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Robustness and Aging – A Systems-Level Perspective

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Abstract

The theory of robustness describes a system level property of evolutionary systems, which predicts tradeoffs of great interest for the systems biology of aging, such as accumulation of non-heritable damage, occurrence of fragilities and limitations in performance, optimized allocation of restricted resources and confined redundancies. According to the robustness paradigm cells and organisms evolved into a state of highly optimized tolerance (HOT), which provides robustness to common perturbations, but causes tradeoffs generally characterized as "robust yet fragile". This raises the question whether the ultimate cause of aging is more than a lack of adaptation, but an inherent fragility of complex evolutionary systems. Since robustness connects to evolutionary designs, consideration of this theory provides a deeper connection between evolutionary aspects of aging, mathematical models and experimental data. In this review several mechanisms influential for aging are re-evaluated in support of robustness tradeoffs. This includes asymmetric cell division improving performance and specialization with limited capacities to prevent and repair age-related damage, as well as feedback control mechanisms optimized to respond to acute stressors, but unable to halt nor revert aging. Improvement in robustness by increasing efficiencies through cellular redundancies in larger organisms alleviates some of the damaging effects of cellular specialization, which can be expressed in allometric relationships. The introduction of the robustness paradigm offers unique insights for aging research and provides novel opportunities for systems biology endeavors.

1. Introduction

Research on the biology of aging has seen a dramatic increase in the scope of experimental work and availability of molecular data. In response to the pluralism in observations and study of compartmentalized mechanisms integration efforts using systems biology approaches have been suggested (Kirkwood, 2011; Kriete et al., 2011; West and Bergman, 2009). Systems biology in its core seeks to develop computational, mechanistic models using the underlying connectivity of components, with the goal to predict the dynamics of biological processes. While some progress has been made elucidating the dynamics of age-related processes, the introduction of modeling into aging encounters more complexities as compared to other disciplines. Not only is aging undoubtedly of multifactorial nature, but it cannot be fully understood without an evolutionary view. In fact, theoretical-evolutionary theories have made important contributions to our understanding of the biology of aging (Kirkwood, 2005; Ljubuncic and Reznick, 2009; Rose et al., 2008). However, such theories are difficult to be implemented into contemporary systems biology, and modeling activities are limited in their capacity to reach out to organizational principles underlying complex biological systems.

What is the conceptual framework allowing us to integrate the diversity of observations, experimental data, models and theories of aging so that different approaches become mutually supportive? The answer to this question is strongly related to the fundamental principle on which this framework should be based. Robustness as a systems level property of complex designs, subject to optimization on evolutionary scales, predicts the occurrence of tradeoffs as unavoidable side effects. Here it is argued that aging is influenced by robustness tradeoffs inherent in evolutionary systems. Robustness is a concept developed in control theory and complexity science (Carlson and Doyle, 1999, 2000) and, like the introduction of feedbacks into biological thinking (Wiener, 1948), it is poised to make inroads to help solving some fundamental problems of biology. This review first introduces the theory of robustness, and discusses tradeoffs as part of evolutionary optimization processes. Subsequently, age-related experimental data, models and theories are reexamined in their support of a robustness-tradeoff framework, such as the occurrence of aging in asymmetric cell division, fragilities of feedback control mechanisms in cell stress responses, and robustness expressed by allometric relationships. Furthermore, lifespan extension and prior theories are reviewed, lending to a

general robustness-of-aging theory. A concluding outlook provides directions how robustness as a systems function can be involved in the analysis of biological aging.

2. Principles of robustness and tradeoffs in engineering and evolutionary systems

Robustness is a desirable goal in the iterative design of technical systems or processes to improve durability and maintain functionality over a wide range of conditions and reduce system failure. Since system level properties in technical systems converge with properties of those complexities evolved in biological systems (Csete and Doyle, 2002), both technical and biological systems share similarities in robustness which may be studied under a common systems analysis framework (Carlson and Doyle, 1999, 2000, 2002; Csete and Doyle, 2002). Robustness has been postulated as a key property of evolutionary systems providing adaptive and protective mechanisms to intrinsic and environmental challenges (Kitano, 2004). A most common definition describes robustness as a property that allows a system to maintain its function against a spectrum of internal and external perturbations (Kitano, 2007b; Stelling et al., 2004). Stability of a system is not restricted to a return to the original state after perturbation, as in homeostasis, but can also be reached by entering a new and different stable state. The concept has been successfully applied to elucidate robustness of cellular functions (Stelling et al., 2004), metabolic networks (Stelling et al., 2002), biochemical reactions (Morohashi et al., 2002), evolvability (Wagner, 2005b), immunosenescence (Stromberg and Carlson, 2006) and host-pathogen interactions (Kitano, 2007a). Robustness drives the development of internal complexities, but tradeoffs and fragilities in response to perturbations cause dysfunction and systems failure, characteristics we find ubiquitously in aging mechanisms, aging phenotypes and limited lifespans.

Fragility s of a system with a feature or trait t_i, can be determined by evaluating the responses to applicable disturbances d_j. A proper normalization can be introduced to evaluate the probability and degree of failure against a set of perturbations, whereby larger values of s (>1) indicate fragilities, and smaller values of s (<1) robustness. The overall sensitivity S (or fragility) of a system over the entire space of traits T and perturbations D, can be expressed terms of a sensitivity integral:

$$S = \sum_i \sum_j \log | s(t_i, d_j) | \geq 0 \qquad [1]$$

This definition is inspired from a sensitivity function used in technical systems, called Bode sensitivity integral (Bode, 1945), and follows similar definitions made for biological systems (Kitano, 2007b). In the design of technical systems, like amplifiers controlled by feedback loops, sensitivities are determined by transfer functions for different operational frequencies of the amplifier, rather than traits. A property of complex systems is a conservation of sensitivity, i.e., improvement of robustness in one area leads to an increase in sensitivity or fragility in another, preventing the construction of a perfect robust system with $S = 0$ (Eq. 1). It has been suggested that conservation of robustness is a fundamental property in the optimization of complex systems and has been studied in theoretical and computational settings (Carlson and Doyle, 1999, 2002; Csete and Doyle, 2002; Kitano, 2007b). In biology, robustness evolves from a probability-loss-resource optimization schema (Doyle and Carlson, 2000). Hereby environmental perturbations, depending on their frequency and severity, constantly challenge the existing design, discard systems by premature death and loss from the population, and favor mutations from a limited pool of resources providing improved system performance. Of note, the crucial balance between evolutionary innovation and robustness restricting genetic mutations and adaptability is well studied (Wagner, 2005a, b, 2012), but how evolutionary genetics meshes with higher-level tradeoffs in the process of natural selection yet needs to be fully explored and is not discussed here.

However, it is important to realize that evolution and the development of complexities entails allocation of constrained resources, thus evolved systems reside in a highly optimized state characterized by traits and control mechanisms tolerating the most common fluctuations and stressors, but remain fragile to unexpected perturbations. Termed highly optimized tolerance (HOT), this state is reached by evolution in biological systems or by design in technical systems (Carlson and Doyle, 1999). For instance, an engineer is constrained during the construction and optimization of a device in the selection of available materials, resources and control mechanisms, in the consideration of only the most common hazards that may occur over the lifetime of the product, or incompatible design objectives. This inevitably causes a “robust yet fragile” systems property, which is a cornerstone of the robustness paradigm (Carlson and Doyle, 1999, 2000) and is expressed by the conservation of the sensitivity defined by Eq. 1. Fragilities may preferentially occur in response to perturbations not considered in the design

phase. As an example in biology we may consider the substantial responses cells and organisms are able to mount to successfully deal with strong acute perturbations on small time scales. But the very same systems are left fragile to seemingly innocuous damage rates in aging, due to declining forces of natural selection in adult organisms (Hamilton, 1966), leading to a slow accumulation of damage and dysfunction on a longer timescale, up to a point of catastrophic system failure (death). Robustness provides a framework allowing us to reason about such limitations.

According to the multifactorial nature of aging, we should be able to identify multiple of such mechanisms under the robustness paradigm. Figure 1 gives an overview of the different topics being discussed in the following along robustness principles and conceptual formulations in support of the hypothesis that aging is caused and its dynamics shaped by multifactorial robustness tradeoffs.

3. Robustness-performance tradeoff in asymmetric cell division

Many complexities are encountered in studies designed to unlock the dynamics underlying the aging process. For example, accumulating damage such as oxidation of proteins, damage to nuclear and mitochondrial DNA, dysfunctional mitochondria and decline of metabolism and biosynthesis, are well studied. The dynamics of these proximal aging processes need to be seen in context with regulatory mechanisms, such as increase in stress signaling, adaptive changes in gene expressions and epigenetic alterations. Furthermore, cells in proliferative tissues can arrest in a state of replicative senescence, while more severely damaged cells may enter mitochondrial induced apoptosis limiting their detrimental effect to the organism. The reader is referred to a large body of reviews on these topics (Gensler and Bernstein, 1981; Johnson et al., 1999; Kenyon, 2010; Kirkwood, 2005; Kourtis and Tavernarakis, 2011; Kujoth et al., 2005; Navarro and Boveris, 2007). But it appears equally important to study these mechanisms with an evolutionary perspective.

Cellular specialization and performance precede modular building blocks in multicellular organisms, with robustness tradeoffs in repair and damage removal. However, systems with moderate performance are known to cope well with a broad range of moderate perturbations, optimization of performance in specific traits may increase fragilities in others (Kitano, 2004;

Takada et al., 2003). This is the critical difference between cells dividing symmetrically, which do not show mortality, as compared to asymmetric cell division, which exhibits the aging phenotype. The segregation of germ line, stem cells and somatic cells exemplifies an asymmetric property in multicellular organisms. Both the disposable soma theory by Kirkwood and Holliday, which states that organisms must reach a balance between investment in soma maintenance and resources invested in reproduction (Kirkwood, 1977; Kirkwood and Holliday, 1979), and the ontogenetic theory of longevity by Jazwinski (Jazwinski, 1993), describe how progressive cellular specialization and improvement in performance requires distribution of limited resources with predictable genetic consequences and fragilities. Recent experimental data on metabolic performance substantiate these assumptions: Totipotent germ and pluripotent stem cells gain their energy mostly from glycolysis (Zhang et al., 2011), which is also the main source of energy during embryogenesis (Ramalho-Santos et al., 2009). Once somatic cells differentiate they involve mitochondrial respiration more strongly to efficiently meet body size and tissue dependent energy requirements (Benard et al., 2006). High ATP yield by respiration is an advantage for a cooperative use of resources in multicellular organisms (Pfeiffer et al., 2001). At the same time, oxidative phosphorylation constitutes the main source for reactive oxygen species, superoxide O_2^- and diffusible H_2O_2 (Boveris et al., 1972; Chance et al., 1979) leading to protein modifications, lipid oxidation and random point mutations in the mitochondrial and nuclear DNA. Interestingly, this increase in oxidative damage does not seem to be met by an increase in damage repair mechanisms (Saretzki et al., 2008), such as base excision repair, scavenging, proteasomal degradation and autophagy. Thus, improved metabolic efficiency and specialization in somatic cells are traits favored over longevity assurance.

Asymmetric cell division, along with cell polarity and pattern formation, can be traced back to simple prokaryotes like Caulobacter crescentus (Ackermann et al., 2003) and E. coli (Stewart et al., 2005), and have been intensively studied in Saccharomyces cerevisiae (Aguilaniu et al., 2003; Lai et al., 2002). For prokaryotes and bacterial eukaryotes an asymmetric cell division separates accumulated damage and aged parts, like mitochondria, from intact compartments creating “rejuvenated” daughter cells (Ackermann et al., 2007). This allows a phenotypic differentiation of cells in populations by the amount of damage they have accumulated over several cell cycles (Figure 2), and cells become individuals. As the performance of a cell is improved in specific traits, the trait aging becomes more pronounced. Steinsaltz and Goldwasser have discussed the

level of complexity required for a total quality control, which demands significant resource allocations (Steinsaltz and Goldwasser, 2006). Repair mechanisms like protein ubiquitination, proteasomal degradation, autophagy and base excision repair appear to be insufficient for systems of high-performance like most prokaryotes. Kirkwood and co-authors developed a number of elaborate dynamical systems models, showing that, under reasonable conditions, repair sufficient to maintain the cell in perpetuity would absorb most of the energy budget (Kowald and Kirkwood, 1994; Kowald and Kirkwood, 1996; Kowald and Kirkwood, 2000; Sozou and Kirkwood, 2001). Consistent with such considerations it was hypothesized that allowing aging to occur sets resources free otherwise engaged in error correction and repair (Ackermann et al., 2007). This might increase the overall robustness and innovation in traits more critical for survival on evolutionary timespans.

Immortal cells maintain a low level for damage preventing cell death. While improvement in fitness and specialization enhances cellular performance and growth for a young portion of the population, it introduces lower reproductive success and mortality in the older (see Figure 2), which is a robustness tradeoff. The net effect of such dependencies can be gauged in microbial population models using the mathematical formulation of a superprocess (Evans and Steinsaltz, 2007). An additional aspect of robustness concerns the damage cells may receive from environmental sources. In this scenario the likelihood for survival of the population under increased damage load is improved if damage is sequestered unequally among daughter cells (Chao, 2010). Asymmetric cell division is beneficial for robustness of unicellular population, and an ancestral phenomenon in multicellular organisms, but in turn it introduces an aging phenotype and mortality tradeoff to its members.

4. Network limitations in robust feedback control – acute versus chronic stressors

Robustness in networks is often established by negative feedbacks (NFBs). Feedbacks have been widely recognized to play a major role for stabilization and survival by engaging cellular and physiological processes for regulation and control, adaptation and repair (Brandman and Meyer, 2008; Tyson et al., 2003; Zhang and Andersen, 2007). Feedbacks are activated in response to external and internal stressors on any level of biological organization, and are finely tuned to provide optimal responses, from repair of UV induced DNA damage over complex immune responses to physiological thermoregulation.

Computational models considering the role of feedbacks in aging have targeted mitochondrial dynamics (Figge et al., 2012; Kowald and Kirkwood, 2011), protein homeostasis (Proctor and Lorimer, 2011), as well as the modular structure of protein networks and changes of protein connectivity with age (Borklu Yucel and Ulgen, 2011; Soltow et al., 2010; Xue et al., 2007). A network model of mitochondria, aberrant proteins, free radicals and scavengers (MARS model) was a more broader approach to study the interplay between metabolism, damage and repair predicting the progression of aging (Kowald and Kirkwood, 1996). To work optimally, the character, functionality and timing of the NFB response dynamic is important to bring the system back to a desired state. However, activation of feedbacks over longer periods of time may induce tradeoffs. Chronic inflammation and associated diseases in aging are such tradeoffs involving negative feedbacks. It has been suggested that the combination of positive damage-accumulation cycles and negative stress-response feedbacks shapes the overall behavior of cellular and physiological decline by a progressive adaptation (Kriete et al., 2010). Of note, the combination of positive and negative feedbacks may explain plateaus in mortality rates, if individual viability is expressed as a function of constant drift, resembling linear loss of function, combined with a stochastic Gaussian fluctuation (Weitz and Fraser, 2001). The assumptions of this model are in contrast to evolutionary theories (Mueller and Rose, 1996) and reliability models (Gavrilov and Gavrilova, 2001), which do not consider feedback mediated decline in function.

The theoretical conceptualization of robustness has led to suggestions for mathematical models to evaluate complex systems and control (Carlson and Doyle, 1999, 2000, 2002; Csete and Doyle, 2002; Kitano, 2007b), including the sensitivity integral (Eq. 1). With respect to properties predicted by the robustness theory, including the hypothesis that robustness is a limited resource for a designed or evolutionary system (Csete and Doyle, 2002), increase of performance in one part of the (frequency) range may be compensated by fragilities in another. Similarly, robustness provided by pathways such as the retrograde response (RTG) in yeast and the Nuclear Factor kappa-B (NF-κB) pathway, which takes a similar role in higher organisms as a marker of elevated energetic stress and redox state (Srinivasan et al., 2010), evolved to provide adequate responses in acute episodes of stress and mitochondrial dysfunction, but reveal tradeoffs if chronically activated. Concretely, in the absence of sufficient molecular robustness

the ongoing damage from oxidative phosphorylation causes aberrant proteins and damaged DNA to initiate a vicious cycle (Bandy and Davison, 1990). However, cross-sectional studies do not provide indications of an accelerated decline in metabolic and other parameters in cells (Greco et al., 2003), model systems (Even et al., 2001; Gruber et al., 2011) and humans (Black et al., 1996; Hunter et al., 2001; Piers et al., 1998), and only in a few organisms reveal any substantial decline (Martinez, 1998; Moe et al., 2007; Promislow and Haselkorn, 2002). None of these observations is compatible with a vicious cycle, and many of the parameters changing in aging have an early onset. For instance, energy expenditure and resting metabolic rate in humans peak at 20 year of age (Black et al., 1996; Manini, 2010), from which on they decline in a linear fashion. Longitudinal studies are revealing more complex pattern, where ongoing adaptations can change physiological parameters in a nonlinear fashion (Arbeev et al., 2011). In all these cases regulatory feedback mechanisms participate in the dynamics of the aging process.

We can understand feedbacks as barriers designed to prevent a sudden breakdown. The retrograde response, activated upon mitochondrial dysfunction, changes the gene expression adaptively (Butow and Avadhani, 2004; Jazwinski, 2000), extends lifespan, but also causes the accumulation of extrachromosomal circles. Similarly, NF-κB is responsive to a variety of exogenous and endogenous stressors at the core of a bow-tie architecture of an autoimmunity protein network (Kitano and Oda, 2006) and elicits a pro-survival response. This response contributes to low intracellular levels of free radicals by activating the expression of scavenger molecules, improves protein quality (Rivas and Ullrich, 1992), and may contribute to a change in metabolism from anabolism to catabolism and increased protection against protein oxidation by increasing glycolysis (Brand, 1997). Feedbacks architectures provide robustness, but always have fragilities (Csete and Doyle, 2002), which shows in aging when NF-κB becomes constitutively activated by cell-intrinsic “atypical” mechanisms (Evans et al., 1995; Kriete and Mayo, 2009) (**Figure 3**). The chronic activation likely contributing to epigenetic dynamics (Vanden Berghe et al., 2006) and promotion of cellular senescence (Rovillain et al., 2011), while senescent cells themselves express their specific inflammatory phenotype (Coppe et al., 2008). Inflammation is generally considered a major risk factor in age-associated diseases like cancer, arthritis and cardiovascular disease, even if it occurs prenatal (Mazumder et al., 2010), and genetic risk models have confirmed the role of genetic variants of genes associated with NF-κB networks

and longevity (Sebastiani et al., 2012). Consequently, modulation of NF-κB, which is finely tuned, is considered a strategy to influence aging (Adler et al., 2008), and both hyperactivity of NF-κB (Dong et al., 2010), as well as its loss of function (Alcamo et al., 2001; Dong et al., 2008) reduces lifespan.

The observation of an active downregulation of mitochondrial genes coded in the nuclear DNA (Preston et al., 2008; Zahn et al., 2006) is another indicator of the regulatory, adaptive mechanisms during aging. However, ROS levels do not have to increase to cause the accumulation of permanent oxidative damage (Kriete et al., 2010). Akin to the role of regulatory mechanisms, limitation of antioxidants or inhibition of mitochondrial repair pathways does not elevate intracellular ROS levels, but accelerates aging by decline in mitochondrial membrane potential, loss of ATP levels and increase in apoptosis (Echtay et al., 2002; Gruber et al., 2011; Kujoth et al., 2005; Trifunovic et al., 2005). This supports the notion that free radicals are important stress and signal messengers and are tightly controlled (Fedoroff, 2006; Finkel, 2003), and their involvement in caloric restriction and exercise may cause an adaptive response in promotion of mitochondrial quality (mitohormesis) (Ristow and Zarse, 2010).

Thus, the dynamic mechanisms underlying aging are in part determined by evolved responses and the combination of positive with negative feedbacks allows aging to progress in a lock-step fashion (Kriete et al., 2010). As damage accumulates, stress responses counteract, and ROS levels are contained. While RTG genes in yeast and NF-κB in higher organisms shape the aging progression, these pathways have not specifically evolved to be an “optimal” response for aging, nor do they provide sufficient robustness to revert the aging phenotype. Instead, they introduce new vulnerabilities. The antagonistic activity of the pro-survival mechanism NF-κB and the pro-apoptotic function of p53 is another example. The p53 pathway is engaged in DNA repair mechanisms like base excision repair and modulates apoptosis, but competes with NF-κB over a common pool of transcriptional co-activators (Ak and Levine, 2010). In aging, the pro-survival mechanism dominates the repair and apoptotic pathway, so that nuclear damage can progress. Only if p53 is activated by stronger signals, like telomere shortening in proliferating cells (Artandi and Attardi, 2005), the situation changes: cells apoptose or enter a senescent state whereby ROS levels increase (Lawless et al., 2012). Accordingly, constitutive activation of p53 prevents cancer but also shortens lifespan (Donehower, 2002), while low basal levels of p53

activity and normal regulatory control in the "super p53" mouse does not cause premature aging (Garcia-Cao et al., 2002). Thus, the slowly aging intracellular environment tips the balance from a genome protective response to a pro-survival response, which may be beneficial in acute short-term perturbations, but exposes the organism to fragilities such as cancer in the long term.

5. Do lifespan extension experiments validate aging as a tradeoff?

Under the robustness paradigm, organisms residing in a HOT state have developed diverse and connected pathways (Li et al., 2008; Natarajan et al., 2006), providing a balanced robustness against most common perturbations. The spectrum of perturbations and fluctuations biological systems encounter is broad: the abundance and supply of nutrients varies, pathogens hijack cells to replicate, and damaging agents challenge the structural and functional integrity of the cell (UV radiation, oxidative damage, toxins, low and high temperatures), accompanied by cell intrinsic noise (Pedraza and van Oudenaarden, 2005). In order to sense, regulate, adapt and survive under these conditions, cell and organisms have evolved an array of specific pathways improving their robustness in key areas, but may show antagonisms in others. **Figure 4** provides a schematic for specialization and innovation under limited resources during evolution. As part of this process, proteins can take multiple roles in multiple traits, i.e. they become pleiotropic, which keeps the growing complexity at bay but may introduce antagonisms. Similarly, pathways can exhibit an enzymatic cross-talk causing competition (Rowland et al., 2012). Of note, proteins associated with aging show a higher degree of pleiotropy as well as higher connectivity (Criollo et al., 2012; Dong et al., 2010; Fortney et al., 2010; Kriete et al., 2010; Witten and Bonchev, 2007). Assembly of an aging-associated network from proteins known to be influential of aging if perturbed, demonstrates the broad spectrum of protein function (signaling, mitochondrial, metabolism) and protein distribution over most cellular compartments belonging to this network (Budovsky et al., 2007). This network did not evolved to drive aging, but it contains highly connected, evolutionary conserved hubs eliciting pro-survival responses, for instance if activated by caloric restriction (Wuttke et al., 2012). At the same time, higher connectivity may render these proteins experimentally more noticeable (Criollo et al., 2012). Further studies are needed to investigate the function, control and dynamics of age-related networks, such as metabolic flux mode analysis (Gebauer et al., 2012; Stelling et al., 2002). In addition, robustness constraints these networks faced during evolution need to be considered more strongly, which

has proven to be superior to an analysis of attack tolerance based on topology (Doyle et al., 2005).

In the context outlined here, age-related proteins and genes have been hijacked for innovative functions and traits improving robustness in young organisms, rather than tuning their function to longevity assurance, and priorities are allocated to viability, metabolic efficiency, fecundity and immune functions (de Jong and van Noordwijk, 1992; Sheldon and Verhulst, 1996). Due to the pleiotropic nature of proteins associated with aging, any attempt to redistribute resources in a tightly regulated and densely knitted network by genetic or pharmacological interventions may improve the trait lifespan, but dependencies between these proteins and pathways may cause tradeoffs elsewhere. Indeed, both artificial selection experiments and genetic knockouts have shown the ability to extend lifespan, but many reports mention tradeoffs (Jenkins et al., 2004; Rose and Charlesworth, 1980; Van Voorhies et al., 2006). Such fitness costs may be difficult to detect. For instance, unless a knockout is not viable we may not recognize or able to determine the loss of the beneficial role this gene might have in the early development of an organism or during perturbations not always present in lab environments. Sometimes these tradeoffs only surface when the environment becomes suboptimal, i.e. the tradeoff becomes conditional. Examples have been demonstrated for long-lived *Indy Drosophila* and *age-1 C. Elegans* nematode mutants, which reveal decreases in some other fitness traits only when placed under a stressful environment (Marden et al., 2003; Walker et al., 2000). Similarly, IGF-1 mutants show increased lifespan and better stress resistance, but have a reduced competitive Darwinian fitness leading to extinction (Jenkins et al., 2004). The limitations and tradeoffs in any type or target for intervention document a careful distribution of resources under the robustness paradigm. A similar cautionary note may apply to the application of mild stressors activating mechanisms benefiting lifespan termed Hormesis, which is observed in model organisms (Rattan, 2008; Shama et al., 1998). Hormesis often shows a bi-phasic dose response. Accordingly, there is a limit to which life-extending interventions are beneficial. For example, in model organisms both slowing of behavioral rates (Cristina et al., 2009), and reduction of lifespan if caloric restriction was combined with additional pharmacological interventions (Onken and Driscoll, 2010), was observed.

In summary, the overwhelming experimental evidence in *de novo* mutants and pharmaceutical interventions indicates that biological organisms are in an optimized HOT state, and, following the conservation law of robustness, lifespan is "traded" against essential robustness and fitness traits. Other genetic approaches, such as artificial selection experiments aimed to extend the forces of adaptation into later age as carried out by Rose in *Drosophila melanogaster* (Rose, 1984; Rose and Nusbaum, 1994), are undoubtedly a better way to modulate lifespan by altering many genetic loci simultaneously. Transitional tradeoffs observed in such experiments, like loss of fecundity, can be interpreted by complex schemes of molecular rearrangements (Arking et al., 2002). Since tradeoffs are difficult to detect in laboratory environments, the ability to perform genome wide expression studies can at least provide hints where they might exist (Doroszuk et al., 2012). To date, no serious attempt has been carried out to analyze tradeoffs in higher organisms with lifespans extended by artificial selection, other than a small-scale mouse study (Nagai et al., 1995). It remains an open question if higher organisms are amendable to the kind of lifespan extension and tradeoff analysis performed in simpler organisms, despite the substantial value this would have for the understanding of human aging (Rose and Nusbaum, 1994). With respect to refined specialization, control mechanisms and hierarchies in higher organisms, and practical aspects such as longer lifespans, it appears likely that such investigations are more challenging.

6. Body size as a resource for robustness

Complex organisms are not only optimized with respect to a performance of required traits and control mechanisms, but also in terms of physical and physiological structure and function. These optimizations contribute to lifespan as a quantifiable measure of robustness. Lifespan for individuals in a class of species is variable, contributing to the stochastic nature of aging (Herndon et al., 2002) and is determined by multiple failures leading to a catastrophic breakdown, and the process of aging increases the opportunity for combined failures to occur. However, average lifespan is a quantifiable measure in populations, which can be used to define one boundary of the viable state space in which all organisms reside. Average lifespan can by expressed by allometric scaling laws, which define a biological property in relation to body mass (M_b) and a scaling exponent α. The exponent takes multiples of ¼ power, such as basal metabolic rate (α ~3/4), DNA and nucleotide substitution rates (α ~3/4), densities of mitochondria and ribosomes (α ~-1/4), and heart rate (α ~ -1/4), to name a few, and has been

amended by finite size corrections (Savage et al., 2008). West, Brown and Enquist (West et al., 1999) had reasoned that the geometry and function of supply networks (vascular tree, branching in bronchial tree of lung, hepatic, renal, neural but also intracellular systems) are at the root of such relationships. It is well known in physiology that in the design of branching supply systems an increase of cross-sections in branches increases the overall volume of the medium to be transported, while reduction in cross-sections increases resistance, thus there is a physical optimum which minimizes transport related costs. In organisms such relationships provide networks for optimized distribution, space filling, and minimization of energy dissipation to invariant end units (cells) constraining their metabolism, leading to efficiency gains with increasing body size (West et al., 2003). For mammals, allometric scalings extend over 7 orders of magnitude in mass, from shrew (2 g) to whale (200 t), out of 27 orders applicable to biology (West and Brown, 2005). Variation in lifespan for mammals, within a total range of 3 orders of magnitude, indicates an evolutionary optimization of structural and functional properties defining one boundary for robustness in mammalian state space.

For mammalian lifespan the exponent α is approximately 1/4, indicating increase of lifespan with body size and an absolute predictor for organism robustness in terms of lifespan potential (R_{absLS}) is proportional to:

$$R_{absLS} \approx \textit{lifespan potential} \approx M_b^{1/4}. \qquad [2]$$

This measure is inversely related to metabolism per unit weight per day (specific metabolic rate), which is higher in the mouse (133 kcal kg^{-1} day^{-1}) than it is in elephants (7.4 kcal kg^{-1} day^{-1}), determining the rate of aging decline. Interestingly, the density of mitochondria scales with a negative exponent ($M_b^{-1/4}$), which can be directly associated with improvement in lifespan defined by a positive exponent ($M_b^{¼}$) (Kriete et al., 2006).

One characteristic of allometric scaling laws is the emergence of invariant quantities, which includes heartbeats per lifetime for mammals or total number of turnovers in the respiratory complexes. Similarly, we can express a relative measure of robustness (R_{relLS}) by basal energy consumed per uni-mass of an animal over its lifespan potential:

$$R_{RelLS} \approx \textit{basal metabolic rate} * \textit{body mass}^{-1} * \textit{lifespan}^{-1}. \quad [3]$$

This expression for relative robustness of lifespan is invariant and approximately $2 * 10^5$ kcals kg^{-1} lifespan $^{-1}$ for all mammals. Species with similar relative robustness belong to the same optimality class. Increase of robustness in biological and technical systems is not only limited to the optimization of traits and control mechanisms, but can also be achieved by modularity, decoupling and redundancy (Kitano, 2004). The above defined invariance demonstrates that body size obtained by increasing the overall number of cellular units in conjunction with optimized supply systems is a redundancy resource for mammals, which increases lifespan by reducing the (per cell) metabolism, improving energetic efficiency and lessening some of the damaging effects arising from cellular specialization.

However, adding redundancies becomes an increasing burden for the system as a whole and benefits are not growing linearly as more and more resources are being added. For instance, ecological niches for very large animals are sparse and such animals would be constrained by availability of nutrients and risk extinction despite increased metabolic efficiency, which constitutes population-level tradeoffs and reduces the density of larger species (Clauset and Erwin, 2008). While body mass and base metabolism become factors determining longevity, the environmental conditions and their changes, and the finely tuned balance of traits inherited genetically constitute additional factors influencing the rate of aging and lifespan. This introduces a variance around the allometric regression line, reducing its fit (R^2 value), but not its statistical significance (p value). Species diverting from the best-fit line are of primary interest to investigate genetic and environmental factors contributing to aging, such as the bat or naked mole rat in mammals. The long lifespan in humans, exceeding relative robustness by about three times over the predicted average value, emerged only recently by improved living conditions, hygiene, medical support and nutritional balance. In addition to environmental conditions the process of aging is influenced by identifiable proteins and pathways promoting longevity (Li and de Magalhaes, 2011) and further modulated by genetic variants deciphered in long-lived centenarians. These variants appear to introduce a buffer – or robustness – against the detrimental effect of age-related disease genes (Bergman et al., 2007; Christensen et al., 2006; Sebastiani et al., 2012) and may suggest strategies for healthy aging.

7. Robustness in the context of theories and models of aging

Attempts to explain aging have produced a number of different theories, as reviewed in detail elsewhere (Kirkwood, 2005; Ljubuncic and Reznick, 2009; Longo et al., 2005; Rose et al., 2008). In order to position robustness with respect to prior work, some key aspects of most common theories are reviewed, summarized in **Table 1**. August Weismann, at the end of the last century, introduced the idea of mortality as an adaptive and altruistic process (Weismann et al., 1889). The theory claimed a competitive advantage of aging species over populations that do not remove older individuals. The group selection concept received criticism and was later abandoned by Weismann himself in favor of a soma-germ segregation theory (Weismann, 1893). Peter Medawar introduced a mutation accumulation theory (Medawar, 1952), recognizing that diminishing selective force with age may lead to a (passive) accumulation of harmful genes acting later in life. In a further refinement of Medawar's theory, George Williams proposed a model of antagonistic pleiotropy, whereby the selection of some pleiotropic genes benefiting the young organism become detrimental in late-life (Williams, 1957), which is a tradeoff absent in Medawar's theory. Hereby genes contributing to aging are being actively kept in the gene pool due to their beneficial role early in life. The concept of tradeoffs was further explored by Kirkwood and Holliday by postulating a specific class of energy related pleiotropic gene mutations which increase energy expenditure for reproductive tasks, while cutting down on energy required for molecular proofreading and repair in somatic cells (Kirkwood and Holliday, 1979). Known as the disposable soma theory, this concept connects to cellular mechanisms and is further based on the assumption of a constraint in energy expenditure over a life-history.

The related mathematical modeling activities in aging are broad and one thrust of mathematical simulations in aging defines statistical models matching demographic survival rates (Steinsaltz et al., 2012; Vaupel, 2010), reaching out to principles such as reliability theory (Gavrilov and Gavrilova, 2001; Koltover, 1997; Witten, 1985). Models considering optimization aspects can be found in dynamical population models demonstrating the repair–growth–reproduction tradeoffs (Chu and Lee, 2006; Mangel, 2001) or life-history optimization through distribution of limited resources for growth, reproduction and repair (Cichon, 1997; Perrin and Silby, 1993; Schaffer, 1974; Vaupel et al., 2004). Similarly, as discussed earlier, cell population models have targeted

optimization of fitness in asymmetric cell division and survival rates (Ackermann et al., 2007; Chao, 2010; Erjavec et al., 2008; Evans and Steinsaltz, 2007).

There have been attempts to validate aging theories, and specifically the function of antagonistic pleiotropic genes. The prevailing experimental approaches are to alter the force of natural selection by artificial selection experiments, or to knockout single genes having a potential for a pleiotropic effect, as discussed in a previous section of this article. Inconsistencies in the results obtained from these studies have fueled support for Weismann's original idea that aging is an adaptive and "programmed" process (Kenyon, 2010; Longo et al., 2005). Others have demonstrated partial interactions of the phenomena suggested by Medawar's and William's theories (Tatar et al., 1996), or refuted the significance of mutation accumulation or programmed aging on the basis of theoretical considerations, modeling studies and experiments (Austad, 2004; Danko et al., 2012; Rose and Charlesworth, 1980). These intricacies not only suggest a cautious view in the interpretation of experiments (de Magalhaes, 2005; Flatt and Promislow, 2007; Kirkwood, 2005), but also prevented the broader acceptance of a specific aging theory.

The antagonistic pleiotropy and disposable soma theories have already recognized the role of tradeoffs in aging, and as such they are critical cornerstones in the development of a more generalized systems view under the robustness paradigm (see table 1). A more recently developed theory considers hyper-function of key regulatory pathways, such as insulin/IGF and TOR, as the proximal cause of aging (Blagosklonny, 2012; Gems and Partridge, 2013). The theory is consistent with the weakening of adaptations and lack of corresponding adaptive genomic information required to provide more appropriate responses to the aging phenotype (Rose, 2009). Accordingly, caloric restriction or pharmacological inhibitions of the TOR pathway can expand lifespan, but only modulate aging without abrogating or reversing the process. The discussion of the NF-κB pathway in a previous section fits into this concept, and is explained by the specialization and tuning of control mechanisms under the robustness paradigm. We therefore need to consider new tradeoffs any interventions may cause, specifically with respect to the role of both TOR and NF-κB pathways in immune functions (Baeuerle and Henkel, 1994; Thomson et al., 2009).

The introduction of the robustness paradigm into the biology of aging builds on characteristics of complex systems, the control theory in engineering, and transport phenomena in physics, which leads to the conclusion that the ultimate cause for aging is not rooted in mechanisms specific for biology. However, these characteristics have been established and extensively studied in many areas, bringing a solid foundation to the theory of aging providing guidance in deciphering proximal aging mechanisms and appropriate development of models.

8. Discussion and outlook

Highly optimized systems have fragilities and design flaws that can be liberated by seemingly minute disturbances. Prime examples in biology are some single gene mutations, minimalistic changes with respect to the overall structural complexity of an organism, but highly disruptive for the phenotype as manifested in premature aging syndromes like Hutchinson-Gilford Progeria. In contrast to such rare mutations, aging evolved as fragility due to multifactorial robustness tradeoffs in cellular performance and specialization, antagonistic control and limitation in resources. The insight that aging is more than a lack of adaptation, but a tradeoffs during optimizations on evolutionary scales offers a new perspective not only for the mathematical modeling of aging, which is an opportunity for systems biology, but also for a further development of evolutionary aging theories. Aging theories that considered tradeoffs like antagonistic pleiotropy, and more so the disposable soma theory introducing an energetically relevant system constraint, lend themselves to a more general concept outlined here as summarized in Table 1. The underlying hypothesis assumes a conserved property in the relation between robustness and fragility, as proposed by Csete and Doyle (Csete and Doyle, 2002), for which biological mechanisms influential for aging can be defined. Furthermore, this view is consistent with the nonexistence of the Darwinian daemon; a hypothetical organism possessing eternal life and infinite capabilities for reproduction while embracing unrestricted resources. It remains to be explained how biological systems exactly evolve structural and functional properties restricted by resources, or develop asymmetric features, control mechanisms and modularity. It appears that many questions could be tackled by collaborations between systems engineers and evolutionary biologists.

The attempt to define robustness tradeoffs with respect to properties of biological organization as demonstrated here can only be a first step in this direction. However, this review reveals that

biological systems reside in a state of highly optimized tolerance providing robustness to many traits, but the "robust, yet fragile" duality neglects others including limited damage control causing fragility and aging. In particular, asymmetric cell division and specialization leads to performance-robustness tradeoffs, which is not only of relevance for some unicellular organisms, but appears to be at the root of aging in somatic cells. Thus, the onset of aging may be positioned at an early differentiation into somatic cells under selective pressure. Second, evolved feedbacks respond as barriers against rapid breakdowns and shape the aging dynamics in cellular networks into the evolutionary shadow after reproduction. While these evolved control mechanisms support the system to regain stability during acute episodes of external stress, their chronic activation in aging "lock" the system into a slow decline, but does not revert the aging phenotype. Third, body mass appears to be a resource limiting the cellular metabolic load in organisms, alleviating some of the damaging processes caused by cellular specialization, which extends lifespan.

Frequently observed tradeoffs in artificial selection experiments and knockout models designed to extend lifespan remind us of the optimized state, and such limitations are also apparent in humans. For instance, later reproduction seems to be associated with neurodevelopmental and behavioral disorders such as autism (Rahbar et al., 2012) and pharmacological substitution of growth hormones increases risk for developing cancer (Bartke, 2008). Phenotypic manipulations such as caloric restriction to delay aging have been successful in mice (Weindruch et al., 1986), but did not show success in monkeys (Mattison et al., 2012), and in humans even moderate caloric restriction beneficial for obese patient populations can cause adverse clinical effects in lean persons (Fontana and Klein, 2007). Since age-related disease greatly increase in prevalence, extending a healthy lifespan remains a desirable but complex issue and further progress will require a tight integration of data, observations, models and theories to make sound interpretations and predictions. It is likely that consideration of robustness will make a contribution in shaping the consistency in these efforts.

At the same time, the mathematical foundation of robustness still needs to be developed further to find broader applicability, and will likely include elements of game theory to solve conflicting optimization problems (Perc and Szolnoki, 2010; Pfeiffer et al., 2001; Requejo and Camacho, 2011). Previously conducted mathematical modeling approaches for those unicellular

organisms sequestering damage unequally between daughter cells are prime examples to explore fitness optima. However, experimental observations should not be restricted to population growth as the main fitness parameter. Similarly, artificial selection and knockout experiments extending lifespan can reveal tradeoffs in specific phenotypical functions, and herewith validate the concept of robustness. But to decipher these complexities in a more systematic fashion, an evaluation of responses over a spectrum of exogenous perturbations is required. This would move the analysis closer to the core definition of robustness, i.e. the ability of an organism to maintain functionality over a wide spectrum of conditions and perturbations, which can be framed in terms of a sensitivity integral. Since robustness is deeply rooted in engineering it should also mesh well with synthetic biology. Current experimental designs already use elements of synthetic biology to actively interfere with aging mechanisms, such as synthetic circuits introduced to create older populations in yeast cultures (Afonso et al., 2010), or utilize modification of multiple genes in model organisms (Sagi and Kim, 2012). Furthermore, stability and maintenance of function is also a general concern in the design and optimization of synthetic cells (Noireaux et al., 2011). A related question of interest would be if and how robust non-aging organisms with synthetic genomes can be engineered, which will require complexities at or above genome sizes considered minimal (Mushegian and Koonin, 1996). In other words, one would examine the question whether the tradeoff aging is a necessity by design, as hypothesized here. Furthermore, projects investigating the balance of performances and aging tradeoffs in connection with evolutionary genetics would be desirable, linking genotypes to phenotypes (Dalziel et al., 2009). In summary, multiple opportunities can be identified for approaches to investigate robustness and optimality in aging and should be considered more strongly. After all, evolution solved a complex optimization puzzle to ensure survival and performance of biological systems constrained by multiple objective functions. While life is an expression of robustness, aging is an omnipresent tradeoff resulting from this optimization process.

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Figures

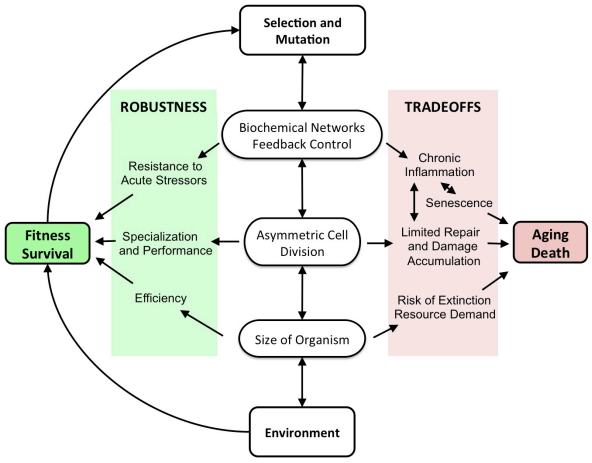

Figure 1: Robustness and tradeoffs. Robustness and multifactorial tradeoffs relevant for aging can be identified across biological scales. While robustness traits lead to fitness, their tradeoff counterparts contribute to an aging phenotype. Tradeoffs include damage accumulation and senescence arising from cellular specialization beneficial to the performance of biological systems. Limitations in feedback control contribute to the chronic progression of aging, which evolved to provide optimal responses for survival in phases of acute perturbations. Cellular redundancy is a source of robustness supporting longer lifespans in multicellular organisms by increasing efficiencies, which alleviates some of the consequences of cellular specialization, but very large body sizes increase the risk of extinction.

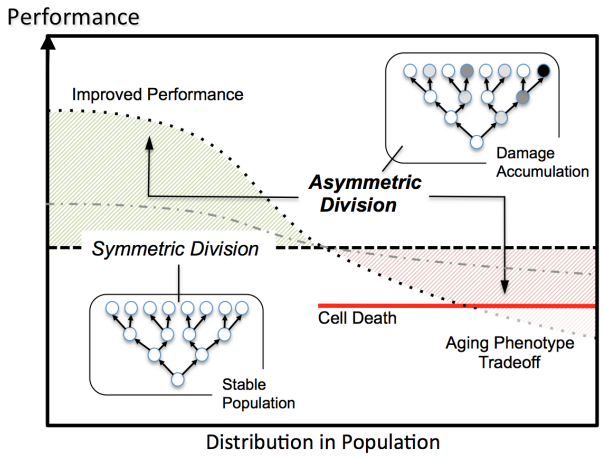

Figure 2: Robustness-performance tradeoff in asymmetric cell division. The graph depicts performance distributions (in terms of metabolic efficiency, accumulated damage) in cell populations. Symmetric cell division in low performance cell populations maintains structural fidelity and repair to prevent the population to die out. Asymmetric cell division improves robustness efficiency in traits advantageous for the population as a whole, but also causes aging through limitation in repair and cells become discernable by a different degree of damage and dysfunction (depicted by darker shades in the insert), before they reach a limit at which they are not viable anymore. Since robustness is conserved, cell lines developing traits of higher performance (from dashed to dotted lines) increase the tradeoff aging, as compared to cells with a more moderate performance and never accumulate significant damage to die out. This is an example for "Robust yet fragile" behavior in evolving biological cell systems.

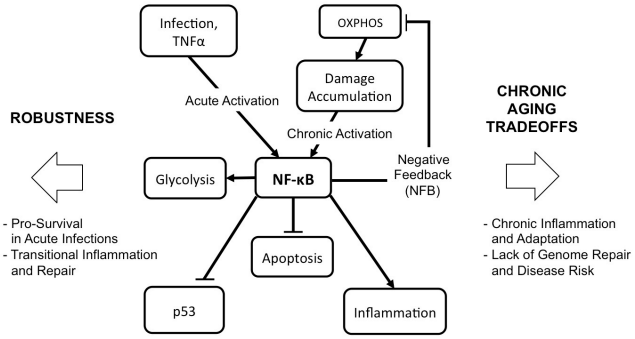

Figure 3: Limitations in systems control. This graph illustrates relationship of components involved in the NF-κB pathway. The pathway evolved to provide benefits in acute, transitional infections, including stimulations by TNFα. In aging, manifestations of oxidative damage elicit a chromic low-grade NF-κB response. This constitutes a negative feedback (NFB) counteracting a positive feedback or vicious cycle of damage progression, and involves a metabolic shift from mitochondrial activity to glycolysis. While a vicious cycle of decline is prevented, the combined positive and negative feedbacks advance aging in a lock-step fashion. Chronic NF-κB activation does not revert the aging phenotype and has tradeoffs, such as suppression of genome repair and inflammation, which are known risk factors for many age-related diseases.

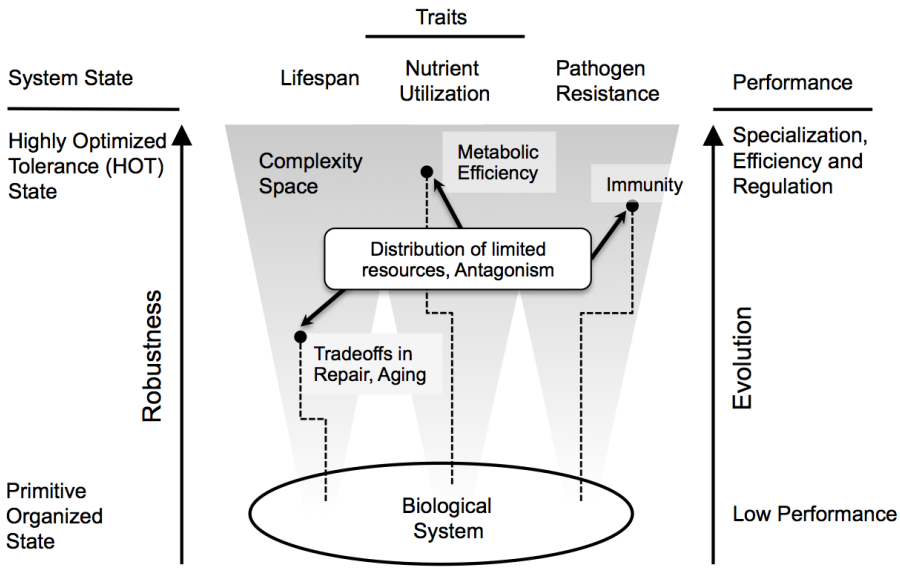

Figure 4: Evolution of phenotypical traits. Biological systems evolve phenotypical traits and pathways to increase performance, efficiency and improved responses to environmental and internal perturbations. Through these innovations cells and organisms reside in a state of highly optimized tolerance (HOT), as compared to a more primitive state sensitive to specific fluctuations. This forms a complexity space shaped by overlapping networks, pleiotropic proteins, and multiple levels of regulation. However, robustness under limited resources causes antagonisms, performance tradeoffs and systems failures particular when experiencing unexpected perturbations. Aging may be a consequence of such tradeoffs. Genetic or pharmacological interventions can improve one pathway or trait such as lifespan, but disturb a symbiotically evolved balance causing deficiencies in other traits, as observed in knockout models.

THEORY	Evolutionary Mechanism	Tradeoff	Proximate Aging Process	Systems-level Property
Weismann (1889)	Active selection of aging genes	Not defined	Aging is programmed, but no cellular mechanism are defined	Altruistic benefit for the population
Mutation Accumulation (Medawar, 1952)	Passive accumulation of genes deleterious later in life	Genes become detrimental later in life	Aging mechanisms not defined	Benefit for population
Antagonistic Pleiotropy (Williams, 1957)	Active selection and maintenance of pleiotropic genes	Genes become detrimental late in life	Aging mechanism not defined	Not defined
Disposable Soma Theory (Kirkwood and Holliwood, 1979)	Active selection of genes to benefit reproduction in young	Insufficient maintenance of somatic cells causes aging	Damage accumulates due to limited resource allocation for repair in somatic cells	Distribution of limited energetic resources over life-history
Robustness and Tradeoffs	Active selection of genes and systems-level properties benefiting robustness in common perturbations	Robustness tradeoffs in fragility, limited resource allocation, robustness tradeoffs in feedback control	Cell specialization and somatic modularity causes damage accumulation - feedback control is inadequate and causes chronic stress	Systems reside in a highly optimized tolerance (HOT) state - robustness is conserved.

Table 1: Overview and classification of aging theories. Theories connect to evolutionary mechanism to explain aging. Early concepts suggested aging to be a benefit for populations, either by program or by allowing a passive accumulation of genes detrimental later in life. The idea of a tradeoff was first introduced in the concept of antagonistic pleiotropy. The disposable soma theory added a system level property in terms of limited energetic resources along with a more mechanistic model of aging. The robustness theory generalizes these concepts and considers different types of systems-level tradeoffs.