Review

Written in development and lost in ageing: the grammar of cellular identity

https://doi.org/10.1038/s41586-026-10955-0

Received: 22 December 2025

Accepted: 27 July 2026

Published online: 30 September 2026

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Ageing has been described through many theoretical frameworks, yet its mechanistic basis remains unresolved. Here we propose that ageing reflects progressive decanalization of mammalian cell identity, driven by erosion of a regulatory grammar written during development. Extending Waddington's epigenetic landscape, development canalizes cell fates through globally coordinated chromatin programs that establish identity constraints across multiple timescales. Subsequently, these constraints can only be maintained through local mechanisms with limited fidelity. The asymmetry between high-fidelity writing and imperfect maintenance generates predictable drift that accumulates with biological time. Antagonistic chromatin pathways, particularly polycomb repressive complex 2 (PRC2)-mediated repression opposed by H3K4/36 methylation and RNA polymerase II binding, enforce identity boundaries through mutual constraint. With age, this balance erodes. Consistent with this framework, the vast majority of age-associated DNA methylation gain in somatic mitotic tissues occurs at PRC2-bound low-methylated regions, indicating that these domains function as conserved coordinates of slow-layer drift. This model explains cross-tissue ageing signatures, developmental timing-to-lifespan correlations and robustness of pan-mammalian epigenetic ageing clocks. It provides testable predictions for interventions that stabilize architecture to preserve cellular identity and function.

Long-lived human cells maintain stable identities for years to decades despite constant molecular turnover, environmental perturbations and metabolic fluctuations[1–4]. This stability is not the product of a single pathway but of a layered regulatory architecture spanning multiple dynamical timescales[5,6]. At the fastest timescales, transcription factor binding, enhancer activation and signalling cascades fluctuate rapidly in response to metabolic, mechanical and inflammatory cues[7–10]. At intermediate timescales, cells transition through activation states, quiescent states and transient stress-induced configurations[11–14]. At the slowest timescales, chromatin architecture and large-scale histone modification landscapes provide long-lived constraints on transcriptional potential[15–18]. Together, these layers define the rules governing how identity is established, maintained and altered over the lifespan.

Ageing perturbs each of these layers[19], but the most stereotyped, cross-tissue and cross-species features of ageing arise from distortions of the slowest processes[20–26]. DNA methylation changes at Polycomb-associated CpGs progress in a predictable manner across 185 mammalian species[20,27]. Moreover, 90% of age-related DNA methylation gain in somatic mitotic tissues occurs within low-methylated regions that are highly bound by PRC2 (ref. 27). Bivalent promoters and developmental regulatory domains show selective erosion of histone modification fidelity with age in multiple tissues[28–31]. Lamina-associated regions become less stably tethered in several contexts[32,33]. Histone variant composition shifts gradually[34]. These slow-layer perturbations correlate with increased transcriptional variability and loss of coordination[35,36], mixed identity states[6] and altered responsiveness to stress signals[37,38], suggesting that drift in the slow layer contributes broadly to age-associated transcriptional and functional changes.

Here we articulate a grammar of cell identity maintenance across these layers. Cell identity, as used here, is the stable regulatory state that restricts a cell's gene expression programs to those of a defined cell type. By grammar, we refer to a framework of constraints, attractors and transition rules that govern how regulatory modules can be combined, how cell identities are stabilized and how perturbations propagate across scales. Identity is maintained through two coupled mechanisms. Lineage-determining transcription factors[39,40] actively sustain cell-type-specific programs, while slow-layer chromatin constraints repress and regulate alternatives. These layers are interdependent. Identity transcription factors require the chromatin accessibility that the slow layer provides, and the slow layer depends on identity transcription factor activity to reinforce its boundaries. We focus primarily on the slow layer because it represents the more vulnerable, less reversible component: identity transcription factors can be re-expressed or re-activated, but once slow-layer memory is lost, the chromatin landscape they require is not recoverable.

The grammar

The regulatory grammar of mammalian identity is built from three interdependent layers (Fig. 1). Each layer operates on characteristic timescales and contributes distinct forms of constraint.

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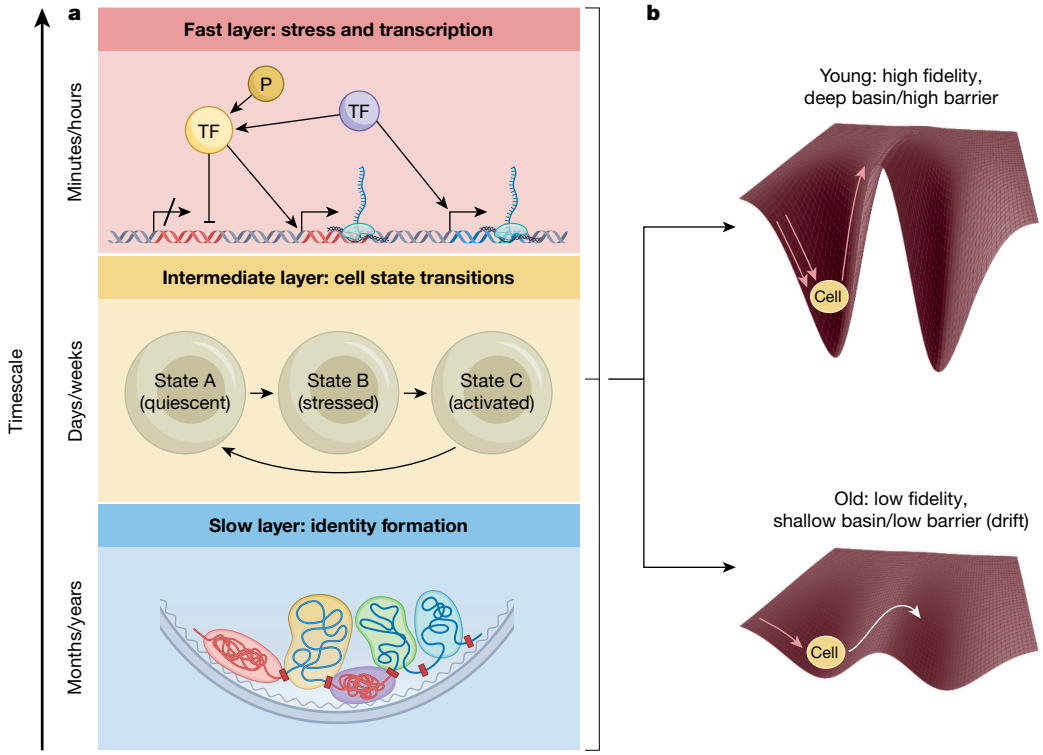


Fig. 1 | A multiscale grammar of cellular identity maintenance. a, Mammalian identity is governed by three coupled layers operating on distinct timescales. The fast layer comprises rapid signalling and transcription factor binding (for example, AP-1) in response to acute stimuli. The intermediate layer represents metastable functional configurations (for example, quiescence versus activation). The slow layer encodes long-term constraints through chromatin architecture, Polycomb domains and nuclear organization. **b**, These layers define an epigenetic attractor landscape. In youth (top), intact slow-layer architecture creates deep basins of attraction, ensuring that fast-layer stochasticity (noise) does not permanently alter cell state. In ageing (bottom), the erosion of slow-layer constraints (for example, PRC2 loss, DNA methylation drift) flattens the attractor basin. Consequently, physiological noise that was harmless in youth now drives the cell into spurious, mixed-identity states (drift). The diagram in **b** was created using BioRender; Yücel, A. https://BioRender.com/sdlia8s (2026).

The fast layer consists of rapid transcription factor dynamics, enhancer activation and context-dependent signalling. Transcription factors bind to and unbind from regulatory elements on timescales of seconds to minutes, and their occupancy reflects both cellular history and acute physiological state. Stress-responsive factors such as AP-1 provide a clear example[41–43]. AP-1 binds broadly to accessible chromatin within minutes of activation, remodels local accessibility, and alters enhancer communities during inflammation, mechanical stress and metabolic challenge[44,45]. These events have central roles in normal physiology, but their impact is constrained when slow-layer architecture is intact. Deeply repressed promoters, insulated domains and lamina-associated regions resist fast-layer invasion, ensuring that acute signals do not compromise identity.

The intermediate layer comprises transitions between distinct functional configurations, such as shifts between quiescence and activation and entry into and exit from stress-induced and inflammatory states. These transitions unfold over days to weeks through coordinated regulatory and metabolic changes[46–49]. The geometry of state space, including the depth of attractor basins, determines how easily cells move between these configurations[47,50]. Basin depth quantifies canalization in the Waddingtonian sense, the buffering of a developmental outcome against perturbation[51]. Shallow basins facilitate rapid shifts in response to extrinsic cues, whereas deep basins maintain identity under fluctuating conditions. The intermediate layer integrates inputs from the fast layer but is anchored by the slow layer. Healthy cells can undergo bidirectional state transitions, while this function declines with age, exemplified by fibrotic states and neuroinflammation[6,52,53].

The slow layer stores long-lived constraints in chromatin architecture. Polycomb-mediated repression, bivalent promoters, DNA methylation, lamina associations and large-scale insulation structures together define the enduring rules that restrict which regulatory programs can be accessed[16,17,54–60]. PRC2 establishes and maintains repression at developmental regulators and alternative lineage genes. PRC2 is recruited preferentially to CpG islands, CG-rich sequences associated with the transcription start sites of approximately 70% of protein-coding genes[61], where it establishes H3K27me3-mediated repression at developmental and lineage-alternative promoters. H3K36 methylation opposes PRC2 activity through a direct structural mechanism[62]. Bivalent promoters carry both H3K4me3 and H3K27me3 in progenitors, poising lineage genes for activation or repression, or stable low expression[63,64]. Lamina-associated domains restrict the spatial proximity between repressive and active compartments[65]. Insulation boundaries constrain enhancer–promoter communication and prevent inappropriate regulatory interactions[66–68]. These elements form the substrate on which faster processes operate. The progressive replacement of canonical histone H3.1/2 with histone H3.3 in postmitotic and slowly dividing cells influences nucleosome stability and recruitment of modifying enzymes, adding another dimension to slow-layer dynamics[34,69].

At fast and intermediate timescales, epigenetic modifications largely respond to and stabilize transcriptional programs initiated by signalling and transcription factor activity. However, at the slow-layer timescale, chromatin architecture constrains which regulatory programs remain accessible, determining not what is expressed but what can be expressed. In the intestinal epithelium, CDX2 controls chromatin

accessibility at identity enhancers, and its depletion collapses the chromatin environment that partner transcription factors such as HNF4A require for binding, disrupting tissue-specific gene expression even though HNF4A protein remains available[70]. Slow-layer perturbations increase susceptibility to stress-driven transcription factor redistribution. When slow-layer architecture remains intact, even substantial intermediate-layer shifts can be reversed. Severe physiological stress transiently increases epigenetic age, with full recovery after stress resolution[71]. Multi-omics analysis across 22 mouse cell types reveals a loss of accessibility at cell identity regulatory elements and gain at stress-associated regions during ageing. Crucially, this same pattern can be phenocopied in young cells either by overexpressing AP-1 factors or by inhibiting EZH2, suggesting that the age-associated change reflects an altered balance between fast and slow layers rather than independent processes[72]. Weakening of Polycomb repression lowers the threshold for AP-1 binding, broadening the set of accessible regulatory elements, while repeated AP-1 activation destabilizes bivalent domains and reduces H3K27me3, linking fast-layer events to slow-layer erosion. This antagonism maintains boundary fidelity in youth. The framework therefore explains why fast-layer fluctuations that are innocuous initially during development produce identity drift in aged cells[6,72]. The same AP-1 activation that was once absorbed by intact slow-layer architecture now propagates into lasting chromatin changes. Recent work reveals the molecular basis of this conversion from acute to chronic. AP-1 activation during colonic inflammation generates *cis*-encoded chromatin memories that persist, are inherited through stem cell divisions and prime cells for oncogenic transformation after subsequent mutation[73]. Similarly, melanoma cells encode AP-1-dependent therapy responses as persistent *cis*-acting chromatin accessibility changes[74]. These findings demonstrate that fast-layer events are not merely transient. When slow-layer maintenance is insufficient to erase them, they accumulate as durable modifications to the regulatory landscape, providing a mechanism through which repeated or prolonged stress converts reversible perturbations into chronic identity erosion.

Writing the grammar

The grammar of identity is written during development through organism-wide coordination. Morphogen gradients, systemic signals and temporal cues direct chromatin remodelling across the organism[75], establishing *cis*-acting somatic memory[18]. These constraints encode identity as analogue epigenetic memory, defined as a regulatory state that maintains heritable and continuous levels of gene expression, not binary states[76]. These programs reach completion as the bistable feedback loops driving bivalent domain resolution settle into stable equilibria. Growth-promoting pathways such as mTOR persist beyond this point[77], but the chromatin-writing programs they participated in have run their course, settling into maintenance states that can only erode. Adult stem cells retain local writing capacity when generating differentiated progeny, but *cis*-regulated memory established during development decays progressively along the adult lineage tree. Each differentiation event proceeds from an already-eroded template, and no endogenous mechanism exists to reverse accumulated slow-layer drift post-differentiation. The critical asymmetry is that developmental writing established these constraints de novo through globally coordinated programs, whereas adult differentiation operates on a substrate that has been maintained, and never rewritten, since maturation[78,79]. Differentiated cells established during development depend on maintenance alone, making analogue memory vulnerable to degradation. This asymmetry is the architectural origin of ageing. This architecture explains why developmental timing, basin depth and adult stability are intertwined. Species that invest more time in coordinated developmental writing establish deeper constraints that erode more slowly under maintenance-only conditions. Here we extend canalization beyond development into adult life. The chromatin architecture that canalizes cell fate during development persists as a slow-layer constraint, continuing to buffer cell identity against perturbation long after the developmental program ends; its progressive erosion produces the loss of cell identity and functional capacity that characterizes ageing. We term this process epigenetic decanalization.

Developmental epigenetics studies illustrate how slow-layer architecture is established before terminal differentiation. Experiments in human embryonic-stem-cell-derived neural systems demonstrate that loss of menin or SUZ12 accelerates the onset of PAX6 expression and developmental timing. This mechanism is shared during definitive endoderm and cardiomyocyte differentiation, pointing to a universal driver mechanism across three germ layers[57]. These perturbations alter the balance of H3K4me3 and H3K27me3 at bivalent promoters, demonstrating that bivalency regulates developmental tempo[57]. More directly, work on human cortical neuron maturation has identified an epigenetic barrier that sets the timing of differentiation. The pace of human brain development is highly protracted compared with most other species; cortical neurons take months to years to develop adult functions compared with only a few weeks in mice. This protracted timing is retained in cortical neurons derived from human pluripotent stem cells even after transplantation into the mouse brain, demonstrating that a cell-intrinsic clock sets the pace of neuronal maturation[80]. This clock operates through EZH2, EHMT1/2 and DOT1L, which together maintain maturation programs at bivalent promoters in a poised state that is gradually released over time[16]. Transient inhibition of these enzymes at the progenitor stage primes newly born neurons to rapidly acquire mature properties[16,81]. These observations reveal that slow-layer constraints, including Polycomb domain formation and bivalent promoter resolution, are encoded during early lineage commitment and set the pace of differentiation[55].

Deep attractor basins require slow and energy-intensive writing. Establishing lineage-specific enhancer communities, repressive domains and spatial genome organization demands high global plasticity, abundant chromatin remodelling and extensive signalling integration[66,82–85]. Species with long developmental periods invest heavily in writing these constraints[16,86,87]. The extended timeline reflects prolonged maintenance of bivalent chromatin states and gradual resolution of epigenetic barriers[16,80,88]. Within the grammar framework, this pattern is naturally interpreted as deeper attractor basins and sharper lineage boundaries in species that invest more in slow-layer writing, although basin depth and its connection to more stable states have not yet been measured directly across species. These differences align with the correlation between developmental time and lifespan observed across mammals[89,90].

Manipulations that accelerate developmental progression demonstrate the cost of shallow basins. Experimental perturbation of bivalent promoter regulation or PRC2 function accelerates differentiation and destabilizes transcriptional programs. Studies in neural and haematopoietic lineages show that reducing bivalency or disrupting core PRC2 components shortens progenitor stages and prematurely resolves fate trajectories[55–57]. Loss of PRC2-dependent repression leads to derepression of lineage-inappropriate genes and breakdown of transcriptional memory[18,91,92]. These outcomes highlight that rapid developmental writing compromises basin depth, increasing susceptibility to later drift. Conversely, embryonic stem cells do not exhibit canonical epigenetic ageing signatures because they lack fully written slow-layer constraints and have highly dynamic chromatin[17,93,94]. Somatic cells largely reset epigenetic ageing marks during reprogramming to induced pluripotent stem cells, whereas direct transdifferentiation tends to preserve age-associated features[95,96]. Induced pluripotent stem cell redifferentiation produces somatic cells that are not only young but also immature[97], because it engages the developmental writing program and resets *cis*-regulated memory[18,98], erasing the marks of ageing in the process. By contrast, direct transdifferentiation is driven by lineage transcription factors such as NGN2 and ASCL1, which install a new

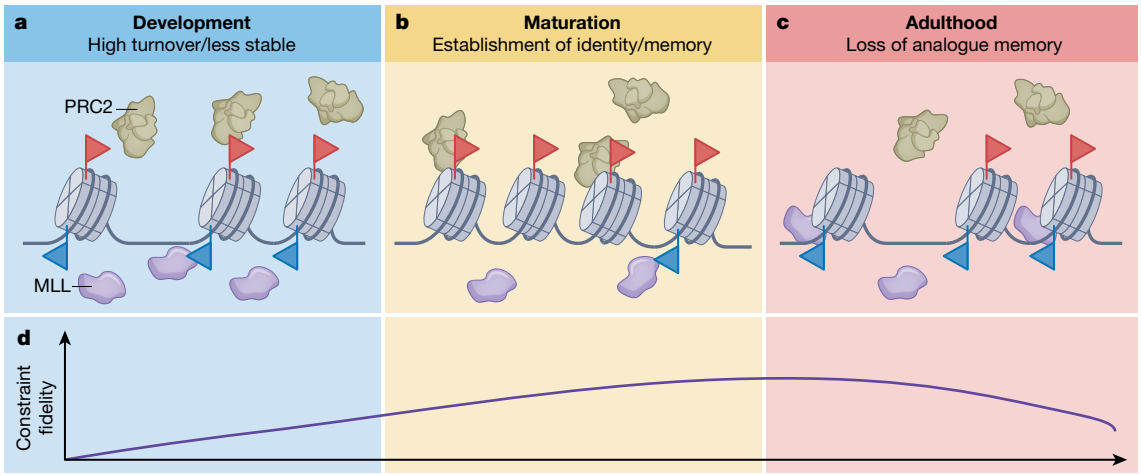


Fig. 2 | The temporal asymmetry of grammar writing versus maintenance. **a**, The slow-layer constraints that define cellular identity are established through a high-energy, globally coordinated process during development, resulting in deep architectural fidelity (for example, robust PRC2 domains, unmethylated CpGs). **b**,**c**, In maturity (**b**) and later life (**c**), there is no global mechanism to rewrite this architecture. Instead, cells rely on imperfect, local analogue maintenance (for example, histone turnover and remodification). Over time, the error rate of maintenance further exceeds repair, leading to a gradual erosion of constraints, evidenced by the loss of H3K27me3, the gain of DNA methylation at Polycomb targets (the epigenetic clock) and increased transcriptional noise. **d**, The graph illustrates this trajectory, showing peak fidelity at maturity followed by inevitable decay due to the maintenance gap.

identity without resetting *cis*-memory. ASCL1 binds to its target sites within hours of expression but activates transcription only in cases in which a permissive trivalent chromatin signature is already present, and the same factors fail to convert cells lacking this chromatin configuration[99]. Induced neurons from aged donors recapitulate features of naturally aged human brain neurons, including RNA-binding-protein dysregulation and chronic stress-response activation, and Alzheimer's disease-associated genes are robustly differentially expressed in induced neurons from patient fibroblasts even though the parental fibroblasts show no such expression difference[96,100,101]. The phenotypic signatures of ageing are therefore downstream of cell identity, while the underlying epigenetic drift is encoded in *cis*, in slow-layer chromatin architecture that lineage transcription factors alone cannot reset.

Together, these observations suggest that developmental tempo influences how strongly adult cell identity is stabilized and how readily it drifts with age (Fig. 2). Epigenetic errors do occur during development as a result of stochastic processes[102], yet developmental errors and post-developmental drift are mechanistically distinct, as the drift described here is a consequence of epigenetic architecture. Writing quality determines constraint robustness, which determines erosion rate. Individuals whose developmental programs executed with higher fidelity enter adulthood with deeper basins that erode more slowly.

Slow-layer drift emerges when the frequency of fast-layer perturbations exceeds the capacity of slow maintenance loops to restore baseline architecture. Each stress-driven burst of AP-1, metabolic fluctuation, double-strand break or transient transcriptional activation creates a small deviation in chromatin state, and analogue repair operates on longer intervals with limited fidelity. Over time, the imbalance between high-frequency perturbation and low-frequency maintenance produces cumulative displacement of PRC2-mediated marks, lamina contacts and insulation boundaries. This rate imbalance converts developmental architecture into a time-integrating variable, generating predictable ageing trajectories without requiring any active ageing program.

Genomic coordinates of slow-layer drift

Among slow-layer features, PRC2 low-methylated regions (PRC2-LMRs) exhibit some of the most consistent age-associated changes across mammals. Analyses across mammals have shown that CpGs gaining methylation with age are disproportionately enriched within PRC2-associated regions, comprising around 90% of age-related hypermethylation in human and mouse. This pattern is observed across multiple tissues and species, suggesting that PRC2-LMR methylation gain represents a conserved genomic coordinate of slow-layer drift[27]. Although PRC2-LMR erosion captures one dominant axis of ageing, slow-layer drift probably reflects the combined failure of multiple antagonistic systems that maintain architectural fidelity. These sites are not independent biomarkers, but are interconnected nodes within a regulatory network of which the coordinated decline constitutes decanalization. Consistent with this, epigenetic editing at individual age-associated CpGs evokes reproducible bystander modifications elsewhere, indicating that age-related changes represent coordinated network responses rather than isolated drift events[103]. However, at specific loci, this erosion has direct functional consequences: the senescence-associated CDKN2A and longevity-associated Klotho genes are both directly regulated by PRC2, linking slow-layer drift to established causal nodes of ageing[104]. Decline in any single component may not be catastrophic, but concurrent weakening across several axes reduces redundancy and increases the probability of identity excursions. This layered vulnerability provides a mechanistic explanation for why ageing progresses gradually rather than catastrophically, and why diverse tissues exhibit convergent epigenomic signatures despite possessing distinct regulatory networks.

These regions combine multiple vulnerability factors: they require ongoing analogue maintenance[76] of developmentally written states, occupy metastable positions sensitive to modification balance[105,106] and sit at bottlenecks in regulatory networks where small changes propagate widely.

The mechanism underlying predictable methylation gain at these sites probably involves declining PRC2 occupancy with age. PRC2 binding protects unmethylated CpG-rich regions from methylation[107], and age-related decline in PRC2 occupancy enables de novo methylation.

Epigenetic clocks capture this slow-layer erosion. The CpGs with the highest predictive value for age across tissues and species are enriched within Polycomb-associated regions[20,21]. We argue that these clocks do not track random methylation but instead largely quantify predictable drift within slow-layer structures. This explains why clocks generalize across mammals with widely divergent lifespans: Polycomb-associated regulatory logic is deeply conserved, and its maintenance is analogue

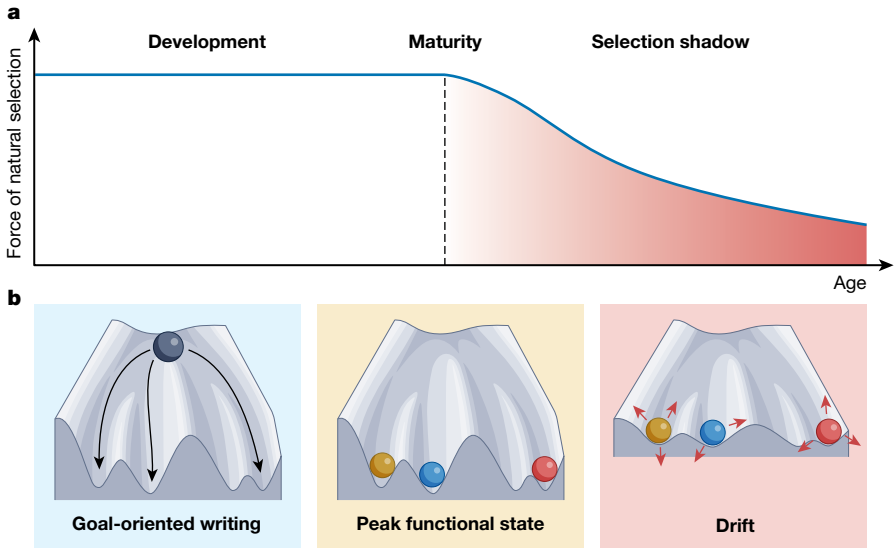


Fig. 3 | The evolutionary origin of epigenetic drift. a, The trajectory of natural selection dictates the stability of the epigenetic landscape. **b**, During development (left), the identity grammar is established through a globally coordinated process selected for high fidelity, creating deep attractor basins. At maturity (centre), the system reaches its peak functional state where established constraints effectively contain cellular identity. As the organism enters the selection shadow (right), the force of natural selection declines, leaving the system reliant on local analogue maintenance. In the absence of selective pressure to strictly enforce the original grammar, the landscape flattens (erosion of constraints), allowing cells to drift stochastically from their defined states.

and drift-prone. Thus, PRC2-LMR methylation gain tracks a conserved form of chromatin drift that accumulates with biological age[27].

An evolutionary perspective on the grammar

Any model of ageing must explain why ageing is widespread across multicellular life and why exceptional species appear to escape or delay it. The multilayered grammar framework offers a unified evolutionary logic for organisms with differentiated somatic lineages. In such organisms, ageing manifests as a necessary consequence of the architectural asymmetry between development and post-developmental states, and the exceptional cases represent life history strategies that circumvent this asymmetry through distinct routes.

Within this framework, ageing reflects imperfect maintenance of slow-layer architecture after completion of the developmental program (Fig. 3). This aligns with the evolutionary concept of a selection shadow, referring to the decline in force of natural selection against age-specific mortality with increasing age[108,109]. As a result, somatic maintenance experiences progressively weaker selection. The gradual transition from a high-fidelity, globally coordinated writing phase to a low-fidelity, locally executed maintenance phase guarantees that slow-layer constraints erode over time, and the phases are expected to be tuned in a way to ensure sufficient function during evolutionarily relevant ages but not necessarily beyond that. The increased occupancy of sites by stress-responsive transcription factors such as AP-1 could be seen as an example of antagonistic pleiotropy in this context. While the process is beneficial in facilitating short-term stress response, it also primes the regulatory landscape for chronic occupancy and permanent changes in cell state during ageing. Processes initiated during development may also escape regulatory constraint if their negative consequences manifest only late in life, beyond the reach of selection. Gradual methylation gain at PRC2-LMRs provides a potential example: these changes may be initiated as byproducts of developmental chromatin dynamics, tolerated because they impose no immediate fitness cost, yet accumulate to compromise identity in aged tissues. The framework therefore predicts that a fixed developmental end point followed by a maintenance-only period produces functional ageing. Organisms that escape or delay this ageing should do so by retaining the capacity for developmental writing beyond the typical end point.

Indeterminate growth exemplifies this strategy. Species that grow continuously throughout life retain active developmental programs in specific tissues: meristems in plants, growth zones in fish and reptiles. These regions do not merely maintain existing architecture but actively write new slow-layer constraints as new tissue is generated. Perennial trees such as *Quercus rugosa* show plateauing mortality while producing new organs throughout life through meristems that maintain developmental plasticity[110]. Among animals, some turtles, tortoises and rockfishes continue growing throughout adulthood, and demographic analyses reveal mortality rates that remain relatively steady with age[111–113]. Mortality is not a perfect read-out of ageing, however, as it can also decrease through reduced predation or disease. More work is needed to establish whether continuous rewriting of slow-layer architecture does functionally slow certain aspects of ageing in these species.

Regeneration represents a related but distinct phenomenon. Organisms with robust regenerative capacity, such as planaria and hydra, can rebuild entire tissues or body regions after injury[114,115]. If regeneration involves re-activation of developmental writing programs rather than mere cellular proliferation, it would allow these organisms to periodically rewrite slow-layer architecture in regenerating tissues[116]. Both planaria and hydra exhibit negligible senescence, consistent with this interpretation. Non-senescent hydra tolerates perturbations in the nuclear lamina, a process that is known to cause progeria in mammals[117]. Continuously active developmental axial patterning in these organisms further suggests ongoing slow-layer regulation rather than static maintenance[118,119]. In pluripotent neoblasts, promoters of stem cell genes exhibit constitutive-like organization characterized by AT-rich sequence composition, weak nucleosome affinity and an Initiator-driven structure that promotes basal accessibility. This architecture enables chromatin remodeller-dependent default expression of pluripotency programs without reliance on a dedicated master transcription factor network. ISWI and SNF2 activity is required to sustain these promoters and support regenerative expansion, indicating that planarian stemness is upheld through ongoing chromatin remodelling rather than a terminally written state[119]. This represents a fundamentally

different strategy from the mammalian system. Planaria circumvent drift by continuously overwriting regulatory architecture; mammals accumulate drift because maintenance mechanisms cannot restore the original written state, only approximate it with decreasing fidelity. Mammalian adult stem cells occupy an intermediate position. Their local writing capacity is established during development, and this architecture itself is drifting during ageing[78,120].

These observations invite a testable prediction. Organisms exhibiting negligible senescence through indeterminate growth or regeneration should show evidence of active chromatin remodelling in growth zones or regenerating tissues even at advanced ages. Direct measurements of chromatin-level drift, PRC2 domain stability and DNA methylation trajectories across these different life history strategies remain sparse, and several alternative hypotheses have been proposed to explain negligible senescence[121,122].

Neurodegeneration as a case study

Neurons exemplify the grammar of identity maintenance and its vulnerabilities. Their identities are established through coordinated developmental programs that set PRC2-regulated bivalent domains, enhancer networks and spatial genome organization before terminal differentiation. Once established, these structures require continuous maintenance in the absence of cell division. Neurons therefore rely heavily on slow-layer mechanisms to preserve subtype fidelity. Neuronal chromatin architecture is established during cortical development through high-level expression of EZH2 in neural progenitors, where PRC2 deposits H3K27me3 across regional, lineage and temporally regulated loci[54,57]. Conditional loss of EZH2 in progenitors abolishes H3K27me3 deposition and prevents establishment of these domains in postmitotic neurons, demonstrating that the chromatin states supporting adult neuronal identity are directly downstream of Polycomb activity during neurogenesis[91]. Beyond identity specification, Polycomb operates in conjunction with EHMT1/2 and DOT1L to form a maturation barrier that constrains the intrinsic pace of human neuronal maturation; transient inhibition of these enzymes accelerates morphological and transcriptional maturation of subsequently born neurons[16].

After terminal differentiation, PRC2 remains required across multiple neuronal subtypes to maintain subtype fidelity and transcriptional coherence[54]. Combined *Ezh1* and *Ezh2* deletion in medium spiny neurons, and PRC2 loss in dopaminergic and serotonergic neurons, eliminates H3K27me3 domains, derepresses alternative lineage programs and produces progressive degeneration[29]. Parallel findings in glutamatergic neurons show that EZH2 loss during differentiation directly alters synaptic and maturation programs into adulthood, whereas newly postmitotic neurons require EZH2-dependent H3K27me3 acquisition to stabilize fate decisions[123]. These genetic models demonstrate that, without ongoing PRC2 activity, H3K27me3 is progressively removed even in postmitotic neurons, implicating active demethylation by KDM6A/B as a mechanism of age-related H3K27me3 erosion in non-dividing cells along with histone turnover[124,125].

KDM1A (also known as LSD1) acts as a co-regulatory boundary enzyme for these Polycomb-repressed domains. Inducible *Kdm1a* deletion in adult forebrain neurons reduces H3K27me3 at affected PRC2-repressed loci, broad H3K27ac spreading and derepression of early developmental, non-neuronal and stress-response genes, producing chromatin and transcriptional signatures that are indistinguishable from naturally aged hippocampus[92]. Together, PRC2 and KDM1A constitute the core identity-maintaining machinery in mature neurons[126].

Lifespan-resolved epigenomic analyses reveal that these Polycomb-mediated programs undergo progressive degradation during ageing. Purified neurons show global declines in H3K27me3 and H3K27ac, with selective loss of H3K27me3 at developmental and identity loci[127]. Multi-omics profiling of the ageing hippocampus demonstrates that regions depleted of histone modifications are disproportionately enriched for Polycomb-target loci, indicating that PRC2-controlled regions are preferentially affected by ageing. Although some loci exhibit gain of H3K27me3 (such as *Bdnf* promoters)[128], the overall pattern is one of redistribution and erosion of canonical Polycomb repression[28]. These changes occur in the absence of cell division, implying active maintenance failure rather than dilution.

Polycomb loss has additional effects through a biochemical mechanism involving EZH2-dependent recruitment of the deubiquitinase USP7. USP7 stabilizes β-catenin, KDM1A, HDAC1 and DNMT1 by reversing their ubiquitination; disruption of EZH2–USP7 interactions lowers β-catenin and KDM1A levels. Thus, PRC2 supports WNT–β-catenin signalling by maintaining β-catenin stability and simultaneously stabilizes KDM1A, thereby sustaining the CoREST complex[129].

β-Catenin is required for induction of the transcriptional repressor REST under stress conditions[130]. REST is minimally expressed in healthy young adult cortical neurons but accumulates in the nuclei of neurons during ageing, where it represses genes associated with apoptosis, oxidative stress, excitotoxicity and Aβ toxicity[131]. REST levels correlate with cognitive resilience and longevity, and nuclear REST is lost in mild cognitive impairment and Alzheimer's disease[130–132]. REST recruits CoREST–KDM1A–HDAC complexes to enact repression[133]; thus, the stability of REST-mediated repression depends on KDM1A abundance[134], which is itself sustained by the EZH2–USP7 axis[129]. This REST–β-catenin–GSK3β module interfaces directly with physiological lithium signalling. Lithium is a direct inhibitor of GSK3β and increases β-catenin by preventing its phosphorylation and degradation. By stabilizing β-catenin, lithium is predicted to enhance REST induction during stress and to suppress GSK3β-dependent degenerative pathways; lithium deficiency in mice elevates GSK3β activity, reduces nuclear β-catenin, impairs REST induction and increases vulnerability to Alzheimer-like pathology[135].

PRC2 and KDM1A also participate in canonical senescence suppression through repression of *CDKN2A/B* and *CDKN1A*. Numerous systems demonstrate that EZH2 loss derepresses *CDKN2A* (encoding p16) and *CDKN1A* (encoding p21) through loss of H3K27me3 at their promoters, triggering senescence programs[136–139]. In proliferative neural or glial contexts, decreases in PRC1/2 and KDM1A predispose cells to senescence through derepression of the p16–p21 axis[140,141]. KDM1A further interacts with PRC2 function in this regard, with KDM1A inhibition contributing to senescence-like chromatin states and loss of proliferative potential[92,142].

Taken together, these data support a model in which ageing promotes a sequential weakening of the PRC2/KDM1A–β-catenin–REST–GSK3β axis. In this model, declines in EZH2 and KDM1A function erode H3K27me3 domains and reduce USP7 recruitment, which destabilizes β-catenin and KDM1A, compromises REST induction and complex assembly and allows unchecked GSK3β activity. Elevated GSK3β then aggravates β-catenin loss and REST failure, creating a self-reinforcing degenerative loop that links slow-layer identity collapse to fast-layer vulnerability. This process promotes tau phosphorylation, synaptic dysfunction and excitotoxic vulnerability[135]. Neurodegeneration, in this view, reflects decanalization of constraints that kept identity coherent for decades. This cascade also has therapeutic implications. PRC2 contributes to slow-layer maintenance through both catalytic H3K27me3 deposition and physical occupancy at target loci, and these functions may be separable. PRC2 presence at developmental promoters could maintain chromatin architecture and prevent inappropriate transcription factor access independently of methyltransferase activity. If so, therapeutic strategies that preserve architectural occupancy without necessarily restoring full catalytic function could maintain identity constraints while reducing the oncogenic risks associated with global H3K27me3 manipulation, such as silencing of CDKN2A-mediated tumour suppression[143,144].

Although the neuronal case study illustrates grammar collapse through this axis, the upstream principle operates across tissues through distinct downstream effectors. PRC2-dependent identity

Box 1

Caloric restriction and epigenetic drift

Mammalian species differ markedly in developmental tempo, and these differences correlate with lifespan, as discussed in the main text. Recent studies have begun to identify the metabolic basis of this variation[150]. Mitochondrial fatty acid oxidation rates are higher in mouse than human cortical progenitors, resulting in elevated acetyl-CoA levels in mouse cells. Acetyl-CoA provides the substrate for histone acetylation, including at H3K27, where acetylation directly competes with PRC2-deposited methylation. When human cortical organoids are supplemented with fatty acids or exogenous acetate, H3K27ac and H4K16ac levels increase, bivalent domain resolution accelerates and late-fate neuronal markers appear precociously. ACLY inhibition, which blocks cytoplasmic acetyl-CoA production from citrate, abolishes this acceleration entirely[151]. These findings reveal that the Polycomb-maintained slow layer does not operate in isolation. Its stability depends on the acetylation pressure it faces from ongoing metabolism. Mouse cells experience greater acetylation pressure, faster bivalent resolution and accelerated maturation. Human cells maintain the Polycomb-dominated state longer, writing deeper constraints over extended developmental time.

This metabolic coupling has implications beyond development. Caloric restriction (CR) extends lifespan across species[152–154], and CR mimetics have been operationally defined as compounds that alter the cellular acetylome through three routes: reducing acetyl-CoA levels, inhibiting acetyltransferases or stimulating deacetylases such as the sirtuins[155]. Long-term CR reduces TCA cycle flux, lowering citrate export and ACLY-mediated cytoplasmic acetyl-CoA production[156]. Conventional explanations attribute CR benefits primarily to autophagy induction and metabolic remodelling. The grammar framework offers a complementary mechanism. Reduced acetyl-CoA relieves pressure on H3K27me3 domains, slowing erosion at the slow layer. Consistent with this interpretation, PRC2-LMRs show reduced methylation under CR conditions[27]. This relationship is bidirectional. Metabolic programs, including mitochondrial function and substrate preferences, are themselves maintained by the transcriptional networks that the grammar constrains. Slow-layer erosion therefore disrupts metabolic identity while metabolic dysfunction simultaneously accelerates slow-layer erosion through altered acetyl-CoA flux, creating a feed-forward loop.

The evolutionary logic suggests that, during famine, organisms must prioritize survival over growth. Maturation and tissue expansion are energetically expensive, and nutrient scarcity favours maintenance over developmental progression. Reduced metabolic flux necessarily reduces acetyl-CoA availability, and this signal is interpreted by the chromatin machinery as a cue to stabilize rather than remodel. We propose that acetyl-CoA availability functions as a metabolic substrate coupling biosynthetic flux to histone acetylation pressure at Polycomb-regulated domains: high levels permit rapid H3K27 acetylation and accelerate developmental transitions, while low levels favour H3K27me3 stability and slow maturation. This coupling is adaptive during development, coordinating growth with nutrient availability. But the same machinery persists after maturation ends. In adulthood, lower acetyl-CoA pressure continues to stabilize PRC2 domains, not because evolution designed an anti-ageing program, but because the developmental–metabolic interface remains in place. CR may extend lifespan in part as a side effect of an evolved famine response that happens to target slow-layer stability. If this model is correct, restoring acetyl-CoA to ad libitum levels during CR should attenuate CR's protective effects on PRC2-LMR drift[27], even while other CR responses such as autophagy and AMPK activation remain intact.

maintenance fails progressively in the haematopoietic system, where it drives lineage infidelity and myeloid bias[55]; in muscle satellite cells, where H3K27me3 at bivalent, lineage-inappropriate promoters safeguards myogenic identity and its loss derepresses alternative-fate regulators[31]; and in the ageing liver, where site-specific loss of H3K27me3 at developmental transcription factor promoters leads to expression of non-hepatocyte markers[145].

Future directions

Ageing emerges from structural features of regulatory architecture shaped by evolution for development and reproductive success rather than for long-term stability. The model does not require any active ageing program. It requires only the combination of deeply written slow-layer rules, analogue maintenance mechanisms with finite precision and long lifespans that exceed the design constraints of the system. Drift accumulates because it is impossible to fully restore developmental architecture, not because any pathway is executing an ageing plan.

Our model provides informational genomic coordinates for ageing but does not constitute a complete mechanistic account. Somatic mutation accumulation, extracellular matrix crosslinking, buildup of byproducts in postmitotic cells, lens crystallin aggregation and many other forms of damage would occur regardless of chromatin state[146–148]. The grammar framework does not replace damage-based models; it explains why diverse damage burdens produce conserved, structured signatures across tissues and species. Somatic mutations accumulate throughout the genome, but their phenotypic consequences are concentrated at loci where slow-layer constraints have weakened. A mutation that derepresses a PRC2-silenced gene is inconsequential within an intact repressive domain but gains functional significance when that domain has eroded. Proteostasis collapse destabilizes chromatin-modifying complexes themselves, directly accelerating grammar erosion, while grammar erosion compromises expression of proteostatic genes, creating positive feedback. Mitochondrial dysfunction alters acetyl-CoA flux and thereby modulates the acetylation pressure on H3K27me3 domains through the substrate coupling described above. The grammar specifies where in the genome perturbations become consequential, why their effects are structured rather than random and how they propagate across regulatory scales.

Molecular damage, such as mutations, oxidative lesions and epimutations, accumulates continuously from mid-embryogenesis. What we propose is that progressive decline of cellular function, as a manifestation of ageing, begins when the developmental programs subside. During maturation, biology actively writes function into cells through the coordinated antagonism of Polycomb and Trithorax systems, establishing identity constraints even as molecular damage accumulates in parallel. The system moves toward peak function despite ongoing damage, much as a structure can be built while simultaneously weathering erosion. Once maturation is reached and the writing program ends, the direction of functional change reverses. Damage continues, but construction does not. The epigenetic changes at PRC2-LMRs are not the totality of age-related damage. They are the specific genomic coordinates where identity-encoding architecture erodes in a measurable, cross-species-conserved manner. Importantly, the model does not predict that all perturbation is detrimental. Mild stress during or after development can reinforce maintenance

systems without exceeding their capacity, consistent with hormetic responses that improve fitness and longevity[149]. The grammar framework predicts that such benefits arise when perturbations strengthen slow-layer maintenance rather than erode it, and that hormetic capacity should decline as accumulated decanalization reduces available maintenance reserves.

This framework generates predictions that distinguish it from existing models. First, because adult cells carry *cis*-acting epigenetic memory, interventions that enhance maintenance fidelity should slow drift without reversing it, while interventions that re-engage writing programs (such as reprogramming factors) should produce actual reversal. This distinction can be tested by comparing PRC2-AgeIndex trajectories under each intervention class. Second, if drift rate reflects both writing depth and maintenance challenge, tissue-specific ageing rates should be predictable from developmental timing and metabolic parameters (Box 1). Third, CpGs with high interindividual variance at birth, reflecting imprecise developmental writing, should exhibit faster age-associated drift in adult cohorts. Fourth, xenografted cells should partially retain donor-species drift rates rather than fully adopting host rates, distinguishing cell-intrinsic constraints from systemic ageing signals. This can be tested using the established xenotransplantation system that demonstrated species-specific developmental timing in human cortical neurons transplanted into the mouse brain. Fifth, repeated acute stress with recovery should be fully reversible until cumulative exposure erodes slow-layer architecture, at which point recovery capacity should decline. This can be measured by tracking bivalent domain changes across stress-recovery cycles.

Key open questions include determining what sets drift rate constants across tissues, how developmental bivalency influences adult maintenance, and whether preventing or tuning slow-layer drift can extend lifespan without altering cellular identity. Resolving these questions will require integrating perturbation experiments, high-dimensional modelling, and comparative analyses across species with diverse developmental schedules and lifespans. The grammar framework provides a common language for unifying observations across scales, from histone modifications to organismal longevity.

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Acknowledgements This work was supported by funding from the National Institute on Aging and Hevolution Foundation (to V.N.G.).

Author contributions A.D.Y. conceptualized the framework and drafted the manuscript with contributions from A.M. on evolutionary biology. V.N.G. extended the framework and supervised this project. All of the authors revised and approved the final version.

Competing interests A.M. is employed by Novartis. The other authors declare no competing interests.

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Peer review information *Nature* thanks Peter Adams, Jessica Proulx and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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