6

Directions for Research

6.1 Orientation

The models and analyses of the preceding chapters have shown that senescence is not inevitable. Much more research is needed to understand why in some species mortality increases after maturity while in others it does not. My results raise an important new question for aging research: when does senescence vs. sustenance evolve?

The study of the evolution of the age-patterns of mortality and fertility is still a wide-open field of research waiting for exploration. In this chapter, I summarize my thoughts about what I think are the most interesting and important parts of the field to explore next.

6.2 Direct Extensions of my Models

In this section I will describe several directions for research that follow naturally from my work described in this monograph.

6.2.1 Linking Burden & Optimization

Whether senescence is due to a burden of deleterious mutations or is a byproduct of optimization among trade-offs has been and still is the subject of intense discussion. In the following, I will outline my ideas of how linking both approaches could help to resolve the debate.

A Future Project

An interesting research project is to develop a model that combines mutational burden and optimization. Using the model developed in

Chap. 5, this could be done by including a mutational load term in the mortality function. Initially, the mutational load would be equal to zero. The optimal mortality and fertility patterns, given zero mutational load, can then be used to calculate selection pressure. The selection pressure plus assumptions about the magnitude and possible age-pattern of the mutation rate will determine the new mutational load. Given the new mutational load, a new round of optimization could be done. With this approach one would be able to analyze what proportion of mortality is due to optimization and what proportion is due to mutational load.

The question is whether the procedure converges. If decreasing selection pressure allows deleterious mutations to accumulate and leads to a rising mortality pattern, then the new selection pressure would fall more quickly, allowing still more mutations to accumulate. As more mutations accumulate, mortality would start rising earlier and earlier. Therefore, this model could shed light on whether the feedback loop between traits and evolution can lead to an unraveling of the life history.

6.2.2 Measurable Quantities and Testable Hypotheses

Evolutionary demographic theory is based on models. Each model is based on assumptions that simplify reality. A set of models can form a theory that illuminates a broad range of the real world because different simple models shed light on different, specific aspects of reality. Some models generate general insights, other models lead to testable hypothesis, and still other models make both contributions. I have developed simple models that contribute general insights to evolutionary demographic theory. In the future I plan to rethink and maybe reformulate my models to get a handle on measurable quantities to derive testable hypotheses from them.

This effort is a direct extension of my work. The parameters k, κ, and δ in the vitality model can be used to set a time and size scale. What is needed is an explicit expression that links vitality and size. This relationship hinges on knowledge about the rate at which cells are lost.

The η parameters capture the costs of maintenance and reproduction and have a major influence on the results of the model. Therefore it is important to understand how to root them in reality. What are the magnitudes of the η parameters for different types of species? This question has to be answered to generate testable hypotheses from the model.

6.2.3 The Diversity of Aging

My work described in this monograph can be viewed as a theoretical exploration of the inter-species diversity of aging, i.e., of how varied aging can be for different species and what factors determine whether a species' strategy involves sustenance or senescence. I believe that the models I developed can also be usefully applied, if somewhat refocused, to studies of intra-species variability of aging patterns resulting from environmental cues or conditions. A further research project that derives from my work is to develop this kind of application of my models.

As an example, consider the article by Mair et al. [116]. This group, from Linda Partridge's laboratory, explored two kinds of phenotypic plasticity of aging in genetically-identical lines of *Drosophila*. They manipulated diet and demonstrated that flies shifted to a restricted diet experienced, for the rest of their lives, the same trajectory of lower mortality as flies kept on the restricted diet all their lives. In terms of my vitality model, this effect is most simply explained by a shift in the parameter b. The "vitality" of a fly is unchanged by the dietary shift: the shift influences how vitality determines mortality. In contrast, Mair et al. [116] show that a reduction in temperature slows the pace of mortality increase with age. This effect can be captured in my model by a change in the deterioration parameter δ, or by a more general change in all the "scale" parameters k, κ, and δ or by a change in the strategy π. Which of these possibilities best captures reality? Collaborative theoretical and empirical research might answer this intriguing question.

A variety of other researchers, including James Carey, Thomas Johnson, James Curtsinger and Marc Tatar, have conducted laboratory studies of how some environmental change alters subsequent age-patterns of mortality and, in some cases, fertility. It may be possible to interpret the results of such studies in terms of changes in the parameters of my models – and this might shed light on mechanisms that underlie the phenotypic plasticity of aging.

6.2.4 The Characteristics of Senescent vs. Non-senescent Species

Species can be classified according to various characteristics. A challenging direction for future research is to identify the characteristics that distinguish senescent from non-senescent species.

The results of my models suggest that species with the capability of continued growth after the onset of reproduction are candidates for

non-senescent life-history strategies. The results of my vitality-based model of Chap. 5 suggest that the costs of growth and maintenance and the costs of reproduction (as captured by parameters η_g and η_r) are the major determinants of senescence vs. sustenance. Developing a theory that identifies the relevant traits in reality that correspond to low vs. high values of η_g and η_r is a promising direction for future research opened up by my work.

In this regard, modularity might prove to be an important trait that can be associated with inexpensive growth and maintenance. The ability to reproduce clonally from segregated body parts, i.e. vegetative propagation, might prove to be associated with inexpensive reproduction. More thought is needed to come up with plausible hypotheses about characteristics that correspond to particular values of η_g and η_r.

A deep understanding of the returns to scale of investment to basic processes of life will shed light on why some species senesce and other species do not. Chap. 5 develops several ideas for exploration: Are there differences in returns to scale for asexual and sexual reproduction? Can the η parameters change with age, maybe being concave early in live and transitioning to convex later in live? Could different levels of organization, from the molecule over the cell to the whole organism be associated with different shapes of trade offs? Much more research is needed to answer all these questions.

The results of Chap. 5 further suggest that the parameters for intrinsic (i.e. state-dependent) and extrinsic (i.e. state-independent) mortality conditions (as captured by parameters b and c respectively) mainly influence the degree of senescence of a life history. What characteristics in a species determines the level of b and c? Williams [212] provides one hypothesis of how mortality conditions should influence the patterns of senescence. Research on this question has been done, e.g. by Ricklefs [164] and Ricklefs and Scheuerlein [165], but further research is needed to understand the influence of mortality components on the evolution of aging.

Mapping typologies of species into a typology of aging would be a major step towards understanding the evolution of senescence vs. sustenance. The simplest typology of aging would distinguish between species with strategies of senescence vs. sustenance. A more elaborate typology could be based on the five age-patterns of mortality and fertility discussed in Chap. 5. In addition to classifying species according to the shape of age-patterns of mortality and fertility, species could also be classified by their time scale: is life measured in hours, days, weeks, months, years, decades or centuries? Similarly, their size scale

could be used: is size measured in nanometers, micrometers, millimeters, centimeters, decimeters or meters? As discussed above, other possible classifications could be growth mode, i.e. determinate vs. indeterminate growth, or the structure of the body plan, i.e. modular vs. non-modular structure.

6.2.5 Alternative Applications

The vitality model is a general model that could also shed light on other aspects of life that influence successful survival and reproduction. One important aspect is learning. If the single state variable in my models is interpreted as including the level of knowledge or cognitive ability, then the change in state can be due to learning or loss in cognitive ability. If more experience and knowledge imply a lower risk of death and more reproductive success, then my model can be extended to apply to the evolution of learning.

6.3 Other Modeling Extensions

In this section, I discuss several other directions for research for developing evolutionary demographic models. Over the past three years, there has been a spate of stimulating research in this area and I cite some pathbreaking recent advances.

6.3.1 Density Effects

Trees do not move. To live they need space to stand on. Therefore population density is crucial in a forest. If all patches are taken, no seedlings can establish themselves. This is true not only for trees in a forest but for many plants in many environments. In a recent working paper, Doncaster and Seymour [50] show that this density effect can explain the evolution of the great longevity of Bristlecone Pines. If seeds can only root themselves on a patch freed by the death of an adult, then longer lived trees have an evolutionary advantage. Their offspring will occupy the space opened by the death of the shorter lived trees whose offspring will not have found space to successfully establish themselves. The density effect favors the evolution of longevity.

Density is not only important for trees. The abundance of individuals in a population can significantly influence the evolution of life-history traits in general. If density effects play a role, then Lotka's intrinsic rate of population increase r is not an appropriate measure

of fitness. Charlesworth [24] suggests using the number of individuals in the so called critical age group instead. Mylius and Diekmann [132] analyze what fitness measure to use, given the specific way density constrains population dynamics. The fitness measure used in the models I developed in Chaps. 4 and 5 is in accordance with the results of Mylius and Diekmann [132, p. 4]. In my models, density affects fertility via the multiplicative parameter φ for all ages equally.

Abrams [3] analyzes theoretically how extrinsic mortality should affect senescence, given different scenarios of density dependence. Williams [212] hypothesized that individuals living under more hazardous conditions should exhibit faster senescence and thereby lower survival than individuals living under more benign conditions. Abrams [3] shows that Williams' hypothesis will not always be valid if density effects alter population dynamics.

Density could also affect the optimal phenotype in a population. This could help to explain a puzzle recently noted by Resznick et al. [163]. They observe that, for a population of guppies living under two different mortality regimes in the wild, individuals from the high-risk environment show better survival when brought into the laboratory than individuals from the low-risk environment, contrary to Williams' hypothesis. However, because fewer individuals survive in the dangerous habitat, density is lower than under safer conditions. Therefore, the optimal high-risk phenotype develops when resources are more abundant, while the low-risk phenotype develops when resources are scarce. If more abundant resources allow for better growth and development and if this influences adult mortality, then the high-risk phenotype can be more robust than the low-risk phenotype. This density effect as well as several other possible explanations for the guppy-puzzle are discussed by Abrams [4].

Bronikowski and Promislow [15] emphasize that, depending on how senescence is defined and what kind of condition-dependent mortality is prevalent, different long-term effects on the evolution of senescence can be expected.

6.3.2 Intergenerational Transfers

Resources are scarce. Therefore, the age-trajectory of resources available to an individual over the life course constrains the evolution of optimal life histories. In this regard, resource flows among individuals are a crucial fitness component. The common fitness measures R and r do not include intergenerational transfers and, in particular, parental

care. This can seriously distort results for species with significant periods of offspring dependence. Indeed, the degree of independence and the level of mortality at birth both reflect initial parental investment in offspring. From this perspective, size at birth relative to size at reproductive maturity is an important quantity. Lee [109] points out that the act of giving birth in itself can be interpreted as a transfer from mother to child. Therefore transfers should generally be captured by any measure of fitness.

Chu and Lee [36] and Robson and Kaplan [168] study conditions under which transfers from adult to offspring can be optimal: they model the co-evolution of longevity and transfers in human populations. Modeling efforts along these lines could explain the decline in mortality during development as well as the modest rather than steep increase at post-reproductive ages.

6.3.3 Environmental Fluctuations

Environmental fluctuations are certain over the life course of nearly all species. But their timing and magnitude can be highly uncertain. Natural selection needs time to work. If the environment changes faster than it takes selection to be effective, then chance plays a major role in favoring one species over another from one moment to the next. Populations can keep on fluctuating and might not reach a stable age-distribution. In variable environments the intrinsic rate of population increase is a poor measure of fitness because it assumes a stable population. Instead, the stochastic growth rate should be used to measure fitness (Orzack and Tuljapurkar [143], for a review see Tuljapurkar [199]). In a changing environment, the intrinsic rate of population increase r can be negative at every point in time but the stochastic growth rate can be positive: r does not capture real population dynamics.

Ripley and Caswell [166] demonstrate that an indicator of selection pressure – namely the relative change in the stochastic growth rate induced by changes in adult growth and survival of soft-shell clams – is strongly dependent on the amount of uncertainty in the recruitment of baby-clams. This state-dependent analysis implies that their indicator of selection pressure can increase with age if this uncertainty is large.

The development of phenotypes depends on the environment. Environmental cues can switch life histories between alternative age-trajectories of mortality and fertility most suitable to current conditions; some phenotypes can have prolonged life expectancy [7, 20, 63]. If life is harsh, nematode worms, for instance, can enter a state of very low metabolic activity, called the dauer state, that enables the worm to

survive long periods of drought. Switching strategies require survival and reproductive patterns to be highly plastic.

In a recent issue of *Science*, Kussell and Leibler [104] offer a new method for approximating long-term reproductive success in fluctuating environments. Organisms can switch phenotypes according to the prevalent environment. Switching rates turn out to mimic the rate at which the environment is fluctuating. Furthermore, two extreme strategies of switching are compared – responsive vs. stochastic switching. Kussell and Leibler [104] show that switching strategies will be responsive or stochastic, depending on whether the costs of sensing the environment match the gains in reproductive success. An important determinant of this decision is the speed at which environments fluctuate. The information content of the environment (entropy) appears explicitly in the optimal solution, pointing to a deep connection between population biology and information theory.

6.3.4 Population Dynamics

It is useful to assume optimal equilibrium when studying whether non-senescence could be optimal at all. Research is needed to relax this assumption to better understand the domain of non-senescence vs. senescence. Given within-species dynamics like frequency dependence, could a non-senescent strategy be invaded by an alternative, senescent variant?

Survival is heavily influenced by the ability to resist diseases. A more or less costly immune system is necessary to fight the threats from the fast-evolving micro world. Given across-species dynamics like the co-evolution of the micro and macro world, how does the never-ending battle with parasites influence the evolution of senescence? More generally, some species are prey and other species are predators. Almost all species compete with other species for food and other resources. How does the competition among species influence age-patterns of mortality and fertility?

6.3.5 Summary

The models developed in this monograph were designed to shed light on whether non-senescent life-history strategies could be optimal. Further research can deepen and extend evolutionary demographic theory in various directions. In the previous sections I have highlighted the directions that I think are of most immediate interest and importance.

In particular, I laid out several research projects that directly derive from my work, namely:

- Integrating optimization and the burden of deleterious mutations in a single model,
- Reformulating my models such that the parameters are measurable and testable hypotheses can be derived,
- Focusing my models so that they can be used to understand how a species responds to changes in laboratory conditions, such as dietary or temperature manipulations,
- Mapping typologies of species into typologies of aging, and
- Applying the general model to alternative questions such as the co-evolution of longevity and learning.

In addition I have outlined five other directions for further evolutionary-demographic modeling, involving

- Density effects,
- Intergenerational transfers,
- Fluctuating environments,
- Intra-species population dynamics, and
- Inter-species population dynamics.

6.4 Prospects for Evolutionary Demography

Evolutionary Demography is an interdisciplinary area of research that has been newly evolving in recent years. In the following sections I highlight three lines along which the field could move forward. First, some canonical ideas need to be rethought. Second, new data, methods and measures are needed. Third, aging – the processes of change over age – can only be understood in the light of both senescence and sustenance together.

6.4.1 Moving Beyond the Burden of "Deleterious Fixations"

The phrase "deleterious fixations" is meant to emphasize that research on aging has been and still is influenced by long-held "truths" that channel thinking into directions that are limited and might even be wrong.

One of these fixations has successfully been rethought. For a long time, lifespan was believed to be strictly limited and specific to a species, i.e. nothing could be done about aging. The origin of the

species-specific, limited lifespan paradigm can be traced back to Aristotle and Buffon. But over the past two decades gerontology has experienced a paradigm shift. Many experiments on flies, worms, yeast, rodents and other species led to the discovery that dietary restriction can prolong survival, helping shape the newly emerging insight that lifespan is not limited but plastic. Vaupel et al. [201] present age-patterns of mortality based on large sample sizes that do not increase steeply but instead level off or even decline at later ages for several species, thereby disproving the limited lifespan paradigm. Research on nematode worms, starting with Klass and Hirsch [99] and Johnson and Wood [89], demonstrates that changes in single genes can radically alter longevity.

One of the most remarkable examples of the plasticity of aging is presented in a paper by Mair et al. [116] that shows that changes in diet enable switching up and down between different mortality curves in *Drosophila*. Vaupel et al. [205] point out that similar patterns of switches have been observed in humans. Vaupel and colleagues show that mortality is plastic in humans even at advanced ages. One illustration is the convergence of mortality patterns in East and West Germany after reunification.

Indeed, a lot can be done about aging. The shift from the limited to the plastic lifespan paradigm is a major step forward in understanding senescence, exemplifying the importance of moving beyond a "deleterious fixation".

In the following, I list some other recalcitrant concepts that have channeled thinking on aging.

- Universal senescence
  Hamilton made the dogmatic claim that the force of selection inevitably declines, thus postulating the universality of senescence. This has restricted creative thinking about possible age-patterns of mortality.
  How universal is senescence?
- Gompertz Law
  It is widely believed that the age-pattern of mortality follows Gompertz law, but is it a law? We do not know what species exhibit this pattern over what range of age.
  How universal is an exponentially increasing hazard of death?
- No senescence in the wild
  It is often asserted that senescence is not experienced in the wild because individuals do not live long enough due to a high extrinsic hazard of death. This conjecture is intuitively appealing but it might

be wrong, as pointed out by Nesse [138] and Carey and Gruenfelder [18]. Carey and Gruenfelder summarize information available on the role of the elderly in primates, elephants and whales. Furthermore, Carey's recent observation of supine behavior in medflies – flies approaching death start lying on their backs, taking a rest once in a while over the remaining days of their lives – indicates that interesting patterns of senescence may be open to study.

Is there senescence in the wild? What are the age-patterns of mortality in the wild compared to those of creatures in captivity?

- Extrinsic hazard of death

  Is it useful to distinguish between "extrinsic" and "intrinsic" hazards of death? The "intrinsic" hazard depends on age or, more generally, on an individual's state or condition. Are there "extrinsic" hazards that are independent of age or condition?

  Extrinsic mortality is sometimes understood to be captured by the difference in mortality patterns of animals in the wild compared to patterns of those in captivity. However, animals kept in the zoo cannot pursue their natural behavior, for instance running long distances. The lack of exercise and of other behaviors performed in natural environments might distort mortality patterns in artificial habitats. Therefore, extrinsic mortality is not captured simply by the difference between mortality patterns in the wild and in captivity.

  Probably most causes of death are condition-dependent. Natural catastrophes that kill all members of a group independently of condition could be seen as extrinsic risk, but such catastrophes may be rare.

  What causes of death are truly condition-independent for a particular species?

6.4.2 The Need for Data, Methods, and Measures

Future theories of the evolution of aging should rest on scientific evidence. So far, the empirical evidence available on the age-trajectories of mortality and fertility for most species is based on small sample sizes [56, 159, 189, 215]. Meaningful age-patterns of demographic schedules, however, need to be based on large numbers of individuals, especially when studying senescence, because the size of the "interesting", later age-groups is progressively diminished by death. Vaupel [202] and Vaupel et al. [201] review the current empirical evidence of age-trajectories of mortality for species that are based on large sample sizes. These

species include humans, *Drosophila*, medflies, three other species of fruit flies, a parasitoid wasp, the nematode worm *C. Elegans*, and yeast.

Serious study of the process of aging requires knowledge about actual patterns across a wide range of very different species. Biologists interested in different species collect a large amount of data on their particular species to answer their particular questions. It would be useful to obtain knowledge about what data are out there and whether people would be willing to contribute their data to a large database that allows for broad comparative studies of life-history patterns. A comparative study of the qualitative age-trajectories of mortality and fertility including candidates from the whole range of species with sufficiently large sample sizes is essential for developing theories of the evolution of aging.[1]

Methods need to be developed and applied that allow extraction of as much information as possible from the data available. Combining information from different data sources can lead to more conclusive results as emphasized by Anatoli Yashin and colleagues [217, 218]. An important step has recently been taken by James Carey and colleagues [130]: they developed a method for constructing life tables for captured cohorts of unknown age.[2] Their method circumvents the necessity to follow individuals longitudinally in the wild from birth onwards.

In addition to the strong need for new data and methods, it is important to develop a deeper understanding of how to measure senescence and sustenance. I suggest defining senescence as was discussed in Chap. 1: senescence occurs if but only if the relative change in mortality with age exceeds the relative change in fertility. I further suggest a general measure for the degree of senescence of a whole life history (Chap. 5): the fraction of life time reproduction that is realized at ages at which mortality increases. When gathering data to get comparative evidence it is essential to agree upon what is to be measured and compared.

[1] The Max Planck Institute for Demographic Research in Rostock has started a project headed by Alexander Scheuerlein to collect data-sets on patterns of mortality, fertility and growth for non-human species, in captivity and in the wild. A related research initiative will be coordinated at Duke University by Cliff Cunningham and will involve Jim Clark, James R. Carey and others. Other researchers, including Shripad Tuljapurkar and Steven Orzack, Susan Alberts and Tim Coulson, are also in the process of building databases on age-trajectories of mortality, fertility, and growth. The ISIS (International Species Information System) provides data for species kept in zoos; these data have recently been used to calculated comparative life tables for selected species of captive animals [100].

[2] This became necessary because the capture-recapture approach is not feasible for some species, including the medflies studied by Carey.

Even though the ultimate interest of evolutionary demography is focused on patterns over age, the deeper causal link is more than likely with stage and not age. Models should be based on stage and incorporate a biologically justified link from stage to age. Empirical observations and theoretical insights should be used to identify the crucial stage-variables that determine mortality and fertility patterns of a species. These variables need to be measured and included in the data sets.

6.4.3 A New Burning Question

A major and very important focus of research over the last decades has been testing which of the two leading theories, mutation accumulation vs. antagonistic pleiotropy, has more power to explain the evolution of senescence. Half a century after Medawar, Williams and Hamilton, evidence has been published both for and against mutation accumulation and antagonistic pleiotropy. The debate has still not been settled. Recent contributions include Charlesworth and Hughes [30], Charlesworth [29], Hughes et al. [84], Partridge and Barton [148], Partridge [147] and Steinsaltz et al. [187].

This monograph shows that senescence and sustenance are two sides of the process of aging. One cannot be deeply understood without the other. The new burning question that arises from my work is: when does senescence vs. sustenance evolve? An overarching theme that could guide theoretical and empirical work is: to what extent are age-schedules shaped by adaptive vs. non-adaptive processes? What I have done in this monograph is to broaden the focus from

- mutation accumulation vs. antagonistic pleiotropy to explain senescence to
- adaptive vs. non-adaptive theories to explain senescence vs. sustenance.

Medawar, Williams and Hamilton developed the basic ideas of the evolutionary theories of aging. The broadened focus suggested here allows us a wider perspective.

Adaptive

Adaptive theories explain aging as a byproduct of evolutionary optimization. Such theories are based on models of optimization constrained by trade-offs. Antagonistic pleiotropy and the disposable soma

theory are adaptive theories of senescence. Senescence, which in itself is always a maladaptive process, is selected for because the trade-offs that constrain the life history are such that the benefits in fitness outweigh the costs due to senescence.

Reliability theory [65, 81, 108, 203] is another adaptive approach to explain senescence. Individuals are adapted to functioning over a sufficient period to guarantee the transmission of their genes. The subsequent senescent process is a byproduct that is determined by the preceding adaptive pattern.

If senescence and sustenance, i.e. aging, is explained by adaptive processes, then understanding is needed of the factors that have a strong impact on selection pressure vs. the factors that change selection pressure only slightly. Identification of the "strong forces" vs. "weak forces" of selection would provide a priority list of factors for understanding what shapes the age pattern of demographic schedules and its underlying variables[3]. For instance, Smith et al. [181, p. 1042, Fig. 5] show that environmental conditions can radically change stage-specific (and thereby age-specific) selection pressure. That is, the factor "environment" changes the importance of the different life-history transitions among states. This means that the variability of the environment is a strong force of selection. Note that, for this example (a threatened floodplain plant), selection pressure is highly state- but not age-dependent.

The list of valuable extensions to evolutionary demographic models given above in Sect. 6.3 is, likewise, a list of strong forces of selection, i.e. variability of the environment, density dependence, resource transfers, dynamics within and across species and probably more. Clearly, these components could interact with each other. Such interactions together with trade-offs among life-history traits at different ages can lead to dynamics that are not captured by the simple age-specific changes assumed in the indicators for the force of selection discussed in Chap. 2.

Non-adaptive

A non-adaptive theory is about what the force of selection cannot achieve. From the viewpoint of a non-adaptive theory, senescence exists because evolution is not strong enough to eradicate it. Sustenance, on the other hand, cannot be explained by non-adaptive theories. Only adaptive approaches have the potential to fully explain the aging process, while non-adaptive theory can partially account for the senescent

[3] I am grateful to Marc Tatar and Daniel Promislow for discussions about this.

side of the story. This indicates that adaptive approaches will be more powerful in explaining the aging process, although non-adaptive approaches could still play some role in explaining senescence.

The theory of mutation accumulation is a non-adaptive theory. The successive weakening of the force of selection for or against mutations implies that these mutations become increasingly neutral. Neutral theory explains the fate of a gene due to genetic drift and this drift strongly depends on population size. In this regard, assumptions about the time-horizon (infinite vs. finite) and the rate at which mutations occur at different ages are crucial to the conclusions from any mutation-accumulation model.

Over the last few years mounting knowledge about the human genome has been accumulating. Sufficient data are now available to check for age-specific gene-expression patterns in humans and also in other species such as *Drosophila*. It is possible to compare the fraction of individuals exhibiting neutral versus non-neutral mutations at young versus old ages. Evolutionary theories of senescence predict that falling selection pressure should make non-neutral mutations look more and more like neutral mutations as age increases. So if the fraction of individuals exhibiting non-neutral age-specific mutations becomes more similar over age to the fraction with neutral mutations, then this would be evidence for senescence being influenced by a non-adaptive process.

Evolution is constrained by phylogenetic history. A species can exhibit a non-adaptive age-pattern because a particular evolutionary path channels traits to a limited, possibly sub-optimal range. These phylogenetic channels could only be overcome in the very long run. So both mutation accumulation and phylogeny are non-adaptive forces shaping aging.

Further Thoughts

Creative thinking about alternative approaches to explain aging is needed. What are possible factors that shape the age-trajectories of mortality and fertility? Williams's hypothesis suggests the crucial importance of the extrinsic hazard of death. His hypothesis has been tested and evidence has been found for and against it. The contradictory evidence shows that this single factor is not enough to explain the pace of senescence. Williams identified one important variable that now needs to be put into perspective with other possible candidates.

What combination of these candidates leads to what qualitative age-pattern? In particular, when does senescence evolve and when sustenance? Clear, testable hypotheses need to be derived from theoretical

models and empirical observations for what qualitative patterns of mortality and fertility are expected and when. My models in Chaps. 4 and 5 are a first systematic contribution to answering this question. My findings suggest that attention should be given to the costs of maintenance and reproduction.

An equally interesting and related question is how plastic the process of aging can be. For instance, studies of human twins have shown that the same genome can be associated with different patterns of senescence due to phenotypic plasticity. Only 25 % of the variation among humans in life expectancy can be attributed to genetic variation [79, 125]. So, how heterogeneous are species with respect to aging? What species have high plasticity, what species have low plasticity, what characteristics determine the degree of plasticity? Understanding the plasticity of senescence and sustenance would provide a strong tool in steering our own process of aging in the most advantageous way, i.e. towards a long and healthy life.

6.5 Conclusion

Senescence and sustenance are described by the age-trajectories of mortality and fertility. The age-trajectories of mortality and fertility are the fundamental demographic schedules: they determine the dynamics and structures of populations. In particular, they determine a population's genetic structure and size. Evolution can be viewed as change in genetic structure and size of populations over time. Changes in genetic structure lead to changes in age-trajectories. Therefore, evolution molds and is molded by demographic schedules of mortality and fertility. To understand the evolution of life it is crucial to study these schedules. Mortality and fertility are deeply interconnected with each other and in particular with the age-schedule of growth. The models developed in the previous chapters shed new theoretical light on the evolution of the age-schedules of mortality, fertility and growth and their interconnections.

My models suggest that a remarkable variety of patterns may be optimal under different circumstances. The limited empirical data available suggests that species may exhibit a rich diversity of age-schedules of mortality, fertility and growth. Current understanding of the biology of aging is largely based on laboratory studies of a restricted range of species. Getting reliable data on a wide variety of species is a crucial research need.

The evolutionary demographic theory of aging should aim at illuminating senescence vs. sustenance through the study of the age-patterns of mortality, fertility and growth. In particular, the research should explain why some species have a quickly or slowly increasing hazard of death and why others have a constant or falling hazard of death. The models I have developed are a first step towards gaining a deeper understanding of the evolution of senescence vs. sustenance. They lead to the general insight that the costs of maintenance and reproduction are the major determinants shaping these patterns.

In addition to exploring alternative qualitative patterns, evolutionary demographic theory should shed light on questions such as why some species live on short time scales and others on long ones, why some species grow large and others stay tiny and why some species produce numerous small progeny while others produce only few large progeny compared to adult body size. Thinking about scales of time and size could aid in the understanding of what kinds of species exhibit senescence vs. sustenance.

These species can be classified according to several characteristics. How such typologies map onto the typologies of senescence vs. sustenance will undoubtedly be a stimulating direction for future research.

Senescence is not inevitable. Life provides an alternative strategy: sustenance. Sustenance can theoretically be an optimal life-history strategy and is empirically observed for some species. Sustenance may be the strategy for a great many species in which mortality appears to fall or be constant over age, at least over an extended period of life after reproductive maturity. More extensive empirical evidence is needed for a broad range of species beyond humans, rodents, flies, nematodes and yeast. My thesis, the central insight of this work, is: to deeply understand why some species senesce, it is necessary to understand why other species do not.