EnM OPEN ACCESS
ENDOCRINOLOGY AND METABOLISM

Editorial

Endocrinol Metab 2025;40:876-878
https://doi.org/10.3803/EnM.2025.2719
pISSN 2093-596X · eISSN 2093-5978

Aging as Entropy: A Quantifiable Framework

Namki Hong[1], Alan A. Cohen[2]

[1]Division of Endocrinology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Environmental Health Sciences, Butler Columbia Aging Center, Mailman School of Public Health, Columbia University, New York, NY, USA

Quantifying the aging process is one of the most important tasks of aging biology and geroscience [1]. Reliable measures of aging would allow rigorous evaluation and comparison of interventions, which remains a major unmet need [2]. The framework to quantify aging needs to be based on the understanding of aging process [3]. While the mechanisms and definition of aging remain controversial [4], there is increasing recognition that aging involves stochastic accumulation of molecular and higher-order damage due to infidelity of repair and maintenance systems [5]. Entropy can be understood variously as the disorder, randomness, lack of structure, lack of complexity, or loss of information in a system. The accumulation of stochastic damage thus equates to increasing entropy in biological systems with time, following the second law of thermodynamics [6,7]. Entropy can generate feedback effects across levels, accelerating the process. Molecular entropy in cells could lead to tissue dysfunction, or entropy in endocrine networks due to chronic stress could lead to molecular damage, leading to deviation from homeostasis and dysfunction at organ and organismal levels. For example, molecular entropy (DNA damage, oxidative stress, etc.) drives chronic inflammation in muscle, liver, and adipose tissue cells, triggering insulin resistance and a sustained, oscillatory elevation in blood glucose (entropy in endocrine networks) [8,9]. The resulting vascular injury and progressive dysfunction of the heart, eyes, brain, skeletal muscle, and kidneys (entropy in organ and organismal levels) then reinforce the process, creating a self-amplifying loop of entropy from molecules to systems [9]. This viewpoint, aging as entropy, provides unique advantages for a framework to quantify the aging process. Entropy of certain traits can be quantified using reliable proxies across multiple layers from genome to protein dysregulation to organ dysfunction in biological organisms. This framework does not rely on the identification of specific etiologies; it nonetheless incorporates them in a broader systemic context.

Several methods have been proposed to measure entropy in biological systems (Fig. 1). Information entropy (Shannon entropy) is higher when a distribution of values has greater variance [10]. Calculation of information entropy requires a distribution of values from multiple measurements within an individual. When individuals have single value for a variable, Mahalanobis distance (D_M) can be used as an appropriate proxy to measure entropy [11,12]. D_M measures how far an individual has deviated from norm (centroid) across multiple variables, considering correlation between variables at the same time [12]. Another term, homeostatic dysregulation index as log-transformed D_M, has been increasingly used in related research [11,13]. Whether information entropy and D_M are fully interchangeable measures of entropy remains to be explored. A recent study proposed new measure of entropy, distance of covariance matrix (DISCO) [14]. DISCO quantifies how far an individual's biological measurement network has drifted from a healthy reference network, by computing a distance from the reference covariance structure.

Received: 20 October 2025, **Accepted:** 28 October 2025

Corresponding author: Namki Hong
Division of Endocrinology, Department of Internal Medicine, Institute of Endocrine Research, Severance Hospital, Yonsei University College of Medicine, 50-1 Yonsei-ro, Seodaemun-gu, Seoul 03722, Korea
Tel: +82-2-2228-2265, **Fax:** +82-2-393-6884, **E-mail:** nkhong84@yuhs.ac

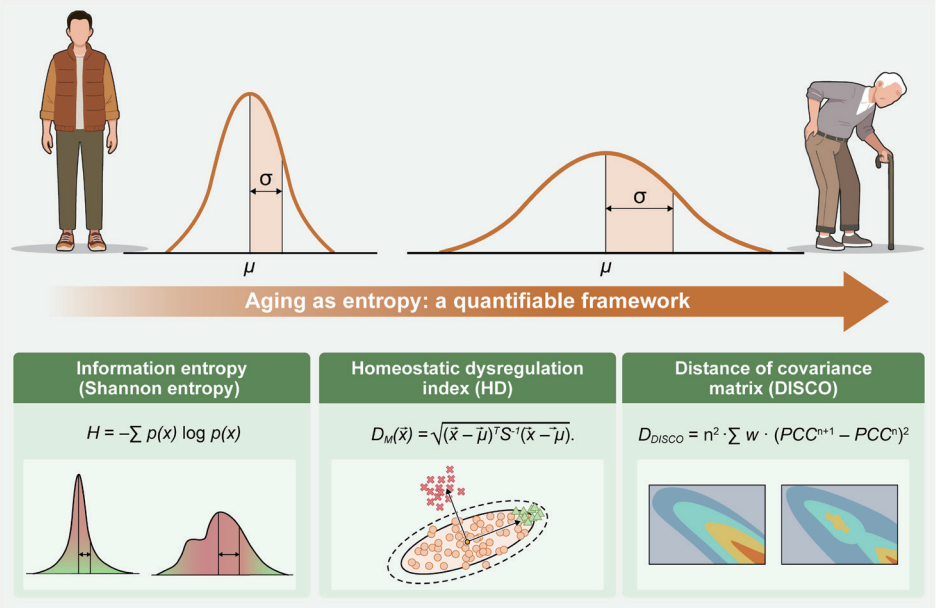

Fig. 1. Aging as entropy: a quantifiable framework.

DISCO showed strong positive correlation with D_M while it demonstrated greater prognostic performance compared to D_M when both were applied to high-dimensional data such as proteomics [14].

Entropy of clinical blood biomarkers throughout the aging process has been extensively studied using D_M [11,13,15]. D_M derived from a complete blood count and chemistry panel increased with age, showing robust prediction for health outcomes and mortality across multiple cohorts with diverse ethnicities. D_M of clinical biomarkers was associated with upstream determinants of health, such as diet and physical activity [16,17]. Of note, the association between D_M and health outcomes was not sensitive to the choice of biomarkers, indicating that D_M robustly detected a system-level property, entropy, even with random sets of markers [13]. A recent study published in *Aging Cell* extended the application of D_M to electrocardiogram (ECG) parameters to measure entropy of cardiac conduction system [18]. In this study, greater ECG entropy was associated with fracture, the consequences of entropic disorder and dysfunction in bone and the neuromuscular system. ECG entropy was also associated with similar changes in multiple systems manifest as an increased total mortality. The association was independent of age, clinical risk factors, and ECG diagnoses. These findings raise the possibility that associations between ECG entropy and outcomes are partly due to the fundamental process of increasing disorder with aging.

The framework of aging as entropy is an emerging research interest, with potential to reshape the landscape of aging science. To achieve this goal, several research questions need to be investigated further. Multiscale entropy from various types of data derived from multiple biological scales could enhance the performance of conventional organ- or system-specific entropy by integrating systemic aging signals at a single time. It remains to be determined whether organ-specific entropy correlates with organismal level multiscale entropy, if this could be measured accurately. Integration of multi-omics profiles in the framework of entropy, along with image-derived features, would be a promising approach to enhance the accuracy and prognostic performance of multiscale entropy [14]. Comparison between entropy and biological age clocks that have been proposed in various domains may be helpful to provide new insight into how these measurements are related.

In summary, testing entropy framework to quantify aging process across various populations and outcomes will advance our understanding of aging and its impacts. Future efforts are needed to build integrated, multimodal entropy tools and examine their prognostic utility for multiple health outcomes related to aging.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Namki Hong *https://orcid.org/0000-0002-8246-1956*

REFERENCES

1. Herzog CM, Goeminne LJ, Poganik JR, Barzilai N, Belsky DW, Betts-LaCroix J, et al. Challenges and recommendations for the translation of biomarkers of aging. Nat Aging 2024;4:1372-83.
2. Cohen AA, Beard JR, Ferrucci L, Fulop T, Gladyshev VN, Moqri M, et al. Balancing the promise and risks of geroscience interventions. Nat Aging 2025;5:4-8.
3. Moqri M, Herzog C, Poganik JR, Justice J, Belsky DW, Higgins-Chen A, et al. Biomarkers of aging for the identification and evaluation of longevity interventions. Cell 2023;186:3758-75.
4. Gladyshev VN, Anderson B, Barlit H, Barre B, Beck S, Behrouz B, et al. Disagreement on foundational principles of biological aging. PNAS Nexus 2024;3:pgae499.
5. Meyer DH, Schumacher B. Aging clocks based on accumulating stochastic variation. Nat Aging 2024;4:871-85.
6. Bortz WM. Aging as entropy. Exp Gerontol 1986;21:321-8.
7. Hershey D, Lee III WE. Entropy, aging and death. Syst Res 1987;4:269-81.
8. Moller DE, Flier JS. Insulin resistance: mechanisms, syndromes, and implications. N Engl J Med 1991;325:938-48.
9. Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2019;7:221-30.
10. Shannon CE. A mathematical theory of communication. Bell Syst Tech J 1948;27:379-423.
11. Cohen AA, Milot E, Yong J, Seplaki CL, Fulop T, Bandeen-Roche K, et al. A novel statistical approach shows evidence for multi-system physiological dysregulation during aging. Mech Ageing Dev 2013;134:110-7.
12. Mahalanobis PC. Reprint of: Mahalanobis, P.C. (1936) "On the generalised distance in statistics." Sankhya A 2018;80 (Suppl 1):1-7.
13. Li Q, Wang S, Milot E, Bergeron P, Ferrucci L, Fried LP, et al. Homeostatic dysregulation proceeds in parallel in multiple physiological systems. Aging Cell 2015;14:1103-12.
14. Hao M, Zhang H, Li Y, Huang Y, Wu J, Zhang S, et al. Distance of covariance (DISCO), a novel measure of network homeostatic dysregulation, reveals organ system interconnections underlying mortality and disease risk. medRxiv [Preprint] 2025 May 6. https://doi.org/10.1101/2025.05.06.25327108.
15. Cohen AA, Milot E, Li Q, Legault V, Fried LP, Ferrucci L. Cross-population validation of statistical distance as a measure of physiological dysregulation during aging. Exp Gerontol 2014;57:203-10.
16. Ghachem A, Dufour F, Fulop T, Gaudreau P, Cohen AA. Effects of sex and physical activity level on serum biomarker-based physiological dysregulation: the impact to predict frailty and mortality in the Quebec NuAge Cohort. Gerontology 2021;67:660-73.
17. Senior AM, Legault V, Lavoie FB, Presse N, Gaudreau P, Turcot V, et al. Multidimensional associations between nutrient intake and healthy ageing in humans. BMC Biol 2022;20:196.
18. Hong N, Cho SW, Kim J, Park H, Kang DS, You SC, et al. Entropy, assessed by homeostatic dysregulation on electrocardiograms predicts fracture and mortality. Aging Cell 2025;24:e70227.