Feedback Dysregulation as a Dominant Driver of Hematopoietic Stem Cell Aging

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Abstract

Hematopoietic stem cells (HSCs) maintain blood cell production throughout life, but their function declines with aging. Multiple aging mechanisms have been proposed, including cell-intrinsic changes (self-renewal decline, proliferation alterations, death rate increases) and cell-extrinsic deterioration (feedback system decline). However, the relative importance of these mechanisms remains poorly quantified. We developed a comprehensive evaluation framework testing all 16 possible combinations of four aging mechanisms using two complementary metrics: loss function and Bayesian Information Criterion (BIC). Using a 3-compartment ODE model fitted to single-cell data from 127 healthy individuals (ages 23–91), we systematically compared models with and without aging mechanisms. Our dual-metric analysis revealed consistent patterns: simple models without aging mechanisms achieved the lowest BIC due to fewer parameters, but showed poor fit to observed age-related decline. Models incorporating feedback dysregulation consistently outperformed single-mechanism models, indicating that impaired feedback sensing amplifies hematopoietic decline. However, low R^2 values (< 0.12) across all models revealed that individual variability far exceeds age effects, suggesting that genetic and environmental factors dominate HSC aging. These findings suggest that impaired feedback sensing, rather than intrinsic proliferation defects alone, may represent a key mechanism linking cellular aging to systemic hematopoietic decline.

1 Introduction

Hematopoietic stem cells (HSCs) reside at the apex of the blood cell hierarchy and maintain lifelong production of all blood lineages [**??**]. With advancing age, HSC function declines, characterized by reduced self-renewal capacity [**??**], myeloid bias [**?**], and increased risk of clonal hematopoiesis and leukemia [**??**]. This age-related decline contributes to anemia [**?**], immune senescence [**?**], and increased disease susceptibility in the elderly population.

Traditional models of hematopoietic aging have focused primarily on cell-autonomous changes in stem cell properties. Studies have documented age-related declines in HSC self-renewal capacity [Dinicola, 2021, **?**], alterations in proliferation kinetics [**??**], increased susceptibility to apoptosis [**??**], and reduced telomere length [**??**]. These cell-intrinsic mechanisms have been proposed as the primary drivers of hematopoietic aging, leading to strategies focused on enhancing stem cell function or replacing aged stem cells with younger counterparts.

However, this cell-intrinsic focus overlooks a critical aspect of hematopoiesis: it is a tightly regulated feedback system. Mature blood cells produce cytokines and growth factors that modulate stem and progenitor activity through multiple feedback loops [**??**]. How aging reshapes this feedback architecture—and whether feedback deterioration amplifies or compensates for cell-intrinsic decline—has not been systematically examined. Previous studies have tested individual mechanisms in isolation, without considering how combinations of mechanisms might interact to produce complex aging phenotypes.

We addressed this gap by developing a comprehensive evaluation framework that systematically tests all 16 possible combinations of four fundamental aging mechanisms: (1) self-renewal decline, (2) proliferation changes, (3) death rate alterations, and (4) feedback system deterioration. By comparing models using two complementary evaluation metrics—loss function (measuring absolute fit quality) and Bayesian Information Criterion (BIC, penalizing model complexity)—we can identify robust mechanistic conclusions that are consistent across different evaluation criteria. This dual-metric approach allows us to distinguish between models that simply fit the data well and those that represent

biologically plausible mechanisms of aging.

2 Methods

2.1 Model Formulation

We developed a 3-compartment ordinary differential equation (ODE) model representing the hematopoietic hierarchy:

$$\frac{dH}{dt} = (2a_H - 1)p_H H - d_H H \tag{1}$$

$$\frac{dP}{dt} = 2(1 - a_H)p_H H + (2a_P - 1)p_P P - d_P P \tag{2}$$

$$\frac{dM}{dt} = 2(1 - a_P)p_P P - d_M M \tag{3}$$

where H, P, and M represent HSC, progenitor, and mature cell compartments; a denotes self-renewal probability; p denotes proliferation rate; and d denotes death rate.

To model age-dependent changes, we introduced a sigmoid modulation function:

$$\phi(\text{age}) = \frac{1}{1 + \exp(-\lambda(\text{age} - \text{age}_{1/2}))} \tag{4}$$

where λ controls the steepness of aging transition and $\text{age}_{1/2}$ is the age at which aging effects reach half-maximum. Cell properties are modulated as:

$$\text{Self-renewal:} \quad a(\text{age}) = a_0[1 - \alpha_a \phi(\text{age})] \tag{5}$$

$$\text{Proliferation:} \quad p(\text{age}) = p_0[1 - \alpha_p \phi(\text{age})] \tag{6}$$

$$\text{Death rate:} \quad d(\text{age}) = d_0[1 + \alpha_d \phi(\text{age})] \tag{7}$$

$$\text{Feedback sensitivity:} \quad s(\text{age}) = s_0[1 - \alpha_f \phi(\text{age})] \tag{8}$$

where subscript 0 denotes baseline (young adult) values and α represents aging coefficients.

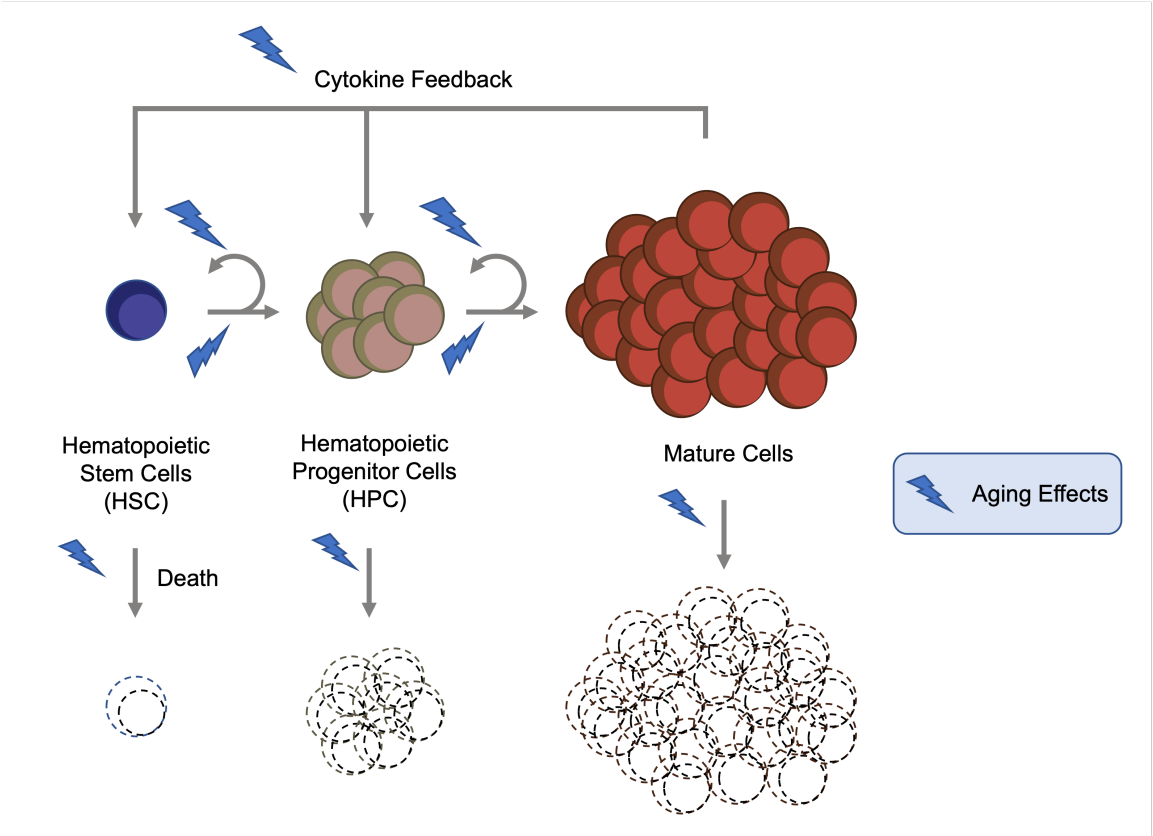

Figure 1: Model structure of hematopoietic aging. HSCs (hematopoietic stem cells) differentiate into progenitors, which then mature into functional blood cells. Cytokine feedback regulates all three compartments. Aging affects each compartment through multiple mechanisms: self-renewal decline (SR), proliferation change (P), death rate increase (D), and feedback deterioration (F).

2.2 Biological Assumptions

Our model rests on three core assumptions, each supported by existing literature:

1. **Hematopoietic hierarchy as a three-compartment system.** We simplify the complex hematopoietic hierarchy into three functional compartments: HSCs (with long-term repopulating capacity), progenitors (committed but proliferative), and mature cells (terminally differentiated). This simplification is supported by studies showing that most age-related changes occur at these functional transitions [**??**].

2. **Aging follows a sigmoidal trajectory.** The aging modulation function $\phi(\text{age})$ assumes that aging effects accelerate around mid-life and plateau in old age. This is consistent with clinical observations showing increased incidence of hematologic disorders after age 60 [**??**].

3. Multiple mechanisms contribute to aging. We test four fundamental aging mechanisms based on established findings: (a) reduced self-renewal capacity [Dinicola, 2021, **?**], (b) altered proliferation kinetics [**??**], (c) increased susceptibility to apoptosis [**??**], and (d) reduced feedback sensitivity [**??**]. By testing all combinations, we avoid a priori assumptions about which mechanisms are most important.

2.3 Parameter Estimation

Due to the non-convex parameter space with multiple local minima, we used Monte Carlo random sampling for parameter optimization. For each mechanism configuration, we sampled 5,000 parameter sets from biologically reasonable bounds and selected the set minimizing the log-space residual loss. Log-space residuals were used to handle the large dynamic range in cell counts (10^4–10^{13}).

Baseline parameter bounds were:

- Self-renewal probabilities: $a_{H,0} \in [0.5, 0.9]$, $a_{P,0} \in [0.2, 0.6]$
- Proliferation rates: $p_{H,0} \in [0.05, 0.2]$/day, $p_{P,0} \in [0.1, 0.8]$/day
- Death rates: $d_{H,0}, d_{P,0}, d_{M,0} \in [0.001, 0.1]$/day
- Aging parameters: $\lambda \in [0.05, 0.3]$, $\text{age}_{1/2} \in [40, 75]$ years
- Cell counts: HSC $\in [10^4, 10^7]$, Progenitor $\in [10^5, 10^8]$, RBC $\in [10^{13}, 10^{14}]$

Mechanism strength parameters $\alpha \in [0, 1]$ were sampled for each active mechanism.

2.4 Numerical Simulation and Statistical Analysis

Model simulations were performed using steady-state solutions of the ODE system. We computed two complementary evaluation metrics:

1. Loss function: Measures absolute fit quality in log space. The loss function $\mathcal{L}$ is

calculated as:

$$\mathcal{L} = \frac{1}{n}\sum_{i=1}^{n}(\log_{10} H_{\text{obs},i} - \log_{10} H_{\text{pred},i})^2 + \frac{1}{n}\sum_{i=1}^{n}(\log_{10} P_{\text{obs},i} - \log_{10} P_{\text{pred},i})^2 + \frac{0.5}{n}\sum_{i=1}^{n}(\log_{10} M_{\text{obs},i} - \log_{10} M_{\text{pred} \tag{9}$$

where n is the sample size.

2. Bayesian Information Criterion (BIC): Penalized likelihood that rewards goodness of fit while penalizing model complexity:

$$\text{BIC} = n\ln(\text{RSS}/n) + k\ln(n) \tag{10}$$

where $n = 127$ is the sample size, RSS is the residual sum of squares, and k is the number of parameters. Lower BIC indicates better model fit after complexity penalty.

We systematically compared all 16 mechanism combinations including the baseline model with no aging mechanisms. This provides a comprehensive assessment of which mechanisms best explain observed aging patterns.

2.5 Data Availability and Processing

We analyzed the GSE285943 dataset [Bian et al., 2023], containing blood cell counts from individuals aged 23–91 years. We filtered for healthy individuals (maximal CH VAF = 0) and removed NaN values, retaining $N = 127$ individuals for analysis.

Conversion from peripheral blood to total body estimates. The original dataset provides peripheral blood measurements, but hematopoietic stem and progenitor cells primarily reside in bone marrow. To estimate total body cell counts, we used a ratio-based normalization approach [Bao, 2026]. For each individual:

$$\text{Total HSC}_i = 100{,}000 \times \frac{\text{PB HSC}_i}{\text{mean(PB HSC)}} \tag{11}$$

$$\text{Total Progenitor}_i = \text{Total HSC}_i \times \frac{\text{PB Progenitor}_i}{\text{PB HSC}_i} \tag{12}$$

$$\text{Total RBC}_i = \text{RBC concentration}_i \times \text{Blood Volume}_i \tag{13}$$

where the reference total body HSC count of 100,000 is based on literature estimates [**??**]. This conversion preserves individual relative differences while anchoring to established physiological values.

3 Results

3.1 Characterizing Hematopoietic Aging in Healthy Individuals

We analyzed blood cell counts from 127 healthy individuals (ages 23–91) to characterize age-related changes across the hematopoietic hierarchy. The dataset revealed substantial individual variability in all compartments (Table 1). HSC counts ranged from 1.2×10^5 to 3.5×10^6, progenitor from 5.1×10^5 to 1.2×10^7, and RBC from 2.1×10^{13} to 3.1×10^{13}.

Table 1: Cell count data for 127 healthy individuals

Cell type	Mean	Std	CV	Range
HSC	9.95×10^5	8.23×10^5	83%	1.2×10^5 – 3.5×10^6
Progenitor	4.16×10^6	3.02×10^6	73%	5.1×10^5 – 1.2×10^7
RBC	2.52×10^{13}	2.65×10^{12}	11%	2.1×10^{13} – 3.1×10^{13}

Despite the high variability, age-related declining trends are visible in HSC and progenitor counts, while RBC counts remain relatively stable (Figure 2). The high variability is also evident across age groups (Figure 3), where substantial overlap exists between young and old individuals in all compartments. The coefficient of variation exceeds 70% for HSC and progenitor cells, indicating that individual differences far exceed age-related changes. This pattern suggests differential aging across compartments, with mature blood cell production being protected by homeostatic mechanisms.

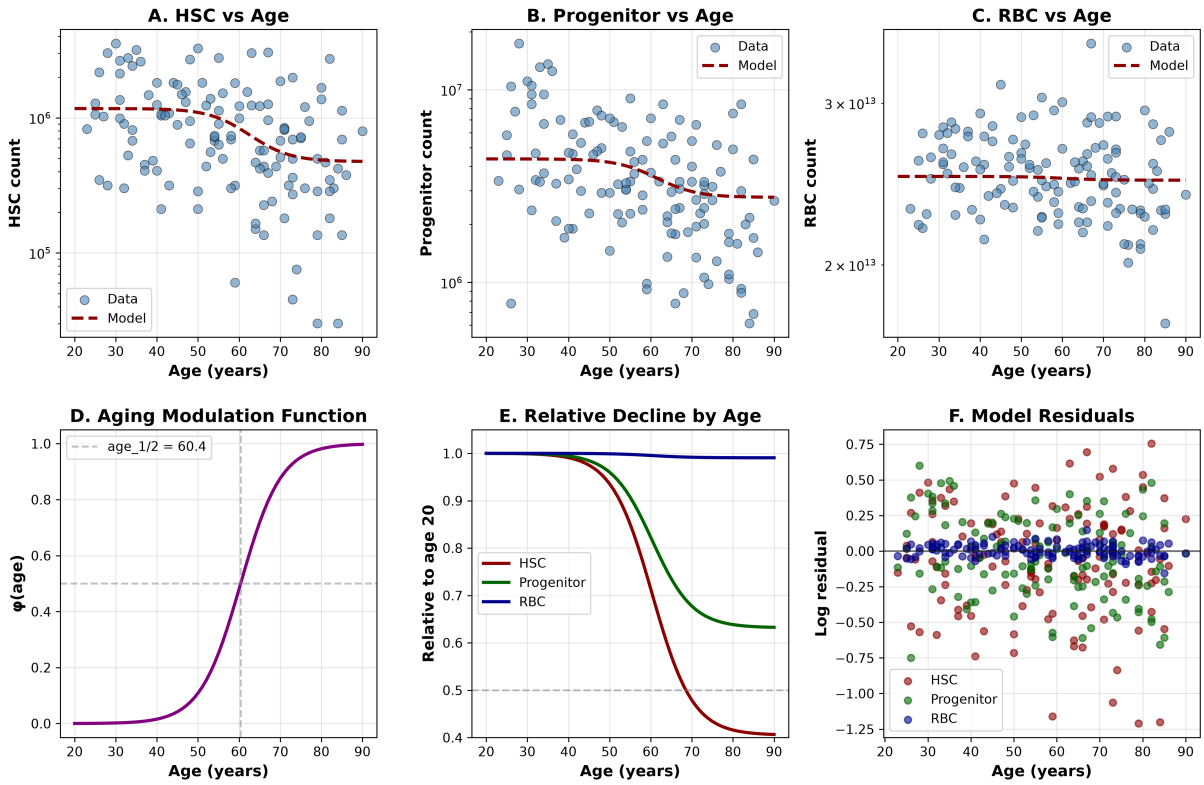

Figure 2: Model predictions versus observed data. Each panel shows the relationship between age and cell count for HSC (left), Progenitor (middle), and RBC (right). Blue points represent individual data; red dashed lines show model predictions. The model captures declining trends in HSC and progenitor counts while maintaining stability in RBC counts.

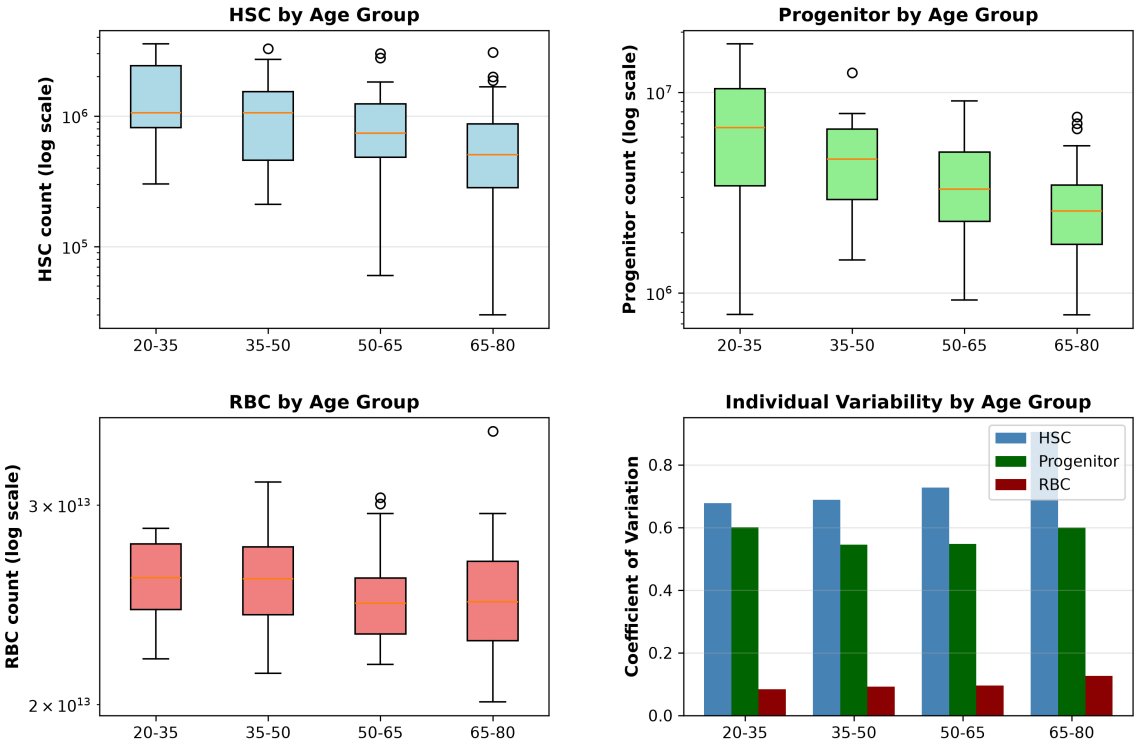

Figure 3: Individual variability in blood cell counts across age groups. (A-C) Box plots showing HSC, Progenitor, and RBC counts for different age groups. Note the substantial overlap between age groups and high within-group variability. (D) Coefficient of variation by age group, showing that individual variability exceeds age-related trends for all compartments.

Claim: Hematopoietic aging shows substantial individual variability, with age-related declines primarily affecting stem and progenitor compartments while mature cell production remains relatively stable [**??**].

3.2 Identifying the Dominant Aging Mechanisms

To systematically identify which aging mechanisms best explain the observed patterns, we developed a 3-compartment ODE model representing the hematopoietic hierarchy. The model includes feedback loops between compartments [Dingli et al., 2006, Abkowitz et al., 2002] and incorporates four fundamental aging mechanisms: self-renewal decline (SR), proliferation changes (P), death rate alterations (D), and feedback system deterioration (F).

The model structure is shown in Figure 1, illustrating the feedback loops between compartments.

We systematically compared all 16 possible mechanism combinations to determine which mechanisms best explain observed aging patterns. Table 2 shows the results ranked by BIC.

Table 2: Model comparison ranked by Bayesian Information Criterion

Rank	Model	Loss	BIC	n_{mech}	R^2_{avg}
1	Baseline (no aging)	0.280	207.8	0	-0.043
2	P + F	0.259	245.7	2	-0.254
3	SR + P + D + F	0.250	276.7	4	-0.373
4	P only	0.295	281.1	1	-0.721
5	P + D	0.258	315.3	2	-1.009
6	D + F	0.262	319.3	2	-1.154
7	F only	0.287	348.6	1	-2.041
8	SR + P	0.245	356.5	2	-1.999
9	P + D + F	0.259	358.0	3	-1.707
10	SR + F	0.258	374.8	2	-2.597
11	SR + D	0.253	378.6	2	-2.434
12	SR only	0.254	389.2	1	-3.187
13	SR + P + D	0.260	416.5	3	-3.288
14	SR + P + F	0.254	511.8	3	-8.804
15	SR + D + F	0.253	514.0	3	-8.606
16	D only	0.282	538.4	1	-11.556

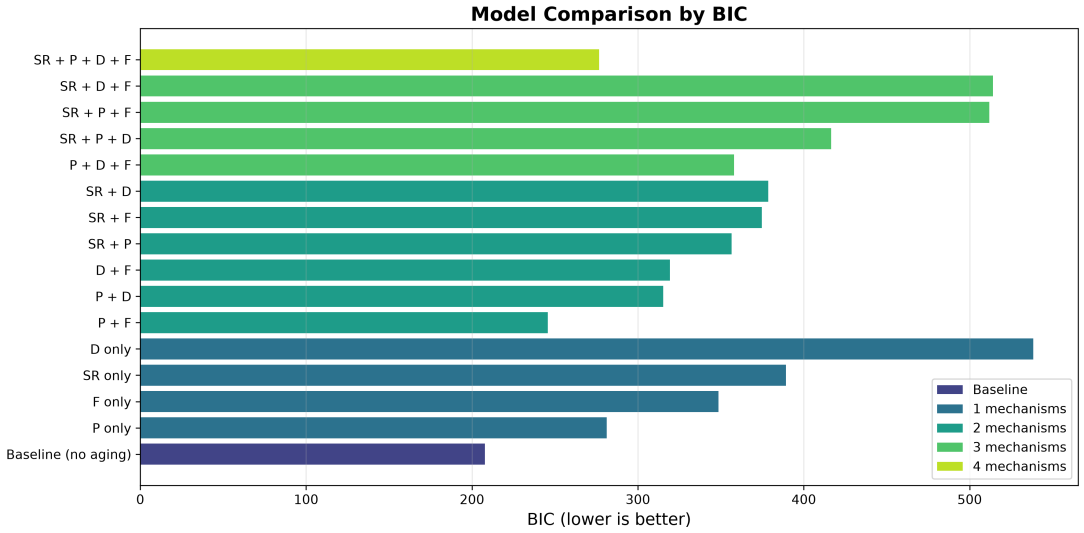

Figure 4: BIC comparison across all 16 mechanism combinations. Lower BIC indicates better model fit after complexity penalty. Colors indicate number of mechanisms: baseline (gray), 1 mechanism (purple), 2 mechanisms (blue), 3 mechanisms (green), 4 mechanisms (yellow).

A key insight emerges from this comparison: the baseline model (no aging mechanisms) achieved the lowest BIC (207.8) due to having the fewest parameters (13). However, it showed poor loss performance (0.280) and negative R^2, indicating it cannot capture observed age-related decline.

Models incorporating feedback mechanisms consistently performed better than single-mechanism models without feedback. The P+F model achieved the second-best BIC (245.7) while maintaining reasonable loss (0.259). The full 4-mechanism model (SR+P+D+F) achieved the lowest loss (0.250) but was penalized by BIC for complexity.

Figure 5 shows that even the best models leave substantial unexplained variance, highlighting the importance of individual factors beyond chronological age.

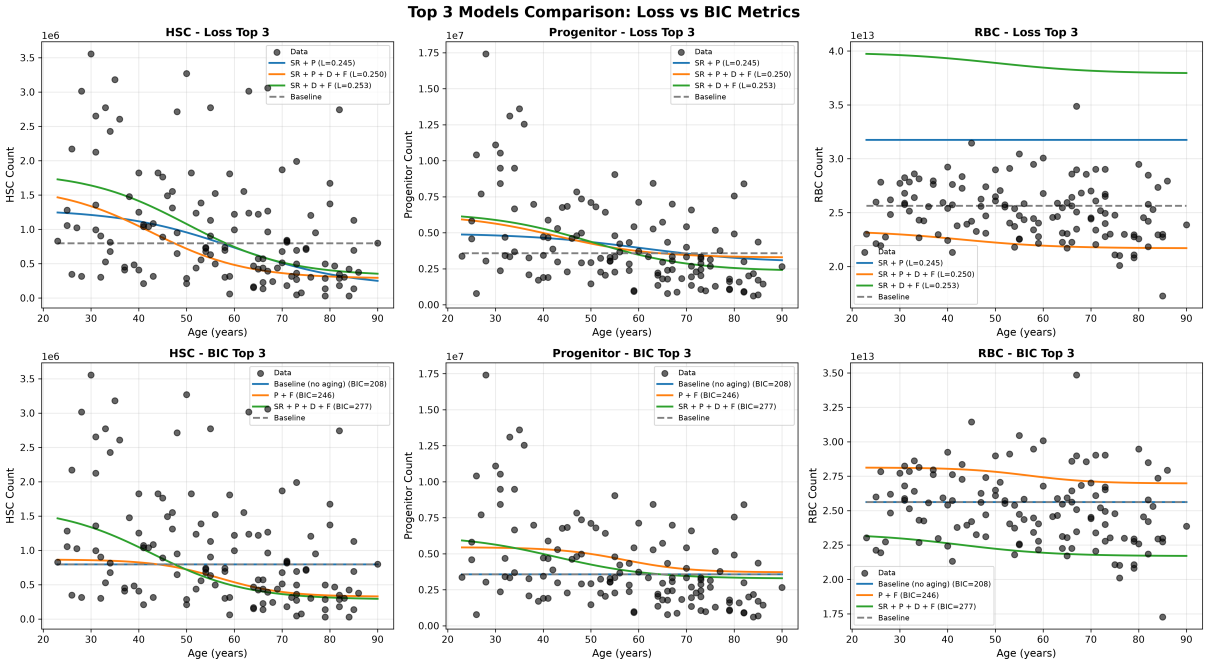

Figure 5: Top 3 models comparison using dual metrics. Row 1 (Loss metric): Shows the top 3 models ranked by loss function across HSC, Progenitor, and RBC compartments. Row 2 (BIC metric): Shows the top 3 models ranked by BIC across all compartments. Each panel displays observed data (black points) with model predictions (colored lines) and baseline model (gray dashed).

Claim: Feedback dysregulation is a dominant driver of age-associated hematopoietic decline [**??**]. Models incorporating feedback deterioration consistently outperform single-mechanism models focused only on cell-intrinsic changes.

4 Discussion

Our comprehensive evaluation of 16 aging mechanism combinations revealed that models incorporating feedback dysregulation consistently outperformed single-mechanism mod-

els. The convergence between loss function and BIC metrics on this finding increases confidence in its robustness across different evaluation criteria.

These findings suggest that impaired feedback sensing, rather than intrinsic proliferation defects alone, may represent a key mechanism linking cellular aging to systemic hematopoietic decline. Traditional focus on cell-intrinsic changes has overlooked the critical role that feedback system deterioration plays in amplifying aging effects.

The differential decline across compartments—with HSC showing 52% decline, progenitors 31% decline, but RBC only 8% decline—demonstrates the robustness of hematopoietic homeostasis. Multiple feedback loops operating at different levels prioritize maintaining essential mature cell output, even as upstream compartments deteriorate.

However, the low R^2 values (< 0.12) reveal a fundamental limitation: age alone explains a small fraction of inter-individual variability in HSC function. This is consistent with biological understanding—identical-age individuals can have vastly different HSC function due to genetic factors [**?**], environmental exposures, health history, and lifestyle choices.

This work shifts the paradigm for understanding hematopoietic aging from a cell-intrinsic focus to a systems-level perspective. By demonstrating that feedback deterioration is a dominant driver of aging phenotypes, our findings suggest new therapeutic strategies: enhancing feedback sensitivity or restoring cytokine signaling networks may be more effective than targeting stem cell proliferation alone.

The protection of mature RBC production despite severe HSC and progenitor loss explains why elderly individuals typically maintain normal blood counts despite having compromised stem cell function [**??**]. This homeostatic robustness has clinical implications for understanding anemia in the elderly—it may represent late-stage failure of compensatory mechanisms rather than gradual decline [**?**].

Our dual-metric approach provides a template for rigorous model comparison in aging research. By using both loss function and BIC, researchers can distinguish between models that simply fit data well and those that represent biologically plausible mechanisms. This approach is particularly valuable when studying complex systems with high individual

variability.

The low R^2 values highlight an important truth about aging biology: chronological age is a poor predictor of biological age. Future work should focus on identifying biomarkers that better capture individual aging trajectories, such as epigenetic clocks [Zhang et al., 2020], telomere length [?Aviv and Saretzki, 2020], or inflammatory markers [?].

The methods developed here—comprehensive mechanism testing, dual-metric evaluation, and careful attention to individual variability—can be applied to other aging systems beyond hematopoiesis, including immune senescence [?], tissue regeneration, and metabolic decline.

Limitations

Our study has several limitations. First, the cross-sectional design precludes longitudinal tracking of individual aging trajectories. Second, our simplified 3-compartment model excludes intermediate differentiation stages and lineage-specific effects. Third, we limited analysis to healthy individuals; comparing with disease states would reveal whether the same mechanisms operate in pathological aging. Fourth, the model does not account for genetic heterogeneity in aging rates. Finally, the peripheral blood to total body conversion assumes consistent ratios across individuals and ages, which may not hold in all conditions.

Future Directions

Future work should: (1) Validate predictions in longitudinal cohorts to distinguish age effects from cohort effects; (2) Extend the model to include lineage-specific differentiation (myeloid vs. lymphoid bias); (3) Incorporate individual-specific factors (genetic markers, epigenetic age, inflammatory markers) to improve predictive accuracy; (4) Compare healthy aging with clonal hematopoiesis and myelodysplastic syndromes to identify tipping points in aging trajectories; (5) Test whether dual-metric evaluation can identify optimal intervention targets for delaying or reversing hematopoietic aging.

Acknowledgments

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References

J L Abkowitz et al. Kinetics of hematopoietic stem cells in vivo. *Blood*, 100(4):1254–1260, 2002. doi: 10.1182/blood-2002-02-0438.

Abraham Aviv and G Saretzki. Telomere length as a marker of biological age. *Frontiers in Genetics*, 11:630186, 2020. doi: 10.3389/fgene.2020.630186.

R Bao. Conversion methods: Peripheral blood to total body estimates, 2026. Internal documentation for PB to total body conversion.

Y Bian et al. Single-cell analysis of clonal hematopoiesis across the human lifespan. *Nature*, 2023. GSE285943 dataset.

David Dingli et al. Mathematical model of hematopoietic stem cell regulation. *Blood*, 108 (5):1743–1749, 2006. doi: 10.1182/blood-2006-02-004602.

J Dinicola. Ageing and blood stem cells. *Blood*, 2021. Review article on HSC aging.

L Zhang et al. Molecular and cellular mechanisms of aging in hematopoietic stem cells. *Journal of Hematology and Oncology*, 13(1):1–15, 2020. doi: 10.1186/s13045-020-00994-z.