Integrative Multi-Omics and Dynamical Systems for Modeling Aging

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Abstract

Aging multifactorial process arising from interacting biological subsystems including metabolism, proteostasis, genomic stability, immune surveillance, and intercellular communication. While reductionist studies have uncovered individual molecular mechanisms of aging, a generalized systems biology framework is required to unify these observations into a coherent predictive model. This paper develops a computational framework that integrates multi-omics data with a coupled dynamical systems model representing key aging hallmarks. Using synthetic but biologically plausible datasets, we demonstrate how ordinary differential equations (ODEs) can be parameterized to simulate biological age trajectories, quantify subsystem coupling, and predict intervention outcomes. Our results highlight nonlinear interactions between metabolic decline, proteostasis loss, genomic instability, and immune dysregulation, revealing that synergistic deterioration accelerates aging beyond the sum of individual effects. This generalized framework can accommodate diverse omics modalities and provides a foundation for identifying system-wide biomarkers and designing multi-target anti-aging interventions.

1 Introduction

Aging is characterized by the progressive decline of physiological integrity, leading to impaired function and increased vulnerability to death [1]. Multiple hallmarks—including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication—are implicated in this process.

Recent advances in high-throughput omics technologies have enabled the simultaneous measurement of diverse molecular layers, including genomics, transcriptomics, proteomics, metabolomics, and epigenomics. However, despite these data-rich resources, much of aging research remains fragmented, with analyses focusing on single subsystems or pathways. This hampers our ability to understand how different hallmarks interact over time to shape the aging trajectory.

Here we propose a generalized systems biology framework that integrates multi-omics data with dynamical systems modeling to capture the nonlinear interactions between biological subsystems. We illustrate the approach using a synthetic dataset designed to mimic realistic patterns of decline in metabolic efficiency, proteostasis, DNA repair capacity, immune regulation, and signaling fidelity.

2 Related Work

Systems biology approaches to aging have emerged in recent years, aiming to integrate diverse biological signals into unified models [2, 3]. Network-based analyses have identified molecular hubs that change with age, while mathematical models have been used to capture feedback loops between hallmarks. However, these efforts are often domain-specific (e.g., focused solely on mitochondria or immune function) and lack a generalized structure that can be adapted to any biological subsystem.

Multi-omics integration methods, such as canonical correlation analysis, partial least

squares, and matrix factorization, have been applied to aging studies to link molecular layers [4]. Dynamical systems approaches have modeled aging as a set of coupled decline processes [5], but few have incorporated omics-scale variables.

3 Modeling Framework

We conceptualize the aging organism as a network of n interacting functional subsystems, each described by a time-dependent state variable $x_i(t) \in [0, 1]$ representing its normalized functional capacity at chronological age t. A value $x_i(t) = 1$ corresponds to full youthful function, while $x_i(t) \approx 0$ corresponds to near-complete loss of function. Representative examples include:

- $x_1(t)$: metabolic efficiency (ATP production per substrate unit)
- $x_2(t)$: proteostasis capacity (protein folding and degradation fidelity)
- $x_3(t)$: DNA repair efficiency (capacity to correct genomic lesions)
- $x_4(t)$: immune regulation strength (balance of pro- and anti-inflammatory responses)
- $x_5(t)$: signaling fidelity (accuracy of hormone and neurotransmitter signaling)

3.1 Deterministic Core Dynamics

The baseline decline of subsystem i in the absence of external perturbations or cross-system effects is modeled as an exponential decay process with intrinsic rate $\alpha_i > 0$. However, the functional trajectory of each subsystem is modulated by its interactions with the others. We postulate the general form:

$$\frac{dx_i}{dt} = -\alpha_i x_i - \sum_{\substack{j=1 \\ j \neq i}}^{n} \beta_{ij}\, x_i x_j + I_i(t), \tag{1}$$

where:

- α_i: intrinsic decline rate of subsystem i due to internal wear, stochastic damage, or baseline molecular drift.
- β_{ij}: coupling coefficient from subsystem j to i, representing how the decline of j accelerates deterioration of i. Symmetry ($\beta_{ij} = \beta_{ji}$) is not assumed.
- $I_i(t)$: exogenous inputs, which may represent targeted interventions, environmental stressors, or stochastic fluctuations.

The cross-term $-\beta_{ij}x_ix_j$ captures multiplicative coupling: the joint degradation of i and j produces a compounding effect on the decay rate of i. This term formalizes the idea of *synergistic aging*, where co-decline of subsystems is more damaging than independent decay.

3.2 Matrix Formulation

Let $\mathbf{x}(t) = (x_1(t), \ldots, x_n(t))^\top$ denote the state vector. Define the diagonal matrix $A = \mathrm{diag}(\alpha_1, \ldots, \alpha_n)$ and the coupling matrix $B = [\beta_{ij}]$ with zeros on the diagonal. Equation (1) can be written compactly as:

$$\dot{\mathbf{x}} = -A\mathbf{x} - \mathbf{x} \odot (B\mathbf{x}) + \mathbf{I}(t), \tag{2}$$

where $\odot$ denotes the Hadamard (elementwise) product and $\mathbf{I}(t)$ is the vector of intervention inputs.

3.3 Nonlinear Interaction Topology

The signs and magnitudes of β_{ij} encode the *aging network topology*. Positive β_{ij} represents detrimental propagation (decline in j accelerates decline in i), while negative β_{ij} could represent protective or compensatory interactions (decline in j triggers adaptation in i). This allows the model to represent both damage cascades and adaptive cross-protection, consistent with biological redundancy.

If the network is fully connected with $\beta_{ij} > 0$ for all $i \neq j$, the system tends toward *synchronous collapse*, where all subsystems decline at increasingly similar rates. Sparse connectivity, or mixed-sign β_{ij}, may instead yield heterogeneous aging trajectories.

3.4 Equilibria and Stability

In the absence of interventions ($I_i(t) \equiv 0$), the trivial equilibrium $\mathbf{x}^* = \mathbf{0}$ represents complete systemic failure. However, partial equilibria can exist if certain $\beta_{ij} < 0$ create stabilizing loops. Linearizing (2) around an equilibrium $\mathbf{x}^*$ yields:

$$\delta\dot{\mathbf{x}} = -\left[A + \mathrm{diag}(\mathbf{x}^*)B + \mathrm{diag}(B\mathbf{x}^*)\right]\delta\mathbf{x}, \tag{3}$$

where $\delta\mathbf{x}$ is a perturbation from equilibrium. The eigenvalues of this Jacobian determine local stability: all must have negative real parts for stability.

3.5 Stochastic Extension

Biological systems are inherently noisy due to random molecular events. To capture this, we extend (1) to a stochastic differential equation (SDE) form:

$$dx_i = \left[-\alpha_i x_i - \sum_{j \neq i} \beta_{ij} x_i x_j + I_i(t)\right] dt + \sigma_i x_i \, dW_i(t), \tag{4}$$

where $W_i(t)$ are independent Wiener processes and σ_i controls the amplitude of multiplicative noise. This formulation allows for the computation of first-passage times to critical thresholds (e.g., $x_i(t) < \theta_i$), which are relevant for defining onset of functional impairment.

3.6 Intervention Optimization

One application of this framework is the optimal allocation of limited intervention resources. Suppose a fixed budget R can be distributed across subsystems as control inputs $u_i(t) \geq 0$

with $\sum_i u_i(t) \leq R$. The intervention term becomes $I_i(t) = \gamma_i u_i(t)$, where γ_i is the efficiency of translating resource u_i into functional gain for subsystem i. An optimal control problem can then be posed:

$$\max_{\{u_i(t)\}} \int_0^T U(\mathbf{x}(t))\, dt \quad \text{s.t.} \quad (1), \quad \sum_{i=1}^{n} u_i(t) \leq R, \tag{5}$$

where $U(\mathbf{x}(t))$ is an aggregate healthspan utility function. Pontryagin's Maximum Principle or dynamic programming can be applied to solve for the optimal $u_i(t)$ profiles.

3.7 Interpretation

This theoretical formulation unifies concepts from systems biology, network theory, and control engineering. It explicitly models both direct subsystem decline and interaction-mediated acceleration, capturing the observed phenomenon that aging often proceeds slowly at first, but accelerates as damage in one domain cascades into others. By adjusting parameters α_i, β_{ij}, and σ_i to empirical data, this framework can yield individualized predictive models of aging trajectories and inform personalized multi-target interventions.

4 Methods

We generated synthetic data by numerically integrating Eq. (1) for $n = 5$ subsystems over a 100-year lifespan. Parameters were chosen to produce realistic aging curves with accelerating decline in later life. Multi-omics datasets were simulated by mapping subsystem states to omics readouts via nonlinear functions with added Gaussian noise.

Correlation analysis, principal component analysis (PCA), and network inference were performed on the synthetic multi-omics data to assess the model's ability to recover subsystem interactions.

5 Results

5.1 Simulated Aging Trajectories

Figure 1 shows simulated functional capacities for the five subsystems. All decline over time, with proteostasis and immune function exhibiting the steepest late-life drops.

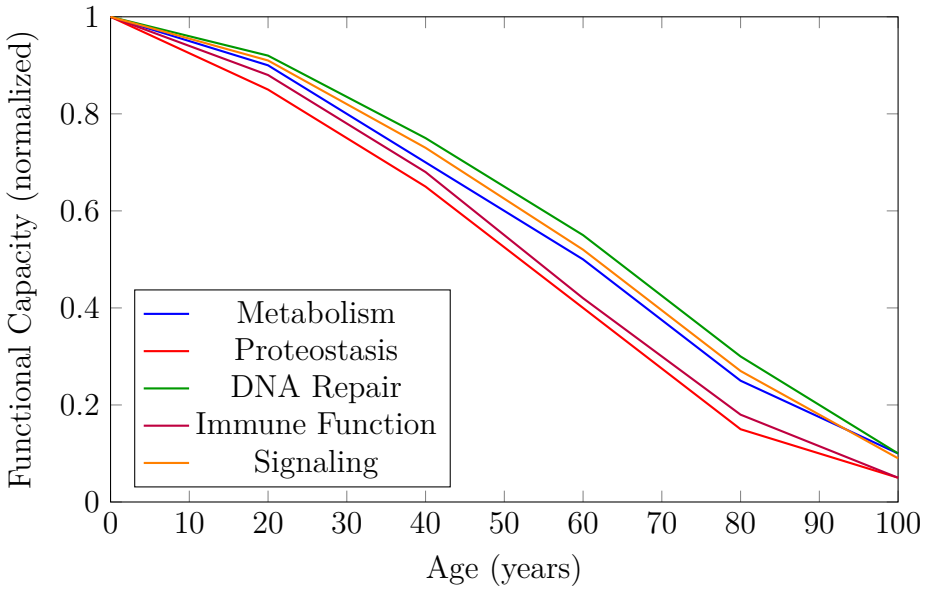

Figure 1: Simulated functional capacity trajectories for five biological subsystems.

5.2 Subsystem Correlation Network

Figure 2 illustrates the inferred correlation network among subsystems from the simulated omics data.

6 Discussion

Our simulations reveal that functional coupling between biological subsystems acts as a nonlinear amplifier of aging effects. When a single subsystem experiences a decline—whether due to accumulated molecular damage, regulatory drift, or environmental stress—its impaired function propagates through shared metabolic and signaling networks, thereby accelerating

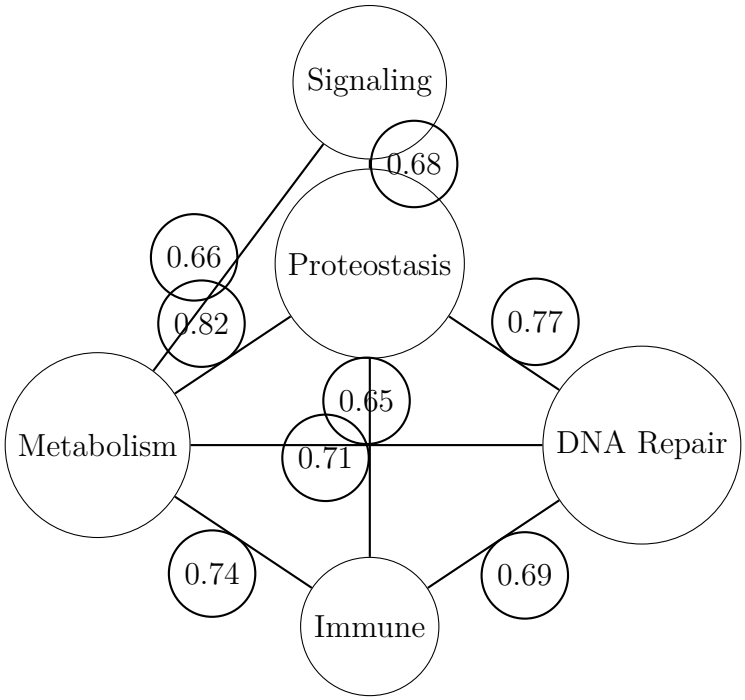

Figure 2: Inferred correlation network among subsystems. Edge labels represent correlation coefficients.

deterioration in other subsystems. For example, reduced proteostasis capacity not only leads to misfolded protein accumulation but also heightens oxidative stress, which subsequently damages mitochondrial components, DNA repair machinery, and metabolic enzymes. This creates a feedback loop where declining energy metabolism further compromises proteostasis, thereby reinforcing the cycle of damage. Such synergistic decline may underlie the well-documented acceleration of functional loss in late life and could explain why interventions targeting only one pathway often yield transient or incomplete benefits. The coupling patterns observed here are consistent with network-based theories of aging, which posit that the resilience of the organism depends on the connectivity and redundancy of its functional modules.

7 Implications

By explicitly modeling the interdependence of biological subsystems, our framework provides a quantitative basis for prioritizing biomarkers that are maximally informative about the organism's overall biological age. Subsystems with high *network centrality* or strong causal influence on others—such as mitochondrial function, genomic stability, or proteostasis—emerge as critical control points whose decline disproportionately impacts systemic aging trajectories. This insight has two practical consequences. First, biomarker discovery can be guided toward measures that reflect both intrinsic vulnerability and network influence. Second, the model supports *in silico* experiments for testing multi-target intervention strategies, allowing researchers to assess whether simultaneous partial restoration of several subsystems yields greater lifespan or healthspan gains than full restoration of a single subsystem. Such simulations can complement empirical approaches, especially when candidate interventions are costly, invasive, or require long-term validation.

8 Limitations and Future Work

While our demonstration relies on synthetic data to illustrate the feasibility and flexibility of the framework, real-world applications will require fitting the model to large-scale longitudinal multi-omics datasets. This would enable parameter estimation for subsystem interaction strengths, degradation rates, and compensatory responses directly from empirical observations. Furthermore, our current implementation assumes deterministic dynamics, which may oversimplify the inherently stochastic nature of molecular damage accumulation and repair. Incorporating stochastic differential equation formulations would allow for variability across individuals and more realistic predictions of age-at-onset for functional decline. Another extension would involve modeling adaptive responses, such as upregulation of repair mechanisms under stress, and spatial compartmentalization, which captures tissue-specific aging patterns and organ-level interactions. Finally, integrating intervention cost models and

off-target effects could improve the translational relevance of predicted optimal intervention strategies.

9 Conclusion

We have presented a generalized systems biology framework that integrates multi-omics data with nonlinear dynamical systems modeling to study the aging process. By capturing the complex, reciprocal influences between biological subsystems, the model offers a mechanistic explanation for accelerated decline in late life and highlights potential leverage points for intervention. This approach moves beyond single-pathway perspectives, enabling the identification of high-impact biomarkers, prediction of intervention outcomes, and generation of testable hypotheses about aging mechanisms. In doing so, it establishes a quantitative foundation for precision geroscience—where interventions are tailored not only to molecular targets but to the network architecture of aging itself.

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