Qeios

Peer Review

Review of: "Aging as Cybernetic Attractor Decay: Beyond the Stochastic-Programmed Dichotomy"

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This is a valuable and interesting work to integrate the longstanding stochastic vs. programmed debate via a cybernetic framework.

My key comments are summarized below.

1. Recent literature could be discussed. There are two recent, relevant empirical studies that speak directly to this perspective:

Tarkhov, A. E. et al. ***Nature Aging*** **(2024).** This study, using single-cell DNA methylation data, distinguishes between co-regulated and stochastic CpG sites during aging. Their finding of a major stochastic component alongside coordinated changes directly parallels and could support your argument for a structured, quasi-programmatic decay of regulatory architectures.

Tong, H. et al. ***Nature Aging*** **(2024).** This paper quantifies the stochastic component of popular epigenetic clocks, estimating that a stochastic process can explain a large fraction (66-90%) of their predictive accuracy. This provides a quantitative benchmark for your argument.

2. The cybernetic attractor framework is conceptually appealing, but it remains somewhat abstract. Could you more explicitly bridge the computational concepts with biological mechanisms? For example, how would the entropy increase in a gene regulatory network for stress response differ mechanistically and in its phenotypic consequences from entropy increase in a network governing metabolic homeostasis? What specific predictions would your framework make about the patterns of gene expression or methylation changes in these different networks? Or, could you propose specific intervention strategies?

doi.org/10.32388/SKL4AI

3. Similarly, what defines a "computational attractor" in molecular terms? Is it a specific combination of transcription factors, a particular chromatin state, or a stable pattern of network interactions?

4. While this may extend beyond the immediate theme, I am interested in whether comparative evidence from other species could inform or challenge the model.

Declarations

Potential competing interests: No potential competing interests to declare.