Aging and the Evolvability of Biological Immortality in Multicellular Organisms

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Orcid: 0009-0004-6762-8748 16.02.2026

Keywords: aging; evolution; evolvability; biological immortality; epigenetics; loss of information

Competing Interests: The authors declare that they have no competing interests related to this work.

Abstract

A lack of consensus persists in aging research about how to define, measure, and explain aging, and mechanistic (molecular) and evolutionary models remain disconnected.
A mechanistic–evolutionary model is proposed that integrates concepts from Kirkwood's disposable-soma theory and Sinclair's information theory of aging, providing a concrete framework for the causes of aging and routes to its reversibility.
The model explains why heterochronic parabiosis benefits older individuals but harms younger ones and why regeneration produces global tissue rejuvenation in aging planarians. Classical evolutionary theories such as antagonistic pleiotropy and mutation accumulation are framed as secondary mechanisms layered atop the central processes described here. This unified perspective on mechanisms, evolution, and reversibility of aging yields a specific, testable prediction: a single differentiated somatic cell (or small graft), serially transplanted once per generation into a clonal youthful host at the previous host's old age, will retain youthful epigenetic and functional states and show a greatly extended lifespan, provided intercellular signals remain coherent and its genome is intact.

Contents

1 Introduction

There is no consensus in aging research on how to define, measure, or explain aging, with fundamental disagreements over its causes, onset, and reversibility. Moreover, a disconnection exists in the literature between mechanistic (molecular) and evolutionary aging models. [1]

Researchers typically search for variables that alter how quickly organisms age by tracking lifespan changes or uncover the exact mechanisms of the functions that are ultimately lost or misregulated with increased age. This strategy generates practical leads on interventions, but it stops short of defining aging itself [2]. It maps modifiers and effects rather than offering a clear, testable account of the underlying process.

Because current theoretical frameworks fail to capture the full complexity of aging and leave substantial gaps, it is both timely and necessary to propose well-motivated speculative hypotheses and to subject them to careful testing against the accumulated empirical evidence.

Resolving how aging emerges from both cellular mechanics and natural selection is essential for predicting which interventions can truly restore function. I therefore develop a simple framework that links cell-level information dynamics to organismal lifespan and testable experimental consequences.

I begin by characterizing the types of damage organisms must withstand to survive and argue that aging represents a fundamentally distinct class. I then propose that the only truly irreparable damage is the loss of information, and that although epigenetic information cannot be reconstructed in the adult organism, it can be restored by re-executing development or a functional equivalent. Under these constraints, I introduce an information-theoretic model in which differentiated cells slow epigenomic degradation through sustained resource investment. This framework offers an explanation for empirical observations that remain poorly accounted for by existing theories, including heterochronic parabiosis and regeneration-associated rejuvenation in planarians. Finally, I show how the model integrates with established evolutionary theories of aging, specifically antagonistic pleiotropy and mutation accumulation.

2 Types of damage to somatic tissue

Damage to somatic tissue can broadly be categorized into two groups. The first are external insults to an otherwise healthy body, for example ultraviolet radiation causing a sunburn, or a laceration or abrasion to the skin, or even a fractured bone. Whenever a particular type of injury recurs frequently within a species, such that it compromises an essential function, there is a clear evolutionary incentive for genes to evolve that restore that function starting from the damaged state. Over time, this pressure can give rise not only to repair mechanisms that patch up minor wounds but to astonishing regenerative feats: an octopus re-growing an entire arm [3], or the human liver restoring itself after substantial tissue loss [4]. At its heart, the process is one of cost versus benefit: only if the energetic and regulatory expense of maintaining and deploying a repair pathway is outweighed by survival or reproductive gain will those genes be retained and refined across generations. When a particular type of injury rarely or never occurs under natural conditions, there is no selective pressure for organisms to evolve mechanisms to repair it.

By contrast, the second category of damage is internal and continuous. Every living cell faces a background of molecular insults, reactive oxygen species generated by normal metabolism that oxidize lipids and proteins, nascent polypeptides that occasionally misfold or aggregate, or metabolic byproducts that, if allowed to accumulate, would become toxic. To counteract this steady trickle of injury, organisms deploy a suite of constitutively active maintenance systems. There are molecular chaperones to shepherd proteins back to their proper shapes, proteasomes and autophagic pathways to clear irreparable debris, and antioxidant enzymes to scavenge free radicals before they inflict further harm. Because these internal threats are unrelenting, any genetic variant that accelerates turnover of damaged molecules or enhances repair capacity or efficiency yields a continuous fitness advantage, driving the evolution of comprehensive, energy-balanced quality-control networks that safeguard cellular integrity around the clock.

Both categories share a crucial feature that the lost function can be fully restored at sufficient energetic cost. A fractured bone will eventually knit back together, and active proteolytic systems can completely clear away protein aggregates. Aging, by contrast, is characterized by a system-wide decline in nearly every physiological system, one that repair pathways cannot wholly reverse. Because the functional losses of senescence never return to their youthful baseline, the damage of aging cannot be neatly slotted into either of the two prior categories. Instead, it represents a unique, cumulative breakdown, in which repair mechanisms themselves gradually lose efficacy.

At first glance, this gradual decline evokes the familiar ”wear and tear” of everyday objects and machinery—material fatigue, abrasion, and corrosion—and aging research often frames its focus in analogous terms. Proteins aggregate like debris in clogged filters, stem cell pools dwindle much like battery capacity, and telomeres shorten as if the bristles on a brush frayed over time. These examples fit neatly into the wear-and-tear paradigm. Yet there is a crucial distinction: unlike inanimate parts, the body continually renews itself. Every cell, protein filament, and tissue type turn over at a characteristic rate far shorter than the organism's lifespan.

For example, the mammalian intestine presents a dramatic case, turning over as rapidly as in two to four days [5]. Despite the remarkable longevity of most mammalian neurons, which can persist for over a century, their molecular components are in constant flux. While the neuron itself is largely irreplaceable, its constituent proteins continuously turn over with the large majority of proteins having a lifetime between 3 and 13 days [6]. Thus, almost all changes, whether an increase or a decrease occurring on the timescale of a human lifetime, are not driven by aggregation or continuous loss, but rather by a change in the rate of production or the rate of removal.

But even this perpetual renewal of all the body parts does not yield ever-fresh components operating at peak performance. One would expect that replacing old parts would restore flawless function, but during aging each renewal cycle simply substitutes a suboptimal element with another of equivalent deficiency. Over years of continuous turnover, these uniformly underperforming replacements accumulate, gradually degrading the system's overall functions.

Aging thus represents a type of damage that, once incurred, cannot be restored. In any self-maintaining system, repair depends on components that carry within themselves the information required to rebuild damaged parts. The only elements that meet the criterion of irreversibility are those whose own blueprint is contained intrinsically. Once that information is destroyed, it cannot be recovered. In other words, if you obliterate a structure along with the self-encoded instructions needed to recreate it, full restoration becomes fundamentally impossible. Across the tree of life, we observe enormous variation in natural lifespans, which suggests that the pace of aging is itself evolvable. If aging truly reflects the gradual build-up of irreparable damage, then some categories of age-related injury must be either minimized or deferred in long-lived species.

3 Loss of information is irrecoverable

One of the most fundamentally irrecoverable information stores in any multicellular organism is its genomic DNA. When somatic mutations disable critical genes, the collective performance of tissues and organs inevitably declines. Fortunately, evolution has equipped cells with a variety of safeguards such as DNA-repair enzymes, proofreading polymerases, chromatin-remodeling factors, and damage-sensing checkpoints, that slow the accumulation of these mutations. Every joule of metabolic energy devoted to nucleotide excision, base-pair correction, or removal of cross-links reduces the burden of DNA damage. By investing resources in these protective and maintenance pathways, organisms can prolong the integrity of their genetic blueprint and, with it, sustain tissue function for a longer span of time.

Another key layer of information that has garnered intense interest in recent years is the epigenome. Like mutations in the DNA sequence, epigenetic alterations (epimutations), such as changes in DNA methylation, histone modifications, or chromatin organization, can impair cellular and tissue function when they stray from the cell-type-specific pattern [7]. The central importance of maintaining epigenetic integrity is underscored by multiple lines of evidence. For instance, in mammals, a lower rate of epigenetic drift correlates with a greater maximum lifespan [8]. In model organisms such as *C. elegans* [9], fruit flies [10], and mice [11], aging is consistently associated with a loss of heterochromatin—regions of tightly packed, transcriptionally silent DNA—which is accompanied by global transcriptional noise. If a fully differentiated neuron, for example, inappropriately expresses genes meant for a stem cell or a muscle cell, it not only wastes energy but also undermines its specialized role. If the function of a particular cell type or tissue declines beyond a critical threshold, other organs or systems that depend on it may also begin to fail, potentially leading to systemic collapse and, ultimately, death. Remarkably, somatic cells from aged individuals, when used for cloning, can give rise to entirely new organisms that develop normally and live full, healthy lifespans [12]. This finding raises the possibility that somatic mutations of the DNA might not be the main cause of aging.

Collectively, these findings are consistent with a central premise of the epigenetic information theory of aging (ITOA) [7]: that the progressive loss of epigenetic structure contributes to the erosion of cellular identity and function. Many aging hallmarks emerge when cells lose stable differentiation and no longer maintain the gene-expression programs that define their function. As regulatory identity degrades, cells fail to coordinate repair, metabolism, proteostasis, and cell-cycle control, leading to senescence, inflammation, mitochondrial dysfunction, and tissue decline. In this view, damage accumulates everywhere, and pathology appears when larger downstream functions degrade or collapse because cells can no longer sustain the coordinated programs required for tissue- and organism-level function.

However, other aspects of the theory remain speculative and are not adopted here. For example, ITOA proposes that cells retain a complete, intact backup of their youthful epigenetic information, which can be restored through partial reprogramming. This notion raises several conceptual and biological concerns. It is unclear how such a backup system could be maintained over time without being subject to the same environmental and molecular insults that drive aging in the first place. Additionally, the hypothesis that activation of endogenous Yamanaka factors could rejuvenate the organism overlooks a key evolutionary question: if such mechanisms exist naturally, why have they not been selectively utilized to preserve function and extend lifespan? This would fall into the other two previously named categories of somatic damage. While whole or partial reprogramming can clear epigenetic marks in experimental contexts, this does not necessarily imply the presence of an innate, organism-wide rejuvenation program.

In principle, the blueprint for the correct epigenetic state resides in the genome itself, yet mature cells lack direct access to the results of the developmental programs that originally established those patterns. During embryogenesis and early differentiation, cascades of developmental transcription factors and signaling pathways choreograph a highly complex program that both specifies cell identity and locks in its epigenetic marks. In this process, cells rely on intercellular communication, with neighboring cells sending instructive signals at precise developmental time points to guide lineage decisions and establish the appropriate epigenetic landscape [13].

Once this program has run its course and a cell settles into its final spatial location with its designated gene expression patterns, it cannot simply replay it on its own to reset its epigenome. The cell would need all the signals it received while the organism developed. Because the original developmental machinery, creating an adult starting from a single cell, cannot be reactivated in adulthood, any epigenetic drift that occurs afterward is effectively irreversible, much like a mutation in the DNA sequence. To counteract this gradual loss of information, organisms must evolve dedicated epigenetic maintenance systems, including genes that encode chromatin-binding proteins, modification enzymes, and structural factors that preserve cell-type-specific patterns. As with DNA repair, such protective mechanisms can only evolve and persist if the benefits of preserving cellular identity exceed the energetic costs. The loss of epigenetic information, therefore, mirrors genomic damage in a fundamental way. Under normal circumstances it cannot be fully reversed once the original state is lost, only slowed down by continuous resource investment.

4 Rejuvenation requires re-execution of developmental programs

A fully ”young” epigenetic landscape in a differentiated cell can only be restored with evolvable biological mechanisms by rerunning, the organism’s developmental program—or by an equivalent process involving complete cellular dedifferentiation followed by autonomous redifferentiation. In effect, one must recapitulate the cascade of transcription factors, chromatin remodelers, and signaling events that originally established lineage-specific epigenetic patterns during embryogenesis. Without such a reset, mature cells have no direct means of erasing accumulated epigenetic drift or repositioning their chromatin to a truly naive, cell-type specific state.

An analogy helps: imagine the assembly manual for a complex LEGO build that was dropped and shattered into many fragments. The original instructions tell you, step by step, which brick to add next and where, but they don’t tell you how to reattach those specific broken fragments. You would need extra pages showing how to piece those fragments back together starting from that damaged state.

Nevertheless, such instructions can evolve, whether as a program to regrow a lost limb or to completely remodel the entire organism. One of the most striking examples of such a reset in the animal kingdom is the so-called “immortal jellyfish,” *Turritopsis dohrnii.* When faced with stress, injury, or senescence, this hydrozoan can revert its mature medusa cells into a cyst-like structure, essentially a colony of pluripotent cells. From this cyst, it can re-differentiate into a new polyp colony, thus jumping back to an earlier point in its life cycle [14]. If no new deleterious genetic mutations arise during its lifetime, the process can, in principle, occur indefinitely, allowing the jellyfish to escape the normal limits of somatic aging.

A parallel phenomenon occurs in many higher plants through vegetative propagation. At the tip of every shoot lies a meristem—a perpetual fountain of undifferentiated cells programmed to generate new leaves, stems, and roots. When a cutting is taken from this young tissue, both the epigenetic age of the cutting and the roots it subsequently produces are effectively reset to zero. Repeatedly planting new cuttings can extend a single genetic individual far beyond the lifespan typical in nature. Some clonal species, like the quaking-aspen colony known as Pando, can survive for thousands of years by continually renewing themselves through the natural formation of genetically identical ramets [15].

In contrast to most vertebrates, certain invertebrates—most famously planarian flatworms—possess a regeneration program that functionally mirrors embryonic development. When a planarian is bisected, each fragment activates its resident totipotent neoblasts to rebuild all missing cell types and structures, restoring the organism to its original size and form [16]. This reconstruction proceeds through waves of proliferation, migration, and differentiation that recapitulate key steps of early development, thereby endowing every newly formed tissue with a fully young epigenetic landscape. Because the epigenome is not merely repaired in place but entirely rewritten as cells re-differentiate, planarian regeneration effectively resets epigenetic age.
Other worm-like species, such as certain nemerteans and annelids, use analogous stem-cell–driven cascades to achieve comparable feats of whole-body renewal [17], demonstrating that a developmentally equivalent program can permanently forestall epigenetic drift so long as the underlying genetic instructions remain intact. The ability to regenerate both anterior and posterior body parts following dissection is often associated with an organism's inherent capacity for fission, a common mode of asexual reproduction in these animals [18]. They therefore possess a genetic program that directs the formation of a new individual through a non-embryonic developmental pathway.

An important point to mention here is that with these species there is a functional decline visible over the timespan prior to fission [19]. Even the "immortal" freshwater planarian *Schmidtea mediterranea* shows alterations in sensory organs, loss of neurons and muscle, loss of fertility and impaired motility with age. But no overall decline of function is visible over successive fissions or after regeneration from injury because it leads to global tissue rejuvenation [20, 21]. There are exceptions if one looks at a successive line of heads. For example, in *Aeolosoma viride* the head part has a definitive lifespan with a number of 57 offspring produced via fission [22]. In *Schmidtea mediterranea* there is evidence that lines of successive heads showed aging and ultimately died out. Conversely, in lines of successive tails, no aging was observed based on uniform fecundity and no recorded deaths [23]. With each fission functionality is fully regained but not for all parts. Mechanisms by which this behavior could be achieved will be explored in the next chapter.

Biological immortality via a mechanism that resets an organism back to an earlier developmental state is extraordinarily rare and when it does occur, it only appears in very small, simple animals. Evolving such a mechanism requires not just small steps evolving over many generations, each of which gives a fitness benefit that can normally be seen in evolution, but the whole program would need to evolve before it gives any benefit at all and could be selected for. This is why no such mechanisms exist in large and complex animals because it is increasingly more unlikely that whole programs evolve for how to turn a fully differentiated body back into an undifferentiated state from where it could build a fully functional body again.

In principle, then, the key to epigenetic youth lies in the capacity to re-execute a developmental program or its functional equivalent, allowing the organism to circumvent the otherwise irreversible drift of its epigenetic landscape. Accordingly, in multicellular sexually reproducing animals the germline periodically induces a state that permits a complete epigenetic reset—thereby rerunning its developmental program to return to its original, youthful condition. With that the germline effectively escapes cumulative epigenetic drift, loss of function and thus functions as an immortal cell lineage of astonishing age.

5 Model for epigenetic repair mechanisms

5.1 Epigenetic stability: biochemical and information-theoretic strategies

There are two broad strategies by which a cell could safeguard its epigenetic information against continual assault. It is important to mention here that those strategies are completely different from programs to build new cells with a youthful epigenetic state, as explained in the previous chapter.

The first is a biochemical stabilization approach. By favoring especially resilient molecular substrates the overall rate of damage and hence of epimutations is kept to a minimum. For example, a lineage might evolve histone variants that are less prone to oxidative modification. This adaptation would effectively fortify the epigenetic code itself, reducing the likelihood that stray chemical insults will permanently corrupt it. To minimize the assault itself, organisms might shield the information from sources of damage, lower the concentration of chemical insults, or reduce metabolic activity, which also falls into this category of biochemical stabilization. For instance, lower temperatures can slow metabolic rates, thereby extending longevity [24].

The second is an information-theoretic or “software” solution, in which redundancy and active maintenance routines continually rewrite and correct the epigenetic record regardless of the underlying damage rate. A straightforward example of this model involves transcriptional regulators that bind to their own enhancers or promoters, thereby reinforcing chromatin states that sustain their own expression. MyoD, a master regulator of the skeletal myogenic program in vertebrates, exemplifies this mechanism. It binds not only to the promoters of many muscle-specific genes [25] but also to its own promoter [26], effectively locking the cell into a differentiated state. This self-reinforcing loop mirrors the behavior described by Waddington's epigenetic landscape model where the cells try to stay in their own valley of differentiation [27].

Similarly, stable cell states can also emerge from small networks of transcription factors that mutually repress and self-activate to create multistable regulatory circuits, as demonstrated in models of T-helper cell differentiation where tristability and hybrid phenotypes arise from coupled regulatory loops [28]. Consistent with this view, Myc-dependent positive feedback in embryonic stem cells has been shown to sustain a self-reinforcing transcriptional regulatory network that establishes an epigenetic memory capable of persisting in the absence of continued upstream signaling [29].

On a smaller scale, molecular marks can also reinforce one another; for example, H3K9me3 is a chemical modification where three methyl groups are added to the ninth lysine residue of histone H3. This mark signals a repressive chromatin state and recruits HP1 (Heterochromatin Protein 1), a protein that helps compact chromatin and silence gene expression. HP1 then attracts SUV39H1, an enzyme that methylates more H3K9 residues, adding additional H3K9me3 marks. This feedback loop creates a self-sustaining silencing environment at specific genomic regions, maintaining stable gene repression over time [30].

Epigenetic marks or transcription regulators that store and reinforce information collectively can be thought of as multiple redundant copies, so that if one is lost due to an epimutation, the others can restore it. Multiple copies of essential epigenetic information also exist at a larger scale, specifically, at the level of cells. When cells of the same type communicate with one another, they may reinforce their epigenetic states, effectively linking their individual epigenomes into a coordinated network. Paracrine signaling and especially targeted extracellular vesicles (EVs) can serve as effective mediators for this information flow.

EVs program the epigenomic profile by remodeling DNA, RNA, and histone modifications in recipient cells. This is achieved by delivering cargoes mainly targeting methyltransferase and demethyltransferase. EVs and epigenomic profiles are closely linked and reciprocally regulated [31]. Even DNA has been found in exosomes, and it has been shown that it can integrate into the genomes of recipient cells [32].

5.2 Binary model of epigenetic maintenance

If one essential gene is silenced by accident in a cell, and all cells continually send information about the genes they express, they can restore the correct gene expression in that cell. In combination with the other self-reinforcing strategies to retain its epigenome, this intercellular communication helps maintain stability and identity across a population of differentiated cells.

To capture these ideas in a simple model, imagine each cell as a 5×5 grid of on/off switches, where each switch represents one gene: on (1) means the gene is expressed, off (0) means it is silenced (Figure 5.1). A perfectly differentiated cell corresponds to a grid in which exactly one entire row of genes is switched on and all others are off. With that, there are 5 different cell types. Random epimutations cause individual switches to flip on or off, and without repair the cell will gradually lose that perfect row, leading to partial or full dedifferentiation. Within this model, the cells depend on the other cell types executing their functions only in that spatial location where they are situated. If too many of the wrong genes are expressed or too many of the right genes are silenced, the system dies.

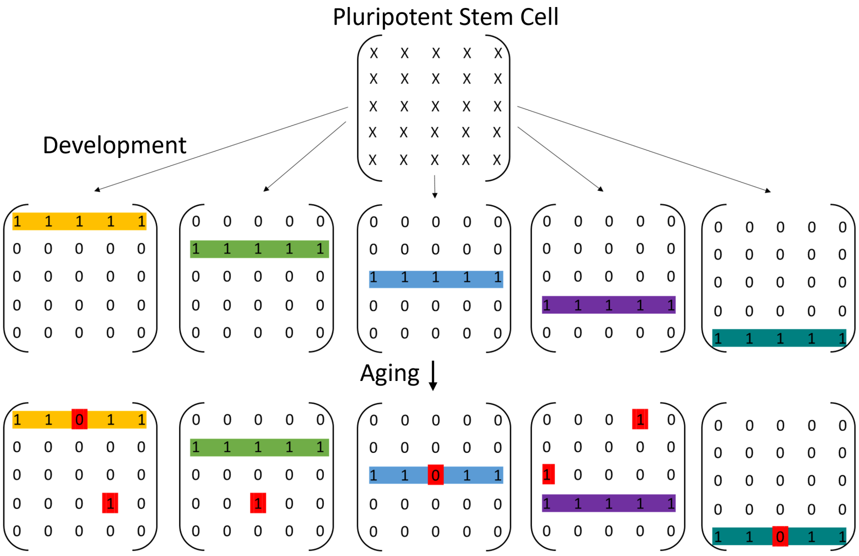

Figure 5.1: Model for development and aging by loss of epigenetic information. A single cell differentiates into many different cell types each with their own spatial location and designated epigenome. With time the epigenome mutates by turning random genes off (0) or on (1).

To conceptually capture the dynamics underlying Waddington's epigenetic landscape [27], I propose a model in which each cell maintains a self-repair signal that depends sigmoidally on the number of active genes within a specific, cell type–defining gene set, represented here as a row in a matrix (Figure 5.2). When most genes in this row are active, the self-reinforcement signal is strong, increasing the likelihood that any temporarily silenced genes are reactivated. As the number of active genes declines, the strength of this signal diminishes steeply, especially below a critical threshold.

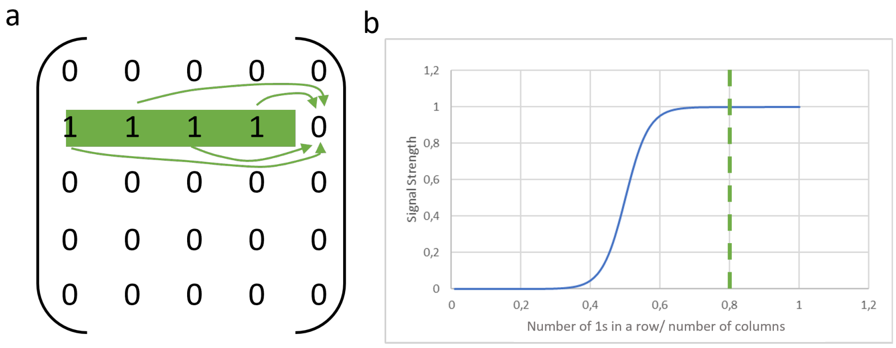

Figure 5.2: Model for behavior of Waddington's epigenetic landscape: active genes in one row influence the activation of the silenced genes of the same row (a) with a signal strength that depends sigmoidally on the number of active genes in that row (b)

In isolation, a single cell subject to random epimutations will lose the ability to maintain this repair signal. Once enough genes in the active row are lost, the signal drops below a functional level, leading to the cell's dedifferentiation. This process has a measurable average lifespan—the time it takes for the cell to cross the tipping point beyond which it can no longer maintain its epigenetic identity.

The fact that epigenetic age can be measured based on specific, predictable changes at defined CpG sites [33], rather than a random erosion of epigenetic information, suggests that aging involves regulated mechanisms that shape the epigenome over time. These mechanisms likely act with varying strength across different genomic regions, leading to site-specific vulnerabilities or biases that, collectively, produce a reproducible pattern of epigenetic drift that can be quantitatively tracked.

Now, in addition, consider a pair of cells of the same type that are coupled via communication—such as through paracrine factors or targeted extracellular vesicles. In this coupled system, each cell receives its repair signal not solely from its own gene activity, but also incorporates input from its neighbor's state, weighted by a coupling strength. For instance, if Cell A's gene set becomes degraded (Figure 5.3) and drops to only two active genes, its self-signal would be weak. However, if Cell B still maintains near-complete activity, its strong signal can compensate, enabling Cell A to recover its gene expression profile. The same applies in reverse. The probability that both cells simultaneously lose their identity becomes substantially lower than the risk of individual failure, thus extending the overall duration of stable differentiation.

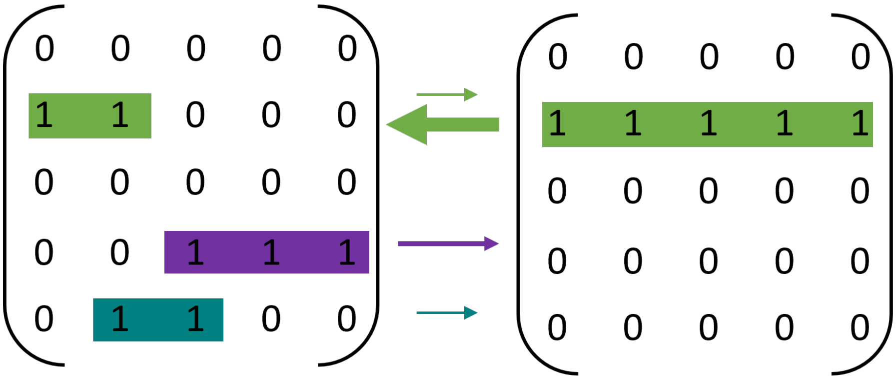

Figure 5.3: If cells share their epigenome by sending information (arrows) to other cells the system becomes more resilient. But if the epigenome of one cell becomes faulty it still broadcasts this faulty information to other cells.

Importantly, cells do not inherently "know" which genes define their correct expression profile. They maintain the configuration given to them during development and propagate it through intracellular and intercellular signaling. If one cell's profile becomes corrupted (Figure 5.3), it still broadcasts this faulty state to others. This principle is exemplified by extracellular vesicle–mediated signaling, where senescent cells release EVs with altered cargo that can induce or accelerate senescence in recipient cells, effectively broadcasting a corrupted cellular state to their surroundings [34].

Over time, this leads to a gradual decline in the average signal shared across the population of cells, and eventually, the system's capacity for self-repair collapses. Once a critical number of cells lose their specialized identity, the tissue or organism may no longer function properly—ultimately resulting in organismal failure and death.

5.3 Strategies to increase lifespan

Within this model, two straightforward strategies can extend the time before such systemic collapse. The first strategy is by increasing the number of genes in the critical row. By expanding the number of actively maintained genes, the system becomes more resilient to random mutations. More events are required for the repair signal to weaken. However, this strategy comes with increased metabolic and genomic costs, as more genes must be expressed. Importantly, with this strategy, aging and the resulting loss of function can only be slowed down and not halted indefinitely, as proposed in the disposable soma theory of aging [35].

One can expect that the activity of these maintenance mechanisms is, at least in part, subject to regulation. For example, they might be downregulated to conserve energy for reproduction during favorable conditions [36]. Conversely, in times of environmental stress or resource scarcity—when the chances of successful reproduction are low, organisms may upregulate these mechanisms to invest in somatic maintenance and longevity, effectively preparing for a more favorable future opportunity to reproduce. This has been shown extensively by caloric restriction and other stress factors extending the lifespan of organisms [37] and reduced fecundity [38].

The second strategy is by increasing the number of cells contributing to a shared signal. By expanding the number of synchronized cells of a given type, the system gains redundancy. When more copies of information synchronize with each other the way described in the model, the time before all the cells lose their differentiation increases, even though the amount of error brought into the system adds up. An interesting observation of this second strategy is that the resource cost per cell required to achieve a fixed lifespan decreases as organism size—and thus cell number—increases.

Beyond interactions within a single cell type, communication between different cell types may also serve a regulatory function in maintaining epigenetic integrity across tissues. Differentiated cells of one lineage can influence the epigenetic landscape of another, effectively adding up the connected cell types even though they are of a different kind. This forms a body-wide, interconnected signaling network through which information about cellular identity is continuously exchanged. It would not only reinforce local identity but also preserve global tissue organization.

If aging is understood as the progressive loss of epigenetic information and consequently, of cellular identity, then the content of these intercellular signals should likewise reflect an organism's age. In this view, aged cells transmit "old" signals that may propagate destabilized or degraded identity patterns, while youthful cells emit young signals that reinforce proper gene expression states. Replacing aged signals with youthful ones would therefore be expected to restore, at least partially, the correct epigenetic configuration in older cells. This conceptual framework is supported by findings from heterochronic parabiosis experiments, in which the circulatory systems of a young and an old animal are surgically joined. These studies show that young animals exposed to aged blood exhibit signs of accelerated aging, while older animals exposed to youthful circulation display molecular and functional rejuvenation [39].

In essence, the systemic exchange of epigenetic signals is dependent on the quality of the signal. For example, extracellular vesicles or tissue-specific signals can impose either a degenerative or regenerative influence [40]. This suggests that aging is not purely a cell-autonomous process, but one shaped by the collective informational environment of the organism. While many studies refer to “youthful factors” as the agents of rejuvenation in heterochronic settings, such terminology often remains mechanistically vague. In contrast, the framework proposed here offers a precise rationale: rejuvenation occurs not through a generic effect, but through the restoration of correct gene expression patterns—an informational reset driven by the reintroduction of accurate signals. It is this informational fidelity—not simply molecular abundance—that distinguishes young from old.

This perspective also helps explain why the previously mentioned freshwater planarian *Schmidtea mediterranea* regains full functionality following regeneration [20, 21]. The newly regenerated body parts are formed through a recapitulation of development-like programs, which inherently establish precise, youthful epigenetic marks. These newly patterned cells do not function in isolation; rather, they engage in intercellular communication with pre-existing tissues, transmitting epigenetic signals throughout the organism. In effect, youthful information is not confined to the site of regeneration but diffuses systemically, progressively rejuvenating the entire organism through coordinated signaling and identity reinforcement. The gradual loss of correct epigenetic information is overshadowed by the inflow of information from the newly built cells.
However, the flow of rejuvenating information may not necessarily be bidirectional—extending from the regenerated posterior to the anterior end. Genes would be needed for each direction in which the information flows. This asymmetry could account for the observation that lines of successive heads in *Schmidtea mediterranea* exhibit signs of aging and ultimately die out [23].
It is conceivable that the quantity of correct epigenetic information originating from the newly formed posterior is insufficient to effect meaningful rejuvenation in the head region and is therefore overshadowed by epigenetic drift. Alternatively, certain specialized cell types within the head may remain functionally uncoupled from the posterior systemic signaling network, rendering them inaccessible to the youthful cues emanating from the tail and thus excluded from the regenerative rejuvenation process. They nevertheless would be able to get rejuvenated if parts of the head would need to regenerate as well.

With this framework—rejuvenating information diffusing from cell to cell—it becomes conceptually plausible that a single differentiated cell could be maintained in a functional, youthful state indefinitely, provided two conditions are met: first, that the intercellular signals reinforcing its identity remain youthful and coherent and second, that the underlying genetic material remains intact and free of deleterious mutations. This hypothesis could be tested experimentally by serially transplanting a cell or small graft from an aged organism into a clonal youthful environment across multiple generations, thereby continually exposing it to a rejuvenating signaling milieu. These somatic cells should retain youthful epigenetic and functional characteristics and have lifespans much longer than that of the normal organism.

Studies where old cells are transplanted into a young host are rare. One study has shown that transplanting an excess of aged hematopoietic stem cells (HSCs) into a young organism largely restored the transcriptional profile of aged HSCs, but not their DNA methylation profiles [41].

To adequately test the mechanisms proposed here, the donor cells must be placed into a host tissue containing a large excess of cells of the same lineage so that host-derived, youthful signals overwhelmingly dominate any deleterious cues emitted by the transplanted old cells. Small grafts—both in absolute cell number and in physical diameter—are therefore preferable, since the speed at which the rejuvenating information transfuses through the transplanted tissue to the core is unknown. Distinct observations may be expected when transplanting long-lived, terminally differentiated cells such as neurons versus multipotent stem cells, including hematopoietic stem cells and their progenitors. The process of differentiation itself may be critical, as it mirrors aspects of development by newly establishing regions of the epigenetic landscape that have not yet been subject to epigenetic drift. In this way, differentiation of stem cells may represent a strategy for minimizing the longevity investment costs.

Extending this principle from a transplanted graft to an entire organism suggests that sustained rejuvenation may be achievable by persistently replacing the signals involved in cell-to-cell communication, so long as the correct epigenetic patterns are reimprinted and stabilized within each cell. Generic, body-wide molecular or genetic interventions are insufficient, as proper rejuvenation demands the spatially targeted delivery of epigenetic information, thereby ensuring that, for instance, liver-specific gene programs are reinstated exclusively within liver tissue. If all cell types are interconnected, it may not be necessary to replace all signals because youthful information introduced into the system could ripple throughout the body and rejuvenate it, provided its renewal rate exceeds the loss from epigenetic drift. It is also important to note that if the renewal rate is smaller than the loss rate, the outcome is likely indistinguishable from interventions that slow the loss rate, such as caloric restriction or knockout of pro-aging genes.

6 Relation to evolutionary genetic models of aging

The mutation-accumulation theory of aging proposes that senescence arises because natural selection grows ever weaker against deleterious mutations whose effects manifest only at advanced ages. Once an individual has survived past its prime reproductive period, the “selection shadow” cast by cumulative mortality renders late-acting mutations effectively neutral, allowing them to accumulate in the genome unchecked. However, a major unresolved challenge for this theory is the absence of any clearly defined mechanism that times the activation of these harmful alleles. As Kirkwood [42] has pointed out, without a credible molecular “clock” to delay expression until late life, the theory remains incomplete and circular, because it must assume just the kind of timing mechanism it tries to explain. The main question shifts from ”What is aging?” to ”What is early and late life?”.

For any model in which gene activity depends on an organism’s age, there must exist some change or signal that reliably marks the transition from one life stage to the next. Antagonistic pleiotropy (AP) likewise rests on the premise that genes can switch their effects between “early-life” and “late-life” states, yielding benefits at one stage and costs at another. Yet this theory does not address why evolution could not favor alleles that simply mirror the beneficial early-life signal indefinitely—thereby reaping only the positive effects and entirely avoiding senescent decline.

A more nuanced perspective emerges once we consider the gradual loss of epigenetic information and the functional impairments that follow. Imagine an AP-gene whose product boosts fitness—for example, by encoding a protein that makes a process more energy efficient—but which naturally degrades over time, requiring cellular clearance mechanisms to remove its breakdown products. Early in life, efficient “cleanup” ensures continued benefit; later, however, as epigenetic drift degrades the very pathways responsible for debris removal, accumulating waste overwhelms the system and generates pathology. Because this failure occurs late and the positive effect persists throughout life, the gene is favored by natural selection. It is also possible for a gene to accelerate aging, but when it also provides a fitness gain that outweighs the negative effects, it will become fixed in the population. A knockout of that gene would result in a longer lifespan.

The same logic applies to mutation-accumulation: a mutation that increases the potential of the byproducts of the protein to aggregate at a certain concentration might escape purifying selection simply because its harmful effects manifest after a lot of reproduction has already taken place. In both cases—antagonistic pleiotropy and mutation-accumulation—the mechanisms they describe are secondary layers atop the fundamental processes that distinguish early life from late life.

This perspective further clarifies why evolution cannot simply recreate the beneficial early-life signals for an AP gene: the signal itself is the function that is progressively lost, making selective retention of only the positive effects impossible.

7 Discussion and Conclusion

By reframing aging as a progressive loss of information—one that evolution can only slow through resource investment or renew via development-like resets—this work provides a unifying mechanistic–evolutionary account that explains otherwise puzzling phenomena such as heterochronic parabiosis and regeneration-mediated rejuvenation. Importantly, the framework yields concrete, falsifiable predictions, making it immediately useful to both theorists and experimentalists.

If information can diffuse between cells, a single differentiated somatic cell could be maintained in a youthful functional state so long as intercellular signaling remains youthful and coherent and the cell's genome stays intact. This is testable: serially transplant a cell or small tissue piece from an aged donor into a clonal youthful host. The transplanted material's epigenome and functional characteristics should become youthful. This could in principle be repeated indefinitely with each generation.

The model is consistent with prior computational simulation studies [43], showing that supplying the correct cell-state information to the correct spatial locations is sufficient to induce durable organ rejuvenation.

In this work, aging was primarily explained as a consequence of epigenetic information loss, but this does not exclude the progressive loss of other forms of biological information. In particular, the accumulation of somatic DNA mutations may still contribute to functional decline over time. Current evidence suggests that the accumulation of single-nucleotide variants alone is unlikely to drive most human aging phenotypes, while the contributions of other forms of genome instability, somatic copy-number alterations and structural variations remain poorly understood and insufficiently studied [44]. For other kinds of information loss to be a driver of aging, the information-depleted state would need either to be restored during development or eliminated by purifying selection.

The here proposed information-theoretic or "software" solution for the preservation of epigenetic information does not have to be limited to signals of only one architecture. RNA that finds the correct DNA regions to construct an R loop triggering chromatin condensation and heterochromatin formation to silence a gene [45] seems like a good mechanism to synchronize the epigenome of multiple cells. For that, the RNA needs to be sent via extracellular vesicles from cell to cell and alter recipient cell gene expression, as has been shown [46].

More generally, any signaling architecture capable of reliably transmitting the information would be subject to evolutionary retention, independent of the specific mediator involved. Bioelectric signals that connect individual cells into large-scale patterning fields [47] could be another mechanism by which the information of correct differentiation is stored and lost over time.

When cells rely strongly on extrinsic cues to establish and maintain their differentiated state, it is reasonable to expect that they exploit robust and persistent environmental signals. One such signal is fluid shear stress, which has been shown to induce differentiation of circulating endothelial progenitor cells toward an endothelial phenotype [48], and may subsequently contribute to the maintenance of that differentiated state. Another constant environmental cue is exposure to sunlight, which can act as an external signal promoting skin-specific cellular identity. Consistent with this idea, skin cells possess molecular mechanisms that enable them to sense and respond to light [49].

Here, it has been argued that the evolutionary explanations of aging — antagonistic pleiotropy and mutation-accumulation — operate as secondary layers that act upon an underlying loss of epigenetic information and function. This provides the much-needed timing mechanism for genes to act upon and therefore be selected for. It is critical to define and distinguish these layers with precision, because aging research should focus primarily on the root causes of functional decline, rather than uncovering the exact mechanisms of the functions that are ultimately lost or misregulated.

A newly developed medicine, such as a molecule that counteracts a specific consequence of aging, offers a novel way to restore a lost function, effectively rebuilding parts of the organism through alternative mechanisms. Current science is nowhere near a systemic understanding of an organism and, with that, far from being able to predict the network of interactions that results from replacing each lost function with a new solution. Therefore, the focus should be on mechanisms that evolution can only reach with difficulty: building a new bridge for the correct and already present youthful information to flow from young to old. Evolution's current bridges to restore functions, development or development-like processes, carries for humans the baggage of death. A new bridge for the information must be built through the substrate of technology.

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