell does not merely return to a fixed set point. It maintains a viable trajectory, shifts between constrained attractor states, and preserves the possibility of recovery after perturbation.

This layered architecture clarifies the specific role assigned to lipid-organized boundary systems in CHP. They do not replace protein, metabolic, bioelectrical, or genomic regulation. Their privileged role is to define the physical feasibility envelope within which those regulatory systems operate. Cell fate, robustness, pathological trapping, and reprogramming potential therefore arise from the dynamic coupling among boundary state, execution networks, and information-bearing memory. This recursive three-layer architecture and its possible state outcomes are summarized schematically in Figure 1.

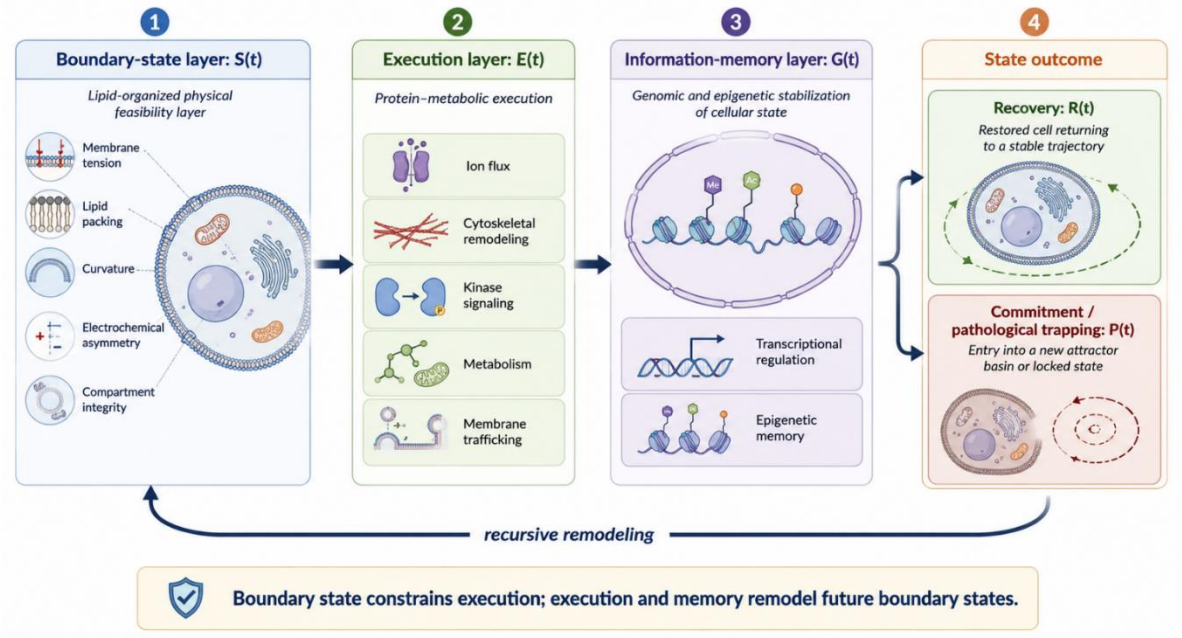

Figure 1. Simplified three-layer recursive model of CHP-mediated cellular state realization. The Central Homeorhetic Principle (CHP) describes cellular state realization as a recursive coupling among the lipid-organized boundary-state layer S(t), the protein–metabolic execution layer E(t), and the genomic/epigenetic information-memory layer G(t). Perturbations that shift boundary-state variables can reshape execution-network activity and information accessibility, thereby biasing state trajectories toward recovery along a viable trajectory R(t) or toward threshold crossing into phenotypic commitment or pathological trapping P(t). The

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feedback arrow denotes boundary remodeling by execution networks and response biasing by information-memory systems, emphasizing a recursive state architecture rather than a one-way hierarchy. (This Figure was drawn by ChatGPT Images 2.0 of GPT-5.4 Thinking).

4. Mechanistic Architecture: Constraint-Sensing-Enactment Closure

A state-constraint principle would be weak if it described constraints without explaining how they become cellular responses. The relevant mechanism is not a hidden central controller. It is a distributed constraint-sensing-enactment loop in which boundary-state variables are continuously read, transformed into thresholds, enacted through regulatory systems, and fed back onto the boundary architecture itself (Kitano, 2004; Montévil & Mossio, 2015).

Sensing occurs through mechanosensitive channels, curvature-sensitive proteins, lipid-binding domains, phosphoinositide enzymes, calcium channels, osmotic and redox sensors, membrane-contact-site proteins, cytoskeletal linkers, and bioelectrical coupling. These systems read variables such as membrane tension, curvature, lipid packing, potential difference, pH, ionic gradients, phase order, and compartmental continuity (Antonny, 2011; Clapham, 2007; Coste et al., 2010; Di Paolo & De Camilli, 2006; Diz-Muñoz, Fletcher, & Weiner, 2013; Levin, 2014; Scorrano et al., 2019).

Evaluation is not a subjective act. It is implemented through physical thresholds and biochemical nonlinearities: channel opening probabilities, phase-separation boundaries, recruitment thresholds, energy barriers, condensate dissolution, cytoskeletal buckling, chromatin accessibility, kinase activation, and metabolic switching. A state becomes viable when it can sustain gradients, energy flux, compartmental integrity, and recovery; it becomes unstable when these coupled requirements fail (Allis & Jenuwein, 2016; Banani et al., 2017; Ferrell, 2012; Kholodenko, 2006).

Enactment occurs through ion fluxes, membrane trafficking, lipid synthesis and remodeling, membrane-contact-site transfer, cytoskeletal reorganization, kinase signaling, metabolic rewiring, transcription-factor localization, chromatin remodeling, and stress-response activation. These responses remodel the boundary state that initiated them, creating recursive closure rather than a one-way causal chain (Di Paolo & De Camilli, 2006; Fletcher & Mullins, 2010; Kholodenko, 2006; Montévil & Mossio, 2015; Scorrano et al., 2019).

Memory is distributed across timescales. Short-term memory can reside in membrane tension, lipid domain persistence, protein clustering, calcium dynamics, cytoskeletal pre-stress, and local metabolic state. Longer-term memory can reside in lipid composition, organelle architecture, membrane-contact-site density, chromatin state, transcriptional attractors, and epigenetic modifications. In this sense, agency-like regulation is measurable as the capacity of a system to sense constraints, transform them into regulatory thresholds, enact adaptive responses, and preserve or revise state trajectories (Di Paolo & De Camilli, 2006; Fletcher & Mullins, 2010; Kholodenko, 2006; Montévil & Mossio, 2015; Scorrano et al., 2019).

5. From Principle to Testable Relationships

5.1. Minimal Causal Scaffold

If the preceding derivation is correct, boundary-state variables should not be treated merely as passive consequences of gene expression. They should have temporal, threshold, perturbational, and recovery relationships to cellular state transitions. These relationships can be expressed with a minimal causal scaffold.

Let S(t) denote a composite boundary-state variable, including membrane tension, curvature stress, lipid packing, phase behavior, electrochemical asymmetry, and compartmental topology. Let E(t) denote execution-network activity, including ion flux, cytoskeletal remodeling, metabolic signaling, kinase activation, membrane trafficking, and repair. Let G(t) denote information-memory state, including chromatin accessibility, transcriptional attractors, RNA processing, and epigenetic memory. Let P(t) denote phenotypic commitment or state-transition probability. Let R(t) denote

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recovery dynamics after perturbation, often measurable as recovery half-time or recovery area under the curve.

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Box 1. Minimal state-feasibility toy model.

A stylized representation is $P(t) = \sigma[aS(t) + bE(t) + cG(t) - \theta]$, where P(t) is commitment probability, S(t) is boundary state, E(t) is execution-network activity, G(t) is information-memory state, θ is the commitment threshold, and σ is a nonlinear threshold-like function.

Boundary-state dynamics can be represented minimally as $dS/dt = -k[S(t)-S0] + u(t) + \alpha E(t)$, where k captures recovery toward a viable trajectory, u(t) is perturbation input, and $\alpha E(t)$ represents remodeling by execution networks.

The purpose of the model is not to simulate all cellular fate decisions. It specifies the relationships that CHP requires: S(t) should shift commitment thresholds, recovery, or reversibility beyond what is predicted by E(t) or G(t) alone.

5.2. Core Predictions

Prediction 1: boundary-state variables should often precede irreversible molecular commitment. During differentiation, reprogramming, epithelial-mesenchymal transition, senescence, or acquisition of non-genetic resistance, CHP predicts that changes in membrane tension, lipid packing, phase behavior, membrane potential, organelle-contact topology, or recovery dynamics should occur before stable commitment by transcriptional networks.

Prediction 2: fate transitions should display threshold-like dependence on boundary state. If membrane tension, curvature stress, lipid order, or recovery capacity crosses a critical range, the probability of transition should rise nonlinearly rather than scale as a simple linear correlate of gene expression.

Prediction 3: selective physical remodeling of boundary state should alter fate thresholds or reversibility without requiring genotype change. This prediction does not require lipids to be the only cause; it requires that changing boundary-state variables changes the accessibility or stability of attractor basins after toxicity, receptor-ligand effects, and nonspecific stress are controlled.

Prediction 4: recovery dynamics should predict resilience. After standardized osmotic, mechanical, oxidative, or metabolic perturbation, recovery half-time, recovery lag, and incomplete return to baseline should predict senescence, pathological trapping, or drug-tolerant persistence better than static composition alone.

Prediction 5: similar molecular programs can yield different phenotypes under different boundary-state architectures. CHP therefore predicts state degeneracy: transcriptomic or proteomic similarity may coexist with different executability, reversibility, and recovery if S(t) differs.

Prediction 6: in protocell models, boundary persistence, selective permeability, deformation resistance, and recovery should constrain the retention and selection of internal catalytic or informational networks. Informational complexity should be harder to stabilize in the absence of viable boundary-state constraints.

Table 1. Expected relationships and weakening patterns.

Relationship	CHP-supporting pattern	CHP-weakening pattern
Temporal precedence	Boundary-state shift precedes irreversible transcriptional or phenotypic commitment.	Commitment repeatedly precedes any measurable boundary-state remodeling.
Threshold behavior	Transition probability rises nonlinearly when defined boundary variables cross critical ranges.	Transition probability is independent of boundary-state thresholds after

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Relationship	CHP-supporting pattern	CHP-weakening pattern
		molecular programs are controlled.
Perturbational causality	Selective remodeling of tension, packing, curvature, or phase behavior shifts fate thresholds or recovery.	Boundary-state perturbation has no effect after toxicity and ligand-like effects are excluded.
Recovery dynamics	Recovery half-time or recovery lag predicts resilience, senescence, or pathological trapping.	Recovery curves fail to predict viability, fate stability, or pathological transition.
State degeneracy	Similar transcriptomic/proteomic states show different phenotypes under different boundary architectures.	Molecular profiles fully predict phenotype independent of boundary state.
Protocell feasibility	Boundary-state properties predict persistence and internal network retention.	Internal informational networks remain selectable without boundary-state constraints.

6. Empirical Anchors

The argument does not rest on metaphor alone. Several empirical domains already show that physical state variables can gate molecular execution, stabilize phenotypic trajectories, or alter recovery. These observations do not prove CHP as a whole, but they identify the kinds of causal relationships that the principle predicts.

Mechanical state can precede and stabilize fate decisions: matrix elasticity directs stem-cell lineage specification, mechanical memory can preserve altered YAP/TAZ activity and chromatin organization after substrate transfer, and mechanical confinement can drive melanoma phenotype switching and drug resistance (Engler, Sen, Sweeney, & Discher, 2006; Hunter et al., 2025; Yang, Tibbitt, Basta, & Anseth, 2014).

Global phase and crowding states can gate transcriptional and metabolic execution: coactivator condensates link super-enhancers to gene control, while metabolic state and macromolecular crowding can alter diffusion, condensate formation and cytoplasmic fluidity (Delarue et al., 2018; Parry et al., 2014; Sabari et al., 2018).

Membrane mechanics provide measurable threshold variables: membrane tension controls curvature-generating protein assembly and gates multiple mechanosensitive channels, including MscS, Piezo1 and mechanosensitive two-pore-domain potassium channels (Simunovic & Voth, 2015; Sorum, Docter, Panico, Rietmeijer, & Brohawn, 2024; Syeda et al., 2016; Zhang et al., 2021).

Membrane topology provides routes for cross-scale propagation: ER–plasma-membrane contact sites support intercompartmental communication, plasma-membrane strain can be relayed to the ER through these contacts, and ER disruption can stimulate nuclear membrane

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mechanotransduction(Chen et al., 2025; Saheki & De Camilli, 2017; Shen, Gelashvili, & Niethammer, 2026).

Bioelectric and lipid-polarity states provide an additional empirical anchor: endogenous membrane potentials regulate non-excitable developmental and patterning processes, while phosphoinositides organize membrane recruitment, polarity and signaling domains (Di Paolo & De Camilli, 2006; Levin, 2014). These observations support the view that boundary-state variables can participate in rapid state integration rather than serving only as passive membrane properties.

Two-dimensional membrane organization changes the rules of protein execution: membrane surfaces can scaffold biochemical reactions and organize receptor signaling domains, including T-cell receptor condensates and membrane-phase-separation-dependent signaling assemblies (Leonard, Loose, & Martens, 2023; Shelby, Castello-Serrano, Wisser, Levental, & Veatch, 2023; Su et al., 2016).

Pathological state trapping provides a translational anchor: drug-tolerant persister cells show ferroptosis-linked lipid vulnerabilities, phosphatidylserine-presenting liposomes can reprogram macrophage responses, and membrane lipid therapy suggests that altered membrane organization can participate in disease-relevant cellular states (Escribá et al., 2015; Hangauer et al., 2017; Harel-Adar et al., 2011).

7. Falsification Criteria

A principle about state feasibility must be vulnerable to failure. CHP would be weakened or narrowed by several classes of evidence (Table 2).

Table 2. Explicit falsification criteria.

CHP claim	Experimental test	Result that would weaken or narrow CHP
Temporal precedence	Live-cell boundary-state imaging combined with time-resolved single-cell multi-omics during fate transition.	Transcriptional commitment repeatedly precedes any detectable boundary-state change.
Perturbational causality	Selective manipulation of membrane tension, lipid packing, curvature, or phase behavior while excluding toxicity and ligand effects.	Boundary-state perturbation does not alter fate threshold, reversibility, or recovery.
Recovery dynamics	Standardized osmotic, mechanical, or oxidative stress followed by recovery-curve measurement in young, senescent, and diseased cells.	Recovery parameters fail to predict viability, senescence, resistance, or pathological transition.
State degeneracy	Compare cells with similar transcriptomic/proteomic profiles but distinct boundary states.	Molecular profiles fully predict phenotype independent of boundary-state variables.
Substrate privilege	Synthetic or cell-free systems testing whether non-lipid architectures can sustain	Protein/nucleic-acid-only systems achieve equivalent nonequilibrium

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CHP claim	Experimental test	Result that would weaken or narrow CHP
	equivalent gradient control, coupling, and recovery.	state control without lipid-like amphiphilic boundaries.
Translational corollary	Boundary-state intervention followed by withdrawal and durable follow-up in plastic pathological models.	Specific boundary-state restoration repeatedly fails to produce sustained functional improvement after confounders are excluded.

8. Translational Corollary: State-Trajectory Restoration

The translational implication of CHP is not that every disease is a lipid disease. The more limited corollary is the State-Trajectory Restoration Hypothesis: when a pathological phenotype is maintained partly by impaired boundary-state feasibility or recovery dynamics, targeted intervention in lipid-mediated boundary-state variables may help move the system from a pathological attractor toward a more physiological trajectory even when the initiating genetic defect, toxic protein, or inflammatory trigger is not completely eliminated (Huang, Ernberg, & Kauffman, 2009; Kitano, 2004).

This corollary applies only to systems with residual plasticity. It does not apply when tissue architecture is irreversibly destroyed, viable cells are lost, terminal genetic collapse dominates, or the rate-limiting cause is independent of boundary-state feasibility. It also requires strict controls. Apparent therapeutic effects cannot be interpreted as CHP-based restoration unless toxicity, receptor-ligand confounding, immune adjuvanticity, and nonspecific stress effects are excluded.

A concise experimental motivation for this view comes from the author's previous work on reconstituted lipid nanoparticles (rLNPs), which are assembled from the whole-lipid fraction of defined cells or tissues and retain a source-specific lipid ensemble. Brain-derived rLNPs showed selective homing to the cerebral ischemic region and improved ischemic-stroke treatment of ischemic brain injury. These observations are not used here as proof of CHP, but they provide a modest experimental clue that physiological lipid ensembles may influence pathological tissue trajectories (Han et al., 2024; C. Wang, 2023).

The corollary may also reframe some effects of engineered lipid systems. Lipid nanoparticles, liposomes, membrane-active agents and membrane lipid therapy may do more than deliver cargo; in selected contexts, they may alter physical constraint architecture that shapes immune activation, macrophage polarization, recovery dynamics or disease-state stability (Escribá et al., 2015; Hangauer et al., 2017; Harel-Adar et al., 2011). The decisive evidence would be durable state correction after specific boundary-state modulation and withdrawal of the intervention.

9. Conclusion and Perspectives

This manuscript proposes the Central Homeorhetic Principle as a substrate-level hypothesis for cellular state realization. The central claim is not that genes are unimportant, nor that the Central Dogma is false in its strict Crickian sense. Rather, the claim is that sequence-derived molecular programs become living function only within a feasible physical state space. In modern aqueous cellular life, lipid-organized boundary systems occupy a privileged but nonexclusive substrate position in defining this space because they integrate selective boundary formation, compartmental topology, electrochemical asymmetry, membrane mechanics, phase behavior, cross-scale coupling, and recovery dynamics.

 doi:10.20944/preprints202603.0083.v3

The scope of CHP is therefore specific. It is most relevant to biological situations in which executability, reversibility, pathological trapping, or recovery depends partly on boundary-state variables. These may include cell-fate transitions, non-genetic resistance, stress memory, senescence, injury recovery, protocell persistence, and selected forms of lipid-state intervention. CHP should not be used as a universal explanation for all phenotypes or diseases. Many outcomes may be dominated by fixed genetic lesions, protein toxicity, metabolic collapse, irreversible tissue destruction, extracellular-matrix constraints, immune context, ecological selection, or other rate-limiting factors. In such cases, boundary-state feasibility may contribute to the phenotype without being the primary explanatory layer.

The framework also carries clear evidentiary burdens. The composite boundary-state variable S(t) is not yet a standardized measurement and must be decomposed into experimentally tractable variables such as membrane mechanics, lipid packing, phase behavior, electrochemical asymmetry, compartmental topology, cross-scale coupling, and recovery dynamics. Correlation between lipid state and phenotype is insufficient. CHP requires temporal ordering, selective perturbation, recovery-curve analysis, and exclusion of toxicity, receptor-ligand effects, immune adjuvanticity, and nonspecific stress responses. If boundary-state variables fail to precede, predict, or perturb state transitions beyond molecular profiles alone, the framework should be narrowed or rejected.

The extensibility of CHP lies in turning cellular state realization into an experimentally tractable problem. Live-cell boundary-state probes, single-cell multi-omics, perturbational lipid-state engineering, synthetic protocells, source-defined lipid ensembles, and recovery-dynamics assays could be used to test whether boundary-state variables constrain molecular execution and state transitions. In translational settings, the same logic may help distinguish lipid systems that merely deliver cargo from those that actively modulate pathological trajectories through boundary-state effects.

The value of CHP will therefore depend on whether its predicted relationships survive rigorous testing. If boundary-state variables precede commitment, shift transition thresholds, predict recovery dynamics, and causally modulate state trajectories beyond molecular profiles alone, CHP would provide a useful extension of state-based biology. If these relationships fail, the principle should be revised, narrowed, or abandoned. Either outcome would sharpen the question that motivates the framework: not only how biological information is encoded or transferred, but under what recoverable physical trajectories such information remains executable as living organization.

Author Contribution: C. W.: Conceptualization, Formal Analysis, Investigation, Methodology, Project Administration, Resources, Supervision, Validation, Visualization, Writing-Original Draft, Writing-Review & Editing.

Acknowledgements: During the preparation and revision of this manuscript, the author used artificial intelligence (ChatGPT-5.4 Thinking) tools to assist with language refinement, literature searching and organization, logical restructuring, and figure conceptualization and synthesis. The author takes full responsibility for the accuracy, integrity, originality, and reproducibility of the final content.

Conflict of Interest: The author declares no conflict of interest.

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