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Epigenetic Noise and Regulatory Entropy in Aging: A Quantitative Systems-Level Framework

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ABSTRACT: Aging is characterized by progressive functional decline and increased susceptibility to chronic disease. While directional epigenetic drift has been extensively documented, accumulating single-cell evidence indicates that aging is also associated with increased stochastic variability in chromatin states and gene expression. Here, we propose a quantitative systems-level framework in which epigenetic noise—defined as non-adaptive stochastic dispersion in regulatory states—contributes to aging by increasing regulatory entropy within gene regulatory networks. We formalize regulatory entropy using information-theoretic and network-based metrics, distinguish biological from technical variability, and outline experimentally testable predictions. Integrating single-cell atlases with methylation entropy, chromatin topology, and disease-associated datasets, we argue that rising regulatory entropy progressively destabilizes cellular identity and network coherence. This framework provides a complementary systems-level perspective on aging biology and suggests that preserving regulatory precision may represent a unifying strategy for extending healthspan.

Keywords: epigenetic noise, regulatory entropy, aging, chromatin architecture, transcriptional variability, systems biology

1. Introduction

The hallmarks of aging framework established a mechanistic taxonomy of aging drivers, including genomic instability, telomere attrition, mitochondrial dysfunction, epigenetic alterations, loss of proteostasis, and cellular senescence [1]. Among these, epigenetic remodeling has emerged as a central and potentially reversible component [2–4].

Most studies emphasize directional changes in mean DNA methylation or histone modification states, commonly termed epigenetic drift [2–4]. However, single-cell transcriptomic and methylomic atlases reveal an additional dimension: increased cell-to-cell dispersion in regulatory states during aging [5–10].

Early evidence of increased transcriptional heterogeneity in aged tissues has been reinforced by multi-organ atlases demonstrating age-associated

increases in transcriptional variance even within phenotypically homogeneous populations [11,12]. These findings suggest that aging involves not only shifts in regulatory setpoints but also a progressive decline in regulatory precision.

2. Operational Definition of Epigenetic Noise

Epigenetic noise is defined as stochastic, non-adaptive dispersion in DNA methylation, histone modifications, chromatin accessibility, and transcriptional output across comparable cells, after controlling for cell identity, cell cycle stage, environmental exposure, and technical variance.

This definition distinguishes noise from directional drift, adaptive heterogeneity, and programmed differentiation variance (Fig. 1).

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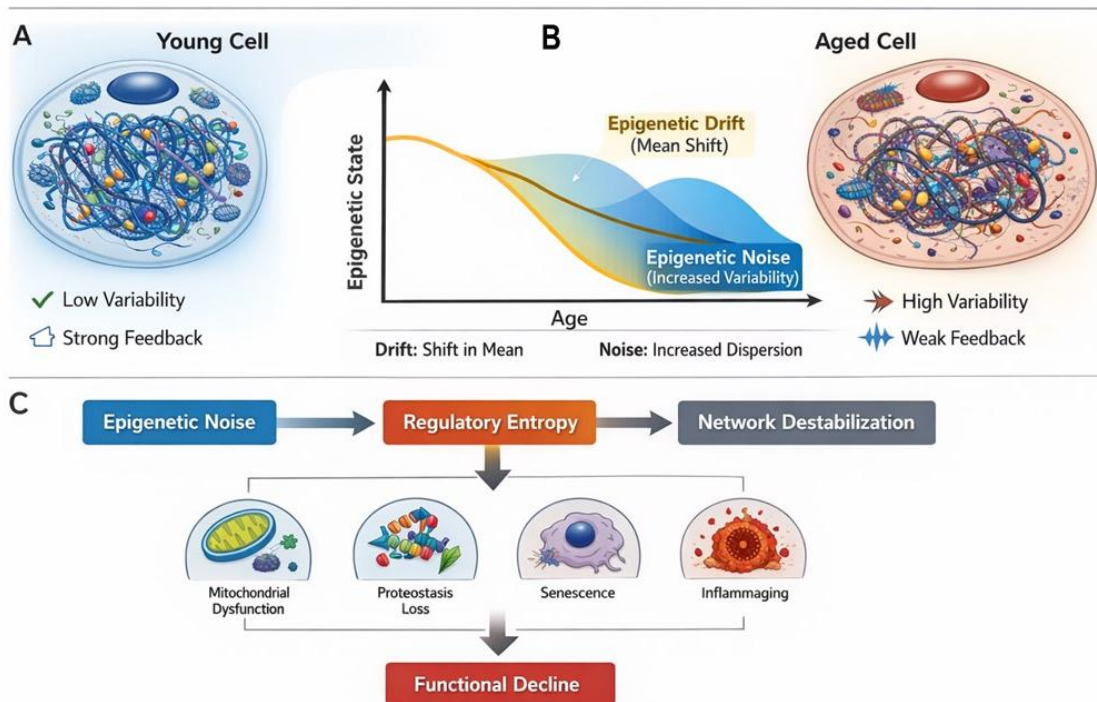


Figure 1. Epigenetic noise as a system-level driver of aging. (A) Young cells maintain low epigenetic variability through compact chromatin architecture, stable enhancer–promoter interactions, and robust feedback loops integrating transcriptional regulatory circuits and mitochondrial bioenergetic control mechanisms. Aging weakens these constraints, leading to relaxed chromatin, impaired regulatory buffering, and increased stochastic variability. (B) Conceptual distinction between epigenetic drift and epigenetic noise. Drift reflects directional changes in mean epigenetic states, whereas noise represents increased dispersion around those means. (C) Proposed systems-level model in which rising epigenetic noise increases regulatory entropy, destabilizes gene regulatory networks, and contributes to hallmark aging phenotypes, ultimately leading to functional decline.

2.1. Biological versus Technical Variability

Single-cell datasets are susceptible to dropout effects, amplification bias, and batch effects [5,6]. Modern variance decomposition approaches allow estimation of intrinsic biological dispersion [6,13]. Importantly, increased variability observed in aging tissues persists after rigorous technical correction, supporting a biological origin [5,7,8].

3. Quantifying Regulatory Entropy

3.1. Gene-Level Shannon Entropy

For a gene with expression probability distribution p_i , Shannon entropy is defined as:

$$H = -\sum p_i \log(p_i)$$

Aging-associated broadening of expression distributions increases H [5,14].

3.2. DNA Methylation Entropy

For methylated (m) and unmethylated (u) states:

$$H_{\text{CpG}} = -[p_m \log(p_m) + p_u \log(p_u)]$$

Information-theoretic analyses demonstrate age-associated increases in methylation entropy independent of mean methylation changes [15,16]. Epigenetic clock models capture mean methylation shifts but do not explicitly incorporate entropy-based dispersion [2].

3.3. Network Entropy

Network entropy quantifies uncertainty in regulatory interactions within gene regulatory networks [17–19]. Increased entropy reflects weakened attractor stability in regulatory landscapes and greater phenotypic variability. Aging-associated increases in network entropy are consistent with progressive destabilization of regulatory coherence [17].

4. Mechanistic Drivers of Rising Entropy

4.1. Chromatin Topology Alterations

Age-associated weakening of three-dimensional genome compartmentalization has been documented in Hi-C datasets [20,21]. Loss of topologically associating domain boundary strength may reduce insulation fidelity and increase transcriptional variability.

4.2. Histone Recycling Fidelity

Replication-associated dilution and imperfect recycling of histone marks contribute to stochastic epigenetic variability [22].

4.3. Mitochondrial Heterogeneity

Mitochondrial and metabolic stochasticity may amplify epigenetic instability through redox-sensitive chromatin remodeling pathways [23,24].

4.4. Feedback Loop Destabilization

Noise within transcription factor circuits propagates nonlinearly across regulatory networks, amplifying entropy at the systems level [9,17].

5. Bidirectional Systems Model

Primary molecular damage, including DNA lesions and mitochondrial dysfunction, reduces regulatory buffering capacity. Reduced buffering increases chromatin accessibility variance and transcriptional dispersion [5,10]. Increased dispersion elevates regulatory entropy [17–19], destabilizing cellular identity and facilitating state transitions. Entropy amplification may further impair mitochondrial function and proteostasis, forming a reinforcing feedback loop [23,24].

6. Disease Implications

6.1. Neurodegeneration

Increased neuronal heterogeneity may precede vulnerability to pathological protein aggregation.

6.2. Cancer

Elevated signaling entropy increases phenotypic plasticity and the probability of oncogenic state transitions [17].

6.3. Immune Aging

Age-associated immune dispersion aligns with inflammaging models [25].

6.4. Metabolic Disease

Transcriptional variance in metabolic tissues correlates with dysregulated glucose and lipid homeostasis.

7. Testable Predictions

This framework generates several experimentally testable predictions. First, longitudinal increases in regulatory entropy may precede frailty progression. Second, entropy metrics may correlate more strongly with functional decline than mean methylation age. Third, interventions that reduce entropy may restore attractor stability. Finally, entropy-based biomarkers may improve prediction of physiological resilience.

8. Methodological Considerations

Key challenges include distinguishing adaptive heterogeneity from stochastic noise, establishing longitudinal single-cell datasets, standardizing entropy metrics, and ensuring cross-platform reproducibility.

9. Therapeutic Implications

Interventions shown to modulate epigenetic age [2,12] may act partially through entropy compression. Future therapies may aim to restore regulatory precision rather than solely reverse mean methylation drift.

10. Conclusion

Aging can be conceptualized as a progressive loss of regulatory precision measurable as rising regulatory entropy. Integrating information theory with single-cell genomics provides a quantitative framework linking stochastic variability to systemic decline. Preserving regulatory coherence may represent a unifying systems-level strategy for extending healthspan.

Conflict of Interest

The authors declare no conflict of interest.

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