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Centrosomal Memory

How mother centrioles record cellular history to dictate fate and disease

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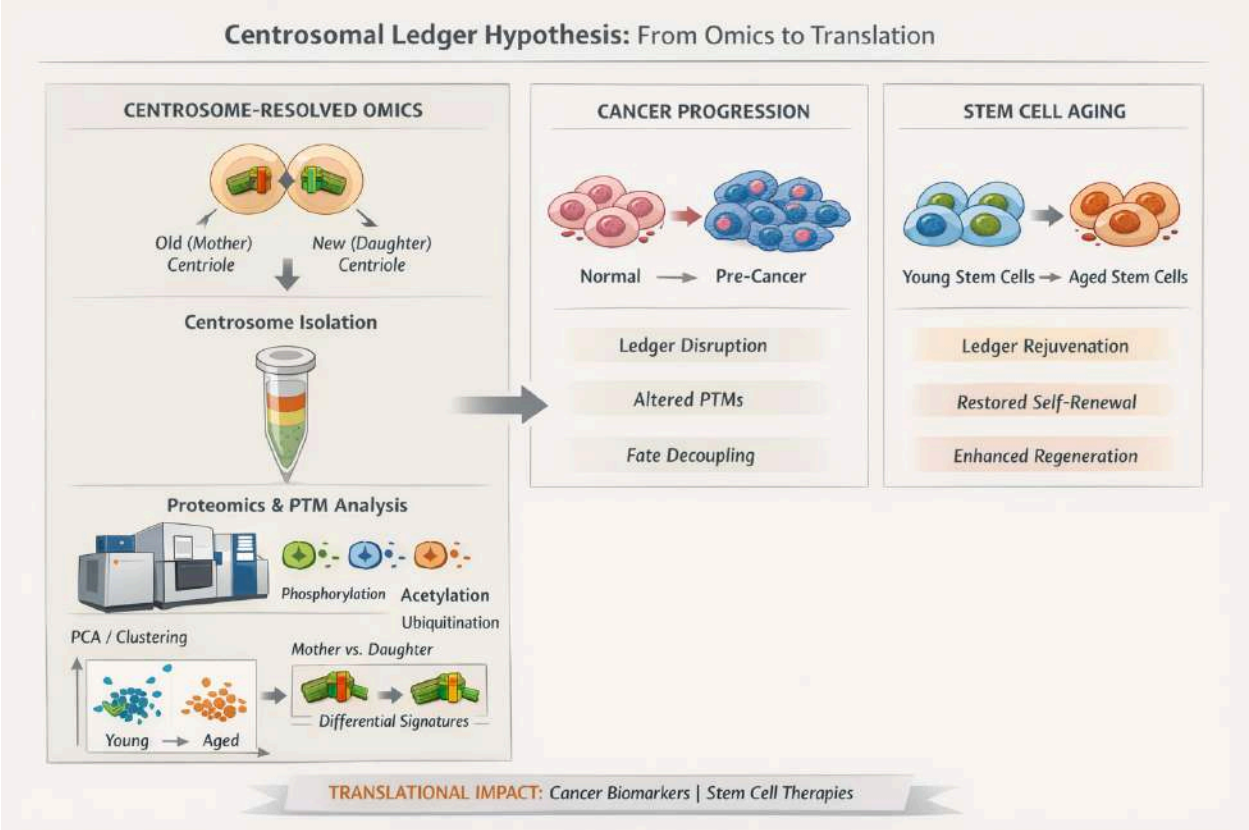
Abstract

The centrosome, classically defined as the primary microtubule-organizing center of the animal cell, is here reconceptualized as a critical organelle for non-genomic cellular memory. We propose the Centrosomal Ledger hypothesis, which posits that the mother centriole encodes a high-dimensional molecular state vector. This distributed memory integrates proteomic composition, post-translational modification (PTM) landscapes, and macromolecular stoichiometries accumulated over a cell's history. Rather than being a passive structural hub, the centrosome actively utilizes this integrated record to guide future cell fate decisions, such as the choice between symmetric and asymmetric division. Crucially, this hypothesis is untestable by traditional bulk-cell molecular biology, as it requires the discrimination of centriole-age-specific molecular signatures. Its rigorous falsification necessitates centrosome-resolved, multi-omic approaches. Furthermore, we argue that dysregulation of this ledger—through corruption or erosion—constitutes a fundamental mechanistic axis underlying oncogenic transformation, where fate instruction is scrambled, and age-associated stem cell decline, where instructive fidelity is lost. This reframing of the centrosome from a cytoskeletal architect to an information-processing device opens novel translational avenues for diagnosing and treating cancer and degenerative diseases by targeting organelle memory.

Keywords: Centrosome, Cellular Memory, Cell Fate, Asymmetric Division, Multi-Omics, Cancer, Aging.



Introduction

For more than a century, the centrosome has occupied a central, yet mechanistically circumscribed, role in cell biology. The classical view defines it as the primary microtubule-organizing center (MTOC) of animal cells, dictating the geometry of the interphase cytoskeleton and bipolar spindle assembly during mitosis (Nigg & Holland, 2018). Closely tied to this structural role is its function as a cell cycle regulator, where it acts as a mandatory platform for the activation of key kinases such as PLK1 and Aurora A, thereby orchestrating the precise timing of mitotic entry and progression (Labbé, Meng, & Hyodo, 2021). This canonical framework portrays the centrosome as an essential but fundamentally reactive structure, a passive executor of cell cycle checkpoints and cytoskeletal blueprints.

However, this paradigm fails to explain a growing body of evidence from developmental and stem cell biology. Many cell types, particularly stem cells, exhibit the asymmetric inheritance of organelles, a process now recognized as a powerful mechanism for distributing non-genetic information and influencing daughter cell fate (Knoblich, 2010). Among these organelles, the centrosome is unique. Unlike mitochondria or other cytoplasmic components, the centrosome is not assembled de novo; it is templated from pre-existing structures. Crucially, the two centrioles within a centrosome are not equivalent. The older mother centriole, distinguished by the presence of distal appendages and enriched subdistal appendages, is often inherited asymmetrically, frequently retained by the stem or progenitor cell during division (Wang & Seydoux, 2013). This consistent, non-random pattern of inheritance suggests that the mother

centriole carries more than just the capacity to nucleate microtubules—it may carry a functional history.

This observation leads to a compelling and testable hypothesis: the mother centriole contains a "structural memory," a persistent record of cellular experiences encoded not in nucleic acids, but in its molecular architecture. We propose that this memory is best understood as a multicomponent vector, a high-dimensional state variable that integrates several layers of information: (1) the specific proteomic composition beyond canonical core components, including transiently associated regulatory factors; (2) a characteristic landscape of post-translational modifications (PTMs) such as phosphorylation, ubiquitination, and glutamylation; and (3) the precise stoichiometry of macromolecular complexes that define its functional maturity (e.g., the ratio of scaffolding proteins to catalytic kinases). The mathematical representation of this state at time *t* could be conceived as:

$S(t) = [P_1, P_2, \ldots P_{\square}; PTM_1, PTM_2, \ldots PTM_{\square}; R(Cplx_1), R(Cplx_2), \ldots R(Cplx_{\square})]$

where P represents protein concentrations, PTM represents modification states, and R represents critical stoichiometric ratios within complexes. This vector S(t) is not static; it is dynamically written and rewritten by signaling events, metabolic states, and cell cycle history, and it is physically transmitted to one daughter cell at division.

The rationale for this study is to move beyond the genetic and epigenetic determinants of cell fate and rigorously investigate these non-genomic, state-dependent determinants embodied by the centrosome. While transcriptional programs and chromatin states are undeniably crucial, they can be slow to enact and are often subject to rapid resetting. In contrast, the centrosomal memory vector offers a potentially faster, more direct, and immediately transmissible mechanism to influence cellular behavior. It could act as a rapid-response integrator, translating past stresses (e.g., DNA damage, oxidative stress) or positional cues into immediate changes in microtubule dynamics, ciliary signaling, or spindle orientation in the subsequent cell cycle. In essence, the centrosome may function as the cell's "flash drive"—a portable, rewritable storage device for operational history.

This concept forces a re-evaluation of cellular decision-making. If the mother centriole's state vector S(t) differs from that of the daughter centriole, the two sibling cells inherit not only identical genomes but also divergent historical records. This could prime them for different fates—self-renewal versus differentiation, proliferation versus quiescence—independent of immediate extracellular signals (Baudoin & Cimini, 2018). Disruptions in the writing, maintenance, or reading of this centrosomal memory could therefore have profound pathological consequences, potentially underlying tissue aging, developmental disorders, and cancer, where cell fate decisions are fundamentally corrupted.

Therefore, this article will explore the evidence supporting the existence of a centrosomal memory vector, detail its proposed molecular components, discuss the experimental paradigms necessary to decode it, and finally, examine the implications of this model for understanding cell identity, plasticity, and disease.

Conceptual Framework: The Centrosomal Ledger

To move beyond the descriptive observation of asymmetric centrosome inheritance, we require a formalized conceptual model. We propose the Centrosomal Ledger, a framework that defines the molecular information stored in the mother centriole not as a single binary marker, but as a multivariate molecular state vector (V). This vector V exists in a high-dimensional space, where each dimension corresponds to a quantifiable molecular feature of the centriolar structure and its immediate pericentriolar environment. Critically, this model posits that the instructive capacity of the centrosome emerges not from any one component, but from the integrated, system-level readout of this vector.

Defining the State Vector: Beyond Single Markers

Traditional models of cellular memory often seek a singular "master regulator" molecule. The centrosomal ledger explicitly rejects this reductionism. Instead, the state of the organelle at a given time *t* is defined by a composite vector V(t), which can be conceptually decomposed into orthogonal but interacting subspaces:

V(t) = [Proteome(t); PTMome(t); Metabolome(t); Stoichiometric Ratios(t)]

Here, Proteome represents the quantitative abundances of both core structural proteins (e.g., CEP135, SAS-6) and dynamically associated regulatory factors (e.g., cell cycle kinases, signaling adaptors). PTMome captures the combinatorial landscape of post-translational modifications—phosphorylation, ubiquitination, acetylation, and the centriole-specific tubulin modifications like glutamylation and glycylation (Janke & Montagnac, 2017). Metabolome accounts for the local concentration of key metabolites (e.g., ATP, Ca^{2+}, reactive oxygen species) known to influence centrosomal activity. Finally, Stoichiometric Ratios encode the precise quantitative relationships between components of functional modules, such as the ratio of PLK1 kinase to its centrosomal scaffold CEP192, a critical determinant of maturation timing (Joukov, De Nicolo, & Rodriguez, 2018). This comprehensive representation underscores that the ledger is inherently multidimensional.

Key Feature I: Distributed Coding

A cornerstone of this model is the principle of distributed coding. The information relevant to a specific cellular history or fate decision—such as "experienced DNA damage two cycles ago" or "is primed for differentiation"—is not stored in a dedicated molecule. Instead, it is encoded across multiple weak, correlated signals within the vector V(t). A past oxidative stress event, for example, might leave a subtle but coordinated signature: a slight increase in the abundance of redox-sensitive chaperones (Proteome), a characteristic pattern of sulfenylation on specific centriolar proteins (PTMome), a persistent local shift in the glutathione redox potential (Metabolome), and an altered CEP152/CEP63 complex ratio (Stoichiometry). Individually, each change may be near the noise threshold of detection and functionally insignificant. In concert, however, they create a robust, fault-tolerant code. This distributed architecture parallels neural

network models of memory, where information is stored in the pattern of synaptic weights, not in single neurons (Gerstner & Kistler, 2002). It ensures resilience against the stochastic turnover of individual components.

Key Feature II: Temporal Integration

The ledger is not a snapshot of the present; it is a temporal integrator. The state vector V(t) reflects the time-integrated history of cellular events, not merely the current signaling milieu. Mathematically, this can be represented as a form of memory with a decay constant. The rate of change of the vector dV/dt is driven by current inputs (e.g., a Wnt signal, DNA damage), but the vector itself, V(t), represents the cumulative effect of past inputs, filtered by organelle-specific turnover rates. For instance, the phosphorylation of a centriolar protein may be rapidly inducible by a kinase, but its dephosphorylation or removal may be slow, causing that "mark" to persist over multiple cell cycles. This creates a hysteresis, where the centrosome's state depends on its trajectory. Experimental evidence for this exists in the prolonged retention of DNA damage response proteins like 53BP1 at centrosomes long after nuclear repair is complete, effectively "remembering" the damage event (Labbé, Meng, & Hyodo, 2021).

Key Feature III: Falsifiability and the Need for System-Level Multi-Omics

A robust scientific model must be falsifiable. The centrosomal ledger model makes a key prediction that distinguishes it from simpler hypotheses: the informational output (cell fate bias) is a non-linear function of the high-dimensional state vector V(t). This cannot be falsified by studying individual proteins or modifications in isolation. Correlating the presence or absence of a single factor (e.g., Ninein) with an outcome is insufficient, as it ignores the distributed code. Therefore, rigorous testing requires system-level multi-omics applied to purified centrosomes. The model predicts that machine learning algorithms trained on high-dimensional datasets—combining centrosome-specific proteomics, phospho-proteomics, and metabolomics from cells with known histories—will be able to predict future cell behavior with significantly higher accuracy than any single-variable model (Slavov, 2021). Failure to find such predictive, correlated patterns in comprehensive centrosomal profiles would constitute evidence against the ledger model.

The Organelle Inheritance Analogy: Memory Drive and Imprint

A useful analogy is to consider the mother centriole as a "memory drive" installed in the cellular hardware. Throughout the cell cycle, the cell's experiences (software operations) write data onto this drive in the form of alterations to V(t). At mitosis, this drive is physically partitioned, with the original (mother) often retained by one cell, and a copied, potentially "fresher" or differently configured version (daughter centriole) passed to the other. Consequently, the two daughter cells boot up with different historical imprints. One inherits the full, accumulated ledger; the other may inherit a default or reset version. This differential inheritance can instantaneously bias downstream processes such as spindle orientation, ciliation potential, or asymmetric protein segregation, setting the siblings on divergent paths from the very onset of their existence

(Buchman & Tsai, 2021). This model elevates the centrosome from a structural organelle to a bona fide computational device in the cellular network, one that carries the legacy of the past into the decisions of the future.

Experimental Strategy: Decoding the Centrosomal Ledger

The centrosomal ledger hypothesis generates specific, testable predictions but demands a departure from conventional methodologies. Bulk cellular analyses are insufficient, as they average the signal from historically distinct mother and daughter centrioles with the entire cytoplasmic and nuclear content. Therefore, a rigorous experimental pipeline must achieve three goals: 1) physically separate centrosomes based on their age and inheritance history, 2) perform deep, multi-layered molecular profiling at the organelle level, and 3) apply systems-level computational analyses to extract predictive patterns from high-dimensional data. The following strategy, summarized in Box 1, outlines a pathway to falsify or validate the model.

Box 1. Experimental Pipeline for Centrosomal Ledger Analysis

1. **Model System Selection**: Utilize well-characterized models of asymmetric cell division.
    - **Neural Stem/Progenitor Cells (NSPCs)**: Primary murine or human NSPCs where centrosome asymmetry correlates with neurogenic vs. self-renewing divisions (Buchman & Tsai, 2021).
    - **Intestinal Stem Cells (ISCs)**: Drosophila or murine ISCs (e.g., Lgr5+ crypt base columnar cells) with defined niche interactions and lineage outcomes (Sugioka & Sawa, 2019).
    - **Hematopoietic Stem/Progenitor Cells (HSPCs)**: Ex vivo cultured HSPCs where division symmetry can be manipulated.
2. **Centriole Age Labeling and Fate Tracking**:
    - **Pulse-chase labeling**: Use stable cell lines expressing inducible, centriole-tethered fluorescent proteins (e.g., SNAP-tagged Centrin) to differentially label old (mother) and new (daughter) centrioles (Wang et al., 2022).
    - **Live-cell imaging**: Track labeled centrioles through one or more divisions while concurrently monitoring cell fate choices (differentiation marker expression, niche localization, functional assays).
3. **Centrosome Isolation and Fractionation**:
    - **Density-gradient purification**: Isolate intact centrosomes from synchronized cell populations using established sucrose/ficoll gradient protocols (Kong et al., 2020).

- **Immunoaffinity purification (optional)**: For specific subpopulations, use antibodies against mother centriole-specific appendage proteins (e.g., CEP164, Ninein) for further enrichment.

4. **Multi-Omic Profiling**:
    - **LC-MS/MS Proteomics**: Quantitative, label-free or TMT-based mass spectrometry to define the full proteome of "mother-centriole-enriched" vs. "daughter-centriole-enriched" centrosome fractions.
    - **PTM-Omics**: Enrichment for phosphopeptides, ubiquitin remnants, or acetylated peptides prior to MS to map modification landscapes.
    - **Metabolomic Profiling (targeted)**: Use LC-MS to quantify a targeted panel of metabolites (e.g., nucleotides, redox couples) co-purifying with centrosomal fractions.
5. **Computational & Multivariate Analysis**:
    - **Data Integration**: Create a unified data matrix where each centrosome sample is a point in a space defined by protein abundances, PTM intensities, and metabolite levels.
    - **Dimensionality Reduction (PCA, t-SNE)**: Visualize global separations between mother and daughter centriole samples.
    - **Clustering & Trajectory Inference**: Use algorithms (e.g., Monocle, PAGA) to identify discrete molecular states and infer transitions related to cell history.
    - **Predictive Modeling**: Train machine learning classifiers (e.g., random forest, neural networks) on the multi-omic data to predict the future fate of the inheriting cell.

Model Systems and Centriole Tracking

The choice of model system is paramount. We propose a focus on asymmetrically dividing stem cells where the functional outcome of division is well-defined. In Drosophila neural stem cells (neuroblasts) and mammalian neural progenitors, the mother centrosome is consistently retained by the self-renewing stem cell, while the daughter centrosome is inherited by the differentiating progeny (Rusan & Peifer, 2021). Similar mechanisms operate in intestinal and hematopoietic systems. These models allow the a priori hypothesis that the molecular ledger V(t) of the mother centriole will differ from that of the daughter and will correlate with a self-renewing signature.

Technologically, a pulse-chase strategy using a covalent label (e.g., SNAP-Cell or HaloTag) fused to a core centriolar protein like Centrin2 enables unambiguous discrimination. A brief pulse labels all existing centrioles; after a chase period covering one full cell cycle, the "old"

mother centrioles retain the label, while "new" daughters do not. Fluorescence-activated cell sorting (FACS) can then separate cells based on which centriole (old/mother vs. new/daughter) they inherited in the previous division, enabling the collection of biologically distinct populations for centrosome isolation (Bazzi & Anderson, 2019).

Centrosome Isolation and Multi-Omic Interrogation

Purifying centrosomes to homogeneity is challenging but essential. Sucrose gradient centrifugation remains the gold standard, yielding preparations sufficient for downstream LC-MS/MS. The critical comparison is not between "centrosome" and "cytoplasm," but between mother-centriole-enriched and daughter-centriole-enriched centrosomal fractions. Even partial enrichment will reveal differential associations if the ledger model is correct.

Mass spectrometry must move beyond cataloging proteins. PTM-omics is crucial, as the information-carrying capacity of PTM combinatorial codes vastly exceeds that of protein abundance alone. Phosphoproteomics will reveal kinase signaling history; ubiquitinomics may reveal degradation cues and regulatory complexes. Furthermore, emerging techniques suggest local metabolite pools influence centrosomal function. Therefore, a targeted metabolomic approach, perhaps following a protocol for isolating metabolite-protein complexes, should be attempted to measure key energetic (ATP/ADP ratio) and redox (GSH/GSSG) parameters associated with the organelle (Zhao et al., 2021).

Multivariate Analysis and Falsification Criteria

The raw output is a high-dimensional dataset. Simple pairwise comparisons (e.g., Protein X is 1.5-fold higher on mother centrioles) are inadequate to test a distributed coding model. Instead, we must employ multivariate analysis.

- Principal Component Analysis (PCA) will determine if mother and daughter centriole samples occupy distinct regions of molecular space based on all measured variables.
- Unsupervised clustering (e.g., hierarchical, k-means) will reveal if there are discrete, recurrent "states" of the centrosomal ledger associated with specific prior histories (e.g., stress-exposed vs. naive).
- Trajectory inference algorithms, commonly used in single-cell transcriptomics, can be adapted to model how the centrosomal state vector V(t) evolves over consecutive cell cycles or in response to a stimulus, mapping a "memory trajectory" (Chen & Wang, 2020).

The ultimate test is predictive power. Can the multi-omic profile of a centrosome isolated before a fate decision predict the outcome of that decision? This requires supervised machine learning. A classifier trained on the molecular ledger data from centrosomes of cells whose fate is known (e.g., remained a stem cell vs. differentiated) must perform significantly better than chance or a classifier based on a single marker.

Clear Falsification Criteria

The ledger model is falsifiable under the following conditions:

1. **Absence of Reproducible Distinction**: If state-of-the-art isolation and multi-omics reveal no statistically significant, reproducible molecular differences between mother and daughter centriole fractions across multiple biological replicates and model systems, the core premise of a distinct historical imprint fails.

2. **Lack of Correlation with Fate**: If molecular distinctions exist but show no consistent correlation—linear or non-linear—with the future behavioral or transcriptional fate of the inheriting cell, then the "ledger" is not instructive. It may be a passive epiphenomenon of assembly kinetics.

3. **Inability to Predict**: If a multivariate classifier trained on the full ledger data performs no better than a trivial model at predicting cell fate, the distributed coding hypothesis is not supported.

By adhering to this stringent, multi-omics-driven strategy, we can move from speculative analogy to rigorous, quantitative testing of whether the centrosome truly functions as a cellular memory device.

Translational Extensions: Cancer and Aging as Diseases of Centrosomal Memory

The centrosomal ledger model is not merely a descriptive framework for normal cell biology. It provides a novel, organelle-centric lens through which to view fundamental pathological processes. If the centrosome indeed encodes a stable, instructive memory of cellular state, then its corruption or erosion could be a direct driver of disease. Here, we extend the ledger hypothesis to two major biomedical challenges: cancer transformation and age-related tissue decline, proposing them as paradigmatic examples of disrupted centrosomal memory with clear translational implications.

Cancer Transformation: Ledger Corruption

The prevailing oncogenic paradigm centers on the sequential accumulation of genomic mutations that confer proliferative advantages. The centrosomal ledger model proposes a complementary, non-mutually exclusive driver: transformation as a state of ledger corruption. In this view, a malignant cell is not only genetically mutated but also suffering from a profound failure in its non-genomic information processing system. The centrosome’s ability to accurately record history and bias fate correctly becomes compromised.

Observable Manifestations of Corruption:

1. **Disrupted PTM Patterning**: The precise, history-dependent combinatorial code of phosphorylation, acetylation, and ubiquitination is scrambled. For instance, the tight regulatory phosphorylation of PLK1 at the centrosome, essential for controlled mitotic entry, becomes constitutive or unresponsive to checkpoints. This has been observed in cancers where centrosomally localized kinases exhibit aberrant activation states (Parker, Knippschild, & Goepfert, 2018). Similarly, abnormal centriolar tubulin glutamylation patterns are linked to genomic instability and invasion (Bodakuntla et al., 2021).

2. **Loss of Mother-Centriole Signatures and Asymmetry**: The molecular distinction between mother and daughter centrioles, crucial for fate asymmetry in stem cells, becomes blurred. In many carcinomas, the mother centriole's distinctive appendage proteins and associated complexes are mislocalized or underexpressed. This loss of centriole asymmetry may force symmetric, expansive divisions irrespective of niche signals. Quantitatively, the state vector V_mother(t) becomes statistically indistinguishable from V_daughter(t) in cancer stem-like cells, representing a loss of instructive information (Godinho & Pellman, 2014).

3. **Decoupled Fate Outcomes**: The correlation between the inherited centrosomal state and the cell's subsequent behavior breaks down. A daughter cell inheriting a centrosome with a "differentiation-primed" ledger might still re-enter the proliferative pool, a direct failure of memory execution. This decoupling manifests as cellular heterogeneity and fate plasticity, hallmarks of aggressive tumors.

Translational Potential:

- **Early Biomarkers**: Detecting specific "corruption signatures" in the centrosomal proteome/PTMome from circulating tumor cells or biopsies could serve as a novel diagnostic or prognostic tool, potentially earlier than genomic instability becomes karyotypically evident.

- **Therapeutic Target**: Instead of targeting a single overactive kinase, the goal would be to correct the ledger corruption. This could involve developing small molecules that restore normal PTM patterning on centrosomal substrates, or chaperones that re-establish proper complex assembly and stoichiometry at the organelle. Compounds that specifically reinstate mother-centriole identity and function could, in theory, re-impose a degree of asymmetric division and differentiation pressure on a tumor.

Aging and Regeneration: Ledger Erosion and Reset

Aging is characterized by a progressive decline in tissue function and regenerative capacity, rooted in stem cell exhaustion. We hypothesize that this reflects the cumulative erosion of the centrosomal ledger in somatic stem cells. Over time, the fidelity with which molecular information is written, maintained, and read at the centrosome declines. The state vector V(t) accumulates noise and errors, losing its precise link to historical cues and fate instructions.

The Mechanism of Erosion:
Aging cells experience widespread declines in proteostasis, increased oxidative damage, and altered metabolism. All these processes directly impact the ledger's components:

- **Proteostatic Collapse**: Misfolded or aggregated proteins may accumulate at the centrosome, disrupting the native proteome. The turnover of key regulatory proteins slows, causing outdated molecular signals to persist.

- **Energetic and Redox Dysregulation**: The local metabolome at the centrosome, dependent on global cellular ATP and redox balance, becomes dysregulated. This impairs the activity of PTM-writing enzymes (kinases, acetyltransferases) and erasers (phosphatases, deacetylases), blurring the modification code.

- **Chaperone Insufficiency**: The depletion of heat-shock proteins and other chaperones with age compromises the proper assembly and maintenance of the large macromolecular complexes that define centrosomal stoichiometry (Fong et al., 2016).

The result is an aged ledger vector V_aged(t) that is a noisy, degraded version of its youthful counterpart V_young(t). When this corrupted vector is inherited by a daughter cell, it fails to provide a clear instruction for self-renewal or differentiation, leading to neutral or faulty fate decisions that ultimately deplete the functional stem cell pool.

Interventions for Regeneration:
The ledger model suggests rejuvenation strategies aimed not at the genome, but at the organelle's information content.

1. **Proteostasis Modulation and Chaperone Activation**: Pharmacological or genetic interventions to boost the protein quality control machinery specifically at the centrosome could clear aggregates and restore proper protein turnover. Upregulating specific chaperones like HSP90, known to regulate centriole duplication and PCM assembly, could restabilize complex stoichiometries (Reyes et al., 2018).

2. **Metabolic Reprogramming**: Interventions that restore youthful NAD+ levels or mitochondrial function could rejuvenate the local energetic and redox environment at the centrosome, allowing for more accurate PTM writing/erasure.

3. **Partial Ledger Reset**: A more radical approach could involve triggering the selective disassembly and de novo formation of the PCM (but not the centriole core) in aged stem cells, effectively wiping the slate clean of accumulated noise while preserving the structural template. This "centrosomal reboot" could allow the cell to re-establish a functional ledger based on current, not historically corrupted, signals.

Observables for Success:

The efficacy of such interventions would be measured by:

- **Rejuvenated Molecular Patterns**: A shift in the multi-omic profile of aged stem cell centrosomes toward a youthful signature—restored PTM patterns, rebalanced stoichiometries.
- **Restored Fate Bias**: The re-establishment of a strong correlation between centrosomal inheritance (mother vs. daughter) and cell fate outcome in asymmetric divisions.
- **Enhanced Regenerative Capacity**: In vivo, this would translate to improved tissue repair, increased stem cell pool functionality, and extended healthspan in model organisms.

In conclusion, viewing cancer and aging through the prism of centrosomal memory dysfunction reframes these conditions as informational diseases. It shifts the therapeutic focus from simply killing bad cells or reactivating genes to correcting corrupted cellular software stored in a key organelle. This represents a profound, if speculative, new axis for translational medicine.

Discussion

The centrosomal ledger hypothesis posits a fundamental shift in our understanding of cellular organization and information processing. By framing the mother centriole as a repository of a multivariate molecular state vector V(t), this model provides a novel and falsifiable mechanistic link between three previously disparate domains of biology: subcellular structural memory, deterministic cell fate decisions, and the phenotypic manifestations of disease and aging. This discussion will contextualize the ledger within existing paradigms, highlight its explanatory power, and outline the new research avenues it demands.

Integrating Structure, Memory, and Fate

A core contribution of this model is its resolution of a long-standing conceptual gap. We have extensive knowledge of epigenetic transcriptional memory and a detailed catalog of structural centrosomal proteins, yet a coherent mechanism linking persistent organelle structure to long-term cell behavior has been elusive. The ledger model bridges this gap. It proposes that the physical continuity and asymmetric inheritance of the centrosome are not incidental but are the hardware prerequisites for a software-like memory function. The structural complexity of the mother centriole—its appendages, scaffold, and PCM—provides the physical substrate with sufficient combinatorial complexity to encode information. This subcellular structural memory is then translated into fate decisions through direct effects on microtubule dynamics, spindle orientation, asymmetric cargo segregation, and ciliary signaling (Pazour & Witman, 2021). For example, a ledger state signifying "recent Wnt exposure" could bias the inheritance of β-catenin regulatory complexes or orient the spindle to position one daughter within a niche permissive for self-renewal. The centrosome thus becomes an interpreter of history, directly influencing the spatial and molecular asymmetries of division.

Contrasting with Genomic and Transcriptomic Paradigms

The centrosomal ledger operates on a fundamentally different logic and timescale than genomic and purely transcriptomic explanations of cell fate. Genomic sequence is essentially static for a somatic cell lineage, while the transcriptome, though dynamic, is highly responsive to immediate signals and can be rapidly reset. The ledger model does not dispute the centrality of these systems but proposes a parallel, complementary layer of control with distinct properties:

- **Speed and Directness**: Altering the centrosomal PTMome or local proteome can occur within minutes of a signal, potentially biasing the very next mitosis. This is faster than many transcriptional responses that require synthesis and nuclear import/export.
- **Spatial Precision**: Information is stored and executed at the exact cellular location where key fate-executing machinery (the mitotic spindle) is assembled. This contrasts with nuclear-centric models where signals must be transmitted across cellular space.
- **Non-Genetic Inheritance**: The ledger provides a robust mechanism for the inheritance of acquired cellular states—a form of Lamarckian information transfer at the somatic cell level—without altering the DNA sequence. This is crucial for explaining how transient environmental exposures can have long-term consequences for a cell lineage.

While transcriptional programs define a cell's potential repertoire, the centrosomal ledger may act as a real-time integrator and executor, selecting from this repertoire based on immediate historical context (Venkei & Yamashita, 2018).

A Unifying Framework for Disease Pathogenesis

The model powerfully unifies disparate pathological observations under the umbrella of informational dysfunction. In cancer, phenomena like centrosome amplification, supernumerary cilia, and mitotic errors are often viewed as downstream consequences of genomic instability. The ledger hypothesis inverts this perspective: ledger corruption may be a primary driver. The chaotic PTM patterns, loss of centriole asymmetry, and stoichiometric imbalances seen in tumor cells (Godinho & Pellman, 2014) constitute a corrupted operating system that produces unreliable fate outputs, fostering heterogeneity and aggressive behavior. This reframes some oncogenic mutations as corruptors of the ledger's "writing" or "reading" mechanisms, rather than just disruptors of proliferation per se.

Similarly, in aging, the decline in stem cell function is frequently attributed to DNA damage accumulation, telomere shortening, or epigenetic drift. The ledger model adds a compelling organelle-centric dimension: aging is, in part, the accumulation of noise in a critical non-genomic memory system. The erosion of proteostatic control, metabolic regulation, and PTM fidelity at the centrosome directly undermines the stem cell's ability to make precise, history-informed decisions, leading to stochastic fate choices and pool exhaustion. This perspective suggests that interventions targeting organelle integrity could have potent rejuvenating effects independent of nuclear manipulations.

Implications for a New Paradigm

If validated, the centrosomal ledger hypothesis necessitates a paradigm shift in several fields:

- **In Cell Biology**: It elevates organelles from static compartments or metabolic factories to active information-processing nodes. The focus would expand from "what does this organelle do?" to "what does this organelle remember, and how does that memory inform its function?" This calls for the widespread adoption of organelle-resolved multi-omics as a standard tool.
- **In Aging Research**: It introduces a new, actionable hallmarks of aging: loss of organelle information fidelity. Therapeutic strategies would aim not only to remove damage (e.g., senolytics) but to restore signal clarity at key cellular control centers like the centrosome.
- **In Cancer Biology**: It proposes a novel class of therapeutic targets: the machinery that writes, maintains, and reads the centrosomal ledger. The goal would shift from simply inhibiting proliferation to reprogramming cell fate by correcting corrupted organelle memory. This could lead to therapies that force differentiation or asymmetric division in tumors.

Future Directions

The centrosomal ledger is a speculative but powerfully synthetic hypothesis. It is grounded in established observations—asymmetric inheritance, centrosomal persistence, and complex PTM regulation—yet extends them into a novel theoretical framework. Its greatest strength is its falsifiability through defined multi-omic experiments, as outlined in Section 3.

Future work must move decisively in this direction. The immediate priority is the technical refinement of centrosome isolation and age-specific fractionation, coupled with deep PTM profiling. Computational biologists must develop new tools to model high-dimensional organelle state vectors and their temporal evolution. Ultimately, the most convincing validation will be causal: demonstrating that the experimental manipulation of a specific ledger component (e.g., forcing a "young" PTM pattern onto an aged centrosome) can predictably alter a cell's long-term fate trajectory.

In conclusion, by proposing that the centrosome functions as a cellular ledger, we are not diminishing the importance of the nucleus but are recognizing the brain-like, distributed nature of cellular intelligence. Memory and decision-making may be properties that emerge from the integrated network of all cellular components. The centrosome, with its unique combination of structural permanence and molecular dynamism, appears to be a privileged node in this network—a keeper of the past and a guide to the future.

Future Directions: A Roadmap for Decoding Cellular Memory

The centrosomal ledger hypothesis establishes a new conceptual landscape, but its validation and full exploration will require a corresponding evolution in experimental and computational methodologies. Moving from a theoretical framework to a robust, predictive branch of cell biology demands a concerted effort across several key frontiers. These future directions outline a roadmap for the systematic interrogation of centrosomal memory, emphasizing technological innovation, causal testing, and clinical translation.

Single-Cell, Longitudinal Centrosome-Resolved Multi-Omics

The fundamental unit of the ledger's operation is the individual centrosome within a single cell. Current bulk purification methods, while essential for proof-of-principle, average signals across thousands of organelles, inevitably obscuring cell-to-cell heterogeneity and the dynamic trajectory of a single ledger over time. The next technological leap must be toward single-cell, centrosome-resolved analysis.

This challenge requires two parallel advancements. First, novel microfluidic or nanopore-based platforms must be developed to isolate single intact centrosomes from individually lysed cells, potentially leveraging antibodies against the mother centriole-specific protein CEP164 for capture (Zheng et al., 2022). Second, ultrasensitive, multiplexed mass spectrometry techniques, such as those employing tandem mass tags (TMT) with carrier channels or emerging single-cell proteomic (SCoPE-MS) workflows, must be adapted for organelle-scale analysis (Slavov, 2021). The goal is to generate paired datasets for individual cells: the centrosomal state vector V_i(t) and the cell's subsequent transcriptional or behavioral fate.

Critically, this must be performed longitudinally. A cell lineage-tracking system, combined with sequential, non-destructive imaging of a reporter for a specific ledger component (e.g., a phosphorylation-sensitive FRET biosensor for PLK1 activity at the centrosome), followed by eventual single-cell centrosome isolation, would allow the direct mapping of how V(t) evolves across generations in response to stimuli. This would move the field from static correlation to dynamic, causal inference about ledger function.

Integration with Metabolomics and Epigenetic Landscapes

The ledger vector V(t) does not exist in isolation. It is both shaped by and shapes the broader cellular context. A comprehensive understanding requires its integration with two other critical information layers: the local metabolome and the epigenetic landscape.

- **Metabolomic Integration**: The centrosome is a hub for kinases, GTPases, and acetyltransferases, all regulated by local metabolite concentrations (ATP, GTP, acetyl-CoA, NAD^+). Quantitative imaging of metabolite biosensors (e.g., ATP, lactate) at the centrosome, coupled with subcellular metabolomic profiling, is essential. We

hypothesize a feedback relationship: Metabolite availability (M) → influences PTM writing on the ledger (V) → altered centrosomal function → changes in cellular metabolism. Disrupting this loop, for instance by depleting local ATP pools, should produce predictable, measurable errors in the ledger's PTM code.

- **Epigenetic Crosstalk**: The most profound implication of the ledger model is its potential interaction with nuclear memory systems. Does a centrosomal state signifying "repeated differentiation pressure" influence the deposition of repressive histone marks (e.g., H3K27me3) on stemness genes in the daughter cell nucleus? Techniques like CUT&RUN or ATAC-seq performed on daughter cells sorted by the age of their inherited centriole could reveal such epigenetic priming by centrosomal history (Buchmann & Bintu, 2019). This would position the centrosome as an upstream instructor of the slower-acting epigenetic machinery.

Functional Perturbation: Causal Testing of the Ledger

Correlative evidence, no matter how detailed, is insufficient. The ultimate test is causal perturbation: selectively modifying specific components of the hypothesized ledger and measuring the outcome against model predictions.

This requires precision tools. Optogenetic systems could be used to recruit a kinase (e.g., Aurora A) or a ubiquitin ligase specifically to the mother centriole at a defined time, artificially "writing" a signal into the ledger. Conversely, light-activated degradation (degron) systems could be used to selectively deplete a mother-centriole-specific protein, erasing a component of the ledger (Natsume & Kanemaki, 2017). The predictions are clear: if the ledger is instructive, these manipulations should bias cell fate decisions in the subsequent division in a predictable manner, overriding genetic identity. For example, artificially adding a "self-renewal" PTM signature to the daughter centriole in a neural stem cell should increase the probability of that daughter adopting a stem-like fate.

Furthermore, machine learning models trained on multi-omic ledger data should be able to in silico predict the outcome of such perturbations. A successful causal test would see close alignment between the model's prediction and the experimental outcome.

Translational Studies: Mapping Disease-Specific Ledger Disruptions

Finally, the translational promise of the model must be tested directly in human pathology. This involves moving from model cell lines to patient-derived cells.

- **Cancer**: Centrosomes should be isolated from primary tumor samples, patient-derived organoids, and circulating tumor cells. Multi-omic profiling will define tumor-specific "corruption signatures" within the ledger. Do glioblastomas show a different corruption pattern than pancreatic ductal adenocarcinomas? Does the ledger state correlate with relapse risk or drug resistance? Critically, comparing centrosomes from matched cancer

stem cells and more differentiated tumor cells could reveal if ledger corruption is hierarchical, driving intra-tumoral heterogeneity.

- **Aging and Neurodegeneration**: Centrosomes from induced pluripotent stem cell (iPSC)-derived neural progenitor cells of young, old, and progeria syndrome donors should be profiled. This will map the trajectory of ledger erosion with chronological and biological age. Similarly, in Alzheimer's disease models, the well-documented deficits in axonal transport and neuronal polarity may be rooted in early centrosomal ledger dysfunction, which could be detectable before overt pathology (Kong & Koushika, 2021).

The outcome of these translational studies would be a new taxonomy of disease—not just based on genomic mutations, but on organelle information states. This could yield novel diagnostic biomarkers from liquid biopsies (detecting centrosomal proteins/PTMs in exosomes) and reveal entirely new therapeutic targets aimed at restoring physiological information flow within the cell. The path forward is technically demanding but holds the potential to redefine our understanding of cellular identity, memory, and disease.

Conclusion

For generations, the centrosome has been defined by its cytoskeletal function. This article has argued for a fundamental expansion of that definition. The cumulative evidence from cell biology, developmental studies, and disease models converges on a provocative conclusion: centrosomes encode a distributed, temporally integrated memory of cellular history. They are not merely executors of the cell cycle but act as sophisticated, non-genomic information-processing devices. The "centrosomal ledger" hypothesis synthesizes these observations into a coherent model, proposing that the molecular state of the mother centriole—a high-dimensional vector integrating proteomic, post-translational, stoichiometric, and potentially metabolic information—serves as a persistent record that guides future cellular decisions. This framework transforms our understanding of the centrosome from a structural scaffold to an active participant in cellular cognition, a keeper of the past that informs the future.

The ledger model's strength lies in its falsifiability and its demand for technological rigor. It moves beyond metaphor by making concrete predictions that can be tested with existing and emerging tools. Critically, it posits that the memory is distributed, relying on weak, correlated signals across multiple molecular layers rather than a single master regulator. It is temporally integrated, reflecting the cumulative effect of past events filtered through organelle-specific turnover rates. These features render traditional, reductionist approaches insufficient. As we have detailed, the hypothesis can only be properly interrogated through centrosome-resolved multi-omics—the isolation and deep profiling of the organelle itself, distinguishing between mother and daughter centrioles, across time and cell states. The failure to find reproducible, high-dimensional signatures that correlate with and predict cell fate would falsify the core premise. The development of single-cell, longitudinal centrosome analysis will be the next critical step in this investigative journey, allowing us to move from population averages to the definitive tracking of information flow within lineages.

The most profound implications of this model are translational. By providing a mechanistic link between subcellular memory and organismal health, the ledger hypothesis reframes major diseases as disorders of cellular information processing. In cancer, we propose that malignant transformation involves not only genomic mutations but also a profound corruption of the centrosomal ledger. The chaotic PTM patterns, loss of centriolar asymmetry, and disrupted stoichiometries observed in tumors are not just side effects; they represent a corrupted operating system that produces unreliable, proliferative fate outputs, driving heterogeneity and therapeutic resistance (Godinho & Pellman, 2014). This suggests novel therapeutic avenues aimed not solely at killing dividing cells, but at "debugging" this corrupted software to restore differentiation or asymmetric division.

Conversely, in aging, the progressive decline in tissue regeneration and stem cell function can be understood, in part, as the erosion of the centrosomal ledger. The age-associated decline in proteostasis, metabolic regulation, and signaling fidelity leads to a noisy, degraded state vector that fails to provide clear instructions for self-renewal versus differentiation (Labbé, Meng, & Hyodo, 2021). Consequently, rejuvenation strategies may find a powerful target in the centrosome. Interventions aimed at restoring proteostatic control, metabolite availability, or precise PTM patterning at this organelle—a partial ledger reset—could, in theory, restore youthful fate bias and regenerative capacity without altering the genomic sequence. This positions the centrosome as a central arbitrator of cellular aging and a novel target for interventions aimed at extending healthspan.

In conclusion, the centrosomal memory hypothesis challenges a nucleus-centric view of cellular identity and fate. It proposes that cells possess a parallel, organelle-based memory system that operates on faster timescales and with direct spatial control over key effectors like the cytoskeleton. By encoding a ledger of past experiences, the centrosome ensures that history is not forgotten but is actively used to navigate future choices. Validating this model will require a concerted interdisciplinary effort, merging advanced cell biology, cutting-edge proteomics, and sophisticated computational analysis. If substantiated, it will establish a new paradigm in cell biology, revealing that memory is a distributed property of cellular architecture, and that its maintenance is fundamental to health, while its dysregulation lies at the heart of cancer and aging. The centrosome, long seen as a simple organizer, may well be the cell's most intricate historian and strategist.

Summary for Perspective

The Centrosomal Ledger hypothesis posits that mother centrioles encode a distributed molecular memory governing cell fate, and its dysregulation drives cancer and aging, testable only via centrosome-resolved multi-omics.

This succinct statement encapsulates the paradigm shift argued for throughout this article. It distills three fundamental and interconnected claims that redefine the centrosome's role.

First, it asserts that the mother centriole is an information-bearing structure. Moving far beyond its role in microtubule nucleation, the centriole is recast as a non-genomic storage device. The

"distributed molecular memory" refers explicitly to the multivariate state vector V(t), a high-dimensional code written in the correlated abundances of proteins, the combinatorial patterns of post-translational modifications, and the precise stoichiometries of macromolecular complexes. This code is not static; it is a dynamic, temporally integrated record of a cell's experiences, from metabolic stress to signaling history.

Second, it posits a direct causal link between this organellar memory and major organismal pathologies. The hypothesis provides a unifying mechanistic framework: cancer is not merely genomic chaos but a state of "ledger corruption," where the instructive code becomes scrambled, decoupling inheritance from proper fate execution and promoting malignant plasticity (Parker, Knippschild, & Goepfert, 2018). Conversely, aging is characterized by "ledger erosion," where the fidelity of this molecular code degrades due to declining proteostasis and metabolic regulation, leading stem cells to make noisy, erroneous fate decisions that deplete regenerative capacity (Fong et al., 2016). In both cases, the dysfunction originates at the subcellular level but manifests at the tissue and organismal scale.

Third, and crucially, it establishes a methodological imperative. The distributed nature of the proposed memory renders it invisible to conventional bulk-cell analyses, which homogenize the critical signal from the centrosome with the vast background of cytoplasmic and nuclear content. Therefore, the hypothesis is falsifiable only through a specific technological approach: centrosome-resolved multi-omics. This demands the physical isolation of centrosomes, preferably with age discrimination, followed by deep, quantitative profiling of their proteome, PTMome, and associated metabolome. Success in this endeavor would not only validate the ledger model but would also establish a new gold standard for organellar biology, moving the field from inference to direct interrogation of organelle-specific states (Slavov, 2021).

This perspective positions the centrosome at the nexus of cell biology, systems theory, and translational medicine. It suggests that understanding cellular decision-making requires us to look beyond the nucleus and the transcriptome to the permanent, information-rich structures that persist through divisions. If correct, the Centrosomal Ledger hypothesis opens a new frontier for diagnostics—by reading disease-specific corruption signatures from patient organelles—and for therapeutics, by developing strategies to correct corrupted codes or rejuvenate eroded ones. The path forward is clear: to test this bold synthesis of ideas, we must build the tools to listen to what the centrosome has remembered.

Computational Modeling Recommendations for Predictive Experimental Design

The empirical validation of the centrosomal ledger hypothesis requires not only advanced wet-lab techniques but also a sophisticated computational strategy. The high-dimensional, multivariate nature of the proposed state vector V(t) necessitates modeling approaches that can handle complexity, infer causality from correlation, and ultimately generate testable, quantitative predictions. Below are specific recommendations for constructing a predictive computational pipeline to guide and interpret the proposed multi-omics experiments.

Data Integration and Dimensionality Reduction Prior to Modeling

The raw output from centrosome-resolved LC-MS/MS (proteomics, phosphoproteomics) and targeted metabolomics will constitute a data matrix with hundreds to thousands of features (proteins, PTM sites, metabolites) across a limited number of biological samples (e.g., mother vs. daughter centriole fractions from different conditions). Direct application of predictive modeling to such wide, sparse data risks overfitting.

- **Recommendation 1**: Multi-Omic Data Fusion. Use methods like Multi-Omics Factor Analysis (MOFA) or integrative Non-negative Matrix Factorization (iNMF) to jointly model all data layers (Argelaguet et al., 2018). These techniques identify latent factors that capture co-variation across different omic types, effectively distilling the distributed ledger code into a smaller set of interpretable, combined factors (LF1, LF2, ... LF_n). These latent factors, rather than individual protein abundances, should serve as the primary input features for downstream predictive models.

- **Recommendation 2**: Trajectory Inference for Temporal Dynamics. For longitudinal single-cell centrosome data, employ trajectory inference algorithms (e.g., Monocle 3, PAGA, or Slingshot). These can model how the latent factor representation of the ledger state LF(t) evolves over time or across cell generations (Chen & Wang, 2020). This allows the hypothesis that the ledger encodes history to be tested by checking if cells with similar histories cluster along the same trajectory branches.

Building Predictive Models of Cell Fate

The core prediction of the ledger hypothesis is that V(t) (or its latent factor representation LF(t)) contains information predictive of a future cellular outcome Y (e.g., self-renewal vs. differentiation, proliferative vs. senescent).

- **Recommendation 3**: Supervised Learning with Regularization. Train supervised machine learning classifiers to predict fate Y from LF(t). Given the likely small sample size of initial studies, use algorithms with built-in regularization to prevent overfitting:
    - **Lasso (L1-regularized) or Ridge (L2-regularized) Regression**: For continuous outcomes (e.g., potency score).
    - **Elastic Net Logistic Regression or Support Vector Machines (SVM) with linear kernel**: For binary fate decisions (Wei & Kusiak, 2015).
    - **Random Forests**: Provide robust performance and inherent feature importance metrics, indicating which latent factors (and by extension, which omic features) are most predictive of fate.

- **Recommendation 4**: Cross-Validation and Strict Hold-Out Testing. Model performance must be evaluated using nested cross-validation. An inner loop optimizes model hyperparameters, while an outer loop provides an unbiased estimate of generalization

error. Ultimately, the model must be validated on a completely independent, hold-out experimental dataset not used in any phase of training.

Generating Causal, Falsifiable Predictions for Perturbation Experiments

A model that merely correlates ledger state with fate is suggestive but not conclusive. The ultimate goal is to build a causal, predictive model that can forecast the outcome of a specific ledger perturbation.

- **Recommendation 5**: Develop a Predictive Equation for Fate Bias. Based on the trained model, derive a simplified, interpretable equation that quantifies the predicted probability of a fate outcome. For instance, using logistic regression coefficients (β), the probability of self-renewal P(SR) could be modeled as:

  $P(SR) = 1 / [1 + \exp(-(\beta_0 + \beta_1 LF_1 + \beta_2 LF_2 + ... + \beta_n * LF_n))]$

  Here, $LF_1...LF_n$ are the values of the key latent factors for a given centrosome. This equation turns the ledger state into a computable fate bias.

- **Recommendation 6**: *In Silico* Perturbation and Prediction. Use the model to simulate experimental perturbations. For example, if a latent factor LF_2 is heavily weighted in the model and is found to correlate strongly with phosphorylation of protein X at site Y, the model can be queried: "If we experimentally increase phospho-Y abundance by 50% (simulating an optogenetic kinase recruitment), what is the predicted change in P(SR)?" This generates a precise, quantitative, and falsifiable prediction for a functional experiment. The success of the model will be judged by how accurately its predictions match the observed outcomes of such targeted perturbations (e.g., using degrons or optogenetic tools as in Natsume & Kanemaki, 2017).

Modeling Ledger Corruption in Disease

To translate the model to cancer and aging, a comparative approach is needed.

- **Recommendation 7**: Differential Network Analysis. Construct correlation networks of ledger features (proteins, PTMs) for healthy/young versus diseased/aged centrosome samples. Use methods like Differential Network Analysis (DNA) or the WGCNA package to identify modules of features whose co-regulation is significantly disrupted in disease (Gysi et al., 2021). This provides a formal definition of "ledger corruption" or "erosion" as a loss of specific regulatory relationships within the state vector.

- **Recommendation 8**: Survival and Prognostic Modeling (Clinical Translation). For patient-derived data, integrate the centrosomal ledger signature with clinical outcomes. Use Cox proportional-hazards models where the predictor variables are key latent factors LF from the patient's tumor centrosome profile. This tests the hypothesis that specific ledger corruption patterns are prognostic biomarkers independent of standard genetic markers.

Computational Strategy

A rigorous computational framework is not an auxiliary component but the very engine for testing the centrosomal ledger hypothesis. By moving from descriptive statistics to predictive, causal modeling, we can transform the high-dimensional multi-omic data into a quantitative theory of centrosomal function. This model-centric approach will generate the specific, falsifiable predictions that are the hallmark of a mature scientific hypothesis, guiding the next generation of experiments aimed at decoding cellular memory.

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