

Perspective

Resilience integrates concepts in aging research

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SUMMARY

Aging research is unparalleled in the breadth of disciplines it encompasses, from evolutionary studies examining the forces that shape aging to molecular studies uncovering the underlying mechanisms of age-related functional decline. Despite a common focus to advance our understanding of aging, these disciplines have proceeded along distinct paths with little cross-talk. We propose that the concept of resilience can bridge this gap. Resilience describes the ability of a system to respond to perturbations by returning to its original state. Although resilience has been applied in a few individual disciplines in aging research such as frailty and cognitive decline, it has not been explored as a unifying conceptual framework that is able to connect distinct research fields. We argue that because a resilience-based framework can cross broad physiological levels and time scales it can provide the missing links that connect these diverse disciplines. The resulting framework will facilitate predictive modeling and validation and influence targets and directions in research on the biology of aging.

INTRODUCTION

Across the tree of life, functional decline and the risk of failure increase with age. These age-related changes occur over diverse spatial scales—from molecules to social networks—and across vast temporal scales—from the milliseconds of molecular phenomena to interspecific differences in lifespan shaped by millions of years of evolution. Across these wide scales, research in the biology of aging can be divided roughly into three domains. First, evolutionary biologists seek to understand the variation in patterns of aging, both within and between species. Second, ecologists examine the demography of aging in lab and natural populations and its relationship with environmental factors. A third body of literature focuses on mechanism, looking at the physiological and molecular causes and consequences of aging.

These three domains share a common focus on the biology of aging, but with a few notable exceptions, there is relatively little overlap in these literatures, and in particular, between those working on mechanisms versus those working on ecological or evolutionary questions. Starting from the premise that a more integrated approach can lead to fundamental improvements in our understanding of the basic biology of aging and its translational potential, here we propose the power of building a bridge between these intellectual domains through the concept of resilience (Box 1).

Resilience defines the capacity of a complex system to rebound from challenges, with responses coordinated across all scales throughout the system. Within the aging field, a considerable literature has explored the relationship between stress and aging, focused in particular around the concept of “allostatic load,” which measures the cumulative physiological burden of stress accumulated over the lifetime (Hadley et al., 2017; Seeman et al., 2001). This material focuses on the clinical perspective. In the face of the cumulative effects of stress, injury, or disease, individuals with a high level of cognitive, psychological, or physiological health are considered to have a high level of resilience. In this literature, resilience might be defined as “a state of adaptation to a lifetime of stress and strain” (Juster et al., 2010) or “the ability to maintain biological and psychological homeostasis under stress” (Lavretsky, 2014). In practice, studies of aging often define resilience in older adults as “the absence of disability” (Lavretsky, 2014), focusing particularly on the effect of allostatic load on disease (McEwen, 1998), cognitive function (Juster et al., 2010), mental health (Kapczynski et al., 2008), or overall age-related physiological functions (Seeman et al., 2001). In this light, resilience reflects the ability to resist and/or recover from stress.

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In this review, we aim to reframe how we think about resilience and aging, inspired in particular by the rich literature on resilience in ecology research spanning decades (e.g., Folke et al., 2010; Holling, 1973). The clinical literature tends to focus on specific disease outcomes and the ability of the organism to adequately respond to stimuli within those systems. Here, we describe the potential benefit of a broader perspective on resilience, exploring how complex molecular networks are linked at different physiological levels, and how responses to extrinsic or internal stressors intersect to produce physiological consequences. We suggest that resilience must be measured not simply as the functional state of the individual (e.g., high cognitive function or lack of disease) but rather as the dynamic, high-dimensional molecular process of stress-induced response and recovery that shapes those broader outcomes. Although several disciplines have advocated for a complex systems approach to resilience (Hadley et al., 2017; Miller et al., 2017; Varadhan et al., 2018), the aging field is yet to embrace these concepts in the broader framework that we propose here, with just a few notable exceptions (e.g., Lahti et al., 2014). We hope not only to inspire more empirical studies on the nature of resilience at a systems biological level but also to support critically important conversations across domains. This broader framework, which encompasses the “resilience of complex systems,” has the potential to guide a more comprehensive approach in biology of aging studies—one that integrates evolutionary, ecological, physiological, and molecular perspectives.

We can measure resilience in response to intrinsic challenges arising from perturbations at the level of molecules, cells, and organs or to extrinsic perturbations in the biotic and abiotic environment, thereby measuring its impact on diverse systems. Moreover, we can consider the evolution of aging as the evolution of age-related changes in resilience. In resilience studies, we define the tipping point as the state of a system at which a perturbation pushes the system into a novel, vulnerable, pathophysiological, or diseased state (Scheffer et al., 2018). Here, we suggest that age-related failure can be understood as the point when an organism reaches a tipping point. In essence, aging undermines the capacity to bounce back from challenges, reducing fitness components, and pushing an organism inexorably toward tipping points (Miller et al., 2017).

The age-related causes and consequences of resilience and tipping points can be considered from the perspective of ecology (environmental risk factors and population dynamic responses), evolution (variation within and between species), and mechanism (molecular, cellular, and physiological causes and consequences). Figure 1 illustrates the relationship between these disciplines and their common connection with resilience. In this perspective, we provide a brief synopsis of aging research within each of these domains. We start with an evolutionary genetic approach to aging and resilience, and then we focus on mechanistic biological concepts of aging studies that are directly relevant to resilience; then we explore how the environment interacts with each of these domains, setting the stage for resilience as a central, integrative concept. We discuss how detailed measures of endophenotypes (genome, epigenome, metabolome, etc.) can be used to study resilience. In this way, we can link these different domains. Finally, we explore what a resilience-based integration of these domains would look like in practice, offering specific questions in aging research that resilience can help to resolve.

AN EVOLUTIONARY BASIS FOR STUDYING RESILIENCE AND AGING

There is a staggering diversity of aging patterns throughout the tree of life, from species that live just a few days to those that live for more than a century (Vaupel et al., 2004). Even within species, we find dramatic variation—consider many ant and bee species, where workers typically live for a few months, whereas queens can live for a decade or more (Keller and Genoud, 1997). Evolutionary approaches attempt to explain why species age and seek to understand how genetic variation for aging is shaped by the external environment, what forces generate and maintain variation within populations, and how aging impacts the short-term ecological and long-term evolutionary dynamics of populations.

Natural variation in any trait is shaped by mutation, genetic drift, natural selection, sexual selection, constraints, and trade-offs. We can encapsulate the genetic architecture that arises from these forces with a simple equation:

$$V_P = V_G + V_E + \text{cov}_{G,E} \quad (\text{Equation 1})$$

where V_P is the total variation in some phenotype (P) within a population and is determined entirely by the sum of V_G (the genetic variation), V_E (the non-genetic or environmental variation), and their covariance (Falconer and Mackay, 1996).

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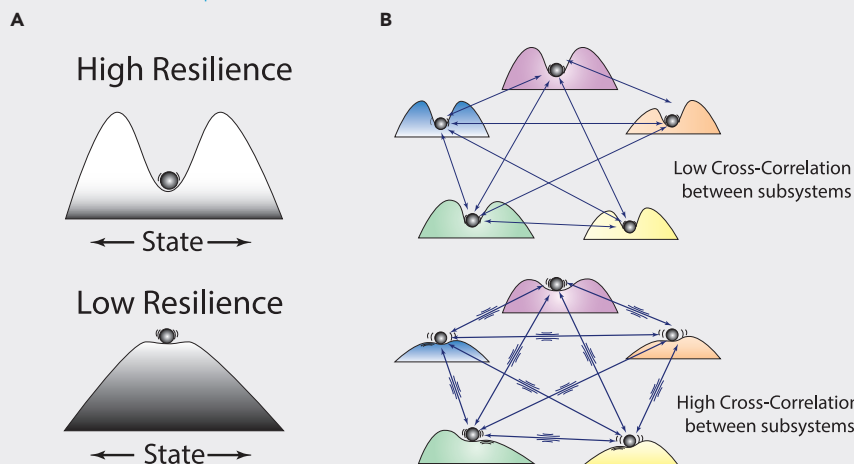
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Box 1. Resilience and Tipping Points

Resilience is a central research topic in ecosystem ecology (Scheffer et al., 2001). Originally arising from Dynamical Systems theory, a considerable body of precise mathematical theory has been developed to interrogate mechanisms underlying ecosystem stability, although the definition of stability has evolved over time (Bersanelli et al., 2020; Grimm and Wissel, 1997). Early on, ecologists quantified resilience (or ‘elasticity’) by measuring the rates of recovery of ecosystems after a perturbation; however, in the 1970’s, ecologists realized that another approach was needed to capture the phenomenon whereby some systems, after a perturbation, would reach a tipping point where they would flip to a fundamentally different state. At its simplest, we can measure resilience as the trajectory that a system follows after a perturbation, initially away from its current state and then back to where it started or alternatively to a new state. As a simple functional example, consider how heart rate increases upon climbing a flight of stairs and then returns back to resting state following recovery. Within an organism, there are an enormous number of processes that exhibit resilience, and this resilience decreases as the organism ages (Scheffer et al., 2018). A key prediction of how aging affects resilience is the emergence of tipping points that lead to fragile homeostatic states.

It was originally thought that loss of resilience in ecosystems could only be determined by measuring the magnitude of the perturbation needed to invoke the shift past the tipping point (to ‘push it over the ridge’) (Holling, 1973). It turns out that characteristic changes in fluctuations of systems may also hint at the proximity of a tipping point, a phenomenon known as ‘critical slowing down.’ There are several specific patterns we can measure that might predict this stage, and which could lend themselves to analysis of aging using modern molecular approaches. 1) At a tipping point, the recovery from tiny, normally occurring perturbations becomes slower, indicating a loss in responsiveness and increased fragility of the system. 2) Over the life course, each system in an organism experiences fluctuations as it is challenged by and recovers from disturbances (Box Figure 1), but loss of resilience leaves an impression on the resulting fluctuations in the state of the system (Carpenter and Brock, 2006; Dakos et al., 2012, 2015; Ives et al., 1999; Scheffer et al., 2009). As the intrinsic recovery rate becomes slower, there is a tendency for more highly correlated states between time points (i.e., rising temporal autocorrelation or ‘memory’), which often goes together with rising variance ((Carpenter and Brock, 2006; Dakos et al., 2015; Dakos et al., 2012; Ives et al., 1999; Scheffer et al., 2009). 3) Although dynamic indicators of resilience are relatively well understood for simple one-dimensional systems, we are only starting to understand how resilience of dynamic networks in complex organisms, and this needs to be assessed (Gao et al., 2016). One idea is that in networks of interdependent elements, an increasing correlation between the functioning of different nodes can arise because of a slower resolution to baseline following perturbation and may be indicative of dwindling resilience (Dakos et al., 2012). Malfunctioning of one element (e.g., glucose level) may affect other elements (e.g., gait) more strongly if the dependent elements have become fragile already. In this way, as subsystems lose resilience, we would expect to see an increase in the correlation among discrete processes that comprise the overall system (Dakos et al., 2012; van de Leemput et al., 2014).



Box 1 Figure. Simple schemas illustrating the ability of a phenotypic state to return to stable state following a perturbation.

States could include, for example, immune reactions, balance, cognitive decision making, molecular network structure, etc.

(A) Above: a deeper valley indicates greater resilience, which is associated with faster recovery and a return to the prestressed or perturbed state. Below: lower resilience is marked by a shallower valley, which indicates a slower recovery and increased possibility that the system may not return to the prestressed state.

(B) Above: If multiple systems are resilient and recover quickly, we expect to observe less correlation across systems. Below: A decline in resilience will lead to slower return rates to equilibrium upon small perturbations. Delay within one element (e.g., glucose level) may impinge on other elements (e.g., gait), leading to a rising cross-correlation between competent and compromised states.

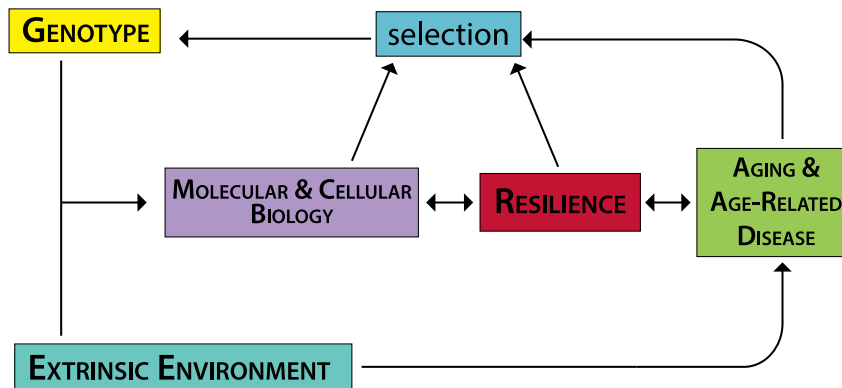


Figure 1. A resilience-centered framework for understanding aging and its evolution.

Variation in aging among individuals is shaped by variation in genotype, environment, and the interaction between the two. Typically missing from this relationship (Equation 1, main text) are the mechanisms by which genes and environment shape phenotype (Molecular & Cellular Biology (MCB), Resilience and Aging & Age-Related Disease (AARD)). Here we propose linking resilience with evolutionary selection and molecular domains directly in a framework that incorporates intrinsic molecular, cellular, and physiological processes – the systems biology of an organism. Briefly, resilience affects and is affected by the intrinsic environment (MCB and AARD) in the form of change in the state of the endophenotypes. At the same time, through its dependence on resilience, homeostasis of the internal environment is vulnerable to aging and disease. Together with aging and disease themselves, resilience influences how selection shapes endophenotypic traits. These states and processes are developed in more detail in Figures 2, 3, and 4 and explanations in the main text.

A rich literature explores the combined role of genes and environment on aging; for example, in many twin studies (e.g., Christensen et al., 2000; Finkel et al., 1995) and the complex interactions between genes and environment that shape aging (e.g., Dato et al., 2017). Historically, the model in Equation 1 that underlies these studies has not included molecular mechanisms. However, to fully understand aging, we need to go beyond measures of natural variation, asking not only what specific genetic and environmental factors shape aging, but also how their influence is exerted. The concept of resilience motivates a set of interesting questions about the evolution of aging and provides means to integrate mechanisms into Equation 1 (Figure 1). First, we hypothesize that variation between species in lifespan can be understood in terms of variation between species in resilience. Thus, the ability to repeatedly return to homeostasis after a perturbation will be much greater for a long-lived species than for a short-lived one. Moreover, by tracking molecular responses to environmental perturbations as measures of resilience, we can identify key cellular and physiological phenomena that account for interspecies variation. Second, we hypothesize that the cumulative effects of inherited mutations proposed to underlie the evolution of aging also alter resilience, changing the timing and sensitivity of tipping points. Third, the concept of trade-offs, central to evolutionary ideas about life history evolution, might also inform our understanding of resilience. Williams (1957) suggested that aging arises from a specific type of trade-off—antagonistic pleiotropy—in which late-acting deleterious alleles are favored by selection because of early-acting beneficial effects. We will consider ways in which trade-offs might also play a part in the role of resilience in aging. Resilience provides a way to explore genetic, environmental, and phenotypic variables in a comprehensive eco-evolutionary framework (Figure 2) and integrate these ideas across disciplines to advance our understanding of the aging process and how it is regulated.

THE BIOLOGY OF AGING: FROM MOLECULES TO CELLS TO PHYSIOLOGY

We now know that within a species, aging is malleable; by altering the function of single genes, we can increase lifespan dramatically (Friedman and Johnson, 1988; Kenyon et al., 1993; Morris et al., 1996; Pan and Finkel, 2017). Moreover, many of the discovered pathways appear to have evolutionarily conserved effects on aging. As shown in Figure 1, molecular, cellular, and physiological aspects of aging are influenced by genotype and by extrinsic environment and shape the pace of aging and the emergence of age-related diseases and disorders. The key to mechanisms of resilience and its decline with age lies within this biology. Below we outline central concepts in aging biology research that relate to resilience and are implicated in aging and longevity regulation.

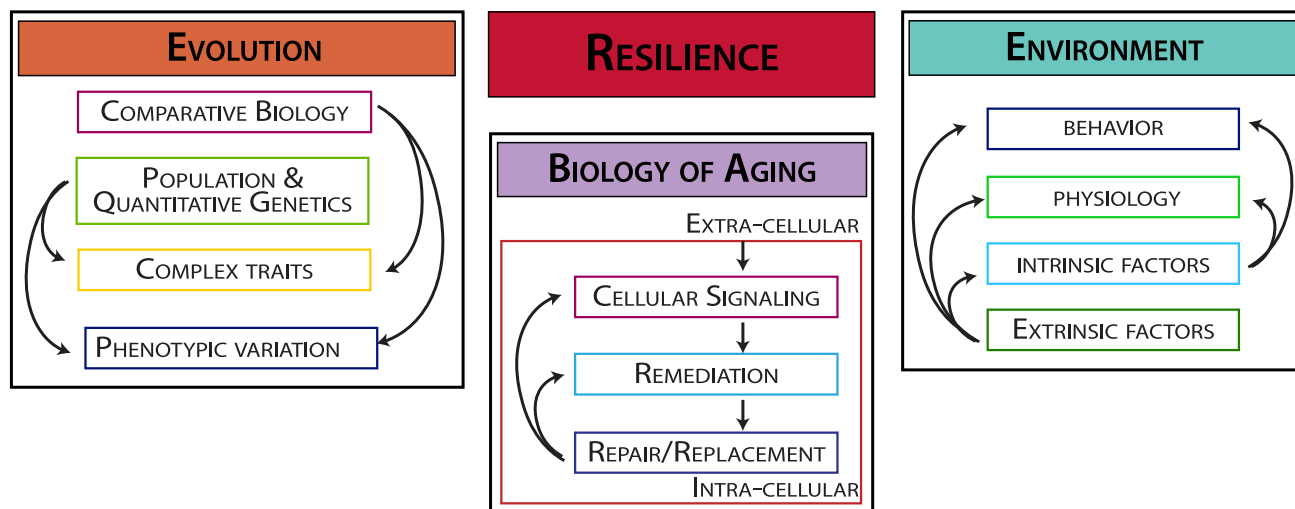


Figure 2. Evolution, Biology of Aging, and Environmental research disciplines are instrumental in the framework of resilience.

Each discipline engages a breadth of approaches to uncover causal factors involved in regulating the pace and the consequence of organismal aging. Each discipline connects to resilience (Figure 1), such that measuring resilience and its upstream causes and downstream consequences can ultimately provide a more comprehensive, interdisciplinary understanding of the forces that shape aging at the individual and population levels. Causal relations in each discipline are discussed in detail in the main text.

Stress pathways and hormesis

The link between longevity and stress resistance is long established and was used in the very early days of mechanistic aging studies to identify longevity-regulating factors. Preliminary screens of resistance to stressors uncovered factors that played a role in lifespan regulation (Imai et al., 2000; Kaeberlein et al., 1999; Lithgow et al., 1995). Since then, the links between cellular stress resistance, damage-activated and stress-activated pathways, and longevity regulation has only gained more traction (Liao and Kennedy, 2014), showing that common features of the stress response include changes in metabolism, RNA processes, protein synthesis, and aspects of cell growth (Gasch et al., 2000). Interestingly, these same pathways have been implicated in the mechanisms of delayed aging by caloric restriction (Rhoads et al., 2018).

Hormesis is a phenomenon where exposure to a small nonlethal stressor can lead to a protective response (Calabrese and Mattson, 2017; Mattson, 2008). By recruiting damage detection, repair, and adaptive response mechanisms, the initial stressor resets the resilience program to be better poised for subsequent exposures. Dietary interventions that prolong health span and survival, including caloric restriction, every-other-day feeding, and time-restricted feeding could be considered a hormetic nutrient stress (Rattan, 2008; Sinclair, 2005). Uncovering the regulatory nodes in these interwoven networks would open up new targets and strategies to improve health.

Routine maintenance, damage, and repair

The ability to repair incidental or inflicted damage to the genome becomes compromised as a function of age. Failure to maintain DNA replication and/or repair is associated with progeria (conditions of accelerated aging) (Liao and Kennedy, 2014), and disruption in DNA damage detection and repair plays key roles in cancer emergence and progression (Roos et al., 2016). A cascade of cell signaling is induced upon damage to implement repair mechanisms, and if that fails, there are exit strategies to remove the afflicted cell from the healthy population (Ogrodnik et al., 2019). Apoptosis, necrosis, and cellular senescence each attract immune and inflammatory response pathways that are themselves subject to loss of functional integrity with age (Franceschi et al., 2017; Hotamisligil, 2017; Pansarasa et al., 2019). Chronic inflammation, in turn, can contribute to disease vulnerability. These pathways of maintenance, damage, and repair are likely important in establishing resilience, and resilience modeling is particularly well suited to complex processes with multiple interacting features such as “inflammaging” (Castellani et al., 2016). Because many players in these individual pathways are well-known, it would be possible to use this framework to establish connections among these pathways, how they link to cell fate, and how aging might impact communication among these pathways to influence resilience.

Growth and metabolism pathways

The earliest longevity pathways discovered relate to growth (Kenyon et al., 1993) and metabolism (Finkel, 2015). In yeast, worms, flies, and mice, attenuation of growth can confer increased longevity (Fontana and Partridge, 2015), whereas delayed aging often results in smaller organisms with reduced growth pathway signaling (Bartke, 2017). Metabolic dysfunction is also observed as a shared feature among common diseases of aging, and metabolism clearly changes as a function of age, leading to the idea that preservation of efficiency and integrity of metabolic pathways is critical for enhanced longevity (Balasubramanian et al., 2017). Exploring the intersection of networks in the context of resilience, where metabolism, growth signaling, remediation, and repair mechanisms are brought to bear (Figure 2), will yield novel insights for aging biology.

ENVIRONMENTAL INTERACTIONS WITH AGING AND RESILIENCE

A comprehensive framework of both aging and resilience requires a nuanced understanding of what we mean by environment and a major consideration in evolutionary concepts that are reported but less often considered in molecular studies. In classic evolutionary theory, long-term environmental exposure influences development, morphology, behavior, physiology and has downstream effects on survival, reproduction, and longevity. Although the environment over evolutionary timescales is recognized as a key component in shaping how a species ages, the immediate environment influences aging over individual lifetimes. Mechanistic studies use a defined or fixed environment, which does not capture how variation in exposures interact with the aging process. The environmental perspective provides a means to view the complexity of aging within a framework of cumulative exposures to stressors over time, and how resilience emerges from interaction with the environment (Figure 2). Integrating across disciplines, it will be possible to identify regulatory nodes that modulate interactions between the environment, age, and resilience. Defining one or more of these interactions would be an important advance in developing new strategies for disease prevention, prognosis, and treatment.

Intrinsic versus extrinsic environments

One of the challenges to a more inclusive framework of aging is in defining the boundaries of the environment. We use the convention of “intrinsic” as processes derived from self and “extrinsic” as exogenous events. Traditionally, discussions about how environment influences aging have focused on exogenous factors (e.g., Orzack and Tuljapurkar, 1989; Shattuck and Williams, 2010), and influence is considered in broad denominations such as “beneficial” or “detrimental”. Although these dichotomies of extrinsic versus intrinsic and beneficial versus detrimental have utility, a binary approach does not reflect actual system complexity. For example, the microbiome can be interpreted as an extended part of ‘self’ and can be included as an endogenous environment. In addition, depending on concentrations and contexts, benefits can become liabilities (e.g., Schreck et al., 1991) and vice versa. Owing to the importance of context, interactions, and dynamics, a simple binary good/bad view of environment or influence has limited scope to explain aging, and why it is accompanied by a loss of resilience.

The aging environment

Age-related decreases in repair (Frenk and Houseley, 2018) may stem from genetic mutations, epigenetic alterations, or alterations to the structure and activity of key enzymes involved in information processing and conveyance. Even under ‘optimal’ conditions, nucleic acid replication is prone to error (Lynch, 2012), and this is exacerbated by environmental insults that can further enhance mutation accumulation (Moskalev et al., 2013). Context is also important. For example, reactive oxygen species can act as critical signaling factors or as damaging agents in age-related disease (Campisi et al., 2019; Ogrodnik et al., 2019). Aging is superimposed on a web of interactions that integrate intrinsic processes with endogenous and exogenous stimuli. Resilience could provide the overarching framework, allowing the roles of intrinsic and extrinsic environments to be integrated into interaction networks (Figure 2) and to solve how aging perturbs the ability of the system as a whole to respond (Gao et al., 2016).

Aging exerts an impact on maintenance and responsiveness across all systems. Viewed through the lens of resilience, the dynamic series of events occurring on different temporal, spatial, and functional scales could be resolved for different stages of lifespan. These scales could account for accumulated exposures and identify the diversity of aging effects among individuals through time (Campisi et al., 2019; Ogrodnik et al., 2019), from communication within cells to interactions among species. Thus, resilience might be

applied to understand how extrinsic environments affect aging and how aging impacts the intrinsic environment.

TOWARD A NETWORK PERSPECTIVE

In the previous sections, we have described how evolutionary, environmental, and genetic factors shape patterns of aging and explored the molecular, cellular, and physiological causes and consequences of aging. Here, we consider how resilience can provide a framework to interrogate aging at all these levels and to develop a more integrated understanding of aging. We can use the tools of network theory and systems biology to understand how interacting molecules, cells, and tissue networks show or fail to show resilience in the face of perturbations and to measure that resilience.

First, consider the elaborate networks that define a living organism. The challenge is to understand cross-talk and information flow within and among molecular pathways, individual cell populations, and tissues, contributing to the integrity, responsiveness, and health status of the organism (Figure 3). On the macroscale, there is the organism as a whole, a collection of organs that communicate through system-wide networks such as the sympathetic nervous system, the vasculature, and inflammatory and immune systems. Beneath that are the behaviors of tissues, heterogeneous population of cells, and extracellular structures that are in constant communication with each other to ensure organ-wide coordination. Extracellular signals are transmitted through suites of factors including metabolites, nucleic acids, proteins, or lipid derived molecules. At the cellular level, networks of signals communicate a requirement for change/adaptation in response to extrinsic signaling to elicit the appropriate response. Within the cells, intrinsic signaling keeps the cellular systems in balance in terms of function, efficiency, and coordination of change/adaptation so that all the cellular systems are appropriately in tune with the prevailing conditions.

At the molecular level, the network of interacting mechanisms recruited by the cell includes transcription regulation, proteostasis, internal signaling through posttranslational modification (PTM), and metabolites that can determine flux through energetic pathways via allostery or ligand activity (Figure 3). For example, epigenetic regulation of gene expression relies on where the gene is in the genome and whether or not that region is accessible. The architecture of the chromatin is determined by modifications both on the DNA itself and on the nucleosomes on which the DNA is wound. Even within the euchromatin, the openness to gene expression is modified through acetylation, methylation, and phosphorylation, modifications that are added by enzymes that use metabolite donors (S-adenosyl methionine, acetyl-CoA) and are themselves sensitive to metabolites such as NAD, alpha ketoglutarate, and succinate. Using resilience as a framework, integrated regulatory mechanisms can be tracked to define how each of these elements respond to external signaling and to each other.

Defining resilience in a simple network system

Although one could measure resilience across many different dimensions, we are particularly interested in the response to perturbation that can be measured within an organism's richly interacting 'endophenotypes' including the epigenome, transcriptome, proteome, metabolome, and microbiome. Small changes in any of countless processes in these molecular domains accumulate, eventually affecting larger-scale functional networks, lowering the reserve that is required to maintain critical parameters such as gait, blood pressure, etc. within safe boundaries (Ayres, 2020). Importantly, the very repair systems that help recovery from perturbations, such as immunity, inflammation, and autophagy, also lose resilience (Hotamisligil, 2017; Labbadia and Morimoto, 2015). Although it is now relatively easy to measure levels of thousands of genes, metabolites, or proteins, to fully understand how these levels change in response to perturbations and to interpret these changes, we will need to place these findings in the context of network theory. One of the ideas emerging from systems biology is to determine how networks respond to perturbations (Levy and Siegal, 2008; Smart et al., 2008; Wagner, 2013). The simplest approach toward understanding how networks of stress response, resilience, and longevity intersect would be to begin with simplified cellular response system models (Figure 4). For example, in Step I, we introduce a nonlethal, low intensity challenge (e.g., H₂O₂, LPS, and TNF). In Step II, we catalog the response in molecular profiles from pre-stimulus to peak response to the final resolution back to either the old baseline or some new baseline. Profiles could include measures of gene expression, metabolomics, proteomics, or other measures of cell state, with each performed as a synchronized time course. Step III would be to integrate the data generated from each domain across the

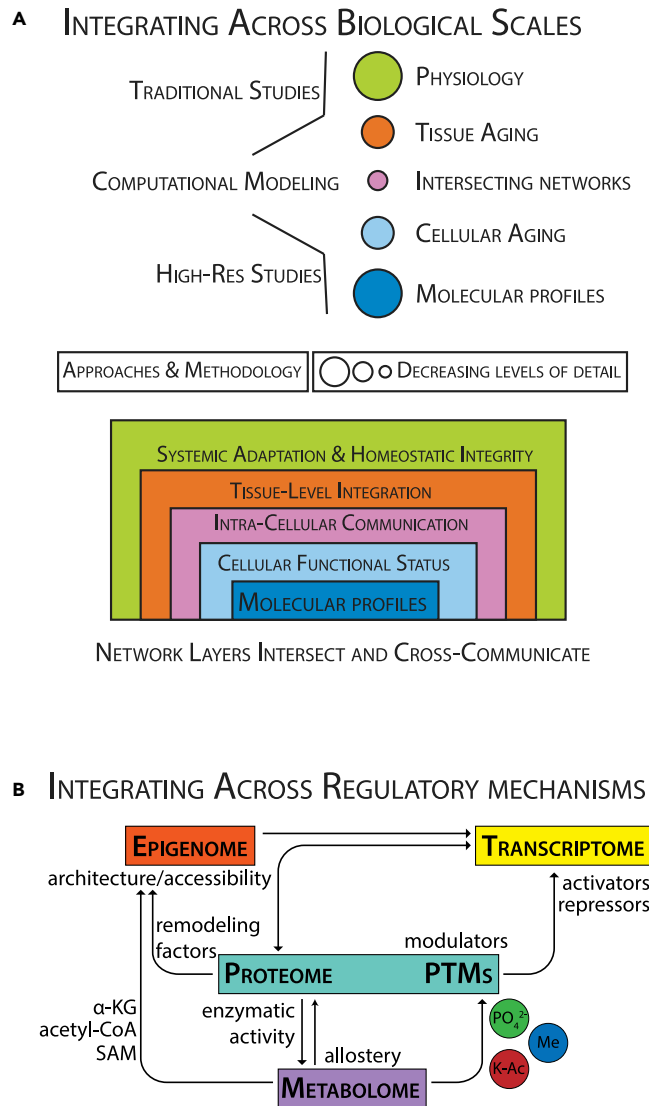


Figure 3. Tools and measurements will help understand interactions over scales (A) and underlying regulatory mechanisms (B), linking aging and resilience.

(A) Above: Knowledge of how networks connect across scales is uneven. Larger circles reflect greater biological detail and conceptual understanding. Below: Layers of networks confer essential traits for whole body homeostasis and plasticity. Integrity of the system relies on the correct response being executed at each level. Circles and rectangles are color-coded to link methods and disciplines (above) to the underlying biology (below).

(B) Interactions among molecules within distinct regulatory mechanisms create a complex set of interdependent outcomes when a system is perturbed. Time course studies of highly defined stimulus and response (i.e., resilience) could delineate the series of causes and effects and how these programs might be sensitive to age.

time course, defining the multidimensional cellular response to challenge and the resolution of that response. Step IV would address how processes with an established role in longevity regulation intersect to influence resilience. This sort of approach is expected to reveal multidimensional mechanistic links between longevity-associated pathways and resilience and bring substantial new insight into the biology of cellular resilience.

A ROADMAP FOR STUDYING RESILIENCE

Taking the perspective that resilience applies across biological levels of organization, we now consider several ways in which measures of resilience could help us to reach an improved understanding of aging.

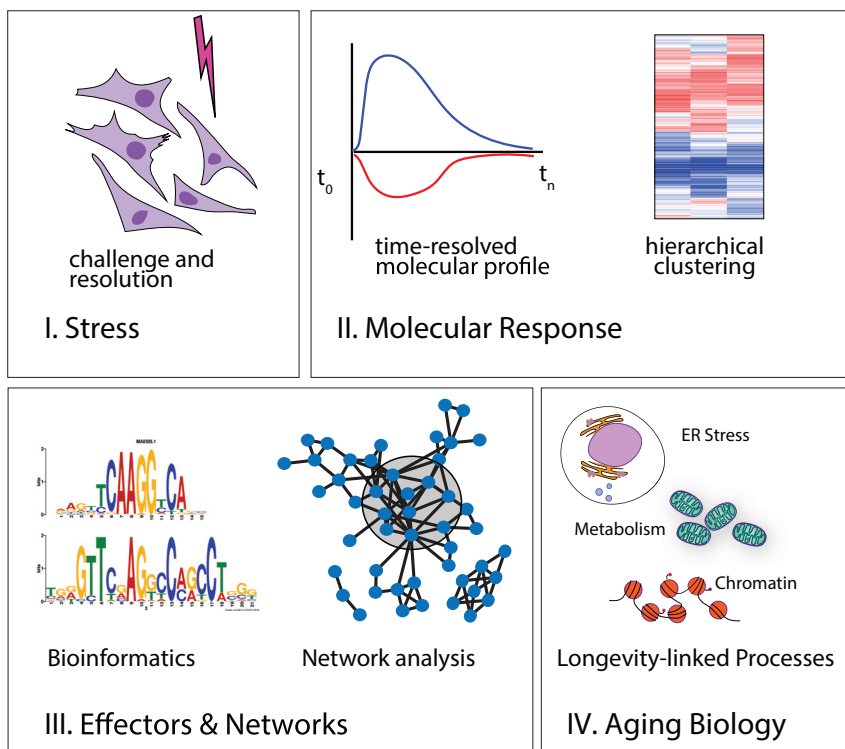


Figure 4. Uncovering aging biology through the study of resilience.

Step I: A nonlethal, low intensity challenge is introduced. Step II: The response to stimulus is quantified at high resolution using multiple platforms, from pre-stimulus to peak response to eventual resolution. Step III: Data integration defines the multidimensional cellular response, effectors in stress, and resilience pathways that are identified using bioinformatics approaches. Step IV: Longevity-associated pathways are superimposed on the resilience framework to identify multidimensional mechanistic links between longevity-associated pathways and resilience.

There are many challenges ahead in creating a more integrated approach to aging studies, but we have already seen some successes. [Box 2](#) nicely illustrates how the concept of resilience can help us understand patterns of age-related change, in this case, in the gut microbiome.

Resilience provides an explicit link between environment and aging via endophenotypes

The concept of resilience focuses our attention on measurable traits that link evolutionary factors with molecular causes, physiological processes, and demographic consequences. Resilience is not limited by the requirement that a single molecule or pathway must explain how an organism responds to a perturbation. Rather, it encompasses a complex network of endophenotypes that form the building blocks of all downstream traits, including the response to upstream environmental perturbations. By using time series analysis, we gain exquisite sensitivity to measure resilience, including how it is impacted by aging and in the presence of age-related disease.

Resilience underscores variation in the impact of aging within and among individuals

Aging is associated with an increase in variation in traits among individuals. Variation among different modules within endophenotype networks is likely linked to resilience. A better understanding on how loss of resilience intersects with these age-related increases in variation could potentially inform our understanding of the causal mechanisms that underlie increases in disease vulnerability with increasing age. Some theories suggest that aging has evolved as part of a trade-off with early-life traits (Kirkwood, 1977; Williams, 1957), and perhaps resilience is at the heart of these trade-offs. For example, individuals primed to respond to a deleterious environmental perturbation (better resilience) might be less poised to benefit from other environmental changes, a concept discussed in the context of psychological resilience (Belsky et al., 2009; Crespi, 2015).

Box 2. A case study: Defining resilience in an organismal network system

Recent work on the gut microbiome offers an excellent example where researchers have used the concepts of resilience and tipping points to understand age-related changes. Complex microbial communities integrate environmental stimuli and modulate host function, promoting homeostasis. Hosts dynamically construct their microbial niche by deploying pro-inflammatory responses against pathogens and promoting immune tolerance toward commensals (Peterson et al., 2007; Yoon et al., 2014). Commensal microbes, in turn, educate the immune system and modulate immune responses against pathogens (Oh et al., 2014). Host-microbial interactions are necessary to ensure host fitness, allowing nutrient uptake, neutralizing toxins, and synthesizing essential biomolecules (Hill, 1997). Together, host-microbiota interactions in healthy individuals are essential to ensure resilience. Challenges to the molecular cross-talk between microbial communities and host epithelia lead to system imbalance, typically associated with immune deficiencies, autoimmune diseases, chronic infections, and aging (Clark et al., 2015; Ray and Dittel, 2015; Rhoades et al., 2019).

One study of the microbiome in people of different ages suggests that the microbiome reaches a tipping point around ages 60–70, shifting to a different state (Lahti et al., 2014). Experiments could be designed to intentionally unbalance microbiota-host interactions and determine tipping points leading to negative health outcomes (Lahti et al., 2014). Other experiments could define the chronology of events leading to restored immune health (Li et al., 2016) or the consequences of transplanting a diverse microbial community from young donors to naturally aged or progeroid hosts (Bárcena et al., 2019; Smith et al., 2017; Stebbeg et al., 2019). Under the umbrella of resilience, investigations of host-microbiota balance and the networks involved in their interactions could span tissues and systems at the organismal level, whereas comparisons of resilience across environments and species allow for integration of ecological and evolutionary perspectives.

Resilience links extrinsic and intrinsic environmental variation

In the classical quantitative genetic model, $V_P = V_G + V_E + \text{cov}_{G,E}$ (Equation 1), we typically think of environmental variation as linked to extrinsic forces, but resilience can also be in response to intrinsic perturbations taking place within cells. Historically, efforts to link environment to aging have remained distinct for evolutionary versus cellular or molecular disciplines. Using a single framework of resilience of endophenotypes, we can gain insight into aging by asking how resilience responds to both extrinsic and intrinsic perturbations, and how each of those responses changes with age.

Resilience, aging, and interdisciplinary integration

There are many unanswered questions that could lead to a better, more integrative understanding of the evolutionary and molecular mechanisms of aging. Among these are the following four: first, does variation in levels of resilience among individuals within populations predict variation in rates of aging? Second, can resilience be considered either a biomarker of age or a risk factor for age-related diseases and conditions? Third, what mechanisms are engaged to establish resilience and at what cost? Fourth, do resilience mechanisms recruited early limit the ability of a system to adjust later in life? As a next step in advancing this conceptual framework for empirical application, we need to establish consensus approaches to measure resilience at the level of molecular networks, cells, tissues, physiological processes, and health/disease. The goal then will be to identify modules within biological networks that are required for resilience and identify structural or functional characteristics of modules that predict levels of resilience. We can also ask whether individuals that are resilient against one type of challenge (e.g., immune insult) are also resilient to other challenges (e.g., nutrient stress) and if greater integration in the ability to both respond to challenges and effectively resolve that response might correlate with healthy aging. In working on these central questions, we will not only develop a better understanding of resilience but also bring together evolutionary, ecological, and molecular approaches to create a more integrated perspective on aging.

CONCLUSION

Over many decades, two large bodies of work have emerged around the study of resilience, one in ecosystem ecology and the other in cognitive and psychological well-being. The concepts and models developed by these fields are particularly well-suited for building a more integrative study of aging biology—one that brings ecologists, evolutionary biologists, systems biologists, molecular biologists, demographers, and others to the table. Under the umbrella of resilience, the ecologist and the physiologist might focus on the extrinsic and intrinsic environmental perturbations, the systems biologist might measure the high-dimensional endophenotype networks that respond to that perturbation, the demographer

might be interested in consequences of this response on age-specific morbidity and mortality, and the molecular biologist might consider the underlying mechanisms that influence these responses. Resilience can integrate these perspectives, leading to powerful questions and more complete answers in the study of aging, thereby allowing us to better understand the factors that determine how and why organisms age.

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AUTHOR CONTRIBUTIONS

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DECLARATION OF INTERESTS

The authors declare no competing interests.

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