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Review

Revamping the evolutionary theories of aging

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ABSTRACT

Radical lifespan disparities exist in the animal kingdom. While the ocean quahog can survive for half a millennium, the mayfly survives for less than 48 h. The evolutionary theories of aging seek to explain why such stark longevity differences exist and why a deleterious process like aging evolved. The classical mutation accumulation, antagonistic pleiotropy, and disposable soma theories predict that increased extrinsic mortality should select for the evolution of shorter lifespans and vice versa. Most experimental and comparative field studies conform to this prediction. Indeed, animals with extreme longevity (e.g., Greenland shark, bowhead whale, giant tortoise, vestimentiferan tubeworms) typically experience minimal predation. However, data from guppies, nematodes, and computational models show that increased extrinsic mortality can sometimes lead to longer evolved lifespans. The existence of theoretically immortal animals that experience extrinsic mortality – like planarian flatworms, panther worms, and hydra – further challenges classical assumptions. Octopuses pose another puzzle by exhibiting short lifespans and an uncanny intelligence, the latter of which is often associated with longevity and reduced extrinsic mortality. The evolutionary response to extrinsic mortality is likely dependent on multiple interacting factors in the organism, population, and ecology, including food availability, population density, reproductive cost, age-mortality interactions, and the mortality source.

1. Introduction

One of the major, unsolved mysteries in biology is the evolution of aging. It remains to be elucidated why there is so much variability in lifespan across the animal kingdom and why aging evolved at all. It is non-intuitive to expect that a harmful process like senescence, which decreases fitness and increases mortality, would be favored by natural selection. The concept of the evolution of aging was introduced into the literature in 1930 by Ronald Fisher (Fisher, 1930). Thanks to Fisher and innovative thinkers like Peter Medawar (Medawar, 1952), George Williams (Williams, 1957), William Hamilton (Hamilton, 1966), Thomas Kirkwood (Kirkwood, 1977), and others, cogent evolutionary theories exist which help explain why aging evolved as well as many of the observed disparities in longevity between different species. According to these classical theories, extrinsic mortality (e.g., predation, disease, starvation, accidents) is a primary evolutionary driver of how quickly or slowly an organism will age. Since most animals in the wild will not survive to old age due to harsh living conditions, there is little to no evolutionary pressure to promote genetic changes that slow aging and increase lifespan. This is certainly true for wild mice, where their major cause of mortality is cold temperature (Berry and Bronson, 1992) and more than 90% of mice will die in their first year of life (Kirkwood, 2005). For these reasons, there should typically be strong evolutionary pressure to encourage genes that promote early survival and more rapid reproduction.

Given high mortality rates in the wild, it is thought that the force of evolutionary selection for self-maintenance will decline with age for most animals (Fig. 1A). This declining selection gradient with age underlies Medawar's "mutation accumulation" theory (Medawar, 1952), which argues that deleterious, late-acting mutations can accumulate passively without resistance (Fig. 1B). Building off of Medawar's work, the later-developed "antagonistic pleiotropy" theory proposed by Williams (Williams, 1957) posits that the rarity of senescence in the wild results in a more active selection for genes that benefit early life but impair late life (Fig. 1C). These theories were formalized mathematically and further developed by Hamilton (Hamilton, 1966). The more mechanical, energy-focused "disposable soma" theory by Kirkwood (Kirkwood, 1977) emphasizes that, because resources are limited, most organisms will fare best if they invest their finite energy into mechanisms that boost fecundity instead of non-reproductive mechanisms (i.e., the soma) that combat aging (Fig. 1D). Both the antagonistic pleiotropy and disposable soma theories expect a trade-off between aging and

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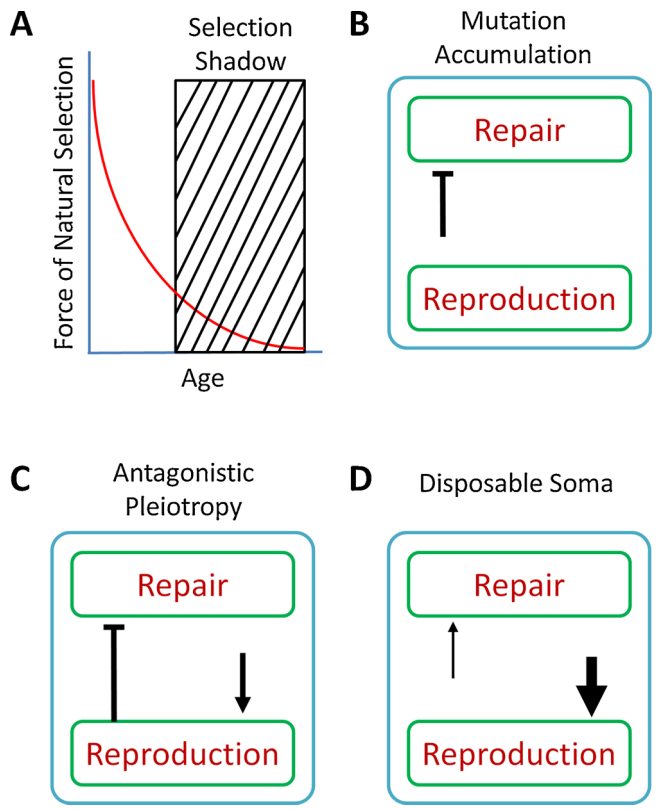

Fig. 1. Classical theories for the evolution of aging. A) Illustration of Medawar's "selection shadow" showing that deleterious mutations are subject to a decreasing selective pressure after sexual maturation. B) The mutation accumulation theory emphasizes the lack of selection against mutations that exert deleterious effects later in life. C) The antagonistic pleiotropy theory argues for the selection of mutations that improve reproduction at the cost of repair, resulting in a direct antagonism. D) The disposable soma theory focuses on mechanistic trade-offs between repair and reproduction through a shared resource pool.

fecundity (Flatt and Partridge, 2018). All three theories predict that an increase in extrinsic mortality should select for the evolution of shorter lifespans and vice-versa.

The bulk of published observations conform to these predictions (Kirkwood and Austad, 2000) and new data continues to emerge that further bolsters these classical evolutionary theories of aging. For example, deep-sea animals live in a stable environment, experience minimal predation, and tend to live significantly longer compared to their shallow-water counterparts. A recent paper reported that large, deep-sea vestimentiferan tubeworms enjoy extreme longevities, regularly obtaining lifespans of 100–200 years and exhibiting a maximal lifespan of over 300 years (Durkin et al., 2017). As an explicit example of the role of predation in the evolution of aging, exposure to the predatory mosquito *Toxorhynchites rutilus* during the juvenile stage has been shown to shorten the lifespan of adults in *Aedes aegypti* mosquitoes. Increased predation also decreased development time and hastened recruitment to the adult stage (Bellamy and Alto, 2018). Further highlighting a trade-off between reproduction and aging, reduced longevity is associated with a high mating rate in wild antler flies (Bonduriansky and Brassil, 2005).

Although significantly rarer, important studies have defied classical predictions by showing that increased extrinsic mortality can select for the evolution of longer lifespans. Two seminal studies performed in guppies (Reznick et al., 2004) and nematodes (Chen and Maklakov, 2012) showed that, in response to an increase in extrinsic mortality, a longer lifespan could be selected for. Using an agent-based, stochastic computational model, we previously demonstrated that whether increased predation selects for the evolution of longer or shorter lifespans can depend heavily on parameters like the cost of mating and energy availability (Shokhirev and Johnson, 2014). The existence of theoretically ageless animals, like planarian flatworms (Sahu et al., 2017), panther worms (Srivastava et al., 2014), hydra (Martinez, 1998), and immortal jellyfish (Schmich et al., 2007) that appear not to undergo senescence create an additional challenge for the evolution of aging. Since these theoretically immortal animals do experience extrinsic mortality, why would they develop such powerful anti-aging mechanisms?

Comparing lifespans between evolutionarily similar animals within the same ecological order reveals how much more we have to learn regarding the evolution of aging. Different species within the order Octopoda, for example, exhibit significantly disparate lifespans. A great illustration of this is the deep-sea octopus *Graneledone boreopacifica*, which has been documented to have a brooding period of 53 months (Robison et al., 2014), making it the longest living known octopus by even the most conservative projection of this animal's full lifespan. Unlike many coastal or shallow water octopuses that reside in protective dens, this species was consistently documented to be brooding out in the open – a strong indication that predators are not a major concern at such oceanic depths (Godfrey-Smith, 2016). The brooding period documented is itself significant, as many shallow water octopuses have a lifespan of approximately one year (Anderson et al., 2002). However, significant variability in lifespan exists between different deep-sea octopus species and between different shallow-water octopus species. This suggests, as expected, that other variables are contributing to these longevity differences other than predation, which is the quintessential example of extrinsic mortality used in discussions involving the evolution of aging. The uncanny intelligence of octopuses paired with their short lifespan also makes them a unique evolutionary puzzle (Godfrey-Smith, 2016), as intelligence is typically associated with reduced extrinsic mortality and longer lifespans (Kirkwood, 2005).

This review summarizes the extant literature both supporting and challenging the three classical evolutionary theories of aging. The role of extrinsic mortality is especially emphasized, as this has been consistently shown to be the predominant variable impacting an organism's evolved lifespan. Other influential variables, such as food availability, fecundity, age-specificity of mortality, and population density, are also discussed. Lastly, we offer new insights which aim to revamp existing evolutionary theories of aging and empower them to coherently integrate all of the existing data. To keep the review a manageable length, we focus on animals with a clear-cut distinction between parents and offspring.

2. Data supporting the classical evolutionary theories of aging

2.1. Field observations and comparative studies

According to the mutation accumulation, antagonistic pleiotropy, and disposable soma theories, we should expect extrinsic mortality and lifespan to be inversely correlated with one another. According to the antagonistic pleiotropy and disposable soma theories, we should also expect to see a trade-off between reproduction and longevity. All three of these theories are compatible with one another and are not mutually exclusive. As such, they can be collectively referred to as classical theories when describing data that supports or contradicts them.

A large array of field data from many different animal species conforms to these classical predictions. Influential work by Steven Austad has shown that an insular opossum population with a four-to five-thousand-year history of insulation showed greater survivorship, reduced litter sizes, slower acceleration of age-specific mortality, and slower aging of tail tendon fibers compared to mainland opossums (Austad, 1993). Unlike the insular environment, opossums in the mainland were subject to greater predation and therefore greater extrinsic mortality (Austad, 1993). In another island study, lifespan in the

extinct, insular bovid *Myotragus balearicus* was ascertained by studying dental durability in fossil samples. Estimated longevity was twice as long as what was predicted given their body mass (Jordana et al., 2012). A separate study investigating fossils of these endemic island goats found that, after settling in an island environment, this animal's brain and sense organs evolved to shrink in size. The reduced brain size and the shrunken sense organs were presumed to be an adaptive strategy to maximize energy use given the lack of predation and the limited availability of trophic resources (Kohler and Moya-Sola, 2004). Bovid longevity increases with sociality for both sexes and this increase is attributed to sociality being a key ungulate strategy to mitigate predation. In only males, bovid longevity was also shown to decrease with male-biased sexual size-dimorphism, an evolutionary trait thought to confer a competitive advantage in contests over mates (Bro-Jorgensen, 2012). These bovid studies conform to classical predications by showing a trade-off between reproduction and longevity and by supporting a causal, inverse link between extrinsic mortality and aging.

Flying animals inhabit a less densely populated ecosystem that is presumed to have less predation and disease compared to the terrestrial environment. Their unique ability to fly also allows them to quickly traverse large swaths of land, thereby granting them access to a much larger food supply. This would be expected to mitigate the risk of starvation as well as allow them to quickly escape hazardous environments. A comparative analysis of longevity among 64 different bat species showed that, on average, a bat's maximum recorded lifespan is 3.5 times longer than that of a land-dwelling placental mammal of similar size (Wilkinson and South, 2002). Many bats, despite their small size, have been documented to live for over 30 years in the wild (Wilkinson and South, 2002). The Brandt's bat can live to at least 41 years (Podlutsky et al., 2005), which is especially noteworthy given that they have a small body mass and that, generally, body size is positively correlated with lifespan (Austad and Fischer, 1991). Among different species of bats, longevity is best predicted by body mass and hibernation. For both hibernators and non-hibernators, longer lifespans are correlated with cave use (Wilkinson and Adams, 2019).

Analogously to bats, birds live about three times longer than an average non-flying mammal of similar size. Despite a rapid metabolic rate and an elevated body temperature, they also show an uncanny resistance to age-related degeneration (Austad, 2011) and an ability to maintain a robust healthspan until the near end of life (Ricklefs, 2010a). It has been suggested that, because of the high aerobic demands of flying, a selection for high aerobic capacity may account for the longer lifespans of birds and bats (Lane, 2011). Notable long-lived examples of birds are the northern fulmar and the Manx shearwater, both of which have a longevity record of 51 years (Austad, 2011). A separate analysis of 271 species of birds found a strongly positive relationship between adult survival rate (i.e., low extrinsic mortality) and relative longevity. Relative longevity was also related to the timing of first reproduction and these two parameters were covaried (Moller, 2006). Across 124 taxonomic families of terrestrial vertebrates, the rate of aging decreases with increasing body mass, age at maturity, gestation period, and possession of flight. Actuarial senescence, or the rate of increase in adult mortality with age, was positively related to extrinsic mortality rate and negatively related to age at maturity and gestation period (Ricklefs, 2010b). Within volant species, lifespan depends on whether the species is active in the day, night, dusk, or dawn and the longest lived birds and mammals tend to be diurnal or nocturnal (Healy et al., 2014). Since fliers active at dusk or dawn would theoretically be predated on by both diurnal and nocturnal predators, this lifespan difference has been thought to stem from disparate rates of predation (Healy et al., 2014).

Among non-fliers, adaptations that would be expected to reduce extrinsic mortality are strongly correlated with boosted longevity. Shattuck and Williams analyzed published data on 776 species and discovered that, assuming common body sizes, arboreal mammals are longer lived than terrestrial animals. This trend was independent of phylogeny and further subclade analyses showed that this trend held true for almost every mammalian subgroup (Shattuck and Williams, 2010). The two exceptions were primates (and their close relatives) and marsupials, both of which experienced a persistent and long evolutionary history in trees prior to transitioning to terrestriality (Shattuck and Williams, 2010). The additional protection from hazards and predators in an arboreal environment further supports the theory that less extrinsic mortality allows for the evolution of longer lifespans. The ability to dig, another trait that could reduce extrinsic mortality levels, is also associated with longer lifespans among terrestrial animals (Healy et al., 2014). In addition, shells and large brains are linked with elongated life and thought to minimize extrinsic mortality sources like predation (Kirkwood, 2005). Theoretically, large brains would be expected to also reduce starvation risk by enabling tool use as well as the ability to obtain and consume more diverse types of food. A detailed analysis is warranted to determine if, akin to traits like flight and arboreality, tool use is positively correlated with longer lifespans.

As a nice illustration of how adaptations that reduce extrinsic mortality are correlated with longer lifespans, the four longest-lived rodents are the eastern grey squirrel, the American beaver, the North American porcupine, and the naked mole-rat (Gorbunova et al., 2008). Squirrels are well known for their ability to deftly evade predators and beavers are the largest rodents in the world that build complex lodges and burrows. Porcupines are massive in size and have the benefit of being covered in sharp, protective quills. They are also adept climbers that spend a portion of their time in trees. Naked mole rats are subterranean, eusocial rodents that live underground in an isolated, dark tunnel environment. All four of these rodents have traits which should increase their odds of surviving to old age (Gorbunova et al., 2008). The naked mole rat, in particular, is a powerful example of an animal that has an incredibly long lifespan for its body size. It also has a remarkable healthspan characterized by negligible senescence, uncanny cancer-resistance, high fecundity until death, and no age-related increase in mortality. Consistent with these traits, genome sequencing of the naked mole rat (*Heterocephalus glaber*) has shown that these animals have unique adaptations in genes involved in cancer resistance, DNA repair, DNA replication, and telomerase function (Kim et al., 2011). While oncogenesis is rare in naked mole rats, it is important to note that they are not completely immune to it. Different forms of cancers have been documented in zoo-housed animals (Delaney et al., 2016; Taylor et al., 2017).

Several studies have explored the link between extrinsic mortality and aging in aquatic animals. In natural populations of sockeye salmon, the fish that showed the slowest progression of senescence were those where brown bears selectively killed fish showing advanced senescence (Carlson et al., 2007). In the live-bearing fish *Brachyrhaphis rhabdophora*, animals in predator environments were found to experience higher overall mortality and proportionally higher adult mortality rates compared to fish from predator-free environments. Within the predator-free environments, the most important life-history stages for population growth occurred late in life. This contrasted with predator environments, where the most important life-history stages for population growth were found early in life (Johnson and Zuniga-Vega, 2009). As would be expected, annual fish of the genus *Nothobranchius* from a dry region were more susceptible to habitat cessation and had shorter lifespans compared to fish from a humid region. Fish from the dry region also accumulated lipofuscin – a pigment that tends to accumulate in organs with age – faster under natural conditions, suggesting that physiological deterioration is more rapid in these animals (Tozzini et al., 2013). Daphnia from temporary ponds exhibit higher juvenile growth, higher early fitness, shorter lifespans, and more rapid senescence compared to daphnia from permanent lakes (Dudycha and Tessier, 1999). A follow-up study found that asexual daphnia clones enjoyed longer lifespans and appeared to age more slowly compared to sexual clones of daphnia, further highlighting a trade-off between aging and fecundity (Dudycha and Hassel, 2013). The African turquoise

killifish (*Nothobranchius furzeri*), which is an emerging animal model for aging research in vertebrates, can enter into a state of damage-resistant diapause in response to external stressors like drought. While in this state, killifish exhibit an exceptional resistance to stress and damage (Hu and Brunet, 2018). This diapause response likely evolved to help survives long droughts, which frequently occur in the habitats of these animals. Interestingly, these fish struggle to survive in a harsh environment and also have one of the shortest – if not the shortest – lifespan among vertebrates (Hu and Brunet, 2018). This association between high extrinsic mortality (i.e., drought) and fast aging lends further credence to traditional predictions.

Clade-focused data from reptiles and amphibians also support classical evolutionary theory. An assessment of 1193 species of non-chemically protected (not venomous or poisonous) and chemically protected (venomous or poisonous) newts, frogs, toads, salamanders, snakes, and fishes revealed that species with chemical protection more frequently exhibited longer lifespans than species without chemical protection (Blanco and Sherman, 2005). This study (Blanco and Sherman, 2005) as well as a later study showed that larger body sizes were positively correlated with lifespan in both amphibians and snakes. In the latter work, maximum lifespan was positively correlated with chemical protection in amphibians but not in snakes. This is potentially due to chemical protection being primarily offensive in snakes and defensive in amphibians (Hossie et al., 2013). Larger body size and chemical protection would both be expected to result in a reduction in predation. Further supporting classical expectations, western terrestrial garter snakes from a low-predation meadow environment evolved longer lifespans than those from a high-predation lakeshore environment (Robert and Bronikowski, 2010). Compared to the short-lived snakes, the long-lived snakes were smaller in size, repaired DNA damage more efficiently, harbored more efficient mitochondria, and had more robust cellular antioxidant defenses. Short-lived snakes from the high-predator lakeshore environment grew faster, matured earlier, and had larger litter sizes compared to long-lived snakes from the low-predator meadow environment (Robert and Bronikowski, 2010).

In humans, mortality data from historical cohorts and subsistence populations from England/Wales and Sweden reveals that slower actuarial aging is associated with reduced extrinsic mortality in longitudinal samples (Gurven and Fenelon, 2009). Using longitudinal demographic records in Utah, it was shown that human reproductive rates have declined over time. As these rates have declined, female lifespan has increased. In contrast, male lifespan has remained largely stable. Since only women pay a major cost to reproduction, it has been theorized that the additional longevity of women in this cohort is a result of reduced reproductive costs (Bolund et al., 2016). A more recent study by Helle did not find strong evidence for a trade-off between post-reproductive mortality and lifetime reproductive effort in a large dataset of 6594 women from pre-industrial, northern Sweden (Helle, 2018). Separate work analyzing fertility and longevity in 6359 women born in the Netherlands between 1850 and 1910 did not find evidence for an initial linear trade-off between these variables (Kaptijn et al., 2015). Prior to any of these mentioned studies, a literature review collated the existing data and assessed whether or not there was a cost for reproduction in human beings. The author concluded that, under natural fertility conditions, longevity and fertility are not inversely correlated. However, some evidence suggests that mortality slightly increases when women have more than five children in modern populations (Le Bourg, 2007). Given the complexity of human culture and its introduction of many confounding variables, it is important to emphasize how challenging it is to assess the relationship between lifespan and mortality in human beings.

2.2. Laboratory studies

Most laboratory studies investigating the evolution of aging have done so in fruit flies. Much like the comparative and field studies discussed above, the bulk of the data indicates that extrinsic mortality and intrinsic mortality (i.e., rate of aging) are negatively correlated and that there is a trade-off between reproduction and longevity.

Work by Stearns et al from 1998 found that artificially increasing extrinsic mortality rates in *Drosophila melanogaster* led to the evolution of shorter lifespans and higher intrinsic mortality rates. 90% or 20% of flies in a cage were killed and replaced each week for the high adult mortality and low adult mortality conditions, respectively (Stearns et al., 1998). Flies subjected to high adult mortality developed faster, hatched at a smaller size, and laid more eggs early in life (Stearns et al., 1998). A subsequent paper by Stearns et al confirmed that higher intrinsic mortality rates and shorter lifespans evolve in response to higher extrinsic mortality. An elevated mortality rate also decreased the age and size at eclosion and shifted peak fecundity to earlier in life. Both larval density and food quality were tweaked during this experiment (Stearns et al., 2000). For both of these studies, population densities were maintained at a constant level by replacing deceased flies under both low- and high-mortality conditions (Stearns et al., 1998, 2000). Separate work by Gasser et al showed that high adult mortality impacted ovariole number, growth rate, and life-body size but did not affect desiccation resistance, starvation resistance, activity, metabolic rate, viability, or body composition (relative fat content). More specifically, there were more functional ovarioles, life-body size was smaller, and growth rate was higher in flies subjected to higher extrinsic mortality (Gasser et al., 2000).

While only a handful of studies have explicitly studied the role of extrinsic mortality in the evolution of aging using flies in the laboratory, several projects have investigated the trade-off between fecundity and aging. Work by Michael Rose has shown that culturing fly populations at later ages (i.e., only allowing surviving older females to reproduce) increases female longevity, enhances late fecundity, and depresses early fecundity (Rose, 1984). Partridge et al bred *Drosophila* from either old or young adults to generate flies that were longer-lived and shorter-lived, respectively, and showed that flies bred from older adults evolved an increase in survival and a decline in early life fertility. No increase in late-life fertility was observed and no correlated responses to selection were observed in larval competitive ability, adult size, or development time (Partridge et al., 1999). Rose and Charlesworth reported that a selection for late fecundity extended female longevity, increased the duration of female reproduction, decreased mean egg-laying rate, and decreased early fecundity (Rose and Charlesworth, 1981). This trade-off between aging and fecundity in flies bred for longevity is further corroborated by data presented by Luckinbill et al (Luckinbill et al., 1984). In a separate study presented by Luckinbill and Clare, the selection of late-life reproductive success required a high larval density. No obvious effect on the evolution of aging was observed when larval density was held low (Luckinbill and Clare, 1985). A more recent paper published in 2015 further confirmed a trade-off between reproduction and aging in *D. melanogaster* by demonstrating that females with a genetic propensity to mate more often live shorter lives (Travers et al., 2015). Important work by Sgrò and Partridge has shown that the sterilization of female flies either by the ovo^{D} mutation or by x-ray irradiation reduces age-related mortality (Sgro and Partridge, 1999). While this list is by no means comprehensive, it serves to show that a trade-off between aging and fecundity is well documented in fruit flies.

In experiments with the freshwater snail *Physa acuta*, snails were reared in the absence or presence of chemical cues from predatory crayfish and mated either early in life or late in life. Both predation risk and age reduced overall reproductive success and this reproductive decline was three times faster under predation risk conditions compared to the no-predator condition. While this initially appears to challenge predictions made by classical theories, this decline in reproductive success was due to a negative effect on post-hatching survival (Auld and Houser, 2015). Therefore, less overall reproduction appeared to occur due to reduced survival rates and a shorter period of

time being available for reproduction. This work highlights the imperative role predation plays in the evolution of aging as it shows that, independent of actual extrinsic mortality, the mere threat of predation is sufficient to affect survival and reproduction. A 2016 study from the same research group compared snails that were either allotted or excluded the offer to mate with an unrelated partner. Mated snails experienced a significant reduction in survival probability, a finding the authors interpreted as a result of shifting resource allocation (Auld et al., 2016). Mate availability was separately shown to reduce final size and juvenile growth rate (Auld and Relyea, 2008). Overall, these experiments bolster classical theories by highlighting mechanistic trade-offs between growth, aging, and fecundity.

Weaver ants are eusocial insects where major, large workers perform risky tasks outside the nest while minor, small workers reside in a highly protected arboreal nest. To assess whether or not intrinsic aging differed between small and large workers, Chapuisat and Keller established experimental colonies of *Oecophylla smaragdina* weaver ants that were collected from Townsville, Queensland, Australia (Chapuisat and Keller, 2002). They discovered that the minor workers from the arboreal, nested environment lived significantly longer than the major workers that performed work outside of the nest (Chapuisat and Keller, 2002). In the larger insect *Melanoplus sanguinipes*, grasshoppers from different populations that occur along an altitudinal gradient in the Sierra Nevada in California were reared in two different thermal culture conditions. Mortality rates increased with age at each temperature and, for each condition, grasshoppers originating from low-elevation populations enjoyed longer lifespans and lower mortality rates than their counterparts from higher elevations. Elevated sites would theoretically be marked by more severe and sudden winter conditions, which could be a source of extrinsic mortality that would explain the observed differences in survival (Tatar et al., 1997).

In the nematode *Strongyloides ratti*, there are distinct free-living and parasitic adults. Rat intestine-dwelling parasitic adults have a maximum reported lifespan of 403 days while soil-dwelling parasitic adults have a maximum reported lifespan of five days. This 80-fold difference in lifespan is presumed to be due to different rates of extrinsic mortality in the intestine and soil (Gardner et al., 2006). In *Caenorhabditis elegans* nematodes, the partial loss of function of the insulin receptor-like protein DAF-2 extends lifespan but results in a heavy fitness cost. DAF-2 mutant worms go extinct more rapidly and show a significant reduction in early fertility (Jenkins et al., 2004). In this same nematode species, a mutation in the *age-1* gene that extends lifespan in *C. elegans* did not have any fitness cost under standard laboratory conditions. When subjected to starvation cycles that could mimic field conditions, however, a fitness cost was revealed in this long-lived mutant (Walker et al., 2000). This is similar to a study done in *Drosophila*, where mutation of the *Indy* gene generates long-lived flies and decreases the slope of the mortality curve, thereby appearing to slow the rate of aging. Under the condition of a decreased-calorie diet, long-lived mutants displayed reduced fecundity. Under standard feed conditions, no reduction in age-specific fecundity was observed (Marden et al., 2003). Data from these latter two studies indicate that standard laboratory conditions may hide significant trade-offs between aging and fitness. If a trade-off is not observed under standard laboratory conditions, various stressors should be tested to determine if there is indeed a fitness cost associated with an extended lifespan.

3. Data challenging the classical evolutionary theories of aging

3.1. Field observations and comparative studies

A significant paper defying standard predictions comes from the Austad laboratory. In this paper, Nussey et al presented evidence of senescence in the wild in 175 different animal species from 340 studies. The evidence of senescence in natural populations of mammals, birds, other vertebrates, and insects (Nussey et al., 2013) suggest that aging may not be exempt from natural selection as much as has been historically assumed. Some field data also do not suggest an inverse relationship between extrinsic mortality and lifespan. Despite its assumed ability to decrease extrinsic mortality, foraging group size was not correlated with maximum longevity in a sample of 421 North American birds. Body mass did, however, increase with longevity in non-passerine birds (Beauchamp, 2010). Although group size would be expected to reduce an individual's risk of predation, a separate analysis of 253 mammalian species found group size to be a poor predictor of maximum longevity across all mammals as well as within rodents and primates. A weak, yet significant group-size effect in the negative direction was found for artiodactyl longevity (Kamilar et al., 2010).

With regards to reproduction, no evidence for a trade-off between self-maintenance and reproduction was observed in the long-lived seabird *Sterna hirundo*, even in old age (Apanius and Nisbet, 2006). Broadly speaking, queens in eusocial colonies with their high longevity and high fecundity defy the traditional prediction of a trade-off between aging and reproduction (Flatt and Partridge, 2018). Similarly defiant of classical expectations, breeders live significantly longer than helpers in social African mole-rats (Dammann et al., 2011). Naked mole rats maintain high reproductive potential throughout old age and, in the Blanding's turtle and the painted turtle, older females lay more eggs and have more consistent annual reproduction than younger adults (Finch, 2009). Impressive work by Jones et al highlights the diversity of animal life histories by contrasting age patterns of mortality and reproduction for 11 mammals, 12 other vertebrates, 10 invertebrates, 12 vascular plants, and a green alga (Jones et al., 2014). The authors show that virtually every combination of mortality and fertility patterns is possible, including bowed, humped, decreasing, constant, and increasing trajectories for both short-lived and long-lived species (Jones et al., 2014). These data make it clear that fecundity and aging can relate to each other in many different ways. Future research should aim to understand what circumstances give rise to the mélange of life history trajectories that exist in nature.

3.2. Laboratory studies

Seminal work directly challenging classical predictions comes from data on guppies from David Reznick and his collaborators. Guppies (*Poecilia reticulata*) in streams were found to have significantly higher predation rates than guppies by waterfalls, where predators are often excluded. Predators increase the guppy mortality rate of all age and size classes and, within the low-predation waterfall site, the odds of surviving for six months is 20–30 times higher than in the high-predation stream site (Reznick et al., 2001a, 1996). High predation localities tended to have higher levels of food availability compared to the low predation localities. Concomitant with this reduction of food availability, guppies from low predation localities had smaller asymptotic body sizes and lower growth rates (Reznick, 1982; Reznick et al., 2001b). In their impactful 2004 *Nature* paper, Reznick et al reared guppies from high predation and low predation localities in the laboratory. As would be expected from classical predictions, high predation guppies reproduced more frequently, produced more offspring in each litter, and matured at a significantly earlier age (Reznick et al., 2004). In addition to having an earlier maturation age, they also ceased reproduction at a later age and sustained a higher rate of offspring production throughout their life. Unexpectedly, guppies from high predation localities enjoyed a lower rate of aging and longer total lifespans. Using a fast start escape response assay to asses neuromuscular performance, it was found that high-predation guppies were significantly faster than low-predation guppies while young but were statistically similar while old. As such, a more rapid age-related deterioration of physiological performance was observed in high-predation guppies. All fish, regardless of predation risk, showed a decrease in neuromuscular performance with age, making this a good marker of guppy senescence (Reznick et al., 2004). In a follow-up study in guppies

from low-predation environments, density manipulation experiments were performed to see if guppies were sensitive to density regulation. Decreased population density resulted in decreased juvenile mortality rates, increased juvenile growth, and an increased reproductive investment by adult females. Increased population density led to increased adult mortality, decreased fat storage by adult females, and reduced offspring size (Reznick et al., 2012).

Another pioneering study defying classical expectations was performed by Chen and Maklakov in the nematode *Caenorhabditis remanei* (Chen and Maklakov, 2012). Although they found that random mortality selected for the evolution of shorter lifespans, they discovered that heat-induced mortality selected for the evolution of longer lifespans. This condition-specific mortality source slows, immobilizes, or kills worms and only the healthiest survivors were therefore transferred to the next generation. Irrespective of the mortality source used (condition-specific vs. random), increased mortality rates resulted in the evolution of females with increased fecundity. Under the conditions tested, the condition-specific lifespan extension was not initially associated with a reproductive trade-off. Nematodes are naturally exposed to higher temperatures and, since increased temperature is associated with increased immunity and thought to increase the proportion of vigorous individuals in the population, the authors theorized that the heat condition uniquely selected for robust, fit individuals (Chen and Maklakov, 2012). While female fecundity was increased in response to increased extrinsic mortality, follow-up work from the Maklakov laboratory discovered that condition-specific mortality resulted in reduced early life and net reproduction in males (Chen et al., 2016). Regardless of the extrinsic mortality source used (random or condition-dependent), the TOR inhibitor rapamycin was able to additively extend lifespan. This would suggest that the evolution of longer lifespans in heat-stressed nematodes occurs, at least partially, via a route independent of the nutrient sensing TOR pathway.

For comparison, a new source of condition-specific mortality was applied in these worms that selected for faster-moving male individuals. Immobilized females were utilized as a pheromone source and only the first 20% of males that arrived at the pheromone spot were maintained in the population and allowed to reproduce. Using this conditional mortality regime, a new population evolved where male chemotaxis was more rapid compared to males evolved under random mortality. Unlike random mortality, where longevity decreased, male longevity evolved to increase in the condition-specific population. Compared to the random mortality condition, male mating proficiency was increased under the condition-specific mortality condition (Chen and Maklakov, 2014). Interestingly, *C. remanei* females are both the shorter-lived sex and the sex with higher learning ability. Young females more rapidly learn a novel association between bacterial food and the odor butanone. Female offspring production and learning ability decline rapidly with age while these traits are maintained at high levels until mid-age for males (Zwoinska et al., 2013). Haphazard extrinsic mortality erodes the sex-based aging difference in these nematodes, where males typically live longer than females (Chen and Maklakov, 2014). These data suggest complex trade-offs between aging, reproduction, movement, and learning ability in *C. remanei*. More broadly, these data indicate that gender roles play an important role in the evolution of aging.

These significant studies in guppies and nematodes make it clear that, contrary to classical predictions, an increase in extrinsic mortality can select for the evolution of longer lifespans (Chen and Maklakov, 2012, 2014; Reznick et al., 2004). While these data corroborate the imperative role extrinsic mortality plays in guiding the evolution of aging, they also make it clear that condition-specific mortality can have distinct effects compared to random mortality. Condition-specific mortality can select for individuals that have more robust internal repair mechanisms, thereby resulting in the evolution of longer life. Moreover, under a regime of a more haphazard mortality (i.e., predation), there are specific conditions that can allow for the evolution of longer lifespans despite an increase in a mortality source. Data from guppies suggest that factors like food availability and population density interact closely with parameters like predation, aging, and fecundity. More specifically, higher rates of predation can decrease the population size, thereby increasing the total number of resources available to each individual.

In our previous stochastic modeling study (Shokhirev and Johnson, 2014), we used a simulated annealing approach to predict what factors might allow for the evolution of longer or shorter lifespans in response to increased predation. When mating costs were relatively low and food was relatively scarce, we found that shorter lifespans evolved in response to increased predation. Conversely, longer lifespans were able to evolve in response to higher extrinsic mortality if energy was available in excess and if the cost of mating was relatively high. We also found that an elevated rate of predation decreased the total population size, increased the shared resource pool, and redistributed energy reserves for mature individuals (Shokhirev and Johnson, 2014). Data from guppies appears to match the predictions of our computational model. High predation guppy localities had an enlarged food supply compared to low predation localities (Reznick, 1982; Reznick et al., 2001b). Likewise, population density was a critical parameter that had to be tinkered with to successfully select for the evolution of longer lifespan in laboratory fruit flies (Luckinbill and Clare, 1985). Population density was also shown to be a potent regulator of mortality, growth, reproduction, size, and fat storage in guppies (Reznick et al., 2012). With regards to the relative cost of mating, guppies are promiscuous fish in which females receive no material benefits and males provide no resources (Evans and Magurran, 2000). In particular, mating increases a female's vulnerability to both predation and parasites as well as leads to a reduction in foraging efficiency (Evans and Magurran, 2000). As predicted by our stochastic model (Shokhirev and Johnson, 2014), a good argument could be made that there is a relatively high cost of mating in these fish.

There are several laboratory studies that challenge the classical assumption of a trade-off between aging and fecundity. In *Cardiocondyla obscurior* ants, for example, queens from single- and two-queen colonies enjoyed both higher fecundity and boosted longevity compared to queens living in associations of eight queens under similar levels of extrinsic mortality (Schrempf et al., 2011). A positive relationship between longevity and reproductive success also exists in reared wild-caught queens from the bumblebee *Bombus terrestris audax* (Lopez-Vaamonde et al., 2009). Combined chemostat cultures containing rotifers from ephemeral and permanent hydroperiods enjoy a 56% increase in asexual fecundity and a 23% decrease in the rate of aging (Smith and Snell, 2014). In daphnia reared from lakes either with or without the predator anadromous alewife, daphnia from predator-containing lakes generated significantly more offspring throughout their lifetime. However, no differences in survival or in age-related declines in fertility were observed (Walsh et al., 2014). In two different mosquito species, transgenically increasing *Akt* signaling not only extended lifespan but also increased yolk protein production (Arik et al., 2015). Although egg production was not significantly impacted, the increase in yolk protein suggests that this aging intervention may offer a mild reproductive benefit in addition to boosting longevity. As an additional indicator that reproduction is not always at odds with aging, neither laser ablation of the entire gonad nor complete sterilization of the already long-lived, fertility-impaired *daf-2* mutant results in life extension in *C. elegans* (Flatt, 2011). Wit et al did not identify a trade-off between early fecundity and lifespan in their longevity selection lines and instead found that females had analogous or higher fecundity throughout life compared to controls. Long-lived flies were also more starvation-resistant (Wit et al., 2013). Similarly, flies with recombinant genotypes have been documented to exhibit an elevation in both longevity and early fecundity (Khazaeli and Curtsinger, 2013). It is important to note that, for any of these studies, a currently unknown trade-off involving reproduction may exist under certain conditions

Table 1
Mean and maximum lifespans of different octopus species.

Octopus Species	Mean Lifespan or Lifespan Range (Months)	Maximum Lifespan (Months)	*N*	Environment	Lifespan Measurement Tool	Reference
Graneledone boreopacifica	≥53	~132.5-212*	1 (female)	Deep sea (observed in the wild, 1397 m deep)	Remote-operated vehicle visits	(Robison et al., 2014)
Enteroctopus dofleini	~54-60**	~60**	NR	NR	NR	(High, 1976)
Bathypolypus arcticus	~36***	≥36***	18	Laboratory flow-through system	Laboratory monitoring	(Wood et al., 1998)
Octopus tetricus	Females: 10.0 Males: 11.2	Females: 17.8 Males: 22.3	Females: 1108 Males: 2384	Collected from a developmental octopus fishery	Stylet weight analysis	(Leporati and Hart, 2015)
Octopus tetricus	Females: 11.5 Males: 11.8	Females: 17.8 Males: 19.8	Females: 732 Males: 2058	Collected from the wild (5-40 m deep)	Stylet weight analysis	(Leporati et al., 2015)
Octopus pallidus	Females: 8.0 Males: 8.5	Females: 15.6 Males: 19.4	503 (409 females and 94 males)	Collected from the wild (26 m deep)	Stylet increment analysis	(Leporati et al., 2008)
Octopus pallidus	8.7	NR	28	Collected from the wild (12-30 m deep)	Stylet increment analysis	(Doubleday et al., 2008)
Octopus cyanea	1.6-10.3	~18	102	Collected from the wild (< 0.6 m deep)	Stylet increment analysis	(Herwig et al., 2012)
Octopus bimaculoides	~15-17	~≥17	40	Closed recirculating seawater systems	Laboratory monitoring	(Forsythe and Hanlon, 1988)
Eledone cirrhosa	Females: 11.2, 10.4**** Males: 8.9, 7.9****	Females: ~17 Males: ~14	122 (60 females and 62 males)	Collected from the wild	Stylet increment analysis	(Regueira et al., 2015)
Octopus tetricus	Females: 2.8-10.1 Males: 2.9-10.3	~11	214 (103 females and 111 males)	Collected from the wild (35-46 m deep)	Stylet increment analysis	(Ramos et al., 2014)
Macroctopus maorum	2.3 – 7.3	7.3	147	Collected from the wild (~ < 20 m*****)	Stylet increment analysis	(Doubleday et al., 2011)

NR = Not reported.
* Maximum lifespan is estimated given known brooding periods and lifespans of other species. The single observed octopus was still alive at the end of the published study.
** Estimated based on the author's personal communications.
*** Estimated based on the observed brooding period as well as prior published data.
**** Two different means are reported and reflect results from two different fishing grounds.
***** Value obtained via personal correspondence with the corresponding author of Doubleday et al., 2011.

3.3. Octopus longevity

Octopuses pose an interesting challenge for the evolution of aging (Godfrey-Smith, 2016) by both bolstering and defying traditional expectations. A comparison of maximum lifespans between different octopus species (Table 1) conforms to the standard predictions of the mutation accumulation, antagonistic pleiotropy, and disposable soma theories. Maximum longevity varies wildly among different species (Table 1) and can fluctuate anywhere from ~7 months to 11+ years (Doubleday et al., 2008, 2011; Forsythe and Hanlon, 1988; Herwig et al., 2012; High, 1976; Leporati and Hart, 2015; Leporati et al., 2015, 2008; Ramos et al., 2014; Regueira et al., 2015; Robison et al., 2014; Wood et al., 1998). Most of the species with documented lifespans have maximal longevities hovering around 1.5 years (Table 1). Of those studied, the longest-lived species are either deep-sea dwellers like *G. boreopacifica* (Robison et al., 2014) and *Bathypolypus arcticus* (Wood et al., 1998) or are atypically large in size like the giant pacific octopus *Enteroctopus dofleini* (High, 1976). As we have already discussed, both deep-sea dwelling and increased size are associated with reduced extrinsic mortality. Relevantly, the longest brooding period documented for any animal – terrestrial or aquatic – was in the deep-sea octopus *G. boreopacifica*. Via repeated remote-operated vehicle visits, a single female was documented to brood for 53 continuous months. The previous octopus brooding record was 14 months and was laboratory-documented in the deep-sea octopod *B. arcticus* (Wood et al., 1998). The estimated lifespan for *B. arcticus* is approximately three years (O'Dor and Macalaster, 1983), which is ~2.5X greater than the recorded brooding stage. Applying this same scaling to *G. boreopacifica*, these longer brooders would be expected to live for ~11 years, making them the longest-lived known octopods. Other octopus species brood for about a quarter of their lifespan (Robison et al., 2014), which would mean that *G. boreopacifica* could theoretically live for over 17 years. Interestingly, the brooding mother was never documented to eat during any of the remote-operated vehicle visits and ignored pieces of crab that were offered to her (Robison et al., 2014). It has been previously theorized that the life-extending effects of caloric restriction (Balasubramanian et al., 2017) evolved as an adaptation to better cope with periods of famine (Kirkwood and Shanley, 2005). In addition to reduced predation, this suggests that food availability and food consumption may contribute to this animal's unique life history.

Although large brains are typically associated with longer lifespans (Kirkwood, 2005), most octopus species are unique, short-lived outliers that possess an uncanny intelligence as well as a remarkable capacity for problem-solving. A typical octopus nervous system will contain about 500 million nerve cells, which is approximately a tenfold increase over the ~50 million neurons found in mice, a fivefold increase over the ~100 million neurons found in rats, and a fourfold decrease compared to the ~2000 million found in rhesus monkeys (Hochner, 2008). A close mammalian counterpart with regards to neuronal density would be the marmoset monkey, a small primate with approximately 590 million neurons (Herculano-Houzel et al., 2007) that can live over 16 years (Tardif et al., 2011). Given that the nervous system of these cephalopods is structured in a radically different way compared to mammalian vertebrates and that their nervous system is poorly understood (Godfrey-Smith, 2016), looking at neuronal count alone may underestimate their actual intellectual capacity. Suggestive of their intelligence, octopuses have been documented to engage in diverse tool use, such as the repurposing of rocks and sand to barricade lair entrances (Mather, 2009). More impressively, octopuses have been documented to carry coconut shell halves and assemble them for shelter when needed. These coconut-carrying octopuses had innovated an awkward, vulnerable method of locomotion to carry the shells while moving, indicating that they were carrying them with the intent of future strategic use (Finn et al., 2009). Further highlighting their unique intellect, octopuses utilize a range of visible displays and signals to communicate with other octopuses (Scheel et al., 2016). Additional work should be done to understand what evolutionary circumstances could have selected for both extreme intelligence and short lifespans in these species. Further confounding the traditional association with longevity and intelligence (Kirkwood, 2005), a recent paper reported that large-brained guppies have lifespans that are 22% shorter compared to small-brained guppies. The authors theorize that the energetic requirements of a larger brain may divert resources away from somatic maintenance (Kotrschal et al., 2019). Thus, it appears we need to broaden our overall understanding of the relationship between intelligence, brain size, and aging.

4. Extreme longevity and potential immortality in the animal kingdom

4.1. Known animals with extreme longevity

Just as there are longevity minimalists – like the mayfly with a lifespan less than two days (Carey, 2002) – there are also rare animals that exhibit extreme longevity. Any similarities among complex animals with atypically long lifespans should reveal something of significance about the evolution of aging. More precisely, it should teach us what circumstances might give rise to such exceptional lifespans.

At the time of writing this review, the longest-lived vertebrate is the Greenland shark (*Somniosus microcephalus*), a large predatory species of the Arctic seas that grows larger over time and has been reported to attain body lengths and masses up to 6.4 m and 1023 kg, respectively. These sharks have been observed both inshore in shallow waters as well as at abyssal depths > 1200 m (MacNeil et al., 2012). Using radiocarbon dating of eye lens nuclei from 28 female sharks, the age of sexual maturity was estimated to be at least 156 ± 22 years old. The largest animal in the study (5.02 m) was estimated to be 392 ± 120 years old (Nielsen et al., 2016). Based on available data for *S. microcephalus* the gestation period has been estimated to be between 8 and 18 years (Augustine et al., 2017). Average ventral aortic blood pressure in these large fish has been estimated to be about 2.3–2.8 kPa, which is much lower than what has been reported in other sharks. Relative to other shark species, *S. microcephalus* are slower moving and are thought to have a relatively low aerobic metabolism (Shadwick et al., 2018). Within the red blood cell-producing Leydig's organ, high chitinase and lysozyme activities were reported in *S. microcephalus* (MacNeil et al., 2012). This suggests that their immune system may be especially robust, which is relevant since the immune system is known to play an important role in aging (Lopez-Otin et al., 2013). For example, flies selected for old age survive fungal, bacterial, and viral infections significantly better than shorter-lived control flies. Similarly, silencing the Toll pathway antagonist *cactus* reduces *Drosophila* lifespan whereas conditional knockdown of the *Toll* receptor extends *Drosophila* lifespan (Fabian et al., 2018).

Before the aging estimates were published for the Greenland shark (Nielsen et al., 2016), the bowhead whale (*Balaena mysticetus*) was a contender for the longest-lived vertebrate and is currently the longest-lived mammal. These whales can weigh up to 100 tons (Keane et al., 2015) and grow as long as 20 m (Nerini et al., 1984). They reach sexual maturity around 25 years (George et al., 1999) and have a gestation period of approximately 13 months (Nerini et al., 1984). By applying the aspartic acid racemization technique to eye globes, age estimates for 42 different bowhead whales indicated that these animals could live as long as 211 years (SE 35 years). Two other especially long-lived whales in the cohort had lifespans estimated to be 172 (SE 29 years) and 159 (SE 27 years). Very few of the whales examined exhibited any signs of obvious pathology (George et al., 1999), which was a noteworthy observation corroborated by a prior report noting that *B. mysticetus* seem atypically free of pathology compared to other species (Philo et al., 1993). The analyzed transcriptome of this cold-adapted baleen whale species was reported in 2014 by Seim et al and, highly relevant to aging biology, changes associated with altered insulin

signaling were found (Seim et al., 2014). Not long afterwards, work spearheaded by the João Pedro de Magalhães laboratory succeeded in sequencing the bowhead whale genome (Keane et al., 2015). Two transcriptomes from different populations were also generated. Numerous mutations in genes linked to cancer and aging were found in addition to gene loss and gain involving genes associated with aging, cancer, cell-cycle, and DNA repair. Changes in genes related to dietary adaptations, sensory perception, immune response, and thermoregulation were also reported. Specific, prominent examples include unique changes in the excision repair gene *ERCC3* and the proteins ERCC1 (involved in nucleotide excision repair), HDAC1 (involved in histone deacetylation), and HDAC2 (involved in histone deacetylation) (Keane et al., 2015). Despite having a body size massively larger than any primate, the lack of correlation between mass and cancer additionally indicates that these larger mammals have evolved especially robust anti-cancer machinery (Caulin and Maley, 2011). This machinery likely overlaps with the same mechanisms that result in this mammal's uniquely long lifespan. Naked mole-rats exhibit an analogous, unique resistance to cancer and these long-lived rodents show positive selection for genes associated with autophagy, inflammation, translation, metal ion homeostasis, and cellular respiration (Sahm et al., 2018).

Yet another oceanic animal that inhabits cold arctic waters, the quahog clam *Arctica islandica* is a bivalve mollusk with a remarkable ability to save energy as well as tolerate long periods of anoxia and hypoxia (Strahl et al., 2011). By assessing annual growth increments in the shells of these bivalve clams from the marine environment north of Iceland, Butler et al identified numerous clams with lifespans exceeding 300 years and a single clam with a lifespan of 507 years (Butler et al., 2013). *A. islandica* are a small animal that grow larger as they age and can exceed 118 mm in length (Kilada et al., 2007). One study comparing weights reported that the largest clam within their sample set weighed 90.8 g (Stott et al., 2010). Work from the Austad laboratory has shown that growth rates, development, and maximum shell size all associate with longevity in various species of bivalve mollusks, including *A. islandica* (Ridgway et al., 2011). A comparison between long-lived *A. islandica* and shorter-lived *Mercenaria mercenaria* clams revealed that *A. islandica* have a lower protein carbonyl concentration in gill tissue, an increased resistance to oxidative stress-induced mortality, and an increased resistance to oxidative stress-induced cell death (Ungvari et al., 2011). A separate study compared the mud clam *A. islandica* to four other shorter-lived sympatric bivalve mollusks with reported longevities of 28, 37, 92, or 106 years. The susceptibility to peroxidation of membrane lipids, which is a marker of oxidative stress damage, decreased with increasing longevity and was significantly lower for *A. islandica*. This decrease was faster for the mitochondrial membrane compared to other cell membranes (Munro and Blier, 2012), which is of note given that mitochondrial dysfunction is a hallmark of aging (Lopez-Otin et al., 2013). Several other papers have corroborated these data by showing that, compared to shorter-lived bivalve mollusks, *A. islandica* have especially robust mechanisms to deal with oxidative stress (Ungvari et al., 2013), produce less mitochondrial H_2O_2 (Munro et al., 2013), and show superior proteome stability (Treaster et al., 2014). They also appear to stably maintain their telomeres irrespective of age (Gruber et al., 2014). Compared to other bivalve mollusks, *A. islandica* are thought to reach sexual maturity at later date. A study of annual internal growth banding in the shells of 39 small clam specimens found that the age of sexually immature clams ranged from four to 14 years (Thompson et al., 1980). These data would indicate that *A. islandica* reach sexual maturity around 15 years of age. A more recent study, however, has suggested that they become sexually mature around 5.8 years of age (Ballesta-Artero et al., 2019).

According to individual-based models paired with size measurements, vestimentiferan tubeworms are another animal thought to be able to live for multiple centuries (Durkin et al., 2017). The cold, deep-sea species *Escarpia laminata* is local to the Gulf of Mexico and inhabits resource-rich seeps between approximately 1000 m and 3300 m deep. According to predictive results from one study, these tubeworms enjoy low mortality rates and regularly achieve lifespans greater than 100 years. Some individuals appear capable of surviving longer than 300 years (Durkin et al., 2017). The vestimentiferan tubeworm species *Seepiophila jonesi* and *Lamellibrachia luymesi* have also been reported to be able to survive for multiple centuries (Cordes et al., 2007). These large worms can grow longer than two meters (Cordes et al., 2007) and do not weigh very much. According to one study, the largest specimen of *Lamellibrachia* collected had a wet weight of 10.2 g, excluding the tube (Duperron et al., 2009). In addition to the deep habitat providing greater stability and less predation compared to shallower waters, cold seeps steadily release resource-rich fluids from the seafloor for thousands of years. These fluids are rich in hydrogen sulfide and/or methane, which allow microbes to flourish. These microbes provide an invaluable energy source for, and are symbiotic with, vestimentiferan tubeworms (Durkin et al., 2017). It is currently unknown how long it takes these slow-aging tubeworms to reach sexual maturity. The faster-growing *Riftia pachyptila* species can reach lengths of 1.5 m and sexual maturity in two years (Lutz et al., 1994). It would be interesting to know whether or not sexual maturity is significantly delayed in the long-lived tubeworms *E. laminata*, *S. jonesi*, and *L. luymesi*.

The rockfish and giant tortoise are also worthy of mention. The maximal lifespan reported for the deeper-dwelling rougheye rockfish *Sebastes aleutianus* is 205 years. Concordant with evolutionary theory, rockfish lifespan increases exponentially with maximum depth of occurrence. The 205 year-old rockfish identified had a recorded depth of 874 m (Cailliet et al., 2001). Based on recorded ages of sexually mature and immature fish, the rougheye rockfish reaches sexual maturity around 19 years of age (Bruin et al., 2004). Giant tortoises can live in excess of 100 years (Quesada et al., 2019) and are thought to be able to live for almost 200 years (Rando, 2006). Unverified age estimates suggest that some individuals may be capable of surviving beyond 200 years. More precise measurements of age are warranted and would be valuable for better understanding the life history of these massive reptiles. Per an assessment in the Aldabra giant tortoise, sexual maturity develops late and occurs in females around 17–23 years. These animals also exhibit a rapid reproductive response to rainfall (Swingland, 1977), a reaction which suggests that their slow aging may be an evolutionary adaptation that allows them to wait out lengthy periods of scarcity. Of relevance, tortoises and turtles are both known for their atypical life histories. Both the Blanding's turtle and the painted turtle become more fecund with age (Finch, 2009) and, for the desert tortoise *Gopherus agassizii*, mortality rates decline with age up until death (Jones et al., 2014). Very recent genome sequencing of the giant tortoise species *Chelonoidis abingdonii* and *Aldabrachelys gigantea* revealed lineage-specific variants affecting genes related to cancer development, inflammatory mediators, and DNA repair (Quesada et al., 2019). These unique investments in repair and maintenance mechanisms are similar to the previously mentioned genomic findings in the bowhead whale (Keane et al., 2015) and the naked mole rat (Sahm et al., 2018).

What do these longevity extremists have in common? A comparison of sexual maturation, gestation, lifespan, length, size, and ecology helps to shed light on how slow aging evolved in these animals (Table 2). The Greenland shark, bowhead whale, and giant tortoise are all uniquely large animals that experience little to no predation due to their size and ecology. The rockfish, vestimentiferan tubeworm, and the Greenland shark can all inhabit deeper waters which are less populated, more stable, and colder compared to more shallow waters. Like the Greenland shark and the bowhead whale, the ocean quahog clam also inhabits colder arctic waters. Unlike the other long-lived animals, it is very small in size but exhibits the longest lifespan of the group. In the study that discovered the 507 year old clam, the studied clams were harvested at a relatively shallow depth of 81–83 m (Butler et al., 2013). Thus, neither size nor oceanic depth is a good explanation for *A. islandica's* exceptional longevity. Either due to its hard, protective shell or

Table 2
Aging, reproduction, and size in animals with extreme longevity.

Animal Species	Age at Sexual Maturity (~Years*)	Gestation Period (~Months*)	Maximum Lifespan (~≥ Years*)	Maximum Length (≥ m*)	Maximum Weight (≥ kg*)	Ecology
Ocean quahog clam	5.8-15	N/A	507	0.118	0.0908	North Atlantic Ocean (including Arctic waters)
Greenland shark	156	8-18**	392	6.4	1023	Arctic seas (shallow water + deep sea)
Vestimentiferan tubeworm	Unknown	N/A	300	2.0	0.0102***	Deep sea seeps
Bowhead whale	25	13	211	20	101,605	Arctic and sub-Arctic waters
Rougheye rockfish	19	N/A	205	0.50	2.0	North Pacific Ocean (including deeper water)
Giant tortoise	17-23	N/A	200****	1.3	120	Tropical islands

N/A = Non-applicable.
* All values included are taken from the relevant papers cited in the manuscript.
** This is an estimate given other known parameters. Empirical work is required to determine a more exact value for the length of the gestation period.
*** Wet weight excluding the tube.
**** This is an estimate. Reliable, quantitative measures of maximum lifespan are needed to better understand longevity in the giant tortoise.

another reason, the adult mortality rate of the oceanic quahog clam has been estimated to be quite low. This combined with a high failure rate for recruitment has been proposed as an explanation for the extreme longevity of this animal (Moorad et al., 2019). The clam's exceptionally slow aging may be an evolutionary adaptation to cope with extended periods marked by limited resources. Alternatively, the cold environment itself may encourage biological adaptations that promote slower aging. Supportive of this, cold temperatures extend lifespan in *C. elegans* via a genetic program led by the cold-sensitive TRPA-1 ion channel (Xiao et al., 2013). The Greenland shark, bowhead whale, and vestimentiferan tubeworm also inhabit colder waters (Table 2), further implicating a relationship between cold temperature and longer lifespans. More broadly, it has been argued that the extreme longevities of some marine animals are due to decreased predatory pressure, lower temperatures, and diminished food availability (Le Bourg and Le Bourg, 2019).

4.2. Theoretically immortal animals

Planarian flatworms are an extraordinary species with impressive regenerative capacity. These animals have the ability to regenerate every single tissue in their body and can develop an entirely new worm from just a small bodily fragment. Making them ideal as a model organism, they harbor complex biological structures translatable to humans, such as an ocular system with two eyes, two optic nerves (which connect the eyes to the nervous system), an optic chiasm (formed by the crossing of the optic nerves), light-sensitive photoreceptor cells, and pigmented cells (Cross et al., 2015; Lapan and Reddien, 2012). Amputating the heads of *Schmidtea mediterranea* planarians while subjecting them to RNAi knockdown against the transcription factor *ovo*, a master regulator of ocular regeneration, results in the formation of new heads without eyes (Lapan and Reddien, 2012). When this knockdown is relieved, the planarians not only grow new eyes but also connect them to their existing nervous system, rendering them functional and light-sensitive (Cross et al., 2015). Also within *S. mediterranea*, a single transplanted adult pluripotent stem cell called a cNeoblast is capable of restoring regeneration capability in lethally irradiated hosts (Wagner et al., 2011). Regeneration in these flatworms is becoming better understood. Currently, we know that their stem cell population is comprised of pluripotent stem cells (cNeoblasts) as well as fate-specified specialized neoblasts. Positional information, which guides stem cell-mediated regeneration and turnover, is harbored primarily in muscle and is constitutively active (Reddien, 2018). This same free-living, non-parasitic, freshwater species of hermaphroditic worms can reproduce either asexually (via regeneration following self-induced fission) or sexually. Asexual, but not sexual, *S. mediterranea* were shown to maintain their telomere length during regeneration. This maintenance is thought to occur over evolutionary timescales (Tan et al., 2012). Because of their limitless potential for asexual self-renewal, planarians may be capable of avoiding aging and have been described as immortal (Sahu et al., 2017). Additional work is required to understand why such potent regeneration evolved in planarians. It is currently unknown what evolutionary pressures would have selected for a flatworm capable of skillfully regenerating any of its body parts.

Like the planarian, the acoel worm *Hofstenia miamia* is capable of whole-body regeneration. The genome of *H. miamia*, also known as the three-banded panther worm, was recently sequenced (Gehrke et al., 2019). In the same study that sequenced the *H. miamia* genome, the *early growth response* gene was identified as a pioneer factor that directly regulates wound-induced genes underlying regeneration. Additional downstream regeneration genes were identified, resulting in the identification of a novel gene regulatory network for regeneration (Gehrke et al., 2019). In a separate study, Bmp-Admp signaling was shown to control regeneration of the dorsal-ventral axis and Wnt signaling was found to dictate regeneration of the anterior-posterior axis (Srivastava et al., 2014). Although acoels evolutionarily diverged from planarians over 550 million years ago, they similarly harbor positional control genes in their muscle cells. These genes play a paramount role in supplying critical positional information that guides the regenerative response (Raz et al., 2017). It would be worthwhile to assess whether or not these acoels exhibit symptoms of aging over time.

An impactful 1998 paper by Daniel Martínez reported that, in the solitary freshwater species *Hydra vulgaris*, mortality rates remained very low and reproductive rates did not vary significantly over a period of four years (Martinez, 1998). These data combined with the fact that the hydra has a robust regeneration program that allows it to constantly renew tissues in its body led to the theory that these animals are biologically immortal (Martinez, 1998). Disrupting the hydra's self-renewal program by downregulating the transcription factor FoxO increases the number of terminally differentiated somatic cells and drastically reduces the population growth rate, suggesting that stem cell self-renewal is integral to this animal's presumed immortality (Boehm et al., 2012). Like the more complex planarian flatworm, hydra can grow an entire new body from a smaller bodily fragment. It has been theorized that this uncanny regenerative capacity may have evolved as a way to survive extreme levels of extrinsic mortality. Predations, storms, strong water currents, and other factors could all lead to hydra being partly consumed or demolished (Schaible et al., 2014). Given that these animals have simple, tiny bodies, radical self-renewal may have adaptively evolved as a way for surviving fragments to continue reproducing. Although the claim that reproductive rates remain invariable over time for *H. vulgaris* has been challenged (Estep, 2010), more recent work by Schaible et al has confirmed that mortality and fertility remain constant with age for long time courses in these animals

(Schaible et al., 2015). A more recent study has found that the loss of neurogenesis occurs with age in the distinct species *H. oligactis* (Tomczyk et al., 2019). It would be helpful to learn why two different species of hydra exhibit such starkly different aging strategies.

The cnidarian *Turritopsis dohrnii* is a hydrozoan that has been dubbed the "immortal jellyfish". These marine animals are capable of undergoing reverse development, a process that can lead a mature adult medusa back to the juvenile polyp stage. Rejuvenation is presumably part of the process of reverse development. Developmental reversal can be induced artificially by different physical and chemical inducers, such as exposure to cesium chloride (Schmich et al., 2007). As shown via selective excision experiments, the transformation of medusae into polyps requires that differentiated cells of the exumbrellar epidermis as well as part of the gastrovascular system are present (Piraino et al., 1996). The reverted lifecycle has been characterized by four different stages based on morphological analysis: healthy medusa, unhealthy medusa, four-leaf clover, and cyst. The four-leaf clover and unhealthy medusa stages were marked by degeneration while the healthy medusa and cyst stages were marked by a higher apoptotic rate (Carla et al., 2003). Compared to planarians, panther worms, and hydra, a lot less is known about this potentially immortal jellyfish. Considerably more work is needed to better understand this organism as well as its unique process of reverse development. It would be useful to have the genome of this jellyfish fully sequenced.

It would be worthwhile to closely monitor these theoretically immortal animals (Table 3) over longer time spans to assess whether symptoms of senescence appear or if these species are truly exempt from the deleterious effects of aging. From an evolution of aging perspective, it would also be useful to learn more about each animal's ecology. Information about interactions between predation, food availability, population density, mortality, and rejuvenative ability would shed light on why such extreme anti-aging strategies evolved. Supportive of the perspective that aging is caused by the gradual accumulation of damage and dysfunction, apparent biological immortality is accompanied by aggressively robust internal maintenance mechanisms. The planarian, whose mechanisms of self-renewal are the best studied, is an excellent example of this with its pluripotent neoblast stem cell population making up approximately 25–30% of all the cells in its body (Reddien and Sanchez Alvarado, 2004). Stem cell exhaustion is a known hallmark of aging (Lopez-Otin et al., 2013) and the unique ability to combat aging in the planarian appears to be primarily, if not exclusively, the result of a tremendous investment in stem cell function. This has interesting clinical implications for potential regenerative medicine therapies (Rohani et al., 2018) in humans.

5. Mathematical and computational modeling of the evolution of aging

While observations of animals in laboratories and the field have provided important insights into potential mechanisms and have resulted in different theories for how aging might have evolved, testing these theories directly remains largely infeasible. Instead, mathematical models and computational simulations have been used as powerful tools for studying the implications of these theories. Since the advent of Medawar's mutation accumulation theory (Medawar, 1952), there have been many different approaches to modeling the evolution of aging. Below we highlight some of the key papers in this field and speculate on the future of such research.

5.1. Intrinsic rate of increase models

In his 1966 paper, Hamilton used the intrinsic rate of increase, r, as a measure of Darwinian fitness based on the Euler-Lotka equation (Hamilton, 1966):

$$\int_0^\infty e^{-rx} l_x f_x \, dx = 1$$

In this equation, l_x is the fraction surviving to age x, and f_x is the age-specific fertility rate at age x. This allowed him to study age-dependent effects of mortality and fertility on fitness and make arguments about how age-dependent changes in mortality are expected to influence fitness. He argued that aging is inevitable in this framework because the force of selection declines with age. Further, he shows that a stable population of immortal beings is expected to favor senescence given genetic variation, while any mutation causing improvement in early fecundity at the cost of aging will have a higher fitness and come to dominate the population. To demonstrate the model, he used mortality and fertility tables to parameterize the model for a Taiwanese farming community with high mortality and fertility rates, and argued that the gradual mortality observed in this population post-reproduction indicated a departure from the mathematical predictions of the theory, leading him to propose that this may be due to the importance of continued parental care in human societies. Further, the high rate of infant mortality was not predicted by the model, which he reasoned could have evolved to ensure that parents would have the chance to try again. This early work demonstrated how relatively simple mathematical models could be used to study the evolution of aging in specific species based on empirical observations and basic assumptions.

Building on the work of Hamilton and others, Abrams showed that density-dependent mortality and fecundity can lead to the evolution of increased and decreased senescence or both, and theorized that extrinsic mortality can also produce these varied outcomes through density-dependent effects (e.g., older or younger individuals being more susceptible to extrinsic mortality) (Abrams, 1993). Later, Caswell reiterated this claim: extrinsic mortality does not affect the selection gradient of populations if the change is age-independent, or stochastic, but can change if the density-dependence is age-specific (Caswell, 2007). More recently, Wensink and coworkers reiterated that mortality need not be the driver of selection gradients (Wensink et al., 2017), as reproduction can also decrease the proportion of older individuals. They reiterate that the classical idea that senescence evolves because survivorship declines with age is not generally supported by computational models and that a more comprehensive set of models and theories are needed to better understand the evolution of aging.

Along similar lines and diving deeper into Hamilton's indicators of senescence, Baudisch showed that different parameterization of the mutation effect can lead to the evolution of a longer lifespan (Baudisch, 2005). She argued that alternative indicators of the force of selection can have both positive and negative changes with age, suggesting that selective pressure can actually increase with age under different assumptions. Further, she models how accumulation of deleterious mutations may affect the force of selection under some basic assumptions. She concludes that under both additive and proportional mutation

Table 3
Potentially immortal animals.

Potentially Immortal Animal	Species Name	Genome Sequenced	Anti-Aging Strategy	Important Molecular Mechanism
Planarian flatworm	*Schmidtea mediterranea*	Yes	Regeneration	*ovo* is a master regulator of ocular regeneration
Panther worm	*Hofstenia miamia*	Yes	Regeneration	*egr* is a pioneer regulator that controls the regeneration response
Hydra	*Hydra vulgaris*	Yes	Regeneration	*FoxO* is integral for stem cell maintenance and renewal
Immortal jellyfish	*Turritopsis dohrnii*	No	Reverse development	Unknown and to be determined

accumulation models, the predicted mutation-associated mortality is low during reproductive age but is then expected to skyrocket dramatically in the forties for humans, which is clearly not the case under protected conditions. Therefore, a model of mutation accumulation would disagree with observations of stabilized mortality post-reproduction. She then argues that this disagreement would imply that age-dependent trade-offs in maintenance are more likely and that mutation accumulation may be relatively unimportant during an organism's reproductive lifespan.

Wensink et al later showed that trade-offs between age-dependent and age-independent mortality can result in the evolution of aging as a function of the interaction between the environment and individual (Wensink et al., 2014). This then suggests that, if an organism can evolve a trade-off between extrinsic and intrinsic mortality, it may be optimal to increase investment into intrinsic mortality as it could allow for lower overall mortality during adolescence. In other words, aging (intrinsic mortality) may be adaptive when it postpones extrinsic mortality, such as when aging corresponds with lower overall mortality for the organism while still young.

5.2. Trade-off models

Assuming the "disposable soma theory", Abrams and Ludwig used dynamic programming to explore senescence in the context of trade-offs between repair and reproduction in individuals (Abrams and Ludwig, 1995). They introduce both discrete and continuous time models of aging and argue that many different trade-off relationships are possible and may be consistent with observations. The authors argue that the disposable soma theory is consistent with the variety of possible relationships that can exist between reproduction and aging (Abrams and Ludwig, 1995).

Building on this model, Cichoń used a dynamic programming model which included trade-offs between growth, reproduction, and repair to explore the effects of resource allocation on optimal reproductive output (Cichoń, 1997). He concluded that repair efficiency and extrinsic mortality are the most important determining factors in the model and that large size is correlated with longer lifespan due to investments in repair and growth early on. Put differently, the author argues that the relationships between body size, maximum lifespan, and age at maturity may be a by-product of optimal allocation strategies. Cichoń's model suggests that investments in repair favor a long-lasting investment in longevity and slow growth, resulting in a larger final body size.

A year later, Ricklefs used a Weibull function to fit age-dependent mortality, arguing that this function is theoretically more appropriate as it assumes that mortality is a sum of extrinsic and age-dependent effects (Ricklefs, 1998). He then uses values for observed survival rates of birds in captivity, which experience lower rates of extrinsic mortality, to show that intrinsic mortality is estimated to be similar to rates expected in the wild using the Weibull distribution but not the Gompertz distribution. Furthermore, while Ricklefs shows that low extrinsic mortality often correlates with low intrinsic senescence in birds and mammals, he argues against the mutation accumulation and antagonistic pleiotropy theories of the evolution of aging. Instead, it seems the fitted models are consistent with the disposable soma theory of aging, in which either repair capabilities decrease with increasing age or early deterioration is more readily repaired. More recently, Burger and Missov showed that the Gompertz function on its own has an inherent correlation between its parameters and that this correlation should not be used to diagnose evolutionary or biological processes (Burger and Missov, 2016). Therefore, choice of function can bias conclusions from modeling studies.

Shanley and Kirkwood explore the implications of calorie restriction on aging in the context of the disposable soma theory (Shanley and Kirkwood, 2000). By parameterizing a dynamic programming model using measured and extrapolated values for mouse mortality, reproduction, maintenance, and environment, they were able to solve for the optimal fitness of a population during periods of lower energy availability. Further, they were able to predict how reproductive overhead and juvenile survival would affect maintenance, showing that both an added upfront cost to reproduction and decreased juvenile survival during famine result in the diversion of resources toward maintenance and that this allocation is inversely proportional with age. Therefore, the diversion of resources away from reproduction toward maintenance is predicted to occur naturally during times of caloric restriction under the disposable soma theory.

Assuming the antagonistic pleiotropy theory as a framework, Williams and Day explored the effects of interactive and non-interactive extrinsic mortality (Williams and Day, 2003). They did this by allowing for interaction terms in their mortality calculations, which allowed for extrinsic mortality to affect differently aged individuals differently. By doing so, they argue that many diverse aging outcomes may be favored. This is similar to the abovementioned work by Abrams (Abrams, 1993), who showed that a diverse set of aging outcomes may be favored when density-dependent extrinsic mortality effects are introduced. However, in the context of antagonistic pleiotropy, Williams and Day argue that "… in response to increased condition-dependent hazard, optimal senescence schedules should often show a pattern of decreased age-specific deterioration early in life, but a steeper rate of change in age-specific deterioration, and possibly greater age-specific deterioration, at late ages." Therefore, the inherent choice of the model used (e.g., antagonistic pleiotropy or disposable soma) may qualitatively bias the predicted conditions leading to the evolution of various aging scenarios.

Drenos and Kirkwood also use a computational model under the assumptions of the disposable soma theory to explore how specific parameters as well as reproduction and mortality schedules affect optimal investment in maintenance (Drenos and Kirkwood, 2005). They show that optimal investment strategies are parameter-dependent. For example, higher juvenile mortality, basal vulnerability to mortality, actuarial ageing rate, and minimum age of maturity serve to increase maintenance while age-independent extrinsic mortality and reproduction rate favor decreases in somatic maintenance. They also show that, under the disposable soma theory, a large range of maintenance values can robustly produce near optimal solutions, arguing that this may be the reason why there is high variability in repair mechanisms within a population.

To explore the interaction between individuals with a shared resource pool, we previously developed an agent-based trade-off model for finite populations of evolving individuals (Shokhirev and Johnson, 2014). Importantly, each individual could accrue resources from a shared pool, allowing us to explore the interaction between individuals in the context of varying extrinsic mortality. We then used an unbiased optimization strategy to see which model parameters may lead to the evolution of short or long lifespans in the presence of extrinsic mortality. We found that increased extrinsic mortality can lead to the evolution of longer lifespan if maturation costs are high and if energy is available in excess, while shorter lifespans evolve when mating costs are low and food is relatively scarce. In other words, high extrinsic mortality can free up additional resources, which can lead to additional investment in repair by the remaining individuals in a population. These results emphasize the importance of taking the interaction of individuals within a finite population into account.

Trade-off models are general enough to be extended toward atypical organisms. For example, Johnson and Mangel explore the implications of the disposable soma theory in single-cell organisms, arguing that they represent good candidates for empirical testing of the theory in the lab (Johnson and Mangel, 2006). In the context of single-cell organisms, they define aging as limited reproduction as a function of age with constant age-independent mortality. They start by building on a non-aging population of single-cells and then introduce a maximum age limit and assume rejuvenation for one of the daughter cells. They find that, in the case of single-cell organisms, investment in shorter doubling

time is considerably more advantageous than investment in higher replicative capacity as the benefit of additional doublings is dwarfed by the doubling lineages produced in the first few generations. Kramer and Schaible later tested trade-offs built into a simple hierarchical model of eusocial insects (Kramer and Schaible, 2013). In this model, workers produce resources for the colony which are in turn invested in either worker or queen maintenance. By optimizing for the number of queens produced at the end of a season, they find that an investment in queens is preferred over an investment in workers as a function of extrinsic mortality, with riskier environments producing very short-lived workers and consequently freeing up resources for the production of queens.

5.3. Reliability theory models

Taking a different approach, Milne modeled aging as a nested binomial model, which is used to approximate random failure of a collection of biological mechanisms with partial redundancy (Milne, 2008). In this context, redundancy decays linearly with age and the probability of mortality is a product of probabilities that any one system fails beyond its redundancy. Milne showed how the parameters affect mortality curves with a simple model and then extended the model to include inter-function (i.e., variability among biological systems within an organism) and inter-individual variation. He then shows that early mortality observed in real populations can be modeled by assuming that redundancy starts out low and then builds (e.g., growth or maturation), and finally decreases again due to failures. Finally, he demonstrates that the plateauing of mortality in old age can be recapitulated if inter-individual variation is positively-skewed or long-tailed.

Laird and Sherratt also modeled senescence in the context of reliability theory at the level of gene products (Laird and Sherratt, 2009). These gene products, or elements, can have multiple redundant copies and are subject to random failure, surviving until all elements are damaged. Unlike Milne (Milne, 2008), Laird and Sherratt allowed for changes in the number of redundant elements in each generation with decreases in the number of elements being more likely than increases (i.e., deleterious mutations are more likely than those that increase redundancy). They find that, even though redundancy has no associated cost, a finite stable equilibrium is reached, thereby suggesting that there need not be a trade-off in costs for senescence to evolve. They also argue that their model matches the following aspects of typical natural populations: 1) an initially low mortality rate that accelerates with age, 2) a plateau of mortality at old age, 3) independence of the mortality plateau height from extrinsic mortality conditions.

5.4. Other models

Moorad and Promislow extend Fisher's geometrical model of adaptation to include a time dimension and use this model to explore how time-dependent mutational effects can affect the evolution of senescence (Moorad and Promislow, 2008). They conclude that aging 1) decreases the likelihood that a mutation is deleterious, 2) makes mutations less deleterious, and 3) makes mutations less variable. The authors argue that the model offers a parsimonious explanation for why juvenile mortality is greater and late-age mortality is lower than predicted by classical theory.

How does sexual conflict and extrinsic mortality affect the evolution of aging? Bonduriansky developed a simple model of female life history with female fecundity being a function of age, reproductive effort, and age-specific costs (Bonduriansky, 2014). By incorporating a male-specific additive cost to female fecundity and a decrease in lifespan (due to external forces), Bonduriansky shows that a male-specific additive cost can actually result in an increase in female fitness with higher extrinsic mortality, suggesting that sexual co-evolution affects life expectancy.

Interested in dissecting acute and chronic sources of mortality, Anderson and coworkers developed a process point of view model that incorporates three sources of mortality: juvenile extrinsic mortality, adult extrinsic mortality, and intrinsic mortality (Anderson et al., 2017). This model was able to fit a Swedish mortality dataset spanning hundreds of years, allowing the authors to associate changes in specific types of mortality with known historical developments in society across time. Because changes in socioeconomic and health factors over the last several hundred years of human history have resulted in specific changes to the three types of mortality defined, the authors conclude that it is important to consider the contexts of population and environment when trying to understand the evolution of aging.

Using a cellular-automata spatial model, Werfel and coworkers demonstrate that intrinsic death could provide long-term advantages to a lineage of creatures living in a finite environment even when intrinsic mortality does not provide direct benefits to the organism (Werfel et al., 2017). They show that this benefit can be delayed, only manifesting after many generations, and show that populations made up of mortal individuals always outcompete immortal populations when introduced into a steady-state model. They use these results to postulate that senescence can itself confer a long-term evolutionary advantage in the context of finite resources contrary to classical theories.

What role does nutrient intake play in the evolution of aging? In a recent work, Hosking and coworkers develop an agent-based model in which individuals of a population and their environment are explicitly modeled (Hosking et al., 2019). As the model simulations progress, individuals obtain specific nutrients from their environment while attempting to reach a specific intake target modulated by the underlying environment with variable nutrient availability. By allowing the intake goal to be evolvable and by imposing increasing levels of extrinsic mortality, they find that populations evolve to favor nutrients that promote fecundity over longevity with increased extrinsic mortality. Although evolved populations tended to shift toward nutrients favoring fecundity with increased extrinsic mortality, the model also predicted a distribution of both longevity- and fecundity-focused intake strategies within a population.

5.5. Perspectives from mathematical and computational studies

Mathematical and computational models provide powerful frameworks for studying the evolution of aging, which often cannot be tested experimentally. Starting from early models based on the intrinsic rate of increase, models have grown in complexity as we labor to account for discrepancies between historical mortality tables and model predictions and as we try to incorporate additional layers of detail and scope. A central theme that emerges is that the evolution of aging need not be a universal constant as predicted by classical theories. Indeed, both shorter and longer lifespans may evolve in the presence of extrinsic mortality depending on the complex interaction between individuals of a finite population and age-dependent forces of selection. Choice of model and indicator can also bias the conclusions drawn and therefore the classical theories of aging are only part of a bigger picture.

New theories for the evolution of aging are emerging which explore additional exciting contexts and challenges to the problem. Models will need to incorporate and reconcile layers of interactions between individuals, their genes, and the environment in which they exist (Fig. 2). To ground these theories, additional biological data will need to be collected across biological scales and integrated using new mathematical and computational frameworks.

6. Assessing the mutation accumulation, antagonistic pleiotropy, and disposable soma theories

Given all of these data, what do we make of the mutation accumulation, antagonistic pleiotropy, and disposable soma theories of aging? As a testament to their predictive power, we've shown that extrinsic mortality and lifespan are almost always inversely correlated. When external mortality sources rise, lifespan tends to shorten. When

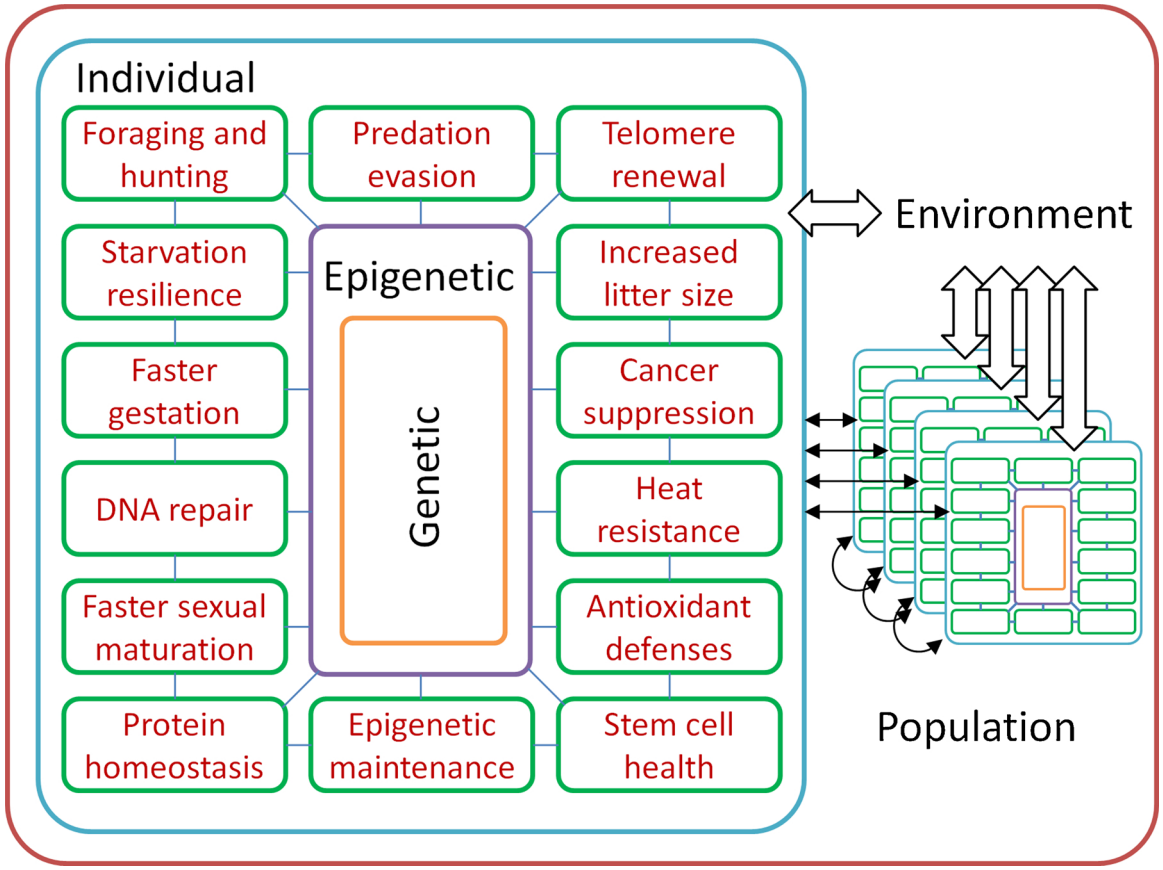

Fig. 2. Multi-level contexts for the evolution of aging. Additional interactions between biological layers can account for discrepancies between recorded observations and classical theories for the evolution of aging. Biological processes are tightly regulated on the genetic and epigenetic levels. These levels influence various aging-relevant aspects of biology, including DNA repair, telomere renewal, protein homeostasis, and stem cell health. They also influence fitness parameters that directly impact survival and fecundity, such as predation evasion and time to sexual maturation. Importantly, the evolution of aging is significantly affected by complex interactions between the environment and individuals within a population.

external mortality sources decrease, lifespan tends to increase.

6.1. Mutation accumulation theory

Despite it being the oldest of the three classical theories, Medawar's mutation accumulation theory remains highly relevant today. Experiments in *Drosophila* have suggested that mutations with late-acting deleterious effects accumulate passively over time and are unopposed by natural selection (Hughes et al., 2002). In 45 killifish species and 231 wild individuals with a geographical distribution throughout sub-Saharan African, Cui et al identified genetic variants associated with positive and relaxed purifying selection. The authors discovered that genetic drift led to the expansion of mitochondrial and nuclear genomes as well as the accumulation of deleterious genetic variants in key genes that regulate aging. Their findings suggest that the relaxation of purifying selection prominently shaped the genomes and influenced the lifespans of these different vertebrate fish (Cui et al., 2019). Separate work by Turan et al assessed 66 multi-tissue transcriptome datasets from five mammalian species. The authors reported that genes that are more upregulated with age among tissues and species are less evolutionarily conserved. These genes, which are relevant to age-associated tissue damage, appear not to be under positive selection (Turan et al., 2019). Recent research from the laboratory of Jan Vijg showed that somatic mutations accumulate significantly with age in human B lymphocytes derived from differently aged healthy individuals. Mutations in sequences relevant to the function of B cells were considerably less common, indicating that humans evolved to allow mutations in non-functional sequences to accumulate passively and to more actively resist mutations in functional sequences (Zhang et al., 2019). These data all suggest that the force of natural selection declines with age and that the evolution of aging is at least partially attributable to the passive accrual of mutations.

Additional support for the mutation accumulation theory comes from the existence of single-mutation diseases that remain stably prevalent despite having a late-onset. A great example of this is the autosomal dominant retinal disease Best vitelliform macular dystrophy. Most cases of this disorder are caused by single nucleotide mutations in the gene *BEST1* and, although the disease can result in severe vision loss or even blindness, symptoms tend to present themselves in later adult life (Johnson et al., 2017). Autosomal dominant Huntington's disease, with an average age of onset of approximately 35 years, is another potential example of mutation accumulation theory (Flatt and Partridge, 2018).

6.2. Antagonistic pleiotropy theory

In the vast majority of circumstances where aging is altered, a clear trade-off with fecundity has been noted. Such a trade-off can manifest as a change in sexual maturation age, length of the gestation period, length of the brooding period, or total number of offspring. The prevalent trade-off between aging and fecundity is highly supportive of the antagonistic pleiotropy and disposable soma theories (Austad and Hoffman, 2018). Genes, such as *daf-2* in *C. elegans*, *InR* in *D. melanogaster*, and *prop-1* in *Mus musculus*, that significantly increase lifespan by at least 50% but also result in either sterility or reduced early life reproduction are compelling examples of genes with pleiotropic effects

(Austad and Hoffman, 2018). High testosterone levels, which can enhance reproduction but also increase the late life risk of prostate cancer, are another possible example of antagonistic pleiotropy (Kowald and Kirkwood, 2016).

6.3. Disposable soma theory

The more mechanism-focused disposable soma theory is heavily bolstered by recent genomic advances. Animals with remarkable longevity consistently show unique changes in genes relevant to known anti-aging mechanisms, such as DNA repair, autophagy, inflammation, and cancer resistance (Keane et al., 2015; Quesada et al., 2019; Sahm et al., 2018). It seems very clear that, whether it's a bowhead whale that can survive for more than two centuries (Keane et al., 2015) or a planarian flatworm with an apparent infinite lifespan potential (Sahu et al., 2017), a resistance to aging is invariably accompanied by more robust internal maintenance mechanisms. In the terms of the disposable soma theory, these long-lived animals have heavily invested in their soma. Moreover, our growing understanding of aging indicates that aging dysfunction is the result of both a gradual accumulation of damage and a concomitant progressive failure of repair mechanisms (Singh et al., 2019). The clearance of damage or the enhancement of repair mechanisms is also sufficient to prolong lifespan and healthspan in animal models (Mahmoudi et al., 2019). The disposable soma theory's emphasis on investments into maintenance and repair mechanisms nicely matches these insights into aging biology.

6.4. Programmed aging

The theory of programmed aging argues that there is a genetic program which facilitates aging. It has been argued that such a program would be evolutionarily beneficial because it would free up resources for younger individuals and would encourage genetic turnover. If this theory were true, it would mean that clinically tackling aging and age-related disease may be as simple as disabling the genetic tools that cause aging. Arguing against this theory, highly compelling data indicate that aging is the result of increasing molecular, cellular, and physiological dysfunction that gradually accumulates over time (Lopez-Otin et al., 2013; Singh et al., 2019). Molecular damage – like genomic instability, telomere attrition, and epigenetic alterations – gives rise to cellular and physiological damage – like cellular senescence, stem cell exhaustion, and altered intercellular communication, which ultimately results in a deleterious aging phenotype (Lopez-Otin et al., 2013; Singh et al., 2019). Moreover, as we have demonstrated throughout this review, animals with longer lifespans frequently exhibit an enhanced ability to resist and repair damage compared to those with shorter lifespans. For example, DNA double-strand break repair is more efficient in longer-lived species (Tian et al., 2019). Even semelparous organisms – those that die rapidly after reproduction (e.g., salmon) – are better viewed as extreme examples of the disposable soma theory instead of evidence for programmed aging (Kirkwood and Melov, 2011). For those interested in a more detailed explanation of why programmed aging is unlikely to help us better understand the evolution of aging, we highly recommend two well-written reviews on this topic (Kowald and Kirkwood, 2016; Vijg and Kennedy, 2016).

7. Expanding the classical theories and looking towards the future

It is important to emphasize that these theories are not mutually exclusive and that they can all work in concert. The antagonistic pleiotropy theory built on the mutation accumulation theory and was refined further with the disposable theory. To accommodate more recent data, it is time for another expansion phase.

All three classical theories of aging relied on a strict conceptual partition between the organism and environment, with attention increasingly focused on the organism. According to Medawar's theory, consistently high-mortality environments negate possible evolutionary pressure that would otherwise select against deleterious aging mutations. Antagonistic pleiotropy focused even more closely on the organism, positing an internal competition of genes favoring early-life against those favoring later-life health. The disposable soma theory specified that these internal competing demands can take shape in a trade-off between reproductive function and self-maintenance. The trend in all three theories has been to designate the organism as the dynamic locus of aging while treating the broader environment as the undifferentiated cumulative source of selective pressures and resources.

This framework implicit in the three classical theories – that the organism is the key dynamic unit that exists in a relatively homogenous environment – has long driven research questions and helped make sense of many experimental results. However, the growing number of recent studies that do not conform easily to the three theories gives cause for reexamining this classic framework. We now know that, under specific conditions, increased extrinsic mortality can select for the evolution of longer lifespans (Chen and Maklakov, 2012, 2014; Reznick et al., 2004). The outcome of increased extrinsic mortality depends on multiple parameters. These parameters include food availability (Reznick et al., 2004; Shokhirev and Johnson, 2014), population density (Luckinbill and Clare, 1985; Reznick et al., 2012), the type of extrinsic mortality (Chen and Maklakov, 2012, 2014; Reznick et al., 2004), and, more broadly, ecology (Tables 1 and 2). How fecundity and mortality rates change over time (Jones et al., 2014) as well as how different age classes are affected by external mortality sources (Abrams, 1993) may also influence the evolved response. How mutations impact an organism over time may also influence the evolution of aging. Maklakov et al have argued that both early- and late-life fitness can be enhanced when the deleterious effects of mutations worsen with age (Maklakov et al., 2015). If the source of extrinsic mortality is one that requires robust anti-aging mechanisms to survive, such as heat stress (Chen and Maklakov, 2012), then this can result in the evolution of individuals with slower aging. Even if an external source is more random, like predation, it is still possible for increased extrinsic mortality to select for prolonged life given a particular combination of circumstances (Shokhirev and Johnson, 2014). As we discussed earlier, high-predation guppy localities have an enlarged food supply (Reznick et al., 2001b) and therefore more resources per capita compared to low-predation guppy localities. The fact that high-predation guppies displayed superior swimming performance (Reznick et al., 2004) also indicates that predation itself, despite being more random, can be a form of conditional mortality. It is possible that the extra availability of per-capita resources allowed for additional investments into both lifespan and fast swimming (i.e., anti-predation). Alternatively, the mechanisms that allowed for the evolution of more rapid swimming may have also resulted in delayed aging as a byproduct.

The lack of a known trade-off between aging and fecundity in some studies additionally requires us to revamp our understanding of the evolution of aging. In any of these studies that do not find a trade-off, it is possible that another trade-off exists, such as one with immunity (Austad and Hoffman, 2018), or that the trade-off has yet to be discovered. As we mentioned before, previously hidden trade-offs have been revealed under harsher laboratory conditions (Marden et al., 2003; Walker et al., 2000). However, it is also possible that, given particular parameters, resources may be available to truly increase longevity without a substantial fitness cost. For example, the typical reduction in fecundity that results from dietary restriction can be overcome in *Drosophila* by adding methionine to their diet (Grandison et al., 2009). In such a circumstance, an organism can enjoy longer lifespans while remaining fecund. More challenging to reconcile, full-diet females allocate more carbon, nitrogen, and essential amino acids into somatic tissues than those on a restricted diet. The ratio of somatic tissue investment relative to egg investment is, however, greatest in diet-restricted females. These and other data have led to the alternative theory that dietary restriction may extend lifespan via somatic

investment relative to how much damage is caused by reproduction, not because of reduced investments in somatic maintenance (Flatt, 2011). As we have discovered to be the case with lifespan and extrinsic mortality, the relationship between aging and fecundity is more complex than a simple inverse relationship and likely depends on the interaction of various factors.

Integrating this growing array of non-conforming studies into a greater theory of aging will, we think, require reconceptualizing the locus at which aging is thought to occur. The dominant tendency has been to see aging as a process happening in/to the discrete organism. While this assumption is intuitive and has proven useful for identifying low-resolution trends, the locus of aging may need theoretical expansion to embrace more of the pathways that link environment, ecology, population, and the organism to each other (Fig. 2). New experimental data, along with the computational models discussed above in Section 5, suggest that it is a confluence of pathways across many levels and scales that determines the average lifespan of any particular species. Aging, on this proposed view, does not happen to a discrete organism affected by its undifferentiated environment, but rather to an organism variably implicated in a multi-dimensional environment involving ecology and population (Laland et al., 2015; Lewontin, 2000).

This shift in perspective prompts different kinds of questions: how do shifting parameters in the broader environment (different kinds of predation, different types of resource availability) interact with population dynamics as well as with the physiological and genetic mechanisms that construct and maintain the organism? Are there discernible trends regarding which levels (environmental, population, physiological, or genetic) initiate changes in senescence? If a set of conditions at one level creates evolutionary pressure on lifespan in a species, how quickly do the other levels respond?

Computational and mathematical modeling has a large role to play in addressing these kinds of questions. This work, which has challenged controlled studies in the laboratory or field, is already yielding a more complex view of the evolution of aging and continues apace (Section 5). Beyond computational models, the field would benefit from studies of aging variation in closely related species. Such studies could explore precisely how longevity has diverged in branching evolutionary histories. Differences among recently divergent species can offer important clues as to how various levels interact to affect and differentiate lifespan. The example of aging differences among closely related octopus species is instructive in the questions prompted (Section 3.3 and Table 1). A better understanding of phylogenetic divergences in longevity may shed new light on the mechanisms of senescence in the organism.

Although beyond the scope of this review's discussion, more aging data for plants and unicellular organisms would be valuable for expanding our understanding of the evolution of lifespan. The seminal, previously mentioned work by Jones et al reveal that mortality and fertility patterns vary drastically among 12 vascular plants and a green alga (Jones et al., 2014). More recent data shows that mortality correlates with parameters like wood density and light requirements among 203 different tropical tree species (Camac et al., 2018). In unicellular organisms, Proenca et al have demonstrated that both physiological immortality and cellular aging can manifest in bacterial populations (Proenca et al., 2018). Aging yeast have been shown to outcompete younger yeast when given non-glucose carbon sources such as galactose, suggesting that aging may sometimes evolve to provide a portion of the population with a competitive advantage under non-traditional conditions (Frenk et al., 2017). Thus, novel insights relevant to the evolution of aging can be gleaned from organisms that have not been historically emphasized by the field.

To clarify, we are not calling here for a full "paradigm shift", nor are we putting forward a new theory. The classical theories remain useful explanations at low resolution. They are still important rules of thumb for the evolution of aging: high mortality environments typically lead to faster average senescence; and there often exist trade-offs between fecundity and longevity, or between longevity and other physiological functions. Nevertheless, research is increasingly driving aging theory to develop greater scope and complexity. Recent studies reveal that senescence has a multi-dimensional character and suggest that ecological and population levels are just as dynamically involved in the evolution of aging as is the organism itself.

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Declaration of Competing Interest

The authors declare that they have no conflicts of interest.

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