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The Evo-Devo Basis of Age-Associated Diseases: Extending the Evolvable Soma Theory of Ageing

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Abstract: The mechanistic and evolutionary origins of age-associated diseases remain incompletely understood. Building on the Evolvable Soma Theory of Ageing (ESTA), which conceptualises development and ageing as a continuous genetically encoded programme of epigenetic change, this work extends the framework to age-associated disease. Advanced age is the strongest risk factor for many diseases, including cardiovascular disease, cancer, neurodegenerative disorders, and metabolic syndrome. The present framework proposes that the age dependence of these conditions may partly reflect their interaction with the regulatory trajectories underlying development and ageing. In this framework, age-associated epigenetic changes may represent regulated components of a lifespan-wide developmental programme, while genetic variation, environmental influences, and stochastic processes contribute to individual disease susceptibility. Disease-associated cellular states are further conceptualised as potential attractors of gene regulatory networks influenced by these trajectories. This perspective provides a theoretical framework for considering common regulatory mechanisms underlying diverse age-associated diseases.

Keywords: ageing; evolution; evo-devo; age-associated diseases

1. Introduction

Ageing remains one of the major unresolved problems in biology, and competing theories continue to debate the relative contributions of stochastic processes and genetically regulated mechanisms. *Stochastic theories* attribute ageing to the cumulative impact of damage arising from environmental stressors and endogenous metabolic by-products, such as reactive oxygen species, drawing an analogy with the progressive wear of mechanical systems. In contrast, *programmed theories* suggest that ageing follows a genetically encoded biological schedule, though its progression may be modulated by external factors (see [1] for a comprehensive review). Despite their differences, many mechanistic frameworks converge on DNA-level alterations [2] or on epigenetic dysregulation [3] as proximal drivers of age-related decline.

Likewise, major diseases such as cardiovascular disease, cancer, neurodegenerative disorders, and diabetes remain major challenges in biology and medicine. Although their epidemiological risk factors and many molecular mechanisms are well characterized, the mechanisms underlying their strong age dependence and their common features across different disease categories remain incompletely understood. A striking commonality among these conditions is their strong association with ageing: as lifespan increases, so does disease prevalence. Together, these age-related diseases account for the vast majority of global mortality, with noncommunicable diseases—including cardiovascular disease, cancer, and diabetes-responsible for over 70% of deaths worldwide [4].

In previous work, the Evolvable Soma Theory of Ageing (ESTA) was proposed, conceptualising development and ageing as successive phases of a developmental programme unfolding throughout the lifespan [5–7]. Here, this framework is extended to age-associated diseases by asking whether disease susceptibility may emerge from the same lifespan-wide regulatory programme. This paper examines evidence for an epigenetic contribution to age-

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associated diseases and explores the hypothesis that some pathological cellular states could correspond to stable or metastable attractors of gene regulatory networks. This disease-focused extension of ESTA is intended to provide a conceptual framework for understanding why susceptibility to diverse diseases increases with age and why particular pathological states may emerge preferentially during later life.

This paper is organised into eight sections. Following this introduction, Section 2 reviews major human diseases, with particular emphasis on their strong association with ageing. Section 3 presents the biological model and the associated hypothesis on the nature of ageing, outlining its core principles and assumptions. Sections 4 and 5 examine the relationship of the epigenetic developmental programme with healthy ageing and age-associated diseases, respectively. Section 6 interprets age-associated diseases as attractor states of the system emerging under perturbations. Section 7 discusses diseases that are not primarily associated with ageing, highlighting their distinct characteristics. Section 8 explores the potential implications of this perspective for the prevention and treatment of human pathologies.

2. Age-Related Diseases

Cardiovascular diseases (CVD), cancer, and neurodegenerative disorders (including dementia) are among the leading causes of death globally, each representing a significant burden on public health. Cardiovascular diseases, including heart attacks and strokes, remain the top cause of mortality worldwide [8]. Cancer, the second leading cause of death, encompasses a wide range of diseases characterised by uncontrolled cell growth, with lung, breast, and colorectal cancers being among the most prevalent [9]. Dementia, particularly Alzheimer's disease, is a growing concern as populations age, leading to progressive cognitive decline and loss of independence [10].

Metabolic syndrome, characterised by a cluster of conditions such as abdominal obesity, hypertension, dyslipidemia, and hyperglycemia, acts as a significant accelerator of the aforementioned diseases. It increases the risk of cardiovascular diseases by promoting atherosclerosis and hypertension [11], exacerbates cancer progression through chronic inflammation and insulin resistance [12], and is linked to cognitive decline and dementia, particularly vascular dementia, by impairing brain structure and function [13]. Together, cardiovascular diseases, cancer, neurodegenerative disorders and metabolic syndrome are referred to by MD Peter Attia as the "four horsemen of death" [14].

Genetic predisposition contributes to all major age-associated diseases, although its architecture is typically complex and polygenic. Genome-wide association studies (GWAS) have identified numerous susceptibility loci, yet, with the exception of a limited number of high-penetrance mutations, most variants individually confer only modest increases in disease risk. Nevertheless, age-associated diseases exhibit clear familial aggregation: individuals with affected parents have an increased risk of developing related disorders, even when the specific clinical manifestations differ [15]. The observation that currently identified genetic variants account for only a fraction of this inherited risk is commonly referred to as the "missing heritability problem" [16].

Subsequent studies have shown that much of this gap can be attributed to the highly polygenic architecture of complex traits, the contribution of rare genetic variants, and limitations in earlier heritability estimates. In particular, recent whole-genome sequencing studies indicate that common and rare variants together account for a substantial proportion of pedigree-based heritability, although some uncertainty remains [17]. This distributed genetic architecture is also consistent with the omnigenic model [18], which proposes that complex traits can be influenced by a large network of peripheral regulatory variants in addition to variants with more direct effects on core disease-related genes.

Besides genetic predisposition, numerous modifiable factors contribute to age-associated diseases through interactions with the genome. Poor diet and physical inactivity promote obesity, hypertension, dyslipidaemia, and insulin resistance, while smoking, air pollution, and excessive alcohol consumption drive chronic inflammation, contributing to cardiovascular disease, cancer, and neurodegeneration. Psychological stress, sleep deprivation, and socioeconomic disadvantage further increase disease risk by affecting metabolic, immune, and behavioural pathways. Collectively, these lifetime environmental influences are referred to as the "exposome" [19].

However, age is the single most significant risk factor for cardiovascular diseases, cancer, neurodegenerative disorders, and metabolic syndrome. For cardiovascular diseases, the risk increases exponentially with age, with individuals aged 60 and older accounting for over 75% of CVD-related deaths globally [20]. Similarly, cancer incidence rises sharply with age (Figure 1), with the vast majority of all cancer cases diagnosed in individuals aged 50 and older, and the median age of cancer diagnosis being 66 years [21]. Dementia prevalence also escalates with age, doubling every 5 years after the age of 65, and affecting over 30% of individuals aged 85 and older [10]. Metabolic syndrome shows a similar age-dependent trend, with prevalence increasing from 20% in individuals aged 40–49 to over 40% in those aged 60 and older [11].

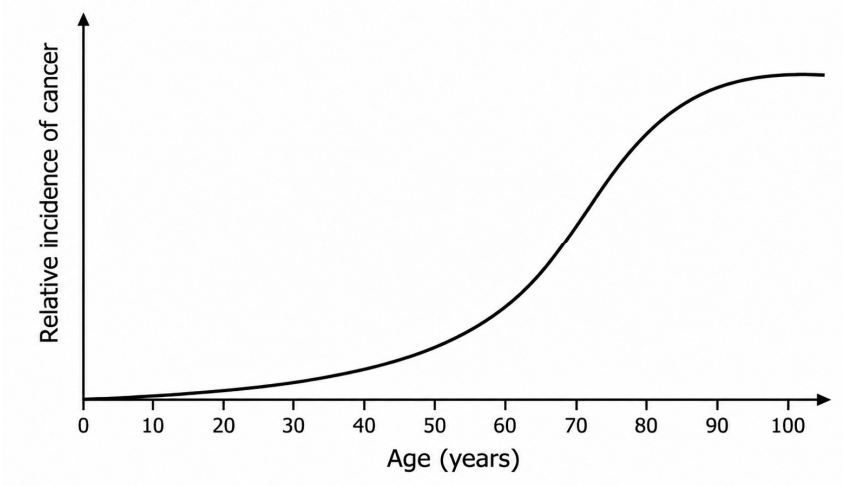


Figure 1. Schematic illustration of the age-related increase in cancer incidence. The curve represents a hypothetical trend intended to illustrate the general increase in cancer incidence with age. It is purely illustrative and does not represent actual epidemiological data or measurements.

Most current theories of age-associated diseases treat the strong correlation between ageing and disease as largely indirect: the passage of time allows molecular damage, somatic mutations, metabolic dysfunction, and other stochastic errors to accumulate, eventually leading to pathology [22]. In this view, ageing primarily acts as a risk factor that increases the probability of disease rather than as its underlying cause. In the remainder of this paper, an alternative perspective is proposed, in which ageing and age-associated diseases are not linked merely by the passage of time, but arise, at least in part, from a common underlying biological driver, alongside other contributing factors.

3. The ESTA Hypothesis

The ageing theory examined here is grounded in a model of development that has provided a framework for interpreting a range of biological phenomena [23]. The model describes development as a process coordinated by a distributed population of *driver cells* that issue commands to *normal cells* (Figure 2, panel A). Cells have a genome that encodes two distinct classes of information: *basic genes*, which produce structural and functional components, and *developmental genes*, which drive development (Figure 2, panel B). The activation of developmental genes is controlled by their associated *timers*, which operate in synchrony with a common *global clock*. Once activated, these genes trigger *change events* that modify the epigenetic state of their target cells. Full model details are provided in [5].

The distinction between basic and developmental genes is primarily functional: the former control cellular behaviour within a given epigenetic state, the latter direct epigenetic state changes. While basic genes are hypothesised to be implemented through protein-coding genes, developmental genes may encompass a broader range of genetic elements, including protein-coding genes as well as long non-coding RNAs, which are increasingly recognised as key regulators of epigenetic states [24,25]. Epigenetic changes comprise a diverse set of chemical modifications that coordinate gene activity across time and space, including the writing, erasing, and interpretation of the "histone code" [26], as well as the establishment and removal of DNA methylation marks.

From an evolutionary perspective, the prevailing view is that ageing is nonadaptive, arising because the force of natural selection declines with age. This leads to reduced investment in somatic maintenance in favour of early-life reproductive success, or to trade-offs mediated by pleiotropic genes with beneficial early-life but deleterious late-life effects [27]. These frameworks, termed for convenience *State-of-the-art Evolutionary Ageing Theory (SEAT)*, typically assume that development is governed by a genetically encoded programme, after which largely non-programmed processes progressively degrade organismal function. Although the age-dependent decline in selection helps distinguish development from ageing, it does not imply a discrete biological boundary between them. No universal event marks when development ends: should it be at 18, 20, 25, or some other age? The transition may instead reflect a gradual shift in the strength and nature of selective pressures.

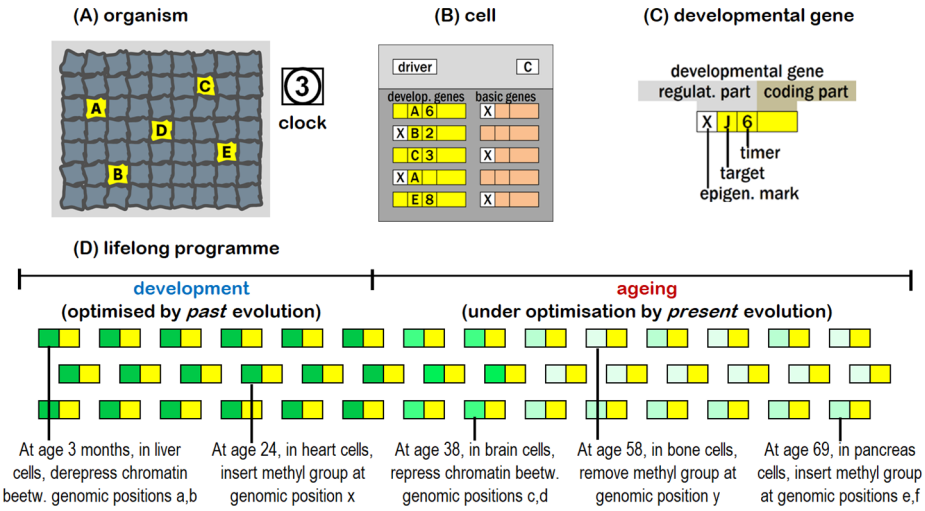


Figure 2. In our model, the organism (panel **A**) consists of a large population of normal cells and a smaller pool of driver cells (highlighted in yellow). The genome is partitioned into basic genes and developmental genes (panel **B**). Developmental genes (panel **C**) comprise a regulatory part, which specifies the timing and target cell types of gene activation, and a coding part, which encodes a change event that modifies the epigenetic landscape of the target cells. In this framework, development and ageing are interpreted as a single continuous programme driven by developmental genes (panel **D**). Development corresponds to the portion of this programme that has been refined by past evolutionary selection, whereas ageing represents the portion that may remain subject to ongoing evolutionary change. The examples of change events shown at the bottom are hypothetical illustrations of the proposed mechanism and do not represent empirical observations.

Our model overcomes this dichotomy by integrating development and ageing into a single, continuous, genetically regulated process: the developmental programme proceeds through a sequence of *developmental steps*, each associated with a specific clock value and a set of coordinated change events (Figure 2, panel D). The *Evolvable Soma Theory of Ageing (ESTA)* [5] posits that development is governed by a portion of the genetic programme already optimised by past evolution, whereas ageing emerges from the action of late-acting genes that are still under evolutionary optimisation. These post-reproductive genetic modifications function as somatic "experiments" that often impair physiological function but can, on occasion, generate beneficial variation on which natural selection may act across generations. From this perspective, ageing is not merely a process of decline, but can be understood as *evolution in action*. Nonetheless, this framework does not exclude contributions to ageing from other, non-programmed factors, possibly induced by environmental agents.

The link between ageing and development is not new. *Hyperfunction theory* [28] proposes that developmental and growth-promoting modules persist beyond their adaptive window, so that processes beneficial early in life become detrimental when they continue later in life. The theory refers to these as *programs*; here, the word *module* is used to denote a component of the developmental *programme*, which refers to the complete set of genetically encoded developmental instructions. ESTA differs in proposing a unified developmental programme extending from conception to death, comprising a sequence of modules with specific spatial and temporal activation patterns, each associated with its own "timer". Thus, ageing does not result from the prolonged activity of the *same* modules that were beneficial during early life, but from the activation of *different, later-acting modules* within the broader developmental programme.

A related developmental theory is the *quasi-program theory* proposed by de Magalhães [29], who argued that some mechanisms of ageing originate during development and involve the persistence of developmental modules into later life, with epigenetic and gene-expression changes providing possible proximal mechanisms. The same distinction outlined above applies here: in ESTA, the modules activated during ageing are different from those that drive earlier developmental stages. An important contribution of de Magalhães was to incorporate epigenetics into this framework, highlighting its potential links to age-associated diseases and pointing to the existence of epigenetic clocks as evidence that ageing may involve a degree of biological programming. ESTA shares this view and, in this sense, both theories can be considered forms of programmatic theories of ageing.

To some extent, both Blagosklonny's hyperfunction theory and de Magalhães's quasi-program theory can be viewed as mechanistic extensions of antagonistic pleiotropy, in which early-life benefits and late-life costs arise from the continued activity of the same developmental modules. ESTA does not require such fixed pleiotropic effects.

Through the regulation of developmental genes by enhancers, silencers, and other regulatory elements, the developmental programme includes temporally and spatially specific patterns of gene activity throughout the lifespan. Antagonistic pleiotropic effects are not excluded by ESTA, but are considered to occur in a limited number of cases and to make a secondary contribution rather than constitute the primary mechanism underlying ageing.

Moreover, neither Blagosklonny nor de Magalhães attributes an adaptive evolutionary function to the late-life activity of the developmental programme, and their models are therefore compatible with non-adaptive accounts such as SEAT. In contrast, ESTA views ageing as *evolution in action*: while most developmental "experiments" may be neutral or deleterious, some may generate phenotypic novelties that can subsequently be refined by natural selection across generations. In this sense, development represents the outcome of past evolutionary innovation, whereas ageing reflects the action of *present* evolutionary experimentation.

The evolutionary interpretation of ESTA places it within the longstanding debate over the relationship between ageing and evolution. Whereas SEAT proposes that evolution is indifferent to ageing, or merely tolerates it, a distinct line of thought argues that ageing itself may have an adaptive evolutionary function. These adaptive-ageing hypotheses propose, for example, that ageing may promote evolvability, population turnover, or ecological regulation [30]. More recent proposals have also explored pathogen-driven explanations for the evolution of conserved ageing mechanisms [31]. ESTA offers a different perspective, by conceptualising ageing as "evolution in action": the unfolding throughout the lifespan of a developmental programme upon which evolution continues to act.

A potential criticism of ESTA is that post-reproductive somatic experiments should have little evolutionary significance, because their effects occur when natural selection is weak or absent. However, the influence of selection generally declines with age rather than disappearing entirely, and late-acting traits may still affect fitness indirectly, through either continued reproduction or kin support. Moreover, under ESTA, the timing of change events is itself potentially evolvable: mutations affecting gene timers could shift a late-acting event to an earlier stage of life in subsequent generations, bringing its effects into a period of stronger selection. Thus, even if a somatic experiment initially has little impact on fitness because it occurs late in life, subsequent evolutionary changes in its timing could increase its exposure to selection and amplify its evolutionary consequences.

4. The Developmental Epigenetic Engine of "Healthy Ageing"

The hallmarks of ageing at the cellular level comprise several interconnected biological processes: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, disabled macroautophagy, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, chronic inflammation, and dysbiosis [32]. The Hallmarks of Ageing framework already classifies genomic instability, telomere attrition, epigenetic alterations, and loss of proteostasis as *primary hallmarks*, reflecting their proposed roles as initial sources of damage. ESTA builds on this classification by proposing that at least some age-associated epigenetic alterations are not merely accumulated damage but genetically controlled components of a lifespan-wide developmental programme.

Epigenetic mechanisms have long been implicated in the ageing process. For example, the Information Theory of Ageing proposes that ageing arises from the progressive loss of cellular identity driven by epigenetic dysregulation and drift [33]. Likewise, epigenetic clocks are based on DNA methylation patterns that change in a highly reproducible manner with age, allowing biological age to be estimated with remarkable accuracy across tissues and individuals [3]. Rather than interpreting these methylation changes solely as passive biomarkers of ageing, the proposed model suggests that they may partly reflect genetically programmed epigenetic modifications executed as part of the developmental programme.

Notably, many age-associated methylation changes are observed consistently across large populations of cells, giving rise to epigenetic signatures rather than isolated alterations in individual cells. The reproducibility of these patterns across individuals and, in some cases, across tissues [34] suggests that age-associated epigenetic changes may involve coordinated regulatory processes in addition to stochastic variation. By contrast, somatic DNA mutations accumulate in individual cells and may undergo clonal expansion when they confer a selective advantage. Although such mutations can have important pathological consequences [35], mutation-based biomarkers have so far proved less accurate than epigenetic clocks for estimating biological age. This difference is consistent with the possibility that epigenetic changes capture aspects of ageing that reflect coordinated alterations in gene regulation, whereas somatic mutations primarily record the history of individual cell lineages.

Besides the action of non-optimised developmental genes, ageing could also be influenced by a biological clock that regulates the timing of the developmental programme. The nature of such a clock remains unknown: it could involve systemic molecular signals, local timing mechanisms, or processes such as telomere dynamics. These possibilities should therefore be regarded as hypotheses rather than established mechanisms. Interventions

known to delay ageing, including caloric restriction [36] and modulation of nutrient-sensing pathways such as mTOR [37], may provide opportunities to test whether such mechanisms influence the proposed clock.

5. The Developmental Epigenetic Engine of Age-Associated Diseases

In this section, the ESTA framework is extended to age-associated diseases by proposing that they may arise from genetically programmed epigenetic modifications occurring during ageing. In this view, healthy ageing and disease represent different outcomes along a continuum driven by the same underlying process. A striking feature of many age-associated diseases is the absence of a simple, recurrent pattern of high-penetrance mutations that could explain most cases. In cardiovascular disease, for example, GWAS have identified numerous associated loci, but individual variants generally have modest effects [38]. Cancer shows a similarly heterogeneous mutational landscape: although mutations in genes such as *TP53*, *BRCA1*, and *KRAS* are recurrently observed, no common mutational pattern accounts for the diversity of cancers across individuals and tissues [39].

The same diffuse genetic architecture is evident in neurodegenerative and metabolic diseases. In late-onset neurodegenerative disorders, numerous risk loci have been identified, but most have modest effects and rarely correspond to recurrent, high-penetrance mutations; Alzheimer's disease is a prominent example, with the *APOE* ε4 allele representing an important exception [40]. Similarly, GWAS of obesity, insulin resistance, dyslipidaemia, and related metabolic traits have identified many associated loci, but no small set of high-penetrance mutations explains the majority of cases [41]. Taken together, these observations suggest that the genetic architecture of many age-associated diseases is highly heterogeneous and may not, by itself, provide a straightforward explanation for their common emergence during ageing.

An alternative explanation is that age-associated diseases may involve coordinated epigenetic dysregulation rather than being driven primarily by recurrent genetic mutations. In cardiovascular disease, increasing evidence implicates epigenetic mechanisms (including DNA methylation, histone modifications, and chromatin remodelling) in processes such as atherosclerosis, cardiac hypertrophy, and heart failure [42]. In cancer, the frequent disruption of epigenetic regulation has led to the proposal that many common cancers may have an important epigenetic component [43]. Similarly, the relative absence of strong, recurrent mutational patterns in neurodegenerative diseases suggests that dysregulated epigenetic processes may contribute substantially to their development [44]. Metabolic syndrome provides another example, with epigenetic alterations implicated in pathways regulating energy balance, glucose metabolism, adipogenesis, and inflammation [45].

Across these disease categories, the genetic evidence therefore points to complex, distributed susceptibility rather than a common high-penetrance genetic mechanism. This does not exclude important contributions from polygenic and rare variants, but suggests that additional regulatory mechanisms may contribute to disease development. Epigenetic alterations are of particular interest as a potential proximal mechanism because they are dynamic, cell-type-specific, and responsive to both intrinsic and environmental influences. Importantly, the involvement of epigenetic dysregulation in age-associated diseases is well established [46] and is not proposed here as a novel observation.

ESTA addresses a different question: why should such epigenetic alterations emerge progressively with age? It proposes that the developmental programme provides an upstream regulatory context in which genetically encoded, age-dependent changes in gene regulation can shape the epigenetic landscape throughout the lifespan. Genetic variation, environmental influences, and stochastic processes may modify these trajectories and contribute to individual differences in disease susceptibility. Thus, ESTA does not posit a genetic-versus-epigenetic dichotomy; rather, it proposes a model in which the developmental programme may influence epigenetic trajectories, while genetic, environmental, and stochastic factors modulate their expression and consequences.

Epigenetic contributions to disease could be interpreted as epigenetic damage or drift. However, the existence of tissue- and organ-specific epigenetic clocks is consistent with a more structured process. The reproducible, tissue-dependent patterns of age-associated DNA methylation suggest that epigenetic ageing is not simply random molecular drift but follows regulated trajectories that differ among cell types and tissues. This is compatible with the hypothesis that age-dependent epigenetic changes form part of a broader developmental programme. Notably, de Magalhães proposed that epigenetic ageing and epigenetic clocks may reflect developmental programmes extending into later life [29]. ESTA extends this concept by proposing a continuous, lifespan-wide regulatory programme with spatially and temporally specific patterns of gene activity.

This perspective does not exclude contributions from other factors. Genetic susceptibility, environmental exposures, metabolic processes, somatic damage and mutations, and stochastic processes may all influence the trajectory toward age-associated disease. These factors may interact with the developmental programme, modifying its effects and contributing to differences in disease susceptibility between individuals. Accordingly,

age-associated diseases are likely to emerge from the combined influence of the lifespan-wide developmental programme and multiple genetic, environmental, metabolic, and stochastic factors.

6. Diseases as System Attractor States

If age-associated diseases are viewed as byproducts of evolutionary experimentation on epigenetic pathways, a natural question arises: why does this process preferentially generate the specific diseases most commonly encountered in clinical practice? The distribution of these diseases is far from random. For example, among age-associated disorders of the central nervous system in developed countries, Alzheimer's disease affects approximately 10% of individuals over the age of 65, whereas frontotemporal dementia affects only 0.1–0.2%, amyotrophic lateral sclerosis has a prevalence of approximately 0.01%, and primary malignant brain tumors affect fewer than 0.05% of the population [47,48]. These large and reproducible differences suggest that ageing does not increase susceptibility uniformly across all possible pathologies.

Dynamical systems theory provides a useful framework for understanding this heterogeneity. An *attractor* is a state towards which a system tends to evolve from a range of initial conditions, known as its basin of attraction [49]. Complex systems can contain multiple attractors, corresponding to distinct relatively stable states. In biology, this concept has been applied to gene regulatory networks (GRNs), where different patterns of gene expression may represent stable cellular states, including distinct cell types [50]. Cell differentiation can thus be viewed as a transition between attractors driven by developmental signals. Quantitative methods have also been developed to reconstruct Waddington's epigenetic landscape and identify early-warning signals of critical transitions [51].

Similarly, age-associated pathological states could represent alternative attractors of cellular GRNs, with network structure influencing their accessibility. A schematic representation of GRN attractor basins for two human cell types is shown in Figure 3. The large central attractor represents a stable physiological state reached during development (25 years of age is shown for illustration). Epigenetic perturbations, hypothesised here to contribute to age-associated cellular changes, need not drive the system toward arbitrary states. Instead, as the regulatory state progressively changes, cellular trajectories may converge toward a limited set of alternative attractors determined by the underlying landscape. Within this framework, age-associated diseases affecting a given organ could be interpreted as stable or metastable attractor states of the GRNs operating in the corresponding cell types, each associated with a distinct basin of attraction.

The idea that disease states can be represented as attractors of gene regulatory networks is not new. It builds on Waddington's epigenetic landscape and Kauffman's early work on attractor states and cell types, and was developed explicitly in the context of cancer by Huang, Ernberg, Kauffman and others [52,53]. Subsequent studies have extended the attractor framework to cancer subtypes, disease progression, and the modelling of transitions between normal and pathological states [54]. These studies provide an important conceptual foundation for the present work. Our proposal builds on this established framework but considers a broader question: whether age-associated diseases more generally can be understood as pathological attractor states emerging from progressive changes in gene-regulatory and epigenetic landscapes during ageing.

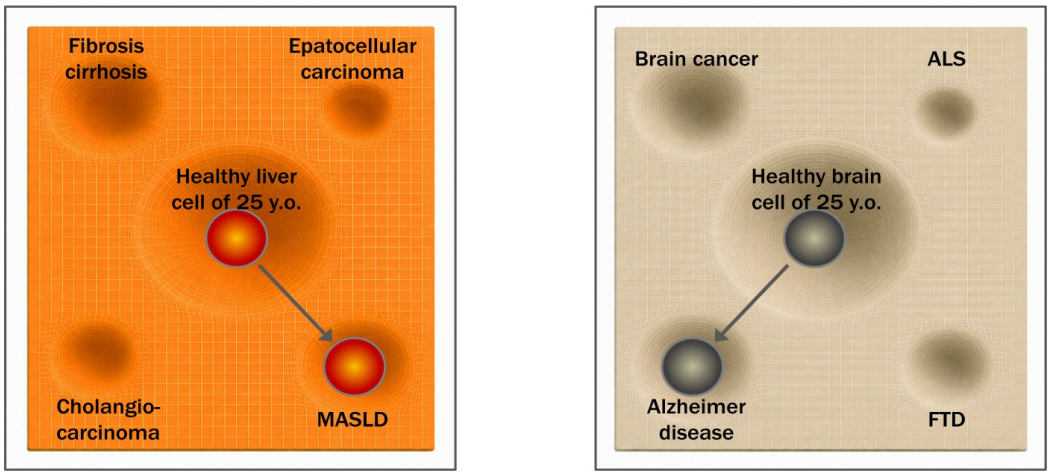


Figure 3. Age-associated diseases as potential attractor states. Schematic representation of GRN attractor basins for two cell types and their corresponding gene regulatory networks. The large central attractor represents a stable physiological state reached during development (25 years of age is shown for illustration). Surrounding attractors represent hypothetical age-associated pathological states. Progressive epigenetic changes may alter the regulatory landscape and shift cellular trajectories away from the physiological state toward alternative states. The figure is

conceptual and does not imply that ageing inevitably leads to disease or that the illustrated attractors correspond to specific actual diseases. The figure is also highly simplified, as actual tissues and disease processes typically involve multiple interacting cell types.

The attractor framework proposed here is conceptual and does not provide an independent measure of attractor basin size. Consequently, the observed prevalence of particular diseases cannot be taken as direct evidence for the geometry of the corresponding regulatory landscape. A rigorous evaluation of this hypothesis would require longitudinal molecular data to determine whether age-associated changes in gene expression, DNA methylation, or other molecular states progressively converge toward disease-associated states, and whether such trajectories are reproducible across individuals. Such analyses are beyond the scope of the present work. The attractor model is therefore presented as a conceptual extension of ESTA and as a hypothesis that could be investigated using existing longitudinal and multiomic datasets, rather than as an empirically established explanation of disease prevalence.

7. Non Age-Associated Diseases

Age-associated diseases account for a large proportion of human pathology. However, not all diseases follow an age-dependent pattern of onset. Infectious diseases, for example, can affect individuals across all age groups, including children and the elderly, as their onset is primarily triggered by external pathogenic agents rather than internal processes. Nevertheless, the host response is strongly shaped by age. With advancing age, the immune system undergoes a gradual decline in efficiency, a process known as immunosenescence, characterised by reduced adaptive immune repertoire diversity, impaired innate immune signalling, and a chronic proinflammatory baseline state ("inflammageing") [55]. These changes contribute to weaker and delayed immune responses to novel pathogens and reduced vaccine efficacy in older individuals. COVID-19 provides a clear example, with age emerging as one of the strongest predictors of severe disease and mortality, even after accounting for comorbidities and exposure risk [56].

The other category of non-age-associated diseases is represented by monogenic diseases, caused by mutations in single (usually protein-coding) genes. These conditions, (including disorders such as e.g., cystic fibrosis, sickle cell anaemia, Huntington's disease, and Tay-Sachs disease) are generally rare, often manifesting with severe clinical phenotypes and an early age of onset. For example, cystic fibrosis, caused by mutations in the CFTR gene, affects approximately 1 in 2500 newborns in populations of European descent [57]. Haemophilia, an X-linked disorder usually caused by mutations in the F8 or F9 genes, impairs the blood's ability to clot and affects approximately 1 in 5000 male births [58]. Also, monogenic diseases can be excluded from the category of conditions driven by programmed epigenetic changes.

Progeroid syndromes are a class of diseases that have been extensively studied in the context of ageing research. These rare, usually monogenic disorders, such as Hutchinson–Gilford progeria syndrome, produce clinical features resembling accelerated ageing, often appearing early in life. Although they share with normal ageing certain manifestations of molecular damage and cellular dysfunction, their underlying mechanisms are fundamentally different. They originate from specific genetic defects that disrupt particular cellular functions, rather than from the complex, multifactorial processes underlying physiological ageing. Thus, despite some phenotypic similarities, progeroid syndromes should not necessarily be regarded as simple accelerated versions of normal ageing. This distinction represents a conceptual interpretation rather than an established conclusion, as the relationship between progeroid syndromes and physiological ageing remains an active area of research [59].

In Section 5, it was proposed that the activity of developmental genes may contribute to the onset of age-associated diseases. By contrast, monogenic diseases can be associated with mutations in basic genes in our model. Whereas evolutionary tinkering with developmental genes, although often detrimental, may occasionally produce beneficial phenotypic variation that natural selection can subsequently refine, mutations in basic genes are far less likely to be advantageous. Because these genes encode proteins with fundamental structural or housekeeping functions required across multiple tissues and developmental stages, a sequence modification that is advantageous in one context is likely to compromise essential functions in others. Consequently, mutations in these genes are often deleterious and associated with severe genetic disorders, thereby limiting their evolutionary flexibility.

The exclusion of monogenic and infectious diseases from the category of conditions potentially associated with programmed epigenetic changes represents a limitation of the scope considered here, rather than evidence in favour of ESTA. These conditions have distinct and often well-characterised causal mechanisms that are not the primary focus of the present framework. Their exclusion does not imply that developmental regulation cannot influence their onset, progression or clinical manifestations, but simply that explaining their origins is beyond the scope of the current analysis.

8. Discussion and Conclusions

Precision medicine aims to tailor prevention, diagnosis, and treatment strategies to individual variability in genetics, environment, and lifestyle, moving beyond the traditional "one-size-fits-all" approach [60]. By integrating genomic, molecular, clinical, and environmental data, precision medicine seeks to improve therapeutic efficacy while reducing adverse effects, particularly in complex, multifactorial diseases that dominate ageing populations. Advances in high-throughput sequencing, biomarker discovery, and data analytics have accelerated this shift, enabling more refined disease stratification and targeted interventions. In the context of age-associated diseases, precision medicine offers a framework to account for heterogeneity in ageing trajectories and treatment responses, thereby improving translational outcomes and long-term patient care. Emerging approaches such as partial epigenetic reprogramming may further expand these possibilities by potentially reversing selected age-associated molecular changes while preserving cellular identity and function.

This perspective is broadly consistent with SEAT, which interprets age-associated diseases as the cumulative outcome of multiple damage-inducing processes acting in the so-called "evolutionary shadow". These include metabolic side-effects, chemical and physical agents, as well as pathogens, leading to stochastic damage affecting organs, tissues and cells, at the genetic, epigenetic and proteomic level (Figure 4, left panel). Genetic factors contribute to these processes in several ways: they influence vulnerability and repair capacity, and, as proposed by antagonistic pleiotropy, some genetic variants that confer fitness advantages early in life can also have deleterious effects later in life. Nevertheless, within the broader SEAT framework, late-life pathologies are generally understood as the outcome of multiple interacting mechanisms operating under conditions of declining selective pressure. Consequently, age-related diseases are thought to arise through heterogeneous causal pathways, do not share a common upstream mechanism, and are typically addressed individually.

In contrast, ESTA proposes an additional upstream perspective on age-associated disease, in which a lifespan-wide developmental programme may contribute to the age-dependent molecular and epigenetic trajectories that influence disease susceptibility (Figure 4, right panel). Within this framework, late-acting developmental processes could interact with genetic variation, environmental exposures, metabolic processes, somatic damage, and stochastic factors to shape the probability of entering particular pathological states. ESTA therefore does not replace existing explanations of age-associated disease, but proposes a developmental and evolutionary framework that may help explain why susceptibility to diverse diseases increases systematically with age.

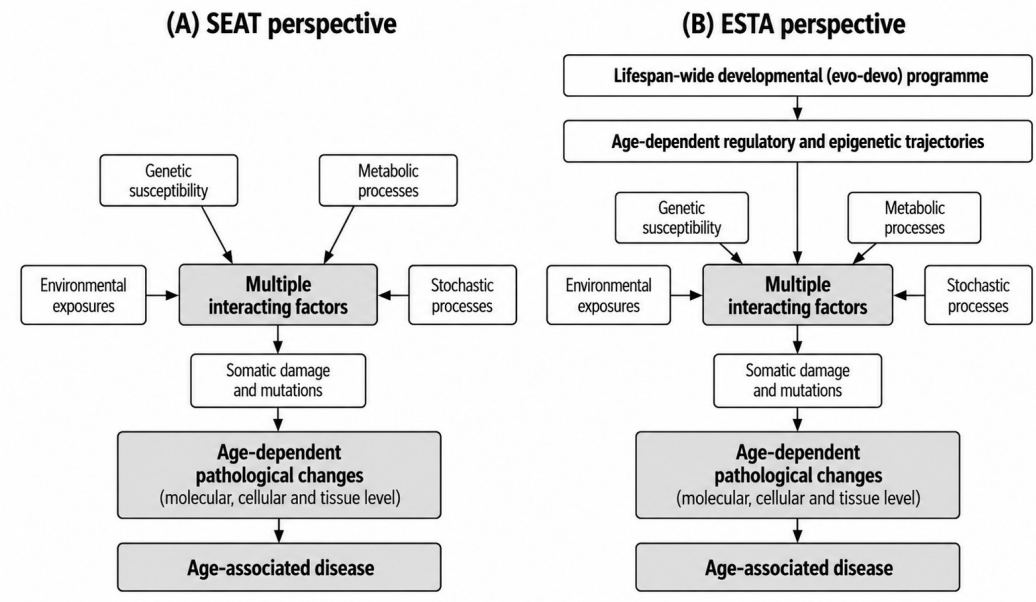


Figure 4. Contrasting perspectives on the origins of age-associated disease. (**A**) Under SEAT, age-associated diseases are understood as the outcome of multiple interacting genetic, environmental, metabolic, stochastic, and damage-related processes whose effects become increasingly apparent with age. (**B**) ESTA proposes an additional upstream regulatory perspective, in which a lifespan-wide developmental programme may shape age-dependent molecular and epigenetic trajectories that influence disease susceptibility. ESTA does not exclude genetic variation, environmental influences, or stochastic processes; rather, these factors may modify the trajectories generated within the broader developmental regulatory framework.

An important question is how ESTA can be tested against alternative theories of ageing. Previous investigations have explored the theory through computer simulations [6] and observations from the natural world [7]. The latter examined three predictions: that species subject to less evolutionary change may age more slowly; that evolutionary innovations tend to emerge towards the end of development; and that changes in reproductive timing may occur over evolutionary timescales. The third prediction is hypothesised to apply to species experiencing different levels of competition and potentially to differences between the sexes. These investigations provided preliminary evidence consistent with the theory.

A further test concerns age-associated epigenetic changes, including those captured by epigenetic clocks. ESTA predicts that at least some of these changes form structured, correlated patterns, following age-dependent trajectories and showing associations with specific disease categories. A further prediction is that methylation changes preferentially affect genes involved in development, consistent with evidence of their enrichment at Polycomb targets and developmental genes across mammalian species [61]. The reproducibility of epigenetic clocks does not in itself demonstrate the existence of a regulated programme, since accurate clocks can also emerge from stochastic epigenetic variation [62]. The distinction therefore lies in whether epigenetic changes exhibit coordinated temporal patterns and relationships that cannot be adequately explained by stochastic drift alone, as predicted by SEAT. Appropriately designed statistical models, with safeguards against overfitting, are needed to distinguish between these possibilities.

Tests also need to be defined to distinguish ESTA from other programmatic theories, particularly hyperfunction and quasi-program theories, with which it shares some conceptual similarities. These theories primarily emphasise the continued or excessive activity of growth- and development-promoting processes, whereas ESTA proposes that ageing involves multiple partially independent developmental modules, each governed by its own timer. These timers may evolve to advance or delay individual events without necessarily affecting the timing of other modules. ESTA therefore predicts that age-associated changes may exhibit temporal coordination among cells within individual organs while evolving relatively independently between organs.

These predictions provide initial directions for distinguishing ESTA from alternative explanations, although their precise formulation and experimental validation remain ongoing challenges. In particular, identifying module-specific timers and demonstrating that their manipulation can selectively alter the timing of corresponding ageing processes would provide a more direct test of the theory. Closer collaboration between ageing research and developmental biology may provide valuable insights into the identification and characterisation of such timers.

Finally, and perhaps most importantly, this perspective may eventually have implications for intervention. If elements of the proposed developmental programme contribute causally to age-dependent disease susceptibility, identifying and modulating these regulatory processes could provide additional approaches to disease prevention or treatment. For example, it might become possible to intervene not only in the downstream molecular damage associated with ageing, but also in the regulatory processes that initiate or coordinate such changes. Such an approach could complement existing strategies aimed at repairing damage or modifying individual disease pathways. At present, however, these possibilities remain hypothetical. Establishing whether the proposed programme exists in the form suggested, and whether its components can be safely manipulated, will require substantial experimental evidence.

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Conflicts of Interest

The author declares that he has no conflict of interest.

Use of AI and AI-Assisted Technologies

During the preparation of this work, the author used ChatGPT to improve the language quality. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the published article.

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