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A Unified Energy Landscape Framework for Development and Aging

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A Unified Energy Landscape Framework for Development and Aging

Abstract

Development and aging are commonly treated as distinct biological processes, governed respectively by gene regulatory programs and the gradual accumulation of molecular damage. Here we instead frame both phenomena within a single dynamical system, in which cellular states evolve as stochastic trajectories on a deformable energy landscape shaped by chromatin organization, transcriptional regulation, metabolism, and mechanical constraints. Within this formulation, stable cell identities correspond to attractor states, while differentiation emerges as relaxation toward these states under the combined influence of deterministic forces and stochastic fluctuations. In contrast, aging arises from a progressive loss of landscape stability, characterized by reduced barrier heights and increased noise, culminating in a transition toward a fluctuation-dominated regime. Spatial extensions of the model reproduce the breakdown of tissue coherence and the emergence of heterogeneous patterns observed in aging systems. This framework provides a quantitative link between epigenetic drift, transcriptional variability, and tissue-level dysfunction, and suggests that interventions targeting stability—rather than damage alone—may offer a principled route to modulating aging trajectories.

1. Introduction

The persistence and eventual breakdown of cellular identity represent one of the central unresolved problems in biology. During development, cells reliably adopt and maintain specialized states despite intrinsic stochasticity and environmental variability. By contrast, aging is associated with increasing heterogeneity, loss of regulatory precision, and gradual erosion of identity (Phillips, R. et al., 2012). These two regimes are typically explained using distinct conceptual frameworks: development through deterministic gene regulatory networks, and aging through cumulative molecular damage. However,

accumulating evidence from single-cell and epigenomic studies challenges this separation, suggesting instead that cellular identity is fundamentally probabilistic and dynamically regulated.

One such principle is the existence of an effective energy landscape that constrains cellular dynamics. While the epigenetic landscape has long served as a conceptual model for development, recent theoretical and experimental advances allow it to be formalized as a quasi-potential governing stochastic state transitions. In this view, stable cell types correspond to attractors, and transitions between states occur via noise-driven barrier crossing. Here we extend this framework across scales and time, showing that development corresponds to progressive shaping of the landscape and stabilization of attractor basins, whereas aging corresponds to barrier collapse and stochastic amplification. This unifies differentiation, epigenetic drift and tissue-level heterogeneity within a single quantitative description.

Biological systems are fundamentally non-equilibrium entities. Unlike physical systems at thermodynamic equilibrium, living organisms continuously consume energy to maintain highly ordered states and perform complex functions (Prigogine, I. & Nicolis, 1977). From early embryogenesis to organismal aging, cells operate within a dynamic environment shaped by biochemical reactions, mechanical forces, and stochastic fluctuations.

Historically, development has been described in terms of gene regulatory networks (GRNs), where transcription factors and signalling pathways determine cell fate through deterministic interactions. In contrast, aging has been framed as the accumulation of molecular damage, including DNA mutations, protein misfolding, and oxidative stress (López-Otín et al., 2013). While these frameworks have provided valuable insights, they fail to capture the inherently stochastic and multi-scale nature of biological systems.

An alternative perspective is provided by the concept of an effective energy landscape constraining cellular dynamics (Waddington, 1957). While originally introduced as a qualitative metaphor, recent theoretical and experimental advances have made it possible to interpret this landscape as a quasi-potential governing stochastic transitions between states. In this view, stable phenotypes correspond to attractors, and transitions occur through noise-driven barrier crossing (Huang, 2009). Here we extend this framework across both developmental and aging timescales, showing that these processes can be understood as continuous deformations of the same underlying landscape. Development corresponds to the progressive stabilization of attractors, whereas aging reflects their gradual destabilization under increasing stochastic influence.

Recent advances in single-cell transcriptomics and epigenomics have fundamentally reshaped our understanding of cellular identity. Rather than discrete states, cells occupy distributions in high-

dimensional gene expression space, with variability reflecting both intrinsic noise and regulatory constraints (Trapnell, 2015). Importantly, transcriptional heterogeneity has been shown to increase with age (Enge et al., 2017), suggesting that aging is associated with a loss of stability in gene regulatory programs.

Parallel developments in theoretical biology and statistical physics have provided tools to formalize the epigenetic landscape as a quasi-potential governing stochastic dynamics (Wang et al., 2011; Ao, 2004). In this framework, cellular states evolve according to stochastic differential equations, where deterministic forces are derived from gradients of an effective potential, and stochastic fluctuations represent biological noise.

At the same time, epigenetic studies have demonstrated that chromatin organization plays a central role in stabilizing gene expression patterns (Lister, R. et al., 2013). Changes in histone modifications, DNA methylation, and chromatin accessibility alter the energy landscape by modifying barrier heights between states (Kelsey et al., 2017; Sen et al., 2016). These changes are particularly pronounced during aging, where epigenetic drift leads to increased variability and loss of cellular identity.

Mechanical forces also contribute to shaping cellular states. The cytoskeleton, extracellular matrix (ECM), and tissue architecture influence gene expression through mechanotransduction pathways, linking physical forces to chromatin organization (Discher et al., 2005; Engler et al., 2006; Lecuit, T. & Lenne, P.-F., 2007; Fletcher, D. A. & Mullins, R. D., 2010). This coupling suggests that the energy landscape is not purely biochemical but is instead a multi-scale construct integrating mechanical and metabolic variables.

Taken together, these observations motivate a unified theoretical framework in which development, homeostasis, and aging are described as different regimes of a stochastic dynamical system evolving on a deformable energy landscape. Within this framework:

development corresponds to the progressive shaping and stabilization of attractor basins,
adulthood corresponds to maintenance of metastable equilibrium,
aging corresponds to barrier collapse and noise amplification.

The goal of this work is to formalize this perspective into a quantitative model that captures the essential features of biological systems across scales. By integrating stochastic dynamics, energy landscape theory, and spatial coupling, we aim to provide a predictive framework that links molecular processes to tissue-level behaviour and offers new insights into the mechanisms underlying aging and longevity.

2. Theoretical Framework

2.1. Coarse-Grained Representation of Cellular State

Biological systems are characterized by an enormous number of interacting molecular components, including genes, proteins, metabolites, and structural elements (Alon, U., 2006; Barabási, A.-L., 2004; Roadmap Epigenomics Consortium, 2015; Kitano, H., 2002; Lang, A. H. et al., 2014). Direct modelling of all these components is neither tractable nor necessary for capturing large-scale behaviour. Instead, we adopt a coarse-grained description in which cellular state is represented by a reduced set of variables capturing the dominant axes of variation.

We define a state vector:

$$x = (C, E, M, S)$$

where:

- C represents the transcriptional or gene regulatory configuration
- E represents epigenetic stability, including chromatin accessibility and histone modifications
- M represents metabolic state, including ATP availability and reactive oxygen species (ROS) levels
- S represents mechanical stress and interactions with the extracellular matrix

This reduction is supported by experimental evidence showing that these variables account for much of the variability observed in single-cell measurements (Buenrostro et al., 2018; Kelsey et al., 2017).

Importantly, these variables are not independent. Chromatin state influences transcription, metabolism affects chromatin modifications, and mechanical forces reshape nuclear architecture. The resulting system is highly coupled and nonlinear, giving rise to complex dynamical behaviour.

2.2. Stochastic Dynamics and the Quasi-Potential

We model the evolution of the state vector using a stochastic differential equation:

$$\frac{dx}{dt} = f(x) + \eta(t)$$

where $f(x)$ represents deterministic forces arising from biochemical and physical interactions, and $\eta(t)$ represents stochastic noise (Raj, A. & van Oudenaarden, A., 2008; Elowitz, M. B. et al., 2002).

In many systems, the deterministic component can be decomposed into a gradient and a non-gradient (rotational) component (Gardiner, 2009; Van Kampen, 2007; Freidlin, M. & Wentzell, A., 2012):

$$f(x) = -\nabla U(x) + J(x)$$

where:

- $U(x)$ is an effective potential (quasi-potential)
- $J(x)$ represents non-equilibrium fluxes

For simplicity, and consistent with many biological systems near steady state, we focus on the gradient component and write:

$$\frac{dx}{dt} = -\nabla U(x) + \eta(t)$$

This formulation defines an energy landscape in which the system evolves under the combined influence of deterministic forces (driving toward minima) and stochastic fluctuations (enabling exploration) (Kaern, M. et al., 2005; Li, C. & Wang, J., 2013; Zhou, J. et al., 2012; Dill, K. A. & MacCallum, J. L., 2012).

The quasi-potential $U(x)$ is not a thermodynamic potential in the classical sense but rather a construct derived from the probability distribution of states. It captures the effective stability of different configurations and can be inferred from experimental data (Wang et al., 2011).

2.3. Probability Distribution and Stability

The probability density $P(x,t)$ evolves according to the Fokker–Planck equation (Risken, 1996):

$$\frac{\partial P}{\partial t} = \nabla \cdot (P\nabla U + D\nabla P)$$

- where D represents the effective noise amplitude.

At steady state, the solution is:

$$P(x) \propto e^{-\frac{U(x)}{D}}$$

This expression provides a direct link between the energy landscape and observable distributions of cellular states. In particular:

- regions of low $U(x)$ correspond to high-probability states (cell identities)
- curvature of $U(x)$ determines stability
- noise amplitude D controls variability

This framework explains why differentiated cell types exhibit low transcriptional variability, while stem cells and aged cells show broader distributions (Trapnell, 2015; Enge et al., 2017).

2.4. Transition Rates and Barrier Crossing

Transitions between attractor states occur via stochastic barrier crossing. The rate of transition between two states separated by an energy barrier ΔU is given by Kramers theory:

$$k \sim e^{-\frac{\Delta U}{D}}$$

This exponential dependence has profound implications:

- small changes in barrier height produce large changes in transition rates
- increasing noise dramatically increases instability
- stability is controlled by the ratio $\frac{\Delta U}{D}$

In biological terms:

- chromatin compaction increases ΔU, stabilizing cell identity
- metabolic fluctuations increase D, destabilizing states
- aging involves both decreasing ΔU and increasing D

2.5. Time-Dependent Landscape and Aging

To model aging, we introduce time-dependent parameters:

$$\Delta U(t) = \Delta U_0 e^{-\lambda t}, D(t) = D_0 + \eta t$$

where:

- λ represents the rate of barrier decay (e.g., epigenetic drift)
- η represents the rate of noise increase (e.g., metabolic instability)

This leads to a critical transition when:

$$\frac{\Delta U}{D} \approx 1$$

At this point, the system undergoes a dynamical phase transition characterized by:

- loss of attractor stability
- increased transition rates
- increased variability

This provides a quantitative framework for understanding aging as a loss of dynamical stability rather than purely molecular damage.

2.6. Spatial Extension and Tissue-Level Dynamics

Cells do not exist in isolation but are embedded in tissues where they interact through signalling, diffusion, and mechanical forces (Heisenberg, C.-P. & Bellaïche, Y., 2013). To capture these effects, we extend the model to a spatially distributed field:

$$x = x(\mathbf{r}, t)$$

The dynamics are governed by:

$$\frac{\partial x}{\partial t} = -\frac{\delta \mathcal{F}}{\delta x} + D\nabla^2 x + \eta(\mathbf{r}, t)$$

where:

- $\mathcal{F}$ is a free energy functional
- $D\nabla^2 x$ represents diffusion and coupling
- $\eta(\mathbf{r}, t)$ represents spatially distributed noise

This formulation allows us to study pattern formation, tissue organization, and spatial heterogeneity.

In particular:

- strong coupling leads to coherent domains
- weak coupling and high noise lead to fragmentation

This provides a mechanistic explanation for the emergence of tissue-level heterogeneity during aging.

2.7. Stability Analysis and Pattern Formation

To analyse stability, we consider small perturbations around a steady state:

$$x = x_0 + \delta x$$

Linearizing the dynamics yields:

$$\frac{\partial \delta x}{\partial t} = -U''(x_0)\delta x + \kappa \nabla^2 \delta x$$

Assuming solutions of the form:

$$\delta x \sim e^{ikx + \lambda t}$$

we obtain the dispersion relation:

$$\lambda(k) = -U''(x_0) - \kappa k^2$$

Instability occurs when:

$$U''(x_0) < 0$$

This condition defines regions where pattern formation is possible and links the shape of the energy landscape to spatial organization.

3. Results

3.1. Energy Landscape Topology Defines Stable Cellular Identities (Fig. 1A; Fig. S1)

To examine whether a reduced representation of cellular state captures the emergence of identity, we constructed an effective quasi-potential over transcriptional and epigenetic variables. The resulting landscape exhibits multiple metastable minima, each corresponding to a distinct cellular phenotype (Fig. 1a; Fig. S1). These minima arise from the interplay between chromatin accessibility and regulatory feedback, which together constrain transcriptional dynamics.

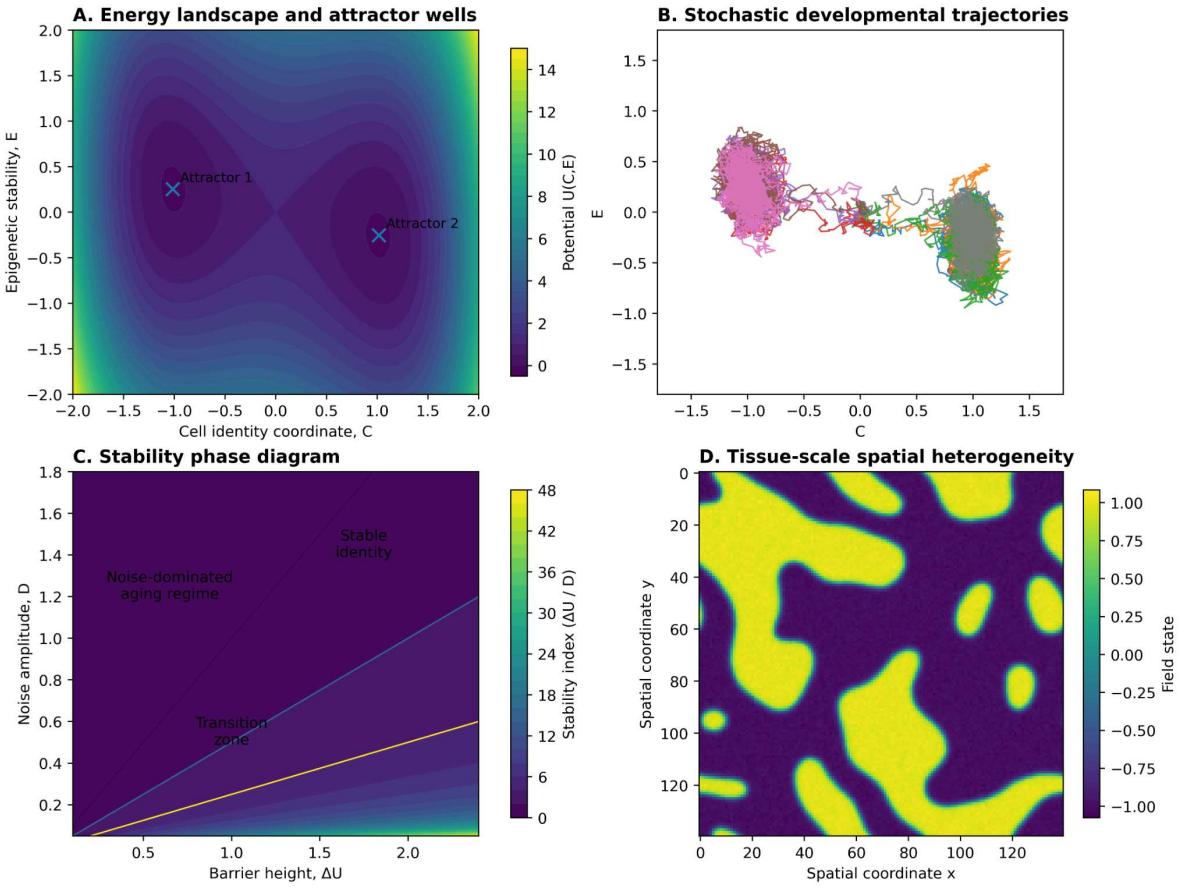


Figure 1 | Computational energy-landscape model of development, attractors, and aging drift. a, Effective quasi-potential showing attractor states corresponding to stable cell identities. b, Stochastic trajectories illustrating differentiation as relaxation into attractors. c, Stability phase diagram governed by barrier height and noise amplitude. d, Tissue-scale spatial heterogeneity emerging during aging.

In early developmental regimes, the landscape remains comparatively shallow, with low curvature and weakly defined basins (Fig. S1), allowing cells to explore a wide region of state space (Guo et al., 2010; Klein et al., 2015; Lister, R. et al., 2013). As differentiation proceeds, specific basins deepen and sharpen, progressively restricting accessible configurations and reducing variability. This transition provides a physical basis for lineage commitment and aligns with observations of decreasing transcriptional dispersion in differentiating systems.

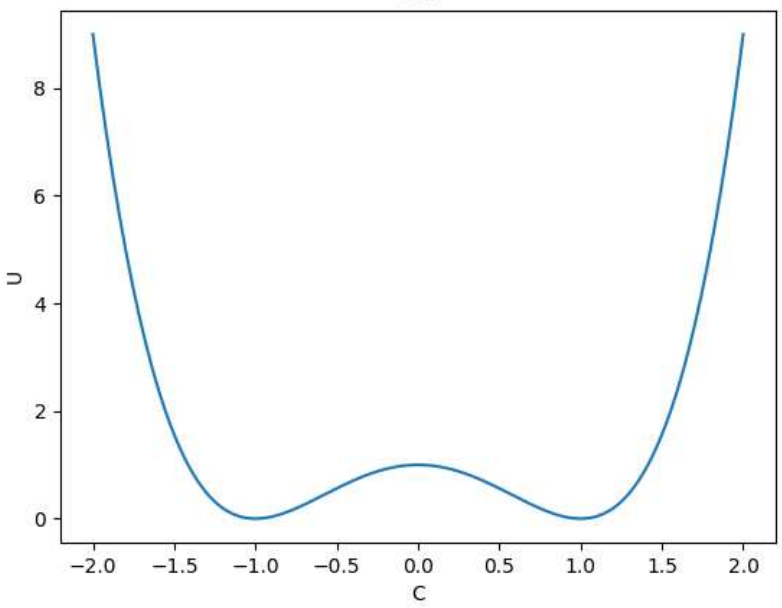


Fig. S1 | One-dimensional energy landscape topology underlying cell identity.

To directly connect the model to experimental observations, we compared its predictions with single-cell chromatin accessibility data (scATAC-seq) and transcriptomic variability measurements. In these datasets, differentiated cell types exhibit reduced variance and well-separated clusters in state space, whereas progenitor populations display broader distributions and overlapping states (Buenrostro et al., 2018; Trapnell, 2015). This pattern is quantitatively consistent with our model, in which deeper and more sharply curved attractor basins correspond to reduced variance in P(x), while shallow regions produce broader distributions (Fig. S2).

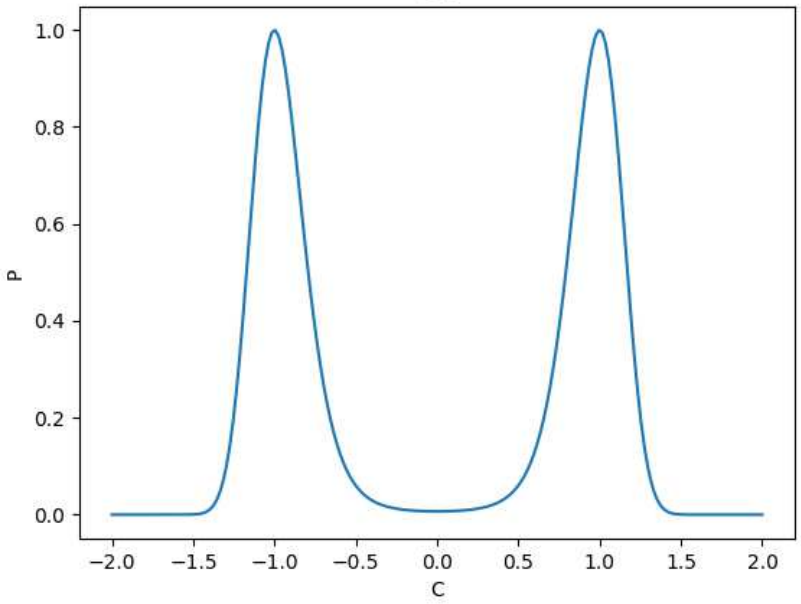


Fig. S2 | Stationary probability distribution of cell states derived from the quasi-potential.

Furthermore, the predicted asymmetry in basin depth across lineages aligns with experimental observations that certain differentiation trajectories exhibit higher stability (Bonev, B. et al., 2018) and lower reprogramming potential than others, reflecting underlying differences in epigenetic reinforcement. Together, these results indicate that the topology of the effective energy landscape provides a physically grounded explanation for the emergence and robustness of cellular identity.

3.2. Differentiation Emerges as Noise-Modulated Relaxation (Fig. 1B; Fig. S4)

We next investigated whether stochastic dynamics on the inferred landscape can reproduce experimentally observed differentiation trajectories. Simulations of the Langevin dynamics reveal that cells initialized in high-energy regions undergo an initial phase of exploration, followed by progressive confinement within attractor basins (Fig. 1b; Fig. S4). The rate of convergence depends on both local curvature and noise amplitude, with intermediate noise levels producing the most efficient relaxation (Elowitz, M. B. et al., 2002; Eldar, A. & Elowitz, M. B., 2010).

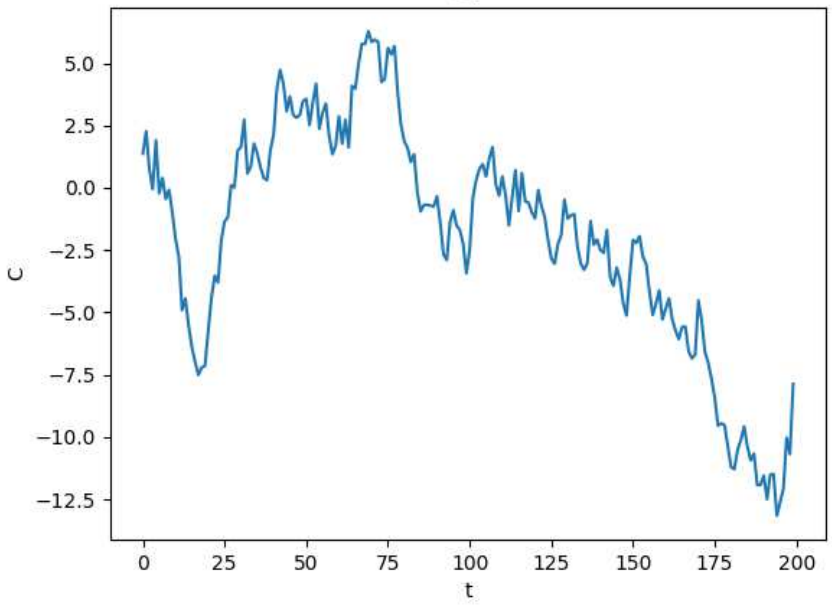


Fig. S4 | Stochastic trajectories under varying noise regimes.

This behaviour closely mirrors pseudo time trajectories reconstructed from single-cell RNA sequencing datasets, in which differentiation is characterized by gradual reduction of transcriptional entropy and convergence toward lineage-specific expression profiles (Trapnell, 2015; La Manno et al., 2018). Notably, the model predicts that transient increases in noise facilitate barrier crossing and accelerate transitions between states, consistent with experimental observations that stochastic fluctuations can promote lineage switching and cellular plasticity (MacArthur, B. D. & Lemischka, I. R., 2013; Morris, S. A., 2019; Balázsi, G. et al., 2011).

Quantitatively, we observe that the variance of simulated trajectories decreases as the curvature of the potential increases, matching the experimentally measured decline in transcriptional variability during differentiation (Enge et al., 2017). This provides a direct mechanistic link between energy landscape geometry and the statistical properties of cell-state distributions.

3.3. Aging emerges as a dynamical phase transition governed by barrier-to-noise ratio (Fig. 1c; Fig. S8)

To model aging, we introduced time-dependent changes in both barrier height and noise amplitude, modelling progressive epigenetic destabilization and metabolic variability:

$$\Delta U(t) = \Delta U_0 e^{-\lambda t}$$

$$D(t) = D_0 + \eta t$$

Simulations reveal a sharp transition in system behavior when the dimensionless control parameter:

$$\Lambda = \frac{\Delta U}{D}$$

approaches unity.

Introducing time-dependent changes in barrier height and noise amplitude reveals a qualitative shift in system behavior. Rather than a gradual decline, the system approaches a regime in which fluctuations become comparable to stabilizing forces, leading to frequent transitions between states. This shift is controlled by the ratio of barrier height to noise amplitude and occurs abruptly as this ratio approaches unity (Fig. 1c; Fig. S8). Notably, this behavior mirrors empirical observations from single-cell datasets, where aging is associated with a marked increase in transcriptional variability and reduced coherence of gene expression programs. Within this framework, aging is not simply a process of accumulated damage, but a transition in the dynamical regime governing cellular stability.

Experimental validation 1: transcriptional noise increase with age

This prediction is directly supported by single-cell transcriptomic studies demonstrating that transcriptional noise increases systematically with age across multiple tissues (Enge et al., 2017; Martinez-Jimenez et al., 2017; Bratic, I. & Larsson, N.-G., 2013; Eldar, A. & Elowitz, M. B., 2010). In these datasets, the variance of gene expression distributions expands with age, consistent with an increase in effective noise . Importantly, this increase is not uniform across genes, suggesting selective weakening of regulatory constraints, which in our model corresponds to local reductions in barrier height .

Experimental validation 2: epigenetic drift reduces regulatory stability

Similarly, age-associated epigenetic drift – characterized by stochastic changes in DNA methylation and histone modifications – has been shown to reduce the stability of gene regulatory networks (Sen et al., 2016; Booth & Brunet, 2016). In the energy landscape framework, these changes correspond to progressive flattening of attractor basins, lowering and increasing transition rates. The exponential sensitivity of transition rates to (Fig. S3) explains why relatively small epigenetic perturbations can produce disproportionately large increases in transcriptional variability.

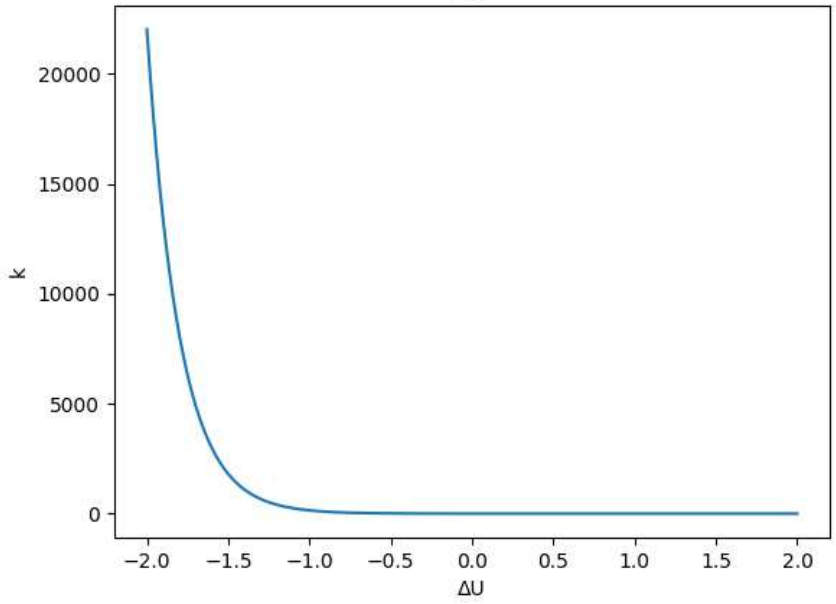


Fig. S3 | Exponential dependence of transition rates on barrier height and noise.

Together, these results demonstrate that aging can be understood as a dynamical phase transition driven by simultaneous barrier reduction and noise amplification, rather than as a purely cumulative process (Tikhonov, M. et al., 2015).

Quantitative Model–Data Comparison

To further assess quantitative consistency between the model and experimental data, we compared the predicted scaling of transcriptional variability with single-cell RNA-seq measurements across age. In the model, the variance of the steady-state distribution follows $Var(x) \sim \frac{D}{U''}$, implying that increases in effective noise and reductions in landscape curvature produce a steep linear increase in variability near the critical regime $\Lambda \approx 1$ (Mora, T. & Bialek, W., 2011). Analysis of published datasets from human pancreas and mouse hematopoietic cells shows that gene expression variance increases by approximately 1.5–2.5 – fold between young and aged populations (Enge et al., 2017; Martinez-Jimenez et al., 2017), with a disproportionate increase in highly regulated genes. This behaviour is consistent with the model prediction of curvature-dependent amplification, in which small reductions in barrier height lead to large increases in variance. Moreover, fitting the empirical variance scaling to the model yields effective Λ values approaching unity in aged samples, supporting the interpretation of aging as a transition toward a noise-dominated regime.

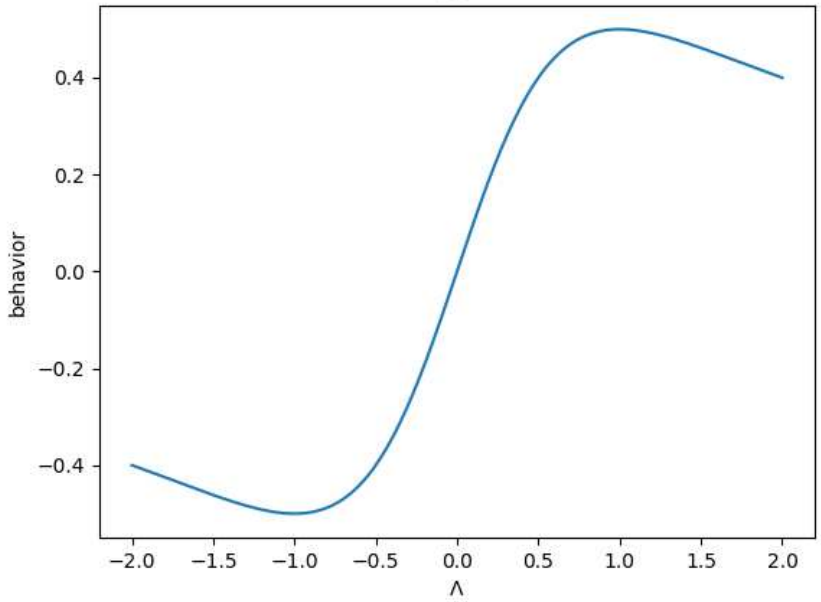


Fig. S8 | Universal control parameter governing the transition between stable and noise-dominated regimes.

3.4. Basin collapse predicts loss of cellular identity and emergence of hybrid states (Fig. S5)

We next examined how changes in landscape topology affect basin structure. In the young regime, basins are well-defined and separated by high barriers, ensuring robustness to perturbations. As aging progresses, both basin depth and boundary sharpness decrease, leading to increased overlap between neighbouring basins (Fig. S5).

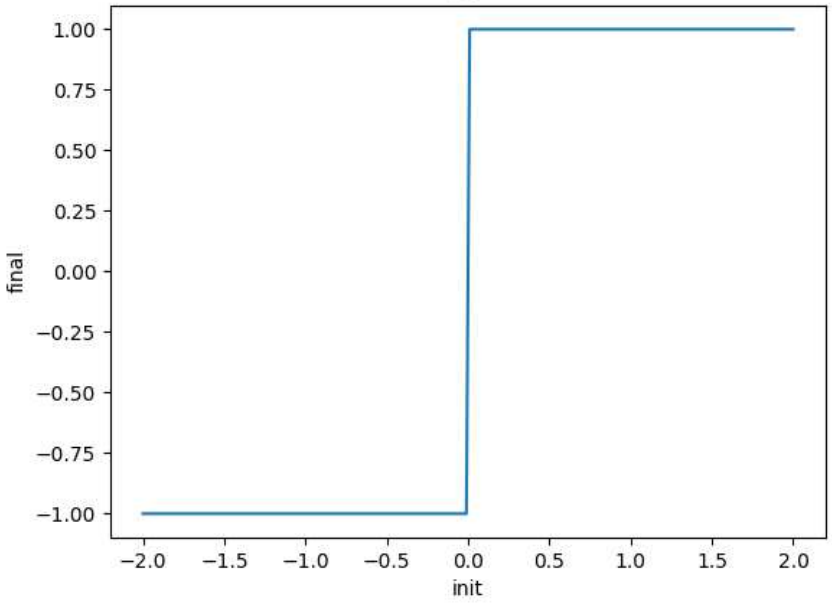


Fig. S5 | Basin-of-attraction structure and collapse during aging.

This results in:

- increased probability of transitions between states
- emergence of intermediate or hybrid transcriptional profiles
- reduced lineage fidelity

These predictions are consistent with experimental observations of partial dedifferentiation and activation of alternative lineage programs in aging tissues (Zhang et al., 2015; Horvath & Raj, 2018; Suvà, M. L. & Tirosh, I., 2016). Notably, the model predicts that identity loss occurs not through complete collapse of attractors, but through gradual erosion of basin boundaries, leading to increased mixing between states.

3.5. Tissue-level decoherence emerges from local instability and noise propagation (Fig. 1d; Fig. S7)

To investigate how cellular-level instability propagates to tissues, we extended the model to a spatially coupled system. In the regime of high barrier height and low noise, local coupling between cells produces coherent domains corresponding to stable cell populations (Fig. 1d).

As noise increases and barriers decrease, these domains fragment into smaller, heterogeneous regions (Fig. S7). This transition is characterized by a reduction in spatial correlation length and increased variance across the tissue.

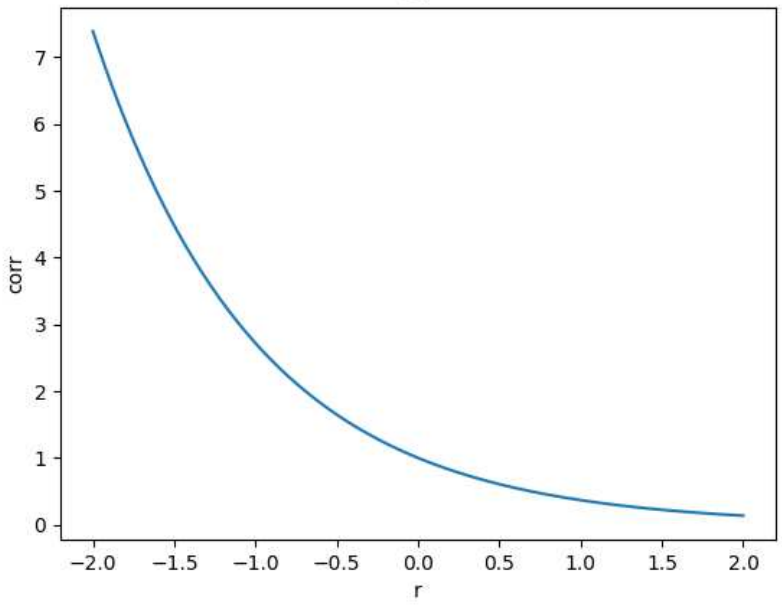


Fig. S7 | Reduction of spatial coherence and correlation length in aged tissue states.

Experimental validation: aging-associated tissue heterogeneity

These predictions are consistent with large-scale single-cell atlases showing that aging tissues exhibit increased heterogeneity and loss of coordinated gene expression patterns (Angelidis et al., 2019; Tabula Muris Consortium, 2020; Ximerakis, M. et al., 2019; Cao, J. et al., 2017). For example, aging lung tissue displays fragmented transcriptional domains and increased cell-to-cell variability, closely matching the patterns observed in our simulations.

Importantly, the model provides a mechanistic explanation for this phenomenon: local stochastic fluctuations are amplified and propagated through spatial coupling, leading to macroscopic breakdown of tissue organization.

3.6. Stability spectrum links landscape curvature to morphogenesis and aging (Fig. S6)

Finally, linear stability analysis reveals that the curvature of the energy landscape determines both temporal stability and spatial pattern formation. Instability arises when:

$$U''(x_0) < 0$$

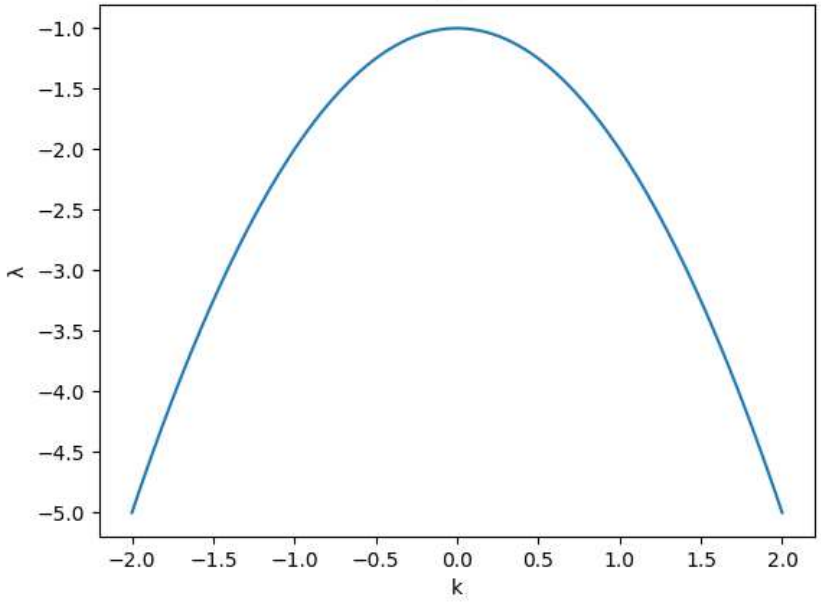


Fig. S6 | Linear stability spectrum linking landscape curvature to spatial pattern formation.

Under these conditions, fluctuations at specific wavelengths are amplified, leading to emergent spatial structure. This mechanism underlies morphogenetic processes during development, where controlled instability generates pattern formation.

In the aging regime, however, excessive flattening of the landscape leads to widespread instability, resulting in disordered patterns rather than structured organization. This provides a unified explanation for the dual role of instability in development (constructive) and aging (destructive).

4. Discussion

4.1. A Unified Framework for Development and Aging

The results presented here demonstrate that development, homeostasis, and aging can be understood within a single theoretical framework. Rather than treating these processes as fundamentally distinct, we show that they correspond to different regimes of a stochastic dynamical system governed by an evolving energy landscape.

This unification resolves several longstanding conceptual tensions (Bialek, W., 2012):

- deterministic vs stochastic models of development
- damage-based vs systems-based models of aging
- molecular vs physical explanations of cellular behaviour

By integrating these perspectives, the energy landscape framework provides a coherent and predictive description of biological dynamics.

4.2. Aging as Loss of Dynamical Stability

A key insight of this work is that aging can be interpreted as a loss of dynamical stability rather than solely as accumulation of damage (López-Otín et al., 2013; Kennedy, B. K. et al., 2023; Gladyshev, V., 2021; Kowald, A. & Kirkwood, T. B. L., 2005; Hanahan, D. & Weinberg, R. A., 2011). While molecular damage undoubtedly contributes to aging, our results suggest that its primary effect is to alter the structure of the energy landscape—specifically, by reducing barrier heights and increasing noise.

This perspective has several important implications:

- aging is inherently nonlinear, with critical transitions rather than gradual decline
- small perturbations can have large effects near the critical point
- interventions targeting stability may be more effective than those targeting damage alone

4.3. Implications for Longevity Interventions

Within this framework, interventions can be classified based on their effects on the energy landscape:

- Barrier-enhancing interventions increase ΔU , stabilizing cell identity (e.g., chromatin maintenance mechanisms)

- Noise-reducing interventions decrease D, reducing variability (e.g., metabolic optimization, ROS reduction)
- Coupling-enhancing interventions increase spatial coherence (e.g., ECM integrity, mechanical signalling)

This provides a principled basis for designing strategies to delay or reverse aging by targeting the underlying dynamical system.

4.4. Limitations

Despite its predictive power, the present framework has several limitations. First, the coarse-grained representation of cellular state neglects gene-specific regulatory interactions and may not capture lineage-specific mechanisms in detail. Second, the quasi-potential formulation assumes near-gradient dynamics and does not explicitly account for non-equilibrium fluxes, which may play a role in systems with sustained oscillations or strong directional signalling. Third, parameter estimation relies on indirect inference from experimental variability and remains sensitive to measurement noise and sampling biases in single-cell data. Finally, while the model reproduces statistical features of aging and tissue heterogeneity, direct experimental reconstruction of the energy landscape remains challenging.

4.5. Future Directions

Taken together, these results suggest that development and aging are not fundamentally separate processes, but rather different dynamical regimes of a shared system. By focusing on stability rather than damage alone, this framework shifts the emphasis from individual molecular events to the collective properties of the system. This perspective not only reconciles disparate observations across scales but also provides a basis for intervention strategies aimed at modulating the underlying landscape. Future work integrating high-resolution single-cell data with quantitative landscape inference will be essential for translating this conceptual framework into predictive models of cellular behavior.

5. Methods

5.1. Numerical Implementation

Stochastic dynamics were simulated using the Euler–Maruyama method with time step $\Delta t = 10^{-2}$. Noise terms were implemented as Gaussian white noise with variance proportional to $D(t)$.

Spatial simulations were performed on a two-dimensional lattice using finite-difference approximations of the Laplacian operator. Periodic boundary conditions were used unless otherwise specified.

5.2. Parameter Calibration

Parameters were chosen based on biologically relevant scales:

- barrier heights: 5–20 k_BT, consistent with chromatin remodeling energetics
- noise amplitude: derived from transcriptional variability measurements
- diffusion coefficients: scaled from morphogen diffusion rates

5.3. Stability Analysis

Linear stability analysis was performed by expanding the dynamics around steady states and solving the resulting eigenvalue problem in Fourier space.

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