



A complex systems approach to aging biology

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Having made substantial progress understanding molecules, cells, genes and pathways, aging biology research is now moving toward integration of these parts, attempting to understand how their joint dynamics may contribute to aging. Such a shift of perspective requires the adoption of a formal complex systems framework, a transition being facilitated by large-scale data collection and new analytical tools. Here, we provide a theoretical framework to orient researchers around key concepts for this transition, notably emergence, interaction networks and resilience. Drawing on evolutionary theory, network theory and principles of homeostasis, we propose that organismal function is accomplished by the integration of regulatory mechanisms at multiple hierarchical scales, and that the disruption of this ensemble causes the phenotypic and functional manifestations of aging. We present key examples at scales ranging from sub-organismal biology to clinical geriatrics, outlining how this approach can potentially enrich our understanding of aging.

The goals of aging biology research are broad and ambitious—to understand how a multitude of genes, pathways and mechanisms at multiple scales contribute to declines in function, health and lifespan in ways that can vary across populations, environments and species. Enormous progress has been made identifying individual genes, pathways, molecules and their connection in mechanisms that modulate aging. However, there has been limited progress in our understanding of how these factors interact to produce a global set of aging processes, or in how these processes combine to produce functional phenotypes of aging such as frailty, or demographic patterns such as the Gompertz mortality curves found across the tree of life¹. Accordingly, research is increasingly focusing on understanding how mechanisms and pathways integrate, drawing on concepts of complex systems such as resilience, homeostasis, networks and interactions. This transition to a complex systems view of aging has been happening piecemeal and is only sometimes explicitly acknowledged; many of the core concepts and methods are unfamiliar to biologists and may be defined in various ways. Here, we provide a theoretical framework and introduction to the key concepts of complex systems theory as applied to aging, as a primer to orient researchers new to the field and in the attempt to offer a unifying vision for how a complex systems approach could be transformative in aging biology research.

In this context, we consider aging to encompass sub-organismal biological processes leading to declines in organismal survival and function with the passing of time, including hierarchical scales ranging from molecular to clinical. We first provide a brief, non-technical motivation for the need to address complexity and then introduce three salient aspects of complex systems in the context

of aging biology—emergence, resilience and networks—providing examples of their use along with appropriate methods.

The history of ecology provides a useful comparison (Fig. 1). In the early 1970s, building on the systems ecology work of Odum², Robert May introduced complex systems theory to ecology^{3–5}. Among other things, this accelerated the transition from notions of ‘food chains’ to ‘food webs’ and led to the complex nature of ecosystems being widely recognized. This generated new key questions, such as how processes could (de)stabilize ecosystems. The transformation of ecology was rapid and thorough, both because previous theory was inadequate, and because emerging data and methods allowed formal analyses of ecosystems as complex systems. This did not negate the impact of straightforward ecological experiments such as predator removal, which continue to be a crucial part of the field⁶; however, they are now conducted in a research framework where the guiding questions presuppose complexity. Theoretical ecology has burgeoned, leading to formalization of notions such as resilience⁷ and critical transitions⁸, both of which have direct implications for aging research and are discussed below. Theoretical advances have also had major impacts on ecological applications, such as management of fisheries (Fig. 1) and forestry^{9,10}.

A similar transformation has started in the field of aging biology. The ideas of multifactoriality or complexity of aging emerged decades ago^{11–14}, and by the 2000s the multifactorial nature of aging was widely acknowledged¹⁵. More recent seminal manuscripts on ‘the hallmarks of aging’¹⁶ and the ‘pillars of aging’¹⁷ implicitly invoked the concepts of networks, feedback loops and nonlinearity—hallmarks of complex systems. We believe that, because of the extreme plasticity and redundancy of aging biology, no specific mechanism

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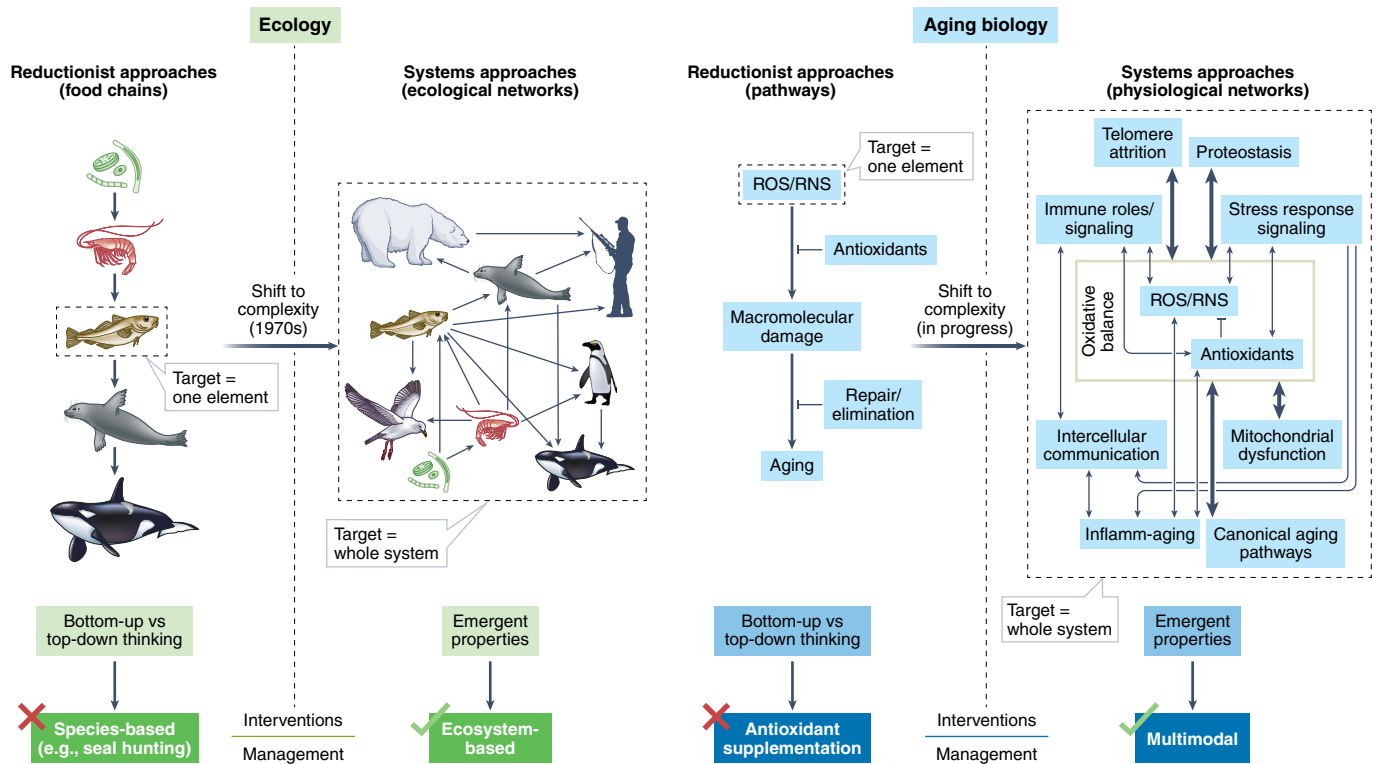


Fig. 1 | Shift to complex systems approaches in ecology and aging biology. In both North Atlantic food webs (ecology) and oxidative stress (aging biology), the failure of linear approaches (food chains/molecular pathways) led to systems approaches with networks that captured the multifactorial and interactive nature of these systems. Bottom-up/top-down thinking gives way to the consideration of emergent properties. Interventions on selected network components, such as seal hunting to restore cod stocks or antioxidant supplements to slow aging, are unsuccessful because they ignore the consequences of propagation to other interconnected parts. RNS, reactive nitrogen species; ROS, reactive oxygen species.

or pathway is fully informative outside the context of the whole organism. Therefore, understanding aging will require detailed knowledge of specific implicated mechanisms contextualized in a 'complex systems' approach, integrating across multiple hierarchical scales to achieve a functional, dynamical understanding of the organism. These approaches complement, but go beyond, classical bioinformatics and functional genomics approaches that are largely focused on high-throughput data in the absence of dynamics and structure, and the systems biology approaches that only tackle small-scale dynamical problems.

Two major challenges in aging biology research are the large volumes of data and lack of an organizing paradigm^{18–20}; both may be aided by two key features of complex systems approaches. First, despite their name, complex systems approaches can be powerful tools for simplification, identifying the essential features in a mass of otherwise indecipherable data and largely unpredictable trajectories. Second, the underlying patterns are driven by broad mathematical and biophysical principles, such that findings in one aspect of aging biology are likely to have direct applications in many others.

Both of these features are clearly evident in a classic example of how complexity science has led to a better understanding of aging and identified novel targets to prevent age-related disease. Lipsitz and colleagues have shown that aging is associated with a loss of structural and functional complexity in a variety of integrated anatomic structures and physiological processes. This loss of complexity impairs an individual's ability to adapt to the stresses of everyday life, leading to disease and disability^{13,21}. Examples of the loss of complexity in anatomic structures with aging and its consequences include the degeneration of fractal-like trabecular networks in bone that leads to fractures, damage to the branching architecture of Purkinje fibers in the heart that leads to conduction

disease, and thinning of the dendritic arbor of frontal lobe neurons that leads to gait disorders and falls. Dynamic physiological systems that lose complexity with aging and are consequently associated with adverse outcomes include heart rate (Fig. 2a), which is a predictor of lethal arrhythmias or cardiovascular disease²¹, systolic blood pressure, which is a predictor of dementia²², moment-to-moment center-of-pressure changes during balance, which is a predictor of falls²³, and the blood oxygenation signal in resting-state functional magnetic resonance imaging, which is associated with slow gait speed in older adults²⁴. The restoration of complex dynamics in various physiological systems through the use of various multisystem interventions can improve functional abilities. For example, Tai Chi exercises improved balance complexity and associated mobility measures in older adults with peripheral neuropathy²⁵. Subsensory vibratory noise applied to the foot soles can improve balance complexity and mobility²⁶. These findings provide preliminary evidence that complexity loss in a variety of anatomic structures and physiological systems is associated with disease and disability, but may be reversible through multidimensional interventions. They also show how complex data (for example, heart rate time series) can be simplified to measure a key underlying property (for example, heart rate complexity), as well as how such principles, once discovered, can generate a range of insights and benefits in different contexts.

The complex systems approach is ultimately a paradigm that reflects what we understand about organismal evolution and function, and major advances can be made by simply adopting this perspective. Indeed, many of the studies in Fig. 2 rely more on a complex systems perspective than on explicit complex systems methods. For example, more than 70 years ago Harman's free radical theory of aging proposed that organisms age because cells accumulate free

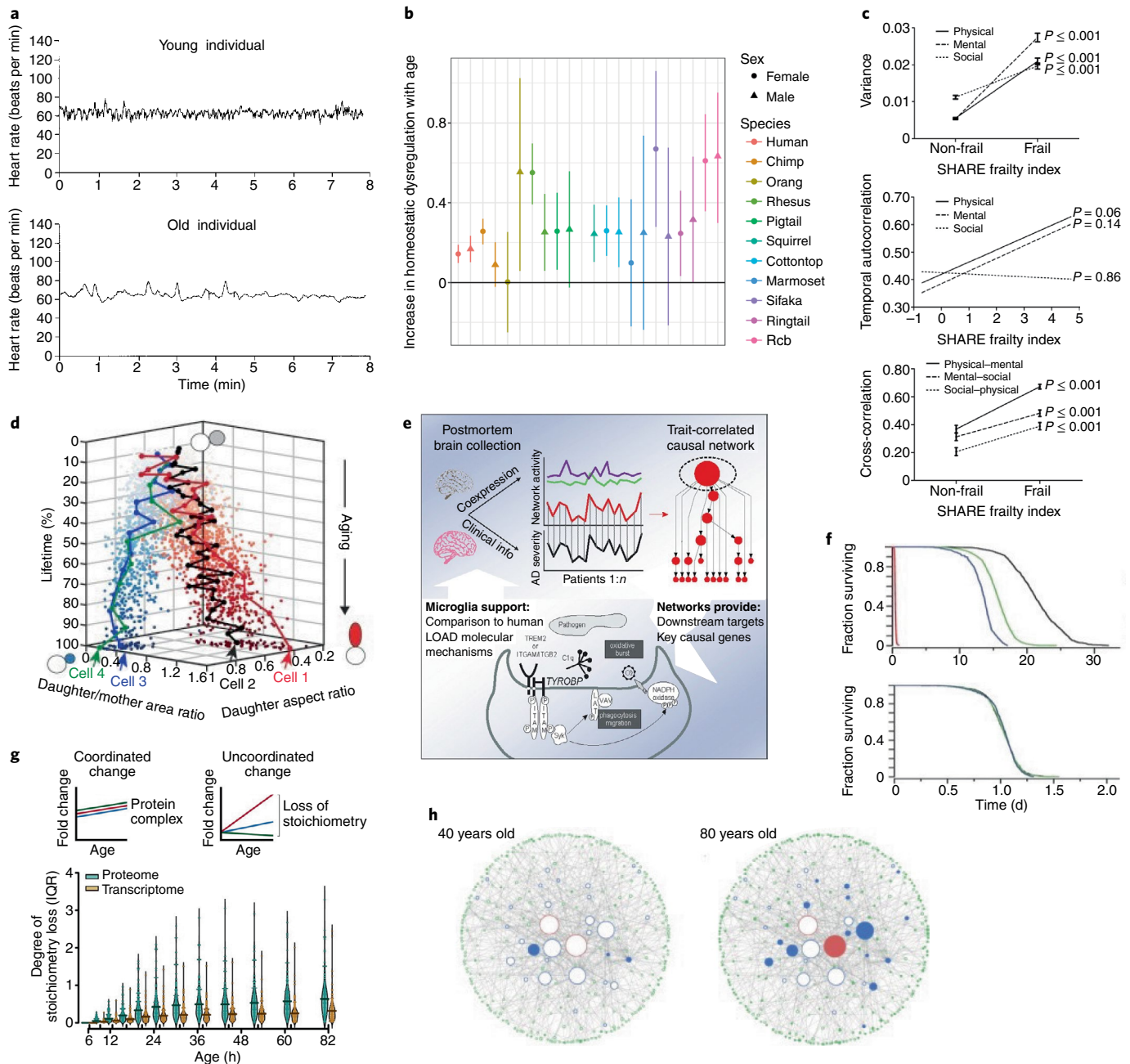
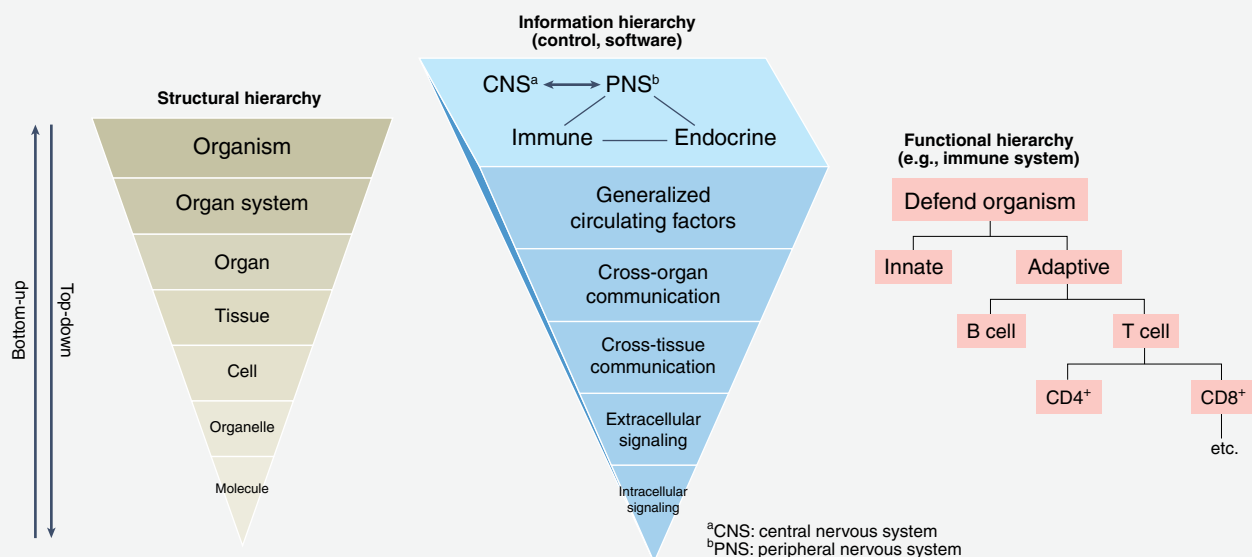


Fig. 2 | Key examples of advances in aging biology using complex systems perspectives or methods. **a**, High complexity in heart rate variability (top) is characteristic of young individuals, whereas decreased complexity is characteristic of older individuals (adapted with permission from ref. ¹³, AMA). This finding led to measures of heart rate variability as indicators of health and aging. **b**, Physiological dysregulation, measured as the Mahalanobis distance of clinical biomarkers, increases with age in similar ways across 11 primate species (reproduced from ref. ¹³³, CC BY 4.0). This shows conservation of physiological signatures of homeostasis and characterizes overall homeostatic state as an emergent property. **c**, Early warning signs of critical transitions, as measured through variance, temporal autocorrelation and cross-correlation in self-rated health data, are strongly associated with frailty status (adapted with permission from ref. ⁸³, Oxford Univ. Press). This confirms predictions that system dynamics change jointly before adverse events. **d**, Different yeast cells show different cell fate trajectories along one of two canalized pathways or ‘modes’ (adapted with permission from ref. ⁵⁶, Elsevier) (see main text). **e**, Bayesian approaches to estimating brain immune and microglial networks provide predictive insights into late-onset Alzheimer’s disease pathophysiology (adapted with permission from ref. ¹³⁴, Elsevier). **f**, Different *Caenorhabditis elegans* survival curves at different temperatures (top) overlap perfectly when adjusted to the temporal scale of the lifespan (bottom) (adapted from ref. ¹¹⁸, Springer Nature Ltd). Accordingly, lifespan can be understood as an emergent property of underlying processes that adjust temporal scale. **g**, Directional network analysis of proteome and transcriptome in yeast shows loss of stoichiometry in protein complexes with aging, implying broadscale reorganization or dysregulation of regulatory networks (reproduced from ref. ¹³⁵, CC BY 4.0). **h**, Simulated networks of interacting deficits propagated across the lifespan recapitulate observed dynamics of frailty and mortality (filled circles indicate damaged nodes) (adapted with permission from ref. ¹³⁶, Elsevier).

Box 1 | Organisms as complex systems

Living systems share many properties with other complex systems^{32,33}, including network dynamics, emergence, hierarchical organization and attractor states. However, they also have unique properties that are key to understanding aging biology:

1. **Optimized for evolutionary fitness.** Living systems have been highly optimized by evolutionary processes over millions of years. This optimization has generated structures and behaviors distinct from less-optimized complex systems such as economies or climate.
2. **Components have dual roles as effectors and as information.** Biological networks are composed of molecules that both perform a function and signal to the rest of the system. For example, ATP serves a function not only as energy, but also as information, inhibiting pyruvate kinase in the pathway that forms it¹³⁸. This dual role is rare in other complex systems. Biological networks are thus also information systems, and information flow is important.
3. **Trade-offs.** Highly optimized complex systems, such as living systems, are forced into trade-offs to maintain robustness at the expense of resource use, performance or control^{42,51,61}.
4. **Plasticity.** Living systems adapt to changing environments and function in a variety of contexts (such as day/night, summer/winter and feeding/starvation), and selection has developed multiple systems that allow such plasticity at different scales.
5. **Larger parts list.** Evolutionary processes generate unparalleled diversity—a typical organism will have tens of thousands of proteins and hundreds of thousands of splicing variants that control an even greater variety of metabolites.
6. **Complex hierarchy.** The parts list, although large, is smaller than expected based on functional complexity. Many layers of biological organization/interactions are still being discovered¹³⁹, and the standard biological hierarchy (molecules, organelles, cells, tissues, organs, organ systems and organism) is only one of several parallel, interacting structures (figure in Box 1). These hierarchies interact over various temporal and spatial scales during aging.
7. **Functionality of attractor states.** Attractor states are discrete states of complex systems to which the system converges, as exemplified by canalization and cell fates^{140,141}. For example, cellular senescence is a relatively discrete state, an alternative to being a healthy cell or to apoptosis. Senescence is thus an attractor state, with many intermediate states within its ‘attractor basin.’ Once an intermediate state is reached, the cell relatively quickly converges toward full senescence¹⁴². While attractor states also exist in undirected complex systems, in biological systems they are generally functional, corresponding to the adaptive needs of the organism (above). Functional non-discrete states (‘attractor gradients’) exist as well (for example, inflamm-aging¹³¹).
8. **Sparse data.** Even with the advent of omics technologies, we are a long way from having a full map of most biological systems¹³⁹, much less being able to measure them simultaneously. Many biological pathways have yet to be discovered!



Parallel biological hierarchies.

radical damage over time²⁷. However, a number of experiments have since demonstrated that free radicals have important signaling roles that are essential for survival, and only when in great excess do they negatively affect cell and organismal survival^{28,29} (Fig. 1). Standard methods showed that intermediate levels of both antioxidants and free radicals are optimal and are therefore tightly regulated³⁰. This fits redox balance neatly into the hormesis paradigm³¹, which relies on feedback loops and homeostasis/dynamic equilibrium, both characteristics of complex systems. We see this repeatedly: the units

we study (molecules, pathways, cells and organs) are part of a larger system, and their behavior cannot be fully understood outside their interactions with its other units and of the state and dynamics of the system as a whole. Each element of the system, such as a metabolite or a protein, has multiple biological effects, which is incompatible with an assumption of simple pairwise interactions between molecules. Rather, biology is an ensemble of signaling pathways with a collective ‘voice’ that results from their combined interactions. During aging, the state of equilibrium of this complex system

evolves through different levels of relative stability until homeostasis is no longer possible and the organism dies.

Organisms as complex systems

Complex systems can be as diverse as ecosystems, economies, traffic systems and even the internet^{32–34}, but are often surprisingly similar in their characteristics and behavior. Core hallmarks of complex systems include: (1) networks of interacting elements (for example, interactions among molecules in key aging pathways such as hypoxia-inducible factor (HIF)-1, AMP-activated protein kinase (AMPK), mechanistic target of rapamycin (mTOR), sirtuins, insulin-like growth factor (IGF)-1R and forkhead box O (FOXO)³⁵ (Fig. 2c,e,h); (2) feedback/feedforward loops (for example, adaptive loops such as blood pressure regulation³⁶ and maladaptive or runaway loops such as cellular senescence increasing the senescence-associated secretory phenotype (SASP), which increases cellular senescence through paracrine signaling^{37,38}; Fig. 2d); (3) a multi-scale or modular hierarchical structure (for example, organelles, nested in cells nested within tissues nested within organs, together with how damage propagates up, down or across such structures during aging^{39,40}); (4) nonlinear dynamics (for example, accelerating decline in multiple systems at the end of life⁴¹; Fig. 2a,c,f); and (5) emergent properties, which are properties of a system that cannot be directly or additively inferred by examining its component parts (for example, cognitive decline or loss of mobility cannot be understood simply as the sum of multiple aging cells; Fig. 2a,b,d,f).

There can be little doubt that both organisms and their subsystems such as cells behave as complex systems^{42,43} (Box 1), but, despite some key studies^{44–46}, the literature on organisms as complex systems is not yet fully integrated into current biological research practice. A starting point, as Theodosius Dobzhansky famously said, is that ‘Nothing in biology makes sense except in the light of evolution’⁴⁷. Unlike in most other complex systems, natural selection has fine-tuned biological complex systems over billions of years, generating biological software for ‘life maintenance’, at least into adulthood (Box 1). As such, organisms are not random collections of interacting molecules, but are highly optimized fitness-maximizing systems with redundancy, flexibility and resilience⁴². A crucial aspect of such fitness is the ability to maintain a state of dynamic equilibrium²¹, which encompasses homeostasis, homeodynamics, allostasis, robustness and resilience: can the organism maintain, adjust, and if perturbed return to whatever state is currently best for it^{48–52}? Aging is thus a set of processes that occur within a complex system: in interacting networks structured by selection to maintain dynamic equilibrium, yet eventually failing to do so. Accordingly, we could add that ‘Nothing in aging biology makes sense except in the light of dynamic equilibrium,’ and conclude that we must eventually understand the interplay between evolution and dynamic equilibrium to fully understand aging.

Emergence: understanding the interplay between different scales of organization in aging

What is emergence? Geriatricians are intimately familiar with frailty, falls and delirium, three phenomena that are clinically important but that do not have simple underlying causal pathways^{41,53}. Numerous interventions have nevertheless been identified to prevent, treat or manage them—notably complex or multimodal interventions. All three conditions are classic examples of emergent properties, properties of a system that cannot be understood by simply combining lower-scale features of the system⁵⁴. In the case of frailty, for example, a relatively coherent phenotype emerges from underlying contributing processes, even though not all individuals with those underlying processes will become frail⁴¹.

Canalization and emergence. One common way that emergence arises is through canalization (Box 1), the tendency of the system to converge toward one of a limited number of discrete states. A striking

example of canalization is the finding of two distinct cell fates in yeast aging (Fig. 2d). Yeast replicative aging is a genetically tractable model that encompasses many conserved hallmarks of aging, such as genomic instability, loss of proteostasis, reactive oxygen species and mitochondrial dysfunction⁵⁵. These damage and stress factors were long studied independently and implicitly assumed to contribute more-or-less additively to the physiological declines and death of aged cells. When studied together by microfluidics coupled with time-lapse microscopy, isogenic BY4741 and W303 yeast cells show two different forms of aging: one with decreased ribosomal DNA silencing and nucleolar decline (mode 1), and the second with heme depletion and mitochondrial decline (mode 2)^{56–58}. Intriguingly, the aging trajectories of mode 1 and mode 2 cells, quantified from molecular and cellular changes, are mutually exclusive. Distinct ending states correspond to discrete attractor states within complex systems theory. This canalization view of yeast aging nicely complements and extends population-level analyses showing that caloric restriction extends lifespan via various parallel pathways⁵⁹. We anticipate that this dynamic, stochastic view of aging will open up strategies to rationally rewire gene networks and reprogram aging dynamics more effectively and robustly than simple gene deletions or overexpression.

Canalization and emergence often arise because biological networks can achieve robustness through redundancy, and so become buffered against perturbations—they are able to maintain a dynamic functional stability even when environmental or internal conditions change^{21,60,61}. This buffering often means that the same functional result can be achieved by multiple alternative pathways, strategies or system states. For example, because of the effect of androgens, men often have higher muscle strength than women and rely on peak strength to optimize gait performance, while women more often rely on optimization and refinement of the motor program⁶². Furthermore, during skeletal muscle aging, impaired chaperone-mediated autophagy appears to be compensated by upregulation of macro-autophagy⁶³. A growing list of examples from diverse hierarchical scales suggests that, in the context of aging, alternative physiological and biochemical strategies are routinely used to compensate for deficits, but that these ‘compensatory strategies’ may be less efficient or effective.

Emergence, hierarchical structure and their characterization.

Frailty, inflamm-aging and yeast cell fates are examples of how core aspects of aging emerge at different scales of organization. Furthermore, mechanisms can emerge at higher scales (for example, tooth wear⁶⁴) or can have effects from higher scales to lower scales (for example, impacts of psychological stress on telomere length⁶⁵). A long-term goal in aging biology research should be a multi-scale mapping of emergent aging phenomena and mechanisms at each scale, and how they influence each other. For example, Kuo et al⁴⁰, recently proposed that functional aspects of human aging such as declines in cognition can be mapped to changes in phenotype during aging, which in turn can be mapped to basic biological processes. Whereas traditional approaches have often examined inter-scale relationships between one or two factors at a time⁶⁶, the complex systems approach emphasizes the need for more integrative models. A good example is the maintenance of immune function during aging. The common conception that immune function declines with age is based on observations such as thymic involution, decreased production of naïve T cells, and impaired antigen presentation by dendritic cells⁶⁷. However, at a functional level, otherwise healthy older adults generally mount sufficient immune responses to infections; further, when properly formulated, most vaccines can be just as effective in older adults, including for severe acute respiratory syndrome coronavirus 2 (refs. 68–71). Accordingly, there is no good one-to-one mapping between individual changes in the immune system with age and overall immune system functionality: overall

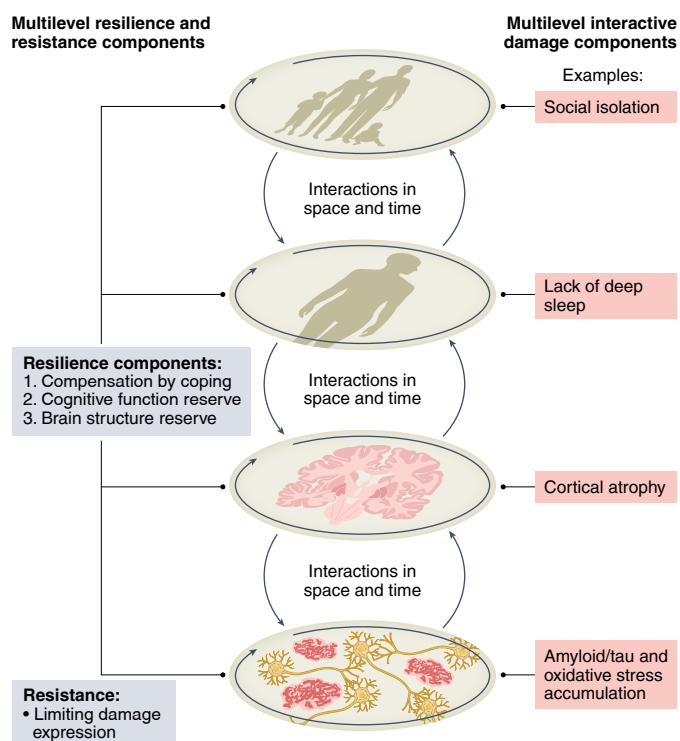


Fig. 3 | Multi-scale causality: the example of Alzheimer's disease.

Dementia provides one illustration of how the science of complex systems can help us better understand dementia's biological processes. First, healthy brain function can be viewed as an emergent property of a complex system, requiring interactions across multiple scales from neurons to networks to social and environmental components, while disease (in this case dementia) arises from the breakdown of these interacting components. Thus, dementia may result from the loss of complex interactions among determinants of healthy cognitive function operating on different scales in time or space. This includes the breakdown of components shown here, including at a cellular scale (interactions among neuroinflammation, the immune context and the accumulation of amyloid and tau that disrupts neuronal integrity); at a tissue scale (brain atrophy); at a person scale (decreased sleep, reduced physical activity, depression and cardiovascular risk factors); and at a societal scale (social isolation, environmental toxins and other influences)¹³⁷. The complex nature of healthy function enables compensation and resiliency, which protects against cognitive decline until the loss of complexity reaches a threshold at which overt disease and disability emerge. This Alzheimer's disease model is an example of the hierarchical principles in the figure in Box 1, but remains speculative.

functionality appears to be largely buffered. Appropriate understanding of how lower-scale changes percolate up to higher-scale effects will thus require complex systems approaches such as simulations, modeling and high-dimensional analyses, all integrated with targeted experimental approaches tailored to this framework.

Discrete system states, such as cell fates or phenotypic frailty⁴¹, or continuous system states, such as inflamm-aging or metabolic syndrome⁷², reflect attractor basins or gradients as organizing biological principles that may be key to understanding aging. An intuitive analogy is that, driving past a cornfield, the corn can appear to be randomly planted until one sees the structure of the rows. When applied with a complex systems perspective, standard statistical/bioinformatics tools such as principal-component analysis⁷³, *t*-distributed stochastic neighbor embedding (*t*-SNE)⁷⁴ and cluster analysis⁷⁵ can uncover structure and become tools for simplification. Many such attractor structures are yet to be identified⁷³. This framework

of defining emergent phenomena could help make major progress on longstanding challenges in aging research. For example, Figure 3 shows what this might look like in the case of Alzheimer's disease and related dementias, and shows how Alzheimer's disease could be regarded as an emergent phenomenon akin to frailty or delirium rather than as a direct product of pathways such as amyloid- β . Additionally, studying whether frailty is an attractor state or an attractor gradient could help to resolve the ongoing debate on phenotypic versus deficit accumulation definitions of frailty^{41,76}.

Resilience and critical transitions: legacies from theoretical ecology

The dynamics, and in particular the resilience, of complex systems is a fundamental problem of many disciplines. In system dynamics, resilience is measured by the capability and the rate at which a system converges to or departs from its equilibrium after a disturbance. Ecology has been influential in this field with the study of the network properties conferring resilience. May⁷⁷ and others⁷⁸ proposed that resilience decreases with network complexity (size, number of connections between nodes and interaction strength) but that regular and organized features such as the existence of modules buffers the spread and impacts of perturbations. May's theory is, however, limited because it applies to deterministic systems that are only very rarely disturbed, while in nature stochastic variations in the environment keep the system moving out of equilibrium. A stochastic theory of resilience was therefore proposed⁷, and was used as the backbone of critical transition theory⁸. Instead of looking at the asymptotic behavior of the system, this theory investigates the distribution of the system around equilibrium. The variance and temporal autocorrelation of time series are expected to increase as resilience decreases.

These insights from ecological systems provide a useful intuition to understand aging. If physiological systems are networks of interacting elements, then we can apply stochastic resilience theory to interpret dynamics of a whole suite of biological markers with aging. A key feature providing resilience to interacting networks is self-regulation within modules, while interactions among them might decrease resilience (but see ref. ⁷⁹). One could therefore ask how these two fundamental quantities change during aging. In particular, the variance of individual markers and the temporal covariances among them are expected to increase with age. Theory also proposes that a sudden increase in these properties can be used to anticipate critical changes in the state of the system.

Resilience and critical transitions are indeed both gaining increasing attention in the aging literature^{80–84}. The formal definition from ecology agrees well with common conceptions of resilience in the aging literature, and allows us to build on the stressor–response paradigm. The literature on frailty and resilience hypothesizes that deleterious changes in homeostatic mechanisms may be hidden in the absence of external stressors such as infection, injury or organ-system-based illness. Consequently, frail and non-frail individuals may differ more in how they respond dynamically to stressors than in their baseline status^{85,86}. Varadhan⁸⁵ proposed a dynamical systems modeling approach, based on the stimulus–response experimental paradigm, to study loss of resilience associated with frailty. This approach successfully distinguished older frail and non-frail women in the Women's Health and Aging Study by response to various physiological stimuli^{86,87}. Similar approaches to resilience have been developed in mouse models⁸¹.

Critical transitions are abrupt changes in the state of a complex system, often toward collapse. While simpler systems often show linear changes in function or state, complex systems often have the internal buffering mechanisms mentioned above that help to maintain function such that any crash occurs suddenly. Predicting critical transitions usually requires detailed time series data but not experimental intervention, and can be quite powerful. For example,

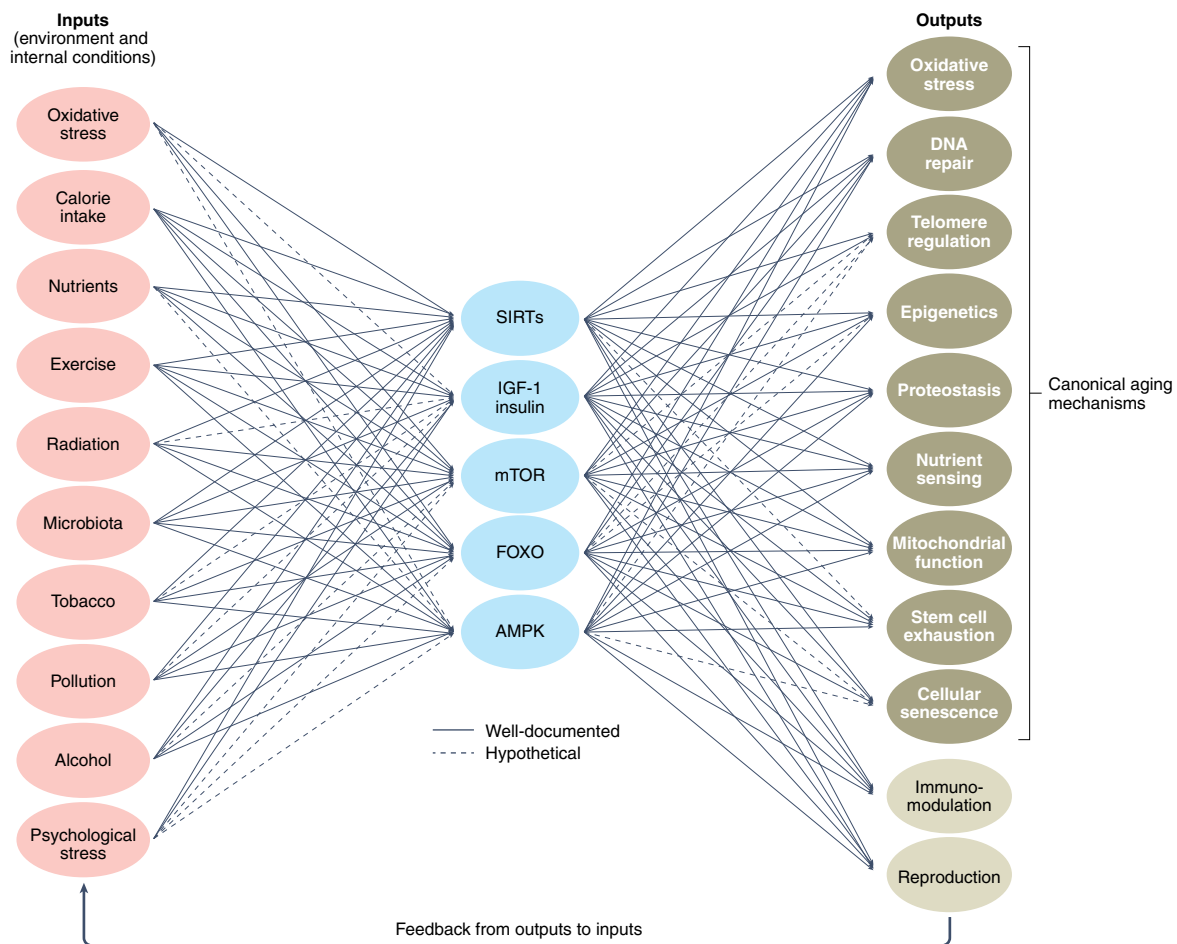


Fig. 4 | Bowtie structure of aging pathways. Numerous upstream signals (pink) are integrated via a limited number of intermediate pathways (blue) to simultaneously adjust multiple downstream outputs (olive) in a coordinated fashion. Many of the downstream components are related to aging, and the result is that this network fine-tunes many molecular aspects of aging. This is a computationally efficient way to optimize many outputs simultaneously, and is similar to a neural network autoencoder. This representation is qualitative: inputs and outputs are not exhaustively listed, and the actual structure of pathways is a bit more complicated (for example, interactions among inputs and among outputs). Adapted from ref. ⁹⁷, CC BY 4.0; see also ref. ⁹⁸.

resilience in postural balance and self-rated health is associated with successful aging and protection against frailty^{83,88}, and early warning signs of critical transitions can strongly predict mortality and frailty in individuals undergoing hemodialysis^{84,89,90}. Current work has barely scratched the surface of what paradigms of resilience and critical transitions might teach us about how ensembles of underlying mechanisms collectively wear down internal buffering mechanisms during aging.

Networks

An important characteristic of many biological complex systems is their organization into networks of interacting molecules, neurons, tissues and so forth. Network science is relatively well developed, with early applications in social networks and traffic systems⁹¹, and is also being applied to biological networks^{92,93}. A challenge in biology has been the enormous number of molecules and the difficulty in fully mapping all the potential interactions, but large-scale experiments to generate protein–protein interaction networks are making headway⁹⁴. We first discuss some theoretical implications of networks for aging, and then discuss approaches to studying them.

Information flow and multi-causality in networks. Biological systems can be considered as information systems (Box 1). Most biological molecules have multiple downstream targets, meaning

they represent information that the biological system incorporates. Because biological regulatory networks are fine-tuned by natural selection to optimize dynamic equilibrium, internal decisions of the network—such as how much ATP to produce, or how inflamed to get—need to incorporate as much relevant information as possible. To do this successfully, networks have evolved specific structures that allow the system to synthesize large numbers of inputs, make an informed decision and then subsequently regulate large numbers of outputs, while still maintaining evolvability^{12,45}. One such information structure is a ‘bowtie’^{95,96}, with fewer components in the middle where the decision is made than inputs or outputs (Fig. 4). Having few intermediate pathways is known as ‘degeneracy’, in the sense that each pathway serves multiple functions. While actual biological pathways are usually more complex, from a schematic and information-theory perspective the bowtie motif recurs often, including with canonical aging pathways, which coordinate an array of signals related to energy metabolism⁹⁷. The example in Figure 4 shows a qualitative representation of how selected extrinsic and intrinsic factors influence multiple aging-related pathways that interact to regulate multiple aging-related mechanisms, as well as other processes^{35,98,99}.

A conventional view of these pathways observes how they influence aging/lifespan, without asking why the network is structured this way. Bowties and similar structures explain why information

from multiple pathways must be integrated for the network to take an appropriate 'decision'. Indeed, multiple pathways integrate to make multiple decisions in parallel. For example, inflammation both activates and is regulated by the mTOR pathway. At the cell scale in fibroblast-like synoviocytes, for example, tumor necrosis factor senses environmental gradients and activates mTOR, which shifts inflammation from nuclear factor- κ B (NF- κ B) pathways to STAT1 pathways¹⁰⁰. In rats, at the organism and tissue scale, lipopolysaccharide-induced inflammation activates mTOR and NF- κ B pathways¹⁰¹. Likewise, sirtuins (notably SIRT1) both are mediated by inflammation and in turn control it, with SIRT1 activating tumor necrosis factor and NF- κ B during sepsis¹⁰². This perspective may explain findings that are otherwise hard to explain: (1) findings of 'causality' or 'control' in signaling pathways are often highly dependent on the cell type, organism and experimental conditions; (2) bidirectional feedback loops, that is, inflammation \rightarrow X \rightarrow inflammation; (3) inflammation affects multiple pathways; and (4) multiple pathways affect inflammation. Accordingly, it is hard to predict how interventions might affect inflammation, and the answer may vary across timescales.

The same pathways that are implicated in inflammation are also implicated in regulating oxidative stress, cancer, reproduction and metabolism. This is a natural consequence of the network's degeneracy and its integration of information to optimize dynamic equilibrium. This implies that we will not always succeed in elucidating molecular pathways by studying them one at a time: inflammatory responses are the result of a balance of numerous inputs filtered through multiple pathways, and the role of each thus depends on all the others simultaneously. In this context, traditional notions of causality break down¹⁰³: when causality is sufficiently circular or contingent, it no longer makes sense to claim that A causes B. For example, depending on their cellular context, calpains may either activate caspase 3, leading to apoptosis, or degrade caspase 3, preventing apoptosis¹⁰⁴. At a more macro level, various types of dietary restriction impact various pathways, which interact to coordinate responses that impact longevity¹⁰⁵. In this case, the question is no longer, 'How can we intervene in pathway X to regulate lifespan?' but rather, 'How do pathways X, Y and Z coordinate to affect longevity-related mechanisms, and are there ways to optimize jointly to create broad health benefits, adapted as needed to the underlying genotype and state of the individual?' This implies a more subtle, complex systems notion of causality, and is one of the key actionable insights in aging research from complex systems theory: a traditional perspective suggests that single-molecule interventions will be found that substantially slow aging, and indeed many researchers are pursuing such approaches. A complex systems perspective emphasizes that there are high-dimensional trade-offs that the system is balancing, and that interventions appearing to have benefits for one or several aspects of aging are likely either to have costs elsewhere, or to have effects that are highly dependent on conditions. For example, several canonical anti-aging interventions have shown countervailing effects on various age-sensitive phenotypes¹⁰⁶. These kinds of considerations may explain why it is so hard to generalize successful interventions in animal models (Alzheimer's disease¹⁰⁷ and anti-aging^{108–110}) into humans: context is crucial for understanding the impact of an intervention. Appropriate modeling combined with experimentation, however, might elucidate multimodal interventions that dynamically optimize aging processes with minimal side effects⁹⁸.

Methods to map and organize biological networks. Direct dynamical systems modeling is feasible when the number of pathways or variables being integrated is small. However, explicit models of complex networks in aging biology are still far from feasible in omics-based approaches with thousands or even millions of distinct variables. Luckily, the redundancy and interconnectedness of

biological networks noted above mean that higher-order patterns can be generated through emergence; these higher-order patterns can then be quantified. Unsupervised graph-based approaches are one method for accomplishing this. They transform similarity or connectedness of nodes in a network into an adjacency or correlation matrix. Various methods can then be applied to glean biological insight from these matrices, such as clustering algorithms to group nodes into clusters or modules. One example of this is a method called weighted gene correlation network analysis (WGCNA)¹¹¹, which performs hierarchical clustering on a transformed adjacency matrix. In WGCNA, after modules are identified, the components of each can be combined into a single value called an 'eigengene', allowing the testing of associations between a whole network of genes and an outcome. Recently, WGCNA was applied to CpG methylation data to identify conserved epigenetic aging modules across tissues¹¹², showing that module-scale information is more relevant than CpG-scale information. Nonlinear alternatives to WGCNA also exist. Manifold learning has been widely used in popular single-cell visualization tools, such as *t*-SNE⁷⁴, uniform manifold approximation and projection (UMAP)¹¹³ and PHATE¹¹⁴. For instance, PHATE can be extended to identify new trajectories that cells take during differentiation using single-cell RNA-sequencing data¹¹⁴. These network tools offer exciting opportunities for studying complex dynamics of biological entities.

Computational dynamical modeling. Computational dynamic models can be used to simulate key aspects of network behavior, at scales ranging from cellular/molecular to the broad health state of an organism. On the cellular scale, the mathematized MARS (mitochondria, aberrant proteins, radicals and scavengers) model describes the breakdown of cellular homeostasis in a networked approach¹². Similarly, the effects of mitochondrial dysfunction on key energy and stress signaling sensors such as AMPK, PTEN and sirtuins have been modeled¹¹⁵, revealing a conflict between immediate survival and long-term cellular maintenance. More complete mechanistic models are emerging for limited, well-characterized networks⁶⁰, and will continue to improve in both breadth and mechanistic detail.

Top-down computational models with discrete health states interacting with simple explicit networks^{116–118} have demonstrated how population-level measures such as survival curves can be generated from conceptually simple models of damage propagation within a complex system. While these models can be trained with detailed cross-sectional data to describe specific health measurements¹¹⁹, they are not well suited to model continuous-valued experimental data. For electrophysiological measurements, dynamical causal modeling makes similar simplifications¹²⁰. Recent advances in machine learning have allowed general dynamics of continuous longitudinal data to be modeled by deep neural networks for more than 29 covariants¹²¹. Ultimately, we are interested in fundamental questions of aging at the organismal scale, and computational models will be needed to tie between scales, like risers tying steps together into a staircase. Pragmatically, this multi-scale approach can start where the good data lies. This is the 'middle-out' strategy of systems biology^{122,123}.

The way forward

Complex systems approaches will lead naturally to a more formal and generalizable understanding of aging. Molecular-scale changes during aging occur not in isolation but within ensembles of interacting components, allowing for the emergence of collective processes. This challenges traditional notions of causality: Aging is not necessarily traceable to discrete molecular/cellular processes, but could emerge from breakdowns in the interactions of many processes within and across organizational scales. Such breakdowns might arise from: (1) problems with information flow in the

networks, impeding the organism's ability to optimize regulation; (2) compensatory strategies, features of network robustness where a suboptimal regulatory strategy is adopted to mitigate one problem, but may create others; and (3) from trade-offs between robustness and other key features such as function or resource use over evolutionary timescales, including trade-offs between cancer protection and functional integrity. These principles may apply to aging biology broadly, but also to sub-phenomena such as cognitive decline and inflamm-aging.

A complex systems perspective will accelerate progress in the field not just methodologically, but also conceptually, leading us to ask questions about systems, networks and emergence that complement and integrate findings on components, pathways and discrete mechanisms. It also holds substantial potential to explain one of the key features of aging: its heterogeneity. While most research on aging naturally focuses on what is common or universal, a complex systems framework lends itself to explaining why aging can differ so much across individuals, populations and species. This heterogeneity underlies intrinsic predictive uncertainty in aging processes and is crucial to understand if we wish interventions to be effective and safe for diverse populations.

A complex systems perspective leads to several actionable insights for the field, notably:

1. Identify and study emergent processes at intermediate biological scales. Use of omics data should be guided by the perspective that the countless biological molecules are not independent data points but windows into functional processes at higher scales of biological organization, many of which have yet to be identified. The methods mentioned above, when applied thoughtfully, can help identify such processes and study them as they relate to aging and as they change in different contexts.
2. Consider the joint effects of multiple aging processes. In particular, consider (a) how various aging processes may interact with each other via networks of effects, (b) how there may be trade-offs among different aging processes, (c) how effects may propagate up or down scales of hierarchical organization, and (d) how buffering may or may not mitigate the impacts of individual mechanisms, and how individual mechanisms or damage profiles may wear down global buffering. This may help us finally untangle the relationship between aging and disease.
3. Develop novel approaches to quantifying resilience, buffering, critical transitions and information flow. Pathway-based biomarkers may be less actionable because they risk ignoring synergies, antagonisms and correlated effects among pathways. Global metrics of system state are thus needed, and these are likely to be based on system dynamics and interactions across components. Such approaches are now in their infancy.
4. Integrate experimental approaches with modeling and theory. Many bench biologists and theoreticians should continue the trend toward integration not just of big data, but also of simulations and mathematical models that help contextualize experimental findings within and across species, and in the context of medical intervention.
5. Accelerate collection of more complex data. Current trends toward big data^{124,125} should explicitly attempt not just to maximize data quantity, but also to simultaneously collect data on as many as possible of (a) interaction networks, (b) dynamic time series data, (c) stimulus–response or perturbation experiments and (d) cross-scale effects. Key insights will come from integrating across these data types.
6. Develop multimodal interventions that target systemic effects rather than individual molecules³⁸. Targeting individual pathways or molecules risks playing whack-a-mole with aging-related processes. Lifestyle interventions or combination lifestyle/pharmaceutical interventions are particularly promising

as more holistic approaches, and might eventually be highly personalized based on the metrics of underlying system state mentioned above, which could serve as surrogate endpoints in trials.

Many of these insights are already starting to be applied but could be accelerated. To do so, we may also need more coordination of the research effort through centralized databases, collaborative networks and structured calls from funders to establish teams.

Perspectives and conclusions

While we are far from the first to link complex systems ideas to aging^{13,41,61,126–130}, aging biology research has arrived in a position similar to ecology 50 years ago and is starting to integrate complex systems perspectives into all types of research. Mechanistic, reductionist research has provided profound insights—identification of key pathways, genes, mechanisms and processes. However, in the absence of a clear framework to integrate these insights, researchers are increasingly feeling compelled to break out of mechanistic silos (for example, protein homeostasis, DNA damage, inflamm-aging and telomeres). Going forward, reductionist and complex systems approaches will need to work hand-in-hand to elucidate the ecosystem of interacting aging processes. Fortunately, appropriate methods are beginning to arrive, and numerous studies show that their application changes both our questions and our conclusions^{13,58,83,118,119,131,132}. The shift toward complex systems thinking is well underway. Our hope is that this article will provide a common framework to accelerate this process and highlight the tools and perspectives available so that theoretical, clinical, quantitative and bench scientists reach out to complementary experts and, through collaboration, integrate the diverse knowledge in our field to better respond to the challenges aging presents for science and society.

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Author contributions

This work emerged from a workshop on complex systems and aging organized by A.A.C. and in which all authors except D.G. participated. A.A.C. drafted the initial document and coordinated efforts. All authors contributed extensively to writing, editing and approving the final version.

Competing interests

A.A.C. is CEO and founder at Oken Health.

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