A Minimal Model Explains Aging Regimes and Guides Intervention Strategies

Peter Fedichev*
GERO PTE. LTD., 133 Cecil Street 14-01 Keck Seng Tower, Singapore 069535

Jan Gruber†
1 Healthy Longevity Translational Research Program,
Yong Loo Lin School of Medicine, National University of Singapore, Singapore and
Department of Biochemistry, Yong Loo Lin School of Medicine, National University of Singapore, Singapore

Aging varies widely across species yet exhibits universal statistical regularities, such as Gompertzian mortality and scaling laws, challenging efforts to link microscopic mechanisms with macroscopic outcomes. We present a minimal phenomenological model that captures these patterns by reducing complex physiology to three variables: a dynamic factor characterizing reversible physiological responses to stress, an entropic damage variable reflecting irreversible information loss, and a regulatory noise term. This framework reveals two fundamental aging regimes. In *stable* species, including humans, aging is driven by linear damage accumulation that gradually erodes resilience, producing a hyperbolic trajectory toward a maximum lifespan. In *unstable* species, such as mice and flies, intrinsic instability drives exponential divergence of biomarkers and mortality. Model predictions agree with DNA methylation dynamics, biomarker autocorrelation, and survival curves across taxa. Crucially, this regime-based view informs intervention strategies at three levels: (i) targeting dynamic hallmarks, (ii) reducing physiological noise, and (iii) slowing or reversing entropic damage—offering a roadmap from near-term healthspan gains to potential extension of human lifespan beyond current limits.

I. INTRODUCTION

Aging displays remarkable diversity across species [1]. Short-lived animals such as flies or medflies often show late-life mortality deceleration and plateaus [2, 3], whereas humans typically retain Gompertz-like acceleration until very late life [4–6]. Some species—such as certain turtles, rockfish, and the naked mole-rat—exhibit *negligible senescence*, showing little or no acceleration of mortality with age despite body sizes comparable to normally aging animals [7–9]. Across taxa, key indicators of functional health follow broadly shared trajectories: cardiorespiratory fitness, muscle mass and strength, and metabolic efficiency progressively decline; recovery from perturbations slows; homeostatic responses weaken; and longitudinal variability in performance increases [10–12]. These regularities point to the presence of *universal features* in aging dynamics, with distinct regimes—what may be called "normal" aging and negligible senescence—emerging from the same underlying principles [13, 14].

Such universal patterns suggest that aging across species may be captured by a small set of coarse-grained variables with clear biological meaning. In the language of statistical physics, this reflects a separation of scales: on timescales relevant to aging, the microscopic complexity of physiology reduces to a few slow, emergent variables that govern long-term dynamics. Building on our previous work [12, 15–18], we propose a minimal phenomenological model in which health trajectories and mortality are governed by three such variables: (1) a *dynamic response factor* z_0 capturing the level of stress responses and characterized by the recovery time (closely related to resilience), (2) an *entropic damage variable* Z representing configurational entropy or information irreversibly lost during the aging process, and (3) a *regulatory noise strength* D_0 quantifying the amplitude of stochastic physiological fluctuations. The central premise is that z_0 behaves as a fast variable whose stability margin is gradually eroded by the slow, linear accumulation of Z. This separation of timescales naturally yields two regimes: in the *stable* regime, biomarker means, variances, and recovery times all diverge hyperbolically as the stability threshold is approached, thereby defining the maximum lifespan; in the *unstable* regime, the stability margin collapses and both biomarkers and mortality accelerate approximately exponentially.

Crucially, this theoretical understanding helps constrain the achievable effect sizes of anti-aging interventions. Therapies that act only on dynamic age-dependent factors (e.g., targeting specific hallmarks of aging) are inherently limited in stable species like humans, where resilience loss is driven mainly by damage accumulation. Larger and more durable gains would require reducing the systemic noise or slowing the damage accumulation rate itself, the latter offering the potential to shift maximum lifespan. This classification of intervention levels provides a principled map from biological targets to realistic clinical outcomes.

In the following sections, we formalize this framework, linking resilience loss to thermodynamic irreversibility and critical dynamics, and derive its empirical signatures in longitudinal data across species. This manuscript is structured as follows: we first summarize universal fea-

* Correspondence email address: peter.fedichev@gero.ai
† Correspondence email address: bchjg@nus.edu.sg

tures of aging across species (Section III), motivate and justify our approach to constructing a minimal theoretical framework (Section IV), and then derive and validate predictions against experimental data (Section V). Readers primarily interested in the biological and translational implications may skip directly to Sections VI and VII, where we discuss the relationship between aging and the second law of thermodynamics, therapeutic insights, and broader implications for developing effective anti-aging interventions.

II. AGEING AS AN EMERGENT PHENOMENON

Complex systems are hierarchically organised: at each scale, new variables and tools become relevant, reflecting behaviours that emerge from many interacting components. As P. W. Anderson put it, "More is different" [19]: the properties of a large system are not reducible to those of its parts. Classic physics examples include superconductivity (cooperative electron pairing), turbulence (nonlinear hydrodynamics), phase transitions (macroscopic order and critical opalescence), and thermodynamic state variables such as temperature, which are sharply defined in the thermodynamic limit; in small systems, "effective temperatures" exist but fluctuate [20, 21].

A relevant analogy is the second law. Microscopic laws of classical and quantum mechanics are *time-reversal symmetric*, yet in macroscopic aggregates tiny uncertainties amplify under interactions, making reversal effectively impossible and producing a robust arrow of time via entropy increase [22, 23]. In this regime, coarse-grained, collective variables dominate prediction, while microstate details become inessential.

The relationship between macro and micro is highly asymmetric. Over long timescales, a few emergent variables often suffice to describe dynamics, while most microscopic degrees of freedom contribute only through statistical aggregates. This coarse-graining underlies *universality*: many microscopically distinct systems share the same macroscopic laws [24, 25]. Conversely, macroscopic constraints (e.g., conservation laws and boundary conditions) restrict the admissible microstates in a statistical sense, providing an inferential "top-down" influence: as in Jaynes's maximum-entropy principle, where the least-biased microstate distribution is the one that maximises entropy subject to those constraints [26, 27].

Because of this asymmetry, predicting macroscopic behaviour from microscopic details alone is often intractable in practice. Complex systems are more often *observed* in certain states than *engineered* bottom-up. This poses a challenge for drug discovery against macroscopic phenotypes such as ageing and chronic diseases: interventions act on molecular targets, but desired outcomes are organismal, and the micro $\rightarrow$ macro map is indirect and nonlinear.

Ageing exemplifies this situation: a slow, macroscopic process describable by a few effective variables yet arising from myriad microscopic events with clear separation of timescales. Direct inference from micro to macro dynamics is therefore unreliable, which helps explain why target-level interventions can yield unpredictable organism-level outcomes. A coarse-grained, system-level description can bridge molecular action to long-term phenotypic change and thereby support more rational strategies to extend healthspan and longevity.

III. PROBLEM STATEMENT AND EMPIRICAL TARGETS

The variables that determine macroscopic healthspan, resilience, and mortality trajectories are not neatly labelled in any molecular inventory. They are distributed across pathways, context-dependent, and not traceable one-to-one to the microscopic components we can isolate in the laboratory. Rapid interactions and fluctuations at molecular and cellular scales, when integrated over long timeframes, give rise to the slow, large-scale process of organismal ageing. The rules governing this long-term behaviour reside at a different scale of organisation and time. This separation of scales implies that ageing cannot be fully understood—or reliably controlled—by studying molecular or cellular mechanisms in isolation.

From physics, the concept of *universality* is directly relevant: systems with very different microscopic constituents and interactions can exhibit the same large-scale behaviour for certain observables. Once coarse-grained, many distinct microstates map to the same macroscopic description, even though the microscopic details differ. In biology, evolutionary optimisation sculpts species-specific ("private") mechanisms of failure, such as extrachromosomal DNA circles in yeast [28], yet the phenomenology of ageing displays striking regularities across taxa. In many animal species, mortality rates increase approximately exponentially with age over substantial adult ranges, consistent with the Gompertz law [4, 5]. The slope of this rise defines the mortality acceleration and corresponds to a characteristic mortality-rate doubling time.

This pattern stands in contrast to most engineered systems, where reliability theory typically predicts hazards that grow as power laws with age, rather than exponentially [29–31]. Exponential hazard growth is the exception rather than the rule in technical systems, but in biology it is nearly ubiquitous. The widespread appearance of Gompertzian mortality therefore suggests a form of universality: a characteristic large-scale behaviour that emerges in organisms shaped by evolutionary pressures, extrinsic mortality, and internal constraints, despite diversity in life histories, metabolism, regeneration, genome architecture, and lifespan. Deviations from the pattern are especially informative. A small number of species, such as the naked mole-rat, exhibit little demographic acceleration within ob-

served ranges—sometimes described as negligible senescence [8, 9]. In many other taxa, hazards accelerate exponentially at earlier ages but slow at advanced ages, approaching a late-life plateau [2, 3]. Humans are unusual in that Gompertz-like acceleration persists well beyond the average lifespan, with only weak signs of saturation near maximum observed ages [6].

Ageing is also intrinsically stochastic. Even genetically identical individuals raised in controlled environments exhibit broad variation in lifespan, showing that random fluctuations at microscopic scales propagate to macroscopic heterogeneity [10]. Across species, the variance of age-associated measures often increases with age and scales inversely with species lifespan [11, 32]. In humans, some physiological indicators display hyperbolic growth in variance that extrapolates toward approximately 120 years of age [32]. Molecular drift rates also scale with longevity: somatic mutation and DNA methylation drift are lower in longer-lived species [33, 34], and methylation drift persists even in species with weak demographic ageing such as the naked mole-rat [35], indicating that molecular change is not always tightly coupled to acceleration of mortality.

Cross-species scaling further constrains theory. Among mammals, lifespan and developmental times generally increase with body mass, following quarter-power laws [36–38]. Rates of molecular and physiological change—methylation drift, mutation accumulation, oxidative damage, protein aggregation—tend to scale inversely with lifespan [39–41], reinforcing the link between rate processes and longevity.

Patterns in biomarker structure point to low effective dimensionality. Analyses of genomic, molecular, and clinical datasets reveal that age-associated features cluster, with principal component analysis often capturing most of the age-related variance in just a handful of components [42–45]. Measures of organismal performance and resilience, such as frailty indices [46], maximal heart rate [47], lung function [48], and recovery times after sublethal stress [49] tend to decline approximately linearly with age at around one percent per year in humans, while also displaying increasing inter-individual variability.

A satisfactory theory of ageing should therefore accommodate not only average decline but also widening dispersion, as well as the cross-species scaling and universality patterns outlined above.

IV. A MINIMAL AGING MODEL

To meet these empirical constraints, we note that aging is a dynamic process occurring in a strongly interacting, open system operating under noise — a living organism. The exact molecular composition and network of interactions in such a system are vast and hardly ever undentifiable, making a fully reductionist, micro-level theory implausible. Yet therapeutic interventions act precisely at this microscopic level — via small molecules, biologics, or cellular therapies — creating a tension between what we can model and what we can manipulate.

A practical way forward is to build a coarse-grained (phenomenological) model: one that describes aging in terms of a small number of emergent variables — such as resilience, frailty, configurational entropy, and noise strength — obtained by averaging over microscopic degrees of freedom. In this framing, biological age itself is an emergent property. The aim is to identify the minimal set of such macroscopic variables that (i) capture the universal features of aging and (ii) connect meaningfully to molecular levers that can be targeted therapeutically.

Formally, the organismal state can be represented as a point x in a high-dimensional state space, with components x_i denoting features across physical scales (e.g., gene expression, CpG methylation, metabolite concentrations, structural integrity of macromolecules). Although most features are experimentally inaccessible, they form a correlated network shaped by evolutionary constraints, enabling a lower-dimensional representation in terms of coordinated subsystems or "pathways." Activation of such a pathway shifts multiple features coherently away from their homeostatic setpoint.

Dynamical systems theory offers an analogy: a *normal mode*—a collective pattern obtained by linearizing dynamics around a stable equilibrium. In biology, fixed points correspond to homeostatic states, and the Jacobian of the linearized system defines normal modes (eigenvectors) evolving on timescales set by eigenvalues. Modes with eigenvalues near zero are slow (system-level adjustments), while those with large negative eigenvalues relax rapidly. This decomposition underlies dimensionality reduction and, in practice, many leading modes align with known biological modules [50–53].

By changing coordinates from features $(x_1, x_2, \dots)$ to eigenmodes $(z_1, z_2, \dots)$, we write

$$\dot{z}_\alpha = -\frac{dU(z_\alpha)}{dz_\alpha} + J_\alpha + f_\alpha, \tag{1}$$

where $U(z)$ is the effective potential generating a restoring force, J_α represents persistent stress, and f_α is noise. Near equilibrium, $U(z_\alpha) \approx \varepsilon_\alpha z_\alpha^2/2$, with $\varepsilon_\alpha > 0$ indicating stability, $\varepsilon_\alpha = 0$ critical slowing down, and $\varepsilon_\alpha < 0$ instability.

Directly modeling all relevant modes is impossible: the organism approaches the thermodynamic limit with effectively infinite degrees of freedom, and most are unobservable. We therefore focus on the slowest modes (smallest ε_α), which dominate long-timescale dynamics. Fast modes average out and become "enslaved" by slow modes [54], producing smooth back-reaction forces. This yields a coarse-grained framework analogous to Landau–Ginzburg theory, where microscopic detail is absorbed into a few effective parameters.

To derive the effective dynamics, we follow [17] and note that the underlying free-energy landscape is rugged, with numerous local minima. Microscopic

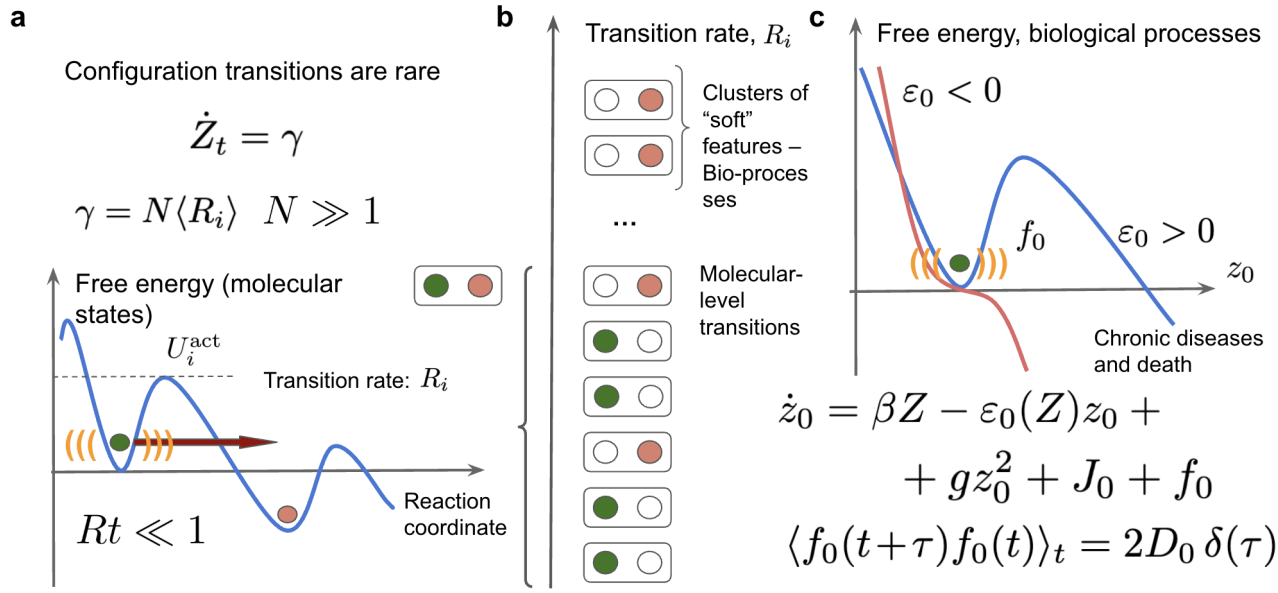

FIG. 1. **Schematic of the minimal aging model integrating entropic damage accumulation, dynamic stability loss, and mortality. (a)** Rare configurational transitions between molecular states are thermally activated processes with high energy barriers. Although individual transitions occur infrequently ($R_i \ll 1$), the cumulative damage rate $\dot{Z}_t = \gamma = N\langle R_i \rangle$ can be substantial because of the large number of degrees of freedom ($N \gg 1$). These events contribute to the slow, approximately linear accumulation of entropic damage Z, interpreted as generalized damage, configurational entropy, or irreversible information loss. **(b)** Transition rates arise from molecular events and clusters of coupled physiological features ("soft modes") across hierarchical biological scales. Their aggregate behavior drives coarse-grained entropic dynamics at the organismal level. **(c)** Entropic damage Z modulates the stability of a critical dynamic variable z_0, which governs resilience, stress response, and ultimately mortality risk. The effective free-energy potential for z_0 depends on its recovery rate $\varepsilon_0(Z)$, which decreases with age. In the stable regime ($\varepsilon_0 > 0$), fluctuations remain bounded; in the unstable regime ($\varepsilon_0 < 0$), fluctuations diverge, leading to systemic collapse. The stochastic dynamics of z_0 are governed by Langevin-type equations with nonlinear terms, persistent stress J_0, and regulatory noise f_0 characterized by $\langle f_0(t+\tau) f_0(t) \rangle = 2D_0\delta(\tau)$.

transitions—mutations, chromatin remodeling, methylation shifts, macromolecular modifications—correspond to moves between these minima (Fig. 1a). Individually rare, such transitions accumulate across billions of molecules and cells at appreciable rates. While their precise history is irrelevant, their cumulative effect matters: we summarize it as a single variable Z representing generalized damage. In the simplest approximation, Z grows linearly in time at rate γ – the damage accumulation rate (DAR).

Assuming that the coupling between modes are small, the coupled dynamics of the slowest mode (z_0) and damage (Z) are:

$$\begin{cases} \dot{z}_0 = \beta Z - \varepsilon_0(Z)\, z_0 + g z_0^2 + J_0 + f_0, \\ \dot{Z} = \gamma, \end{cases} \tag{2}$$

with $\varepsilon_0(Z) = \varepsilon_0 - \beta' Z$. Here β, β', g are small nonlinear couplings, J_0 represents persistent stress, and f_0 is zero-mean white noise with $\langle f_0(t+\tau) f_0(t) \rangle = 2D_0\delta(\tau)$.

Despite its simplicity, Eq. (2) captures a rich phenomenology: critical slowing down, divergence of biomarkers, Gompertzian mortality, and systematic deviations from Gompertz observed in some species. This framework unifies aging as the coupled erosion of resilience and accumulation of damage. In the following, we connect this minimal description to empirical signatures—mortality trajectories, scaling laws, stochastic variability, and biomarker drift—that both motivate and validate the model.

V. AGING PHENOMENOLOGY

The effective dynamics in Eq. (2) admit two qualitatively distinct behaviors, determined by system parameters. In dynamical-systems terms, the nonlinear coupling to accumulated damage introduces a bifurcation: the system can either maintain two fixed points—one stable and one unstable—or collapse to a single unstable point, as illustrated by the blue and red free-energy profiles in Fig. 1b. Biologically, these alternatives correspond to two fundamental regimes of aging.

In the *stable regime*, the presence of a stable fixed point ensures that physiological fluctuations remain bounded and recovery from perturbations is possible, although resilience progressively declines as the stability margin erodes. In the *unstable regime*, only an unstable fixed point exists; trajectories are driven away without restor-

ing forces, producing rapid divergence of biomarkers and escalating mortality risk. In the following, we show how this classification into stable and unstable phases provides a natural theoretical basis for the observed diversity of aging trajectories across species.

A. Class I: "unstable" animals

In the unstable regime, the critical mode z_0 is inherently unstable: at birth, its intrinsic recovery rate is negative, $\varepsilon_0(Z=0) < 0$. When the coupling to damage is weak ($\beta, \beta' \approx 0$), the slow accumulation of generalized damage Z has little influence on dynamics, making mortality trajectories largely independent of Z. As shown in [15], this regime follows a characteristic sequence of phases.

Early in life, stochastic fluctuations dominate, and the variance of z_0 grows until it reaches $z_{\min}^2 \sim D/\alpha$, where $\alpha = |\varepsilon_0|$. Beyond this point, the deterministic force term prevails, and the mode grows exponentially:

$$z_0(t) \sim z_{\min} \exp(\alpha t).$$

Eventually, the system crosses a nonlinear threshold at $z_{\max} = \alpha/g$, beyond which the mode diverges hyperbolically—a state incompatible with survival.

For typical parameters, the ratio $\xi = z_{\max}/z_{\min} \gtrsim 1$, so animals spend most of life in the exponential phase. This prediction is supported by DNA methylation (DNAm) data in mice, which reveal two major signatures: (i) a linear component linked to damage accumulation (Z) and (ii) an exponential trend reflecting intrinsic instability along z_0 [55]. A similar exponential component was recovered from longitudinal blood cell counts in the Mouse Phenome Database [56] using model-based fits of Eqs. (2) in [16], with doubling times matching empirical MRDTs.

In this class, survival probability takes the form $S(t) = \mathrm{Erf}(\xi e^{-\alpha t})$. Near the average lifespan, $t_{\mathrm{ls}} = \alpha^{-1} \ln \xi$, mortality follows an approximate Gompertz law:

$$M(t) \approx 0.6\, \alpha \exp[\alpha(t - t_{\mathrm{ls}})],$$

so the observed mortality doubling rate near midlife equals $\alpha = |\varepsilon_0|$. This implies that hazard curves around the average lifespan can be used to estimate α directly.

Because mortality depends strongly on α but only weakly on ξ, survival curves across conditions collapse under age rescaling by mean lifespan—a property validated experimentally in *C. elegans* [57].

However, the model also predicts systematic deviations from a pure Gompertz trajectory: soon after the average lifespan, mortality acceleration slows and ultimately plateaus at

$$M(t \to \infty) = \alpha.$$

This plateau hazard is numerically close to the inverse mortality rate doubling time. Such deceleration and late-life plateaus have been observed in ultra-large cohorts and across multiple species [3, 15]. In *C. elegans*, the plateau matches the Gompertz slope measured earlier in life across strains with tenfold lifespan differences [58]. Even in mice, data from the ITP show mortality acceleration halting near the average lifespan, followed by a plateau hazard $\approx \alpha$ [16].

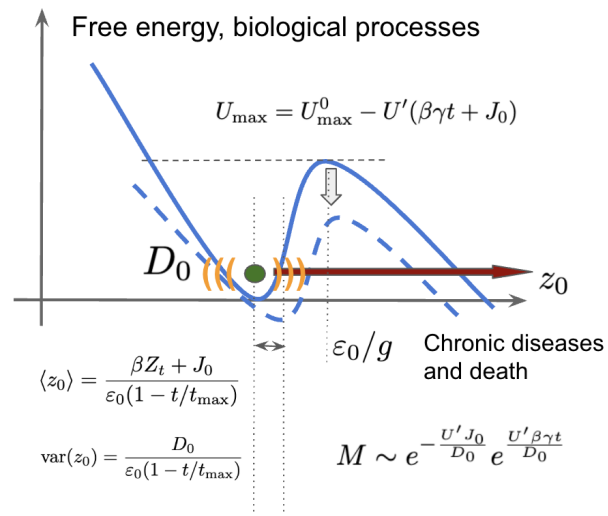

FIG. 2. Stress and damage cumulatively erode the basin of attraction for the critical mode fluctuations. This erosion drives divergence in both the mean and variance of the critical mode while exponentially increasing the probability of escape transitions leading to death. The mechanism provides a natural explanation for the Gompertz mortality law, with the Gompertz exponent (inverse mortality rate doubling time, MRDT) proportional to the damage accumulation rate and inversely proportional to the magnitude of regulatory noise.

B. Class II: "stable" animals

In "stable" animals, all eigenmodes $z_\alpha(t)$ begin life with positive intrinsic recovery rates, $\varepsilon_\alpha(0) > 0$. Such organisms can recover from typical environmental and intrinsic perturbations, returning their physiological state to a healthy setpoint. Early in life, fluctuations of the critical mode z_0 are suppressed by strong restoring forces, and aging manifests primarily through the gradual, linear accumulation of damage Z, which steadily reduces stability.

When no damage has accumulated ($Z = 0$) and external stress is absent ($J_0 = 0$), the free-energy potential exhibits two fixed points: a stable point at $z_0 = 0$ (the minimum, $U_{\min} = 0$) and an unstable point at $z_0 = \varepsilon_0/g$ (the maximum, $U_{\max} = \varepsilon_0^3/(6g^2)$). The unstable point defines the protective barrier beyond which recovery to the stable state is impossible (Fig. 2). As Z increases, $\varepsilon_0(Z)$ decreases approximately linearly, narrowing the gap between these fixed points. At the critical damage level $Z_{\max} = \gamma t_{\max}$, the recovery rate vanishes, $\varepsilon_0(Z_{\max}) = 0$,

Feature	Stable Animals	Unstable Animals
Leading aging signatures	Linear (damage): linear increase of mean and variance. Hyperbolic (critical mode): diverges along with its varaince at maximum lifespan.	Linear (damage): linear increase of mean and variance. Exponential (critical mode): exponentially increasing mean and variance.
Maximum lifespan	Exists in finite cohorts, inversely proportional to damage accumulation rate (DAR).	Does not exist in finite cohorts.
Resilience	Lost at maximum lifespan or via activation transition near average lifespan.	Does not exist for critical mode.
Gompertz exponent α_G	Non-universal, inversely proportional to regulatory noise D and DAR.	Coincides with intrinsic instability rate ε_0.
Mortality acceleration	Exponential until maximum lifespan.	Exponential until average lifespan, plateaus afterward.
Temporal autocorrelation function (TAC)	Quickly decays, the decay rate decreases linearly with age.	No decay (life-long TAC).
Effects of drugs targeting critical mode (z_0) – hallmarks of aging	Reduce aging markers and risk only during application; no lasting effects after stopping treatment.	Lifelong effects from short treatments.
Effects of drugs targeting noise factor (D)	Strong effect: controls difference between mean and maximum lifespan ("squaring" of the survival curve).	Weak or negligible effects.

TABLE I. Summary and comparison of aging characteristics in stable and unstable animals within the minimalistic aging model.

and the protective barrier collapses through a classic saddle–node bifurcation. The corresponding time,

$$t_{\max} = \frac{\varepsilon_0}{\beta'\gamma},$$

defines the species-specific maximum lifespan, set by the initial stability ε_0, the coupling β', and the rate of damage accumulation γ.

As $t \to t_{\max}$, both the mean and variance of the critical mode diverge hyperbolically,

$$\text{mean}(z_0),\ \text{var}(z_0) \sim \frac{1}{t_{\max} - t}.$$

Persistent perturbations (J_0) shift the mean but do not affect variance, which is driven exclusively by aging ($Z \sim t$). This divergence has clear empirical support. Principal component analyses (PCA) of mammalian DNA methylation datasets consistently reveal two major signatures [18]: a linear component reflecting steady damage accumulation, and a hyperbolically diverging component that projects to the species' maximum lifespan (about 120 years in humans [17]). Similar divergence has been observed in mortality-linked biomarkers derived from blood counts, daily physical activity, and composite measures such as PhenoAge [12].

Although systemic stability vanishes only at $t_{\max}$, death usually occurs earlier when stochastic fluctuations drive z_0 beyond the unstable point. According to Kramers' theory [59], mortality is the probability of barrier crossing at age t,

$$M(t) \sim \exp\left(-\frac{U_{\max}(Z, J_0)}{D_0}\right),$$

where $U_{\max}$ is the barrier height between fixed points (Fig. 2). Well before the maximum lifespan, $U_{\max} \approx U_0 - U'Z$ decreases linearly with Z, so mortality risk increases exponentially with age. This mechanism explains the ubiquity of the Gompertz law—exponential growth of mortality rates—even though most forms of damage (oxidative, redox, mitochondrial, etc.) accumulate only linearly [60–62]. The Gompertz exponent,

$$\alpha_G = \frac{U'\gamma}{D_0},$$

is directly proportional to the rate of damage accumulation and inversely proportional to the noise strength D_0.

A key implication is that the gap between average and maximum lifespan depends on the magnitude of physiological fluctuations. In the absence of noise ($D_0 \to 0$), barrier crossing is impossible until the stability margin is fully eroded, and hence the average lifespan would coincide with $t_{\max}$. In reality, stochastic fluctuations ensure that death occurs earlier, producing the observed distribution of lifespans. Empirical estimates of D_0 from DNA methylation fluctuations across mammals support this prediction [18].

C. Dynamic markers of aging and resilience

The distinction between stable ($\varepsilon_0 > 0$) and unstable ($\varepsilon_0 < 0$) regimes can be revealed through the temporal autocorrelation function (TAC) of the critical mode z_0 in longitudinal datasets:

$$C(\tau) = \langle z_0(t+\tau)\, z_0(t)\rangle_t,$$

where $\langle\cdot\rangle_t$ denotes averaging first along a trajectory and then across the cohort.

In the stable regime, the TAC decays exponentially,

$$C(\tau) = \frac{D_0}{2\varepsilon_0}\, e^{-\varepsilon_0 \tau},$$

allowing ε_0 to be estimated directly from data. The inverse, ε_0^{-1}, has the natural interpretation of a recovery time and thus provides a quantitative measure of resilience. Consistent with this prediction, [12] showed that autocorrelation rates derived from human complete blood counts and daily physical activity decline approximately linearly with age, extrapolating to zero around $t_{\max} \approx 120$ years. This agrees with Eq. (2), in which variance diverges as resilience vanishes. The same analysis suggested that D_0 remains roughly age-independent.

By contrast, in unstable species the TAC fails to decay within observational windows. For example, [16] analyzed the Mouse Phenome Database [56] and found TACs to be essentially flat over 14- and 28-week intervals—far exceeding the ∼4-week decay observed in humans. This absence of decay reflects the lack of a restoring force in the unstable regime and underscores the sharp difference in resilience dynamics across species.

Diverging TAC is therefore a dynamic marker of health and vulnerability. In [63], individuals with TAC values exceeding three months—indicative of lost dynamical stability—were identified from longitudinal physical activity data. The fraction of such individuals doubled approximately every seven years, closely matching the human mortality-rate doubling time of about eight years, in full agreement with Kramers' theory of barrier crossing.

The TAC framework also yields testable predictions for interventions. In unstable animals, perturbations of the critical mode z_0 produce persistent effects even after treatment ends, making them detectable in short-term studies. In stable species, however, the TAC decays rapidly, so intervention effects dissipate soon after cessation. A familiar example is smoking: it elevates aging biomarkers, including epigenetic clocks, but these changes reverse quickly upon cessation [12, 63]. Thus, TAC dynamics not only serve as markers of resilience but also determine the interpretability of intervention outcomes across species.

VI. AGING, DAMAGE, AND ENTROPY

Our phenomenological model reduces the complexity of aging to the interplay of two fundamental macroscopic modes. One is a dynamic variable, z_0, representing immediate organismal responses across physiological domains such as immune function, nutrient management, and metabolic regulation. The other is a slow, cumulative variable, Z, representing damage that accumulates approximately linearly with age and gradually destabilizes critical physiological responses. In long-lived, "stable" species whose average lifespan is well below their maximum potential, this progressive damage accumulation is the primary driver of aging dynamics.

Multiple datasets support the hypothesis that damage accumulates linearly with age. Principal component scores from large DNA methylation (DNAm) datasets—spanning mammalian species [64], humans [65], and mice [66]—show variance increasing linearly with age, a hallmark of Poissonian stochastic processes [17, 18, 55]. In such processes, mean and variance grow proportionally, consistent with damage arising from independent molecular transitions.

Single-cell DNAm analysis in aging mice [67] reinforces this view. In [55], mutual information (MI) between CpG sites revealed that CpGs contributing to the exponential (dynamic) aging signature were highly correlated, whereas CpGs from the linear signature had uniformly low MI, implying statistical independence. This independence is exactly what Poisson statistics predict.

The statistical independence of individual damage events implies an exponential growth in the number of accessible microscopic configurations over time. Accordingly, the damage variable Z is proportional to the system's configurational entropy and quantifies cumulative information loss during aging [17]. In macroscopically large systems, Z is large with a high mean-to-variance ratio, justifying a deterministic treatment of its dynamics in Eq. (2).

Site-specific damage rates in DNAm datasets often follow non-Gaussian, exponential-like distributions. This pattern is naturally explained if each event corresponds to a thermally activated transition over a barrier drawn from a Gumbel distribution [18]. Extreme-value statistics predict that kinetics are dominated by the highest barrier among many alternatives, suggesting that aging is driven by rare but consequential failures across otherwise redundant systems.

If Z reflects configurational entropy, its linear growth is a direct manifestation of the second law of thermodynamics—an inherently irreversible process. This explains why reversing accumulated damage is difficult: it would require reordering a vast number of microscopic degrees of freedom with inaccessible initial states. Empirical evidence supports this irreversibility. In mice, heterochronic parabiosis partially restored the dynamic (exponential) DNAm signature but left the linear (entropic) signature unchanged [55, 66]. Thus, while the dynamic mode can

be modulated or even reversed, the entropic mode appears fundamentally resistant to systemic rejuvenation.

Damage is therefore not merely a biomarker but a fundamental state variable of aging. Its Poissonian kinetics, extreme-value rate distribution, and entropic interpretation constrain both theoretical models and realistic expectations for intervention outcomes. Moreover, because Z slowly modulates the resilience variable z_0, it shapes population-level aging trajectories and the timing of resilience collapse. In the next section, we examine how these coupled variables manifest in survival and healthspan patterns across species, and how they inform the broader phenomenology of aging.

VII. INTERVENTION STRATEGIES: THREE LEVELS OF CONTROL

Our model highlights three macroscopic variables as potential levers for intervention: the dynamic stress indicator z_0, the cumulative entropic damage Z, and the regulatory noise strength D_0. Each of these can, in principle, be modulated by biotechnological approaches and identified through phenotypic screening. Based on which variable is targeted, anti-aging strategies can be organized into three conceptual levels, differing in feasibility and expected effect size (Table II).

Level 1: Targeting fast pathways (z_0). Level-1 interventions act on dynamic variables—fast regulatory "pathways" represented by z_0—which dominate the physiological response to stress. This category includes most current approaches in drug development: caloric restriction (CR) mimetics, senolytic therapies, telomerase activators, and cellular rejuvenation strategies. These interventions are highly effective in short-lived organisms, where aging is unstable and fast pathways tightly couple to aging phenotypes. In humans, their greatest promise lies in preventing or delaying major age-related diseases, particularly those with high population impact and market potential. For example, diabetes alone reduces life expectancy by up to eight years depending on age at onset, making metabolic health optimization a key target in this class.

Level 2: Reducing physiological noise (D_0). A second, largely unexplored class of interventions would aim to dampen regulatory noise—random fluctuations that undermine stability near the limits of resilience. Lowering D_0 in our model would reduce stochastic barrier-crossing events, effectively "squaring" survival curves by compressing morbidity without slowing baseline aging processes. Practically, Level-2 strategies could extend healthy lifespan by 30–40 years, bridging the gap between today's average lifespans (70–80 years) and the maximum observed limit (120–150 years). However, these therapies would not substantially slow functional decline or extend the ultimate lifespan ceiling.

Level 3: Controlling entropic damage (Z). The most ambitious interventions would seek to arrest—or even reverse—the slow, cumulative accumulation of entropic damage Z. Success here would not only extend lifespan but fundamentally alter the trajectory of functional decline, pushing the maximum lifespan beyond current natural limits. Achieving this will require novel technologies and experimental frameworks, including robust biomarkers for tracking Z, advanced organ replacement platforms, and new long-lived animal models. While daunting, our theoretical framework demonstrates that this goal, once thought speculative, is analytically coherent and provides a roadmap for prioritizing the necessary innovations.

VIII. DISCUSSION

Our phenomenological model of aging identifies a minimal set of three macroscopic control variables: the dynamic response factor z_0, which captures the leading physiological response to stress; the cumulative entropic damage Z; and the strength of regulatory noise D_0. These variables span distinct temporal and biological scales—from fast, reversible adaptability (z_0) to slow, irreversible damage accumulation (Z)—and together provide a principled framework for classifying anti-aging interventions (cf. Table II).

This hierarchical structure reflects a general principle of complex systems: emergent control variables at each scale cannot be trivially reduced to microscopic laws [19]. The most important example in our framework is cumulative damage Z, closely related to configurational entropy and thus to information irreversibly lost during the aging process. Z aggregates the effects of countless independent microscopic damage events and exerts dominant control over the lifespan of long-lived species, including humans.

Theories positing damage accumulation as the primary cause of aging have a long history, with more than 300 distinct proposals catalogued [68]. Among the most influential is the Free Radical Theory of Aging (FRTA) proposed by Harman in 1956 [69], later refined into the Mitochondrial Free Radical Theory (MFRTA) [70]. This framework emphasized mtDNA damage as both source and target of reactive oxygen species, creating a vicious cycle of exponential damage accumulation. While early studies reported increases in oxidative damage with age [71, 72] and some interventions showed lifespan extension [73, 74], later work challenged the strong form of the MFRTA: large antioxidant trials often failed [75], some long-lived mutants displayed elevated ROS [76], and mutator mice with high mtDNA mutation rates aged prematurely without dramatic ROS amplification [77].

Today, mitochondria remain central to aging biology, but oxidative mtDNA damage is seen as one contributor among many, interacting with altered signaling, metabolic shifts, inflammation, and other hallmarks. This broader perspective aligns with our phenomenological framework: aging is driven not by a single univer-

Property	Level-1	Level-2	Level-3
Mechanism	Targets hallmarks of aging (dynamic variables)	Reduces regulatory noise (variance D)	Reduces/reverses damage (entropic variable Z)
Effect on diseases	Disease-specific, therapeutic (more pronounced in unstable species)	Broad, prophylactic (particularly age-related)	Broad, prophylactic (particularly age-related)
Functional decline	Weakly affected	Weakly affected	Strongly affected/reversed
Lifespan increment	Moderate ($\sim$ 10 years); transient effects of treatments	Large ($\sim$ 40 years); limited by max lifespan	Very large ($\gtrsim$ 40 years); raises max lifespan

TABLE II. Comparison of three classes of anti-aging interventions in long lived species.

sal cause, but by the linear accumulation of rare "flips" in fast variables—generalized forms of damage across many hallmarks—which collectively reshape the dynamics of slower, mortality-linked modes. As the dictum goes, "thermodynamics does not care about the hardware": the precise identity of each microscopic event is less important than its aggregate, coarse-grained effect on macroscopic dynamics.

Examples of such microscopic "flips" include collagen cross-linking, epigenetic drift, chronic inflammation, senescent cell accumulation, and mitochondrial or ROS-related damage. Each is stochastic and infrequent at the molecular level, but together they renormalize the dynamics of system-level variables. By averaging over their effects, the model yields a linearized description of macroscopic outcomes. Without requiring exponential increases in microscopic damage itself, this framework naturally explains the universal exponential rise of mortality captured by the Gompertz law.

In this synthesis, the sum of many distinct processes becomes a quantifiable cause in its own right. Aging cannot be reduced to a single mechanism; it emerges from the coarse-grained sum of many. The resulting effective variables (z_0, Z, D_0) are not abstractions but measurable dynamical phenotypes, each representing the imprint of countless molecular interactions. Indeed, these are the only aging variables we can truly observe, since isolated molecules or cells in vitro do not "age" in a manner homologous to whole organisms. Recognizing and quantifying such system-level phenotypes makes aging both understandable and actionable.

The dynamical form of Eqs. 2 follows from assuming that physiological variables evolve near a critical point separating stable and unstable regimes. This resonates with the concept of systems operating at the "edge of chaos"—such as neural networks or genetic circuits—that maximize adaptability by balancing order and disorder [78]. Renormalization Group (RG) arguments provide further support [79]: in large systems, nonlinear couplings renormalize to small values at macroscopic scales, justifying the simplicity of the effective equations and the empirically small couplings in our model.

Our framework also extends the classical Strehler–Mildvan (SM) theory [80]. It (i) links the SM "vitality deficit" to cumulative damage Z; (ii) identifies z_0 as the reaction coordinate underlying the Arrhenius-like factor that yields Gompertzian mortality under linear vitality loss; and (iii) demonstrates how both Z and z_0 can be inferred from molecular- or physiological-level data. Thus, SM's empirical parameters gain clear physical and biological interpretation, including the temperature-like role of D_0.

Our approach complements mechanistic models such as those of Alon and colleagues [81], which describe saturation of repair pathways (e.g., proteostasis, DNA repair) leading to damage buildup. While both highlight damage as the driver of aging, our framework and the relevant variables are not microscopic, but rather phenomenological or coarse-grained. In our model aging can not be reduced to a single cause. Instead, it is a collective, thermodynamically irreversible process, enabling predictions that scale from molecular autocorrelations to population survival curves.

Eqs. 2, though simple in appearance, give rise to diverse aging regimes and biomarker signatures. Organisms may be fast-aging and unstable—operating near or beyond instability early in life—or long-lived and stable, maintaining equilibrium for much of the lifespan before gradual loss of stability precipitates decline. In the latter, more human-relevant case, aging is dominated by the slow accumulation of Z, leading eventually to critical loss of resilience and rapid mortality acceleration.

The key distinction is that while z_0 dynamics are stochastic and reversible, Z increases in an almost deterministic, linear fashion with age. DNA methylation analyses across species show variance growing linearly with age, consistent with a Poisson process. Single-cell data from mice reveal low mutual information among CpG sites in the linear signature, supporting independence of damage events. This independence implies that the accessible configurational space expands exponentially with time, giving the linearly incrasing Z a natural interpretation as configurational entropy or cumulative information loss. Rare, high-impact failures in redundant networks emerge from this exponential event-rate distribution, consistent with Gumbel statistics.

Although the entropic nature of Z implies macroscopic irreversibility, interventions that slow its accumulation

remain plausible. By altering the rate of damage accrual, such strategies could fundamentally shift human aging trajectories, potentially extending lifespan beyond current limits.

IX. CONCLUSION

In summary, the minimalistic aging model presented here provides a unified framework linking molecular-scale processes to organism-level aging trajectories across species. By framing aging as the coupled evolution of dynamic physiological resilience (z_0) and linearly accumulating, irreversible entropic damage (Z), the model naturally distinguishes **stable** from **unstable** regimes, each with distinct therapeutic implications. While current longevity interventions primarily target age-dependent dynamic features (the hallmarks of aging), our analysis suggests that substantial, durable gains in human lifespan and healthspan will likely require strategies that either reduce regulatory noise (D_0) or slow the rate of entropic damage accumulation.

[1] O. R. Jones, A. Scheuerlein, R. Salguero-Gómez, C. G. Camarda, R. Schaible, B. B. Casper, J. P. Dahlgren, J. Ehrlén, M. B. García, E. S. Menges, *et al.*, Nature **505**, 169 (2014).
[2] J. R. Carey and P. Liedo, Science **258**, 457 (1992).
[3] J. W. Vaupel, J. R. Carey, K. Christensen, *et al.*, Science **280**, 855 (1998).
[4] B. Gompertz, Philosophical Transactions of the Royal Society of London **115**, 513 (1825).
[5] W. M. Makeham, Journal of the Institute of Actuaries **13**, 325 (1860).
[6] N. S. Gavrilova and L. A. Gavrilov, Journals of Gerontology Series A: Biomedical Sciences and Medical Sciences **70**, 1 (2015).
[7] C. E. Finch, Gerontology **55**, 307 (2009).
[8] J. G. Ruby, M. Smith, and R. Buffenstein, eLife **7**, e31157 (2018).
[9] R. Buffenstein, Journal of Comparative Physiology B **178**, 439 (2008).
[10] L. A. Herndon *et al.*, Nature **419**, 808 (2002).
[11] N. Stroustrup *et al.*, Nature **530**, 103 (2016).
[12] T. V. Pyrkov, K. Avchaciov, A. E. Tarkhov, L. I. Menshikov, A. V. Gudkov, and P. O. Fedichev, Nature communications **12**, 2765 (2021).
[13] C. E. Finch, *Longevity, Senescence, and the Genome* (University of Chicago Press, 1990).
[14] T. B. L. Kirkwood and S. N. Austad, Nature **408**, 233 (2000).
[15] D. Podolskiy, I. Molodtcov, A. Zenin, V. Kogan, L. I. Menshikov, V. N. Gladyshev, R. J. S. Reis, and P. O. Fedichev, arXiv preprint arXiv:1502.04307 (2015).
[16] K. Avchaciov, M. P. Antoch, E. L. Andrianova, A. E. Tarkhov, L. I. Menshikov, O. Burmistrova, A. V. Gudkov, and P. O. Fedichev, Nature Communications **13**, 6529 (2022).
[17] A. E. Tarkhov, K. A. Denisov, and P. O. Fedichev, AgingBio **2**, e20240031 (2024).
[18] K. A. Denisov, J. Gruber, and P. O. Fedichev, bioRxiv , 2024 (2024).
[19] P. W. Anderson, Science **177**, 393 (1972).
[20] H. B. Callen, *Thermodynamics and an Introduction to Thermostatistics*, 2nd ed. (Wiley, New York, 1985).
[21] A. I. Khinchin, *Mathematical Foundations of Statistical Mechanics* (Dover Publications, New York, 1949).
[22] J. L. Lebowitz, Physics Today **46**, 32 (1993).
[23] H. Price, *Time's Arrow and Archimedes' Point: New Directions for the Physics of Time* (Oxford University Press, New York, 1996).
[24] K. G. Wilson, Physical Review B **4**, 3184 (1971).
[25] N. Goldenfeld, *Lectures on Phase Transitions and the Renormalization Group* (Addison-Wesley, Reading, MA, 1992).
[26] E. T. Jaynes, Physical Review **106**, 620 (1957).
[27] E. T. Jaynes, Physical Review **108**, 171 (1957).
[28] D. A. Sinclair and L. Guarente, Cell **91**, 1033 (1997).
[29] R. E. Barlow and F. Proschan, *Mathematical Theory of Reliability* (Wiley, 1965).
[30] W. Q. Meeker and L. A. Escobar, *Statistical Methods for Reliability Data* (Wiley, 1998).
[31] L. A. Gavrilov and N. S. Gavrilova, Journal of Theoretical Biology **213**, 527 (2001).
[32] T. Pyrkov *et al.*, Nature Communications **12**, 2765 (2021).
[33] A. Cagan, A. Baez-Ortega, N. Brzozowska, F. Abascal, T. H. H. Coorens, M. A. Sanders, A. R. J. Lawson, L. M. R. Harvey, S. Bhosle, D. Jones, R. E. Alcantara, T. M. Butler, Y. Hooks, K. Roberts, E. Anderson, S. Lunn, E. Flach, S. Spiro, I. Januszczak, E. Wriggled, J. Nicholson, E. Buchalter, F. Maura, A. Degasperi, M. D. Covino, A. Degasperi, X. Zou, H. Davies, J. Lee, M. R. Stratton, I. Martincorena, J. M. C. Tubio, P. J. Campbell, D. R. Fitzpatrick, and Z. Consortium, Nature **604**, 517 (2022).
[34] B. Mayne, O. Berry, and S. Jarman, Nature Aging **3**, 1697 (2023).
[35] D. A. Petkovich *et al.*, Nature Communications **8**, 1 (2017).
[36] J. R. Speakman, Journal of Experimental Biology **208**, 1717 (2005).
[37] G. B. West, J. H. Brown, and B. J. Enquist, Nature **413**, 628 (2001).
[38] W. A. Calder, *Size, Function, and Life History* (Harvard University Press, 1984).
[39] H. H. Ku *et al.*, Proceedings of the National Academy of Sciences USA **90**, 915 (1993).
[40] G. Barja, Trends in Neurosciences **23**, 454 (2000).
[41] X. Tian *et al.*, Science **380**, eabn9235 (2023).
[42] A. Tarkhov *et al.*, bioRxiv , preprint (2024).
[43] S. Fong *et al.*, bioRxiv , preprint (2024).
[44] S. Horvath, Genome Biology **14**, R115 (2013).
[45] G. Hannum *et al.*, Molecular Cell **49**, 359 (2013).

[46] A. B. Mitnitski *et al.*, ScientificWorldJournal **1**, 323 (2001).

[47] H. Tanaka *et al.*, Journal of the American College of Cardiology **37**, 153 (2001).

[48] R. J. Knudson *et al.*, American Review of Respiratory Disease **127**, 725 (1983).

[49] E. Hadley *et al.*, Journals of Gerontology: Series A **72**, 980 (2017).

[50] A.-L. Barabási and Z. N. Oltvai, Nature Reviews Genetics **5**, 101 (2004).

[51] A. Ma'ayan, Science Signaling **4**, tr5 (2011).

[52] S. H. Strogatz, *Nonlinear Dynamics and Chaos: With Applications to Physics, Biology, Chemistry, and Engineering*, 2nd ed. (Westview Press, Boulder, CO, 2015).

[53] J. Guckenheimer and P. Holmes, *Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields*, Applied Mathematical Sciences, Vol. 42 (Springer, New York, 1983).

[54] A. Hutt and H. Haken, *Synergetics* (Springer, 2020).

[55] K. Perevoshchikova and P. O. Fedichev, bioRxiv , 2024 (2024).

[56] M. A. Bogue, V. M. Philip, D. O. Walton, S. C. Grubb, M. H. Dunn, G. Kolishovski, J. Emerson, G. Mukherjee, T. Stearns, H. He, V. Sinha, B. Kadakkuzha, G. Kunde-Ramamoorthy, and E. J. Chesler, Nucleic Acids Research **48**, D716 (2020), rRID:SCR_003212.

[57] N. Stroustrup, W. E. Anthony, Z. M. Nash, V. Gowda, A. Gomez, I. F. López-Moyado, J. Apfeld, and W. Fontana, Nature **530**, 103 (2016).

[58] A. E. Tarkhov, R. Alla, S. Ayyadevara, M. Pyatnitskiy, L. I. Menshikov, R. J. Shmookler Reis, and P. O. Fedichev, Scientific Reports **9**, 7368 (2019).

[59] J. P. Sethna, *Entropy, Order Parameters, and Complexity* (Oxford University Press, Oxford, UK, 2006).

[60] J. Gruber, L. F. Ng, S. Fong, Y. T. Wong, S. A. Koh, C.-B. Chen, G. Shui, W. F. Cheong, S. Schaffer, M. R. Wenk, *et al.*, PloS one **6**, e19444 (2011).

[61] R. S. Sohal and W. C. Orr, Free Radical Biology and Medicine **52**, 539 (2012).

[62] M. L. Hamilton, H. Van Remmen, J. A. Drake, H. Yang, Z. M. Guo, K. Kewitt, C. A. Walter, and A. Richardson, Proceedings of the National Academy of Sciences **98**, 10469 (2001).

[63] T. V. Pyrkov, I. S. Sokolov, and P. O. Fedichev, Aging (Albany NY) **13**, 7900 (2021).

[64] A. Haghani, C. Z. Li, T. R. Robeck, J. Zhang, A. T. Lu, J. Ablaeva, V. A. Acosta-Rodríguez, D. M. Adams, A. N. Alagaili, J. Almunia, *et al.*, Science **381**, eabq5693 (2023).

[65] Å. Johansson, S. Enroth, and U. Gyllensten, PloS one **8**, e67378 (2013).

[66] D. A. Petkovich, D. I. Podolskiy, A. V. Lobanov, S.-G. Lee, R. A. Miller, and V. N. Gladyshev, Cell metabolism **25**, 954 (2017).

[67] M. J. Bonder, S. J. Clark, F. Krueger, S. Luo, J. A. de Sousa, A. M. Hashtroud, T. M. Stubbs, A.-K. Stark, S. Rulands, O. Stegle, *et al.*, bioRxiv , 2023 (2023).

[68] Z. A. Medvedev, Biological Reviews **65**, 375 (1990).

[69] D. Harman, Science of Aging Knowledge Environment **2002**, cp14 (2002).

[70] D. Harman, Journal of the American Geriatrics Society **20**, 145 (1972).

[71] D. C. Wallace, Environmental and molecular mutagenesis **51**, 440 (2010).

[72] A. Linnane, T. Ozawa, S. Marzuki, and M. Tanaka, The Lancet **333**, 642 (1989).

[73] S. SE, Science **308**, 1909 (2005).

[74] S. Melov, J. Ravenscroft, S. Malik, M. S. Gill, D. W. Walker, P. E. Clayton, D. C. Wallace, B. Malfroy, S. R. Doctrow, and G. J. Lithgow, Science **289**, 1567 (2000).

[75] G. Bjelakovic, D. Nikolova, L. L. Gluud, R. G. Simonetti, and C. Gluud, Cochrane database of systematic reviews (2012).

[76] J. Gruber, L. F. Ng, and B. Halliwell, Free Radical Biology and Medicine **86**, S13 (2015).

[77] A. Trifunovic, A. Wredenberg, M. Falkenberg, J. N. Spelbrink, A. T. Rovio, C. E. Bruder, M. Bohlooly-Y, S. Gidlöf, A. Oldfors, R. Wibom, *et al.*, Nature **429**, 417 (2004).

[78] E. Balleza, E. R. Alvarez-Buylla, A. Chaos, S. Kauffman, I. Shmulevich, and M. Aldana, PLoS ONE **3**, e2456 (2008).

[79] K. G. Wilson, Scientific American **241**, 158 (1979).

[80] B. L. Strehler and A. S. Mildvan, Science **132**, 14 (1960).

[81] O. Karin, A. Agrawal, Z. Porat, V. Krizhanovsky, and U. Alon, Nature communications **10**, 5495 (2019).