3

Further Challenges

Hamilton's claim of the inevitability of senescence can be disproved even within his own framework. Furthermore, his framework has several limitations. In this chapter theoretical and empirical issues that weaken his approach as the main explanation for the evolution of senescence will be discussed. Building on Medawar [126] and Williams [212], Hamilton wrote the pioneering *first* chapter on the moulding of senescence.

I draw two main conclusions.

- First, Hamilton's basic notion – that the age-pattern of mortality is an inverse function of the age-pattern of his indicator – is wrong. For both his indicator and the other indicators in Table 2.1 the relationship between the indicator and mortality is so complicated that sophisticated modeling is required.
- Second, several theoretical arguments as well as the bulk of empirical findings suggest that mutation accumulation is of secondary importance in molding the age-trajectories of mortality across the varied species of life. The primary force appears to be adaptation, i.e. the concept that patterns of aging are a byproduct of optimization of trade-offs. Hence, deep understanding of the evolution of aging requires optimization modeling.

3.1 General Problem with All Indicators

Because his indicator declines with age, Hamilton deduced that mortality must increase with age. The relationship between his indicator of selection pressure and the age-pattern of mortality is not a simple one, however. During development his indicator is constant, while mortality,

for many and perhaps all species, is falling. At post-reproductive ages his indicator is zero, while mortality, at least in humans, rises and then slowly levels off. Although the mismatch between indicator and pattern was acknowledged by Hamilton himself, an inverse relation between his indicator and the age-pattern of mortality is commonly assumed. The main justification, from Hamilton onwards, appears to be that there is an inverse relation between his indicator and the age-trajectory of mortality at reproductive ages in humans.

It is well known among plant biologists that many plants are capable of reducing their hazard of death by continued growth after the onset of reproduction. As discussed later in this chapter, various animals show negligibly increasing or declining mortality. I will show in Chaps. 4 and 5 that optimization models can lead to strategies where mortality is constant or keeps on falling after reproductive maturity. Figure 3.1 compares these patterns to Hamilton's inevitably decreasing indicator. It is clear that mortality is not necessarily an inverse function of Hamilton's indicator.

The alternative indicator that I suggested for the force of selection can increase with age, but only if the hazard of death is increasing. The indicator, however, can also decrease when the hazard of death is increasing: whether the indicator increases or decreases depends on how fertility is changing. Furthermore, the indicator decreases if the hazard of death is decreasing. So, as with Hamilton's indicator, the alternative indicator is not necessarily inversely related to the age-pattern of mortality.

But then how are the indicators of the force of selection against senescence related to the shape of the age-pattern of mortality? Hamilton quantified the selection pressure but he did not think carefully about the response to that pressure, although he acknowledges that "what way life schedules will be moulded by natural selection depends on what sort of genetical variation is available" [76, p. 118]. Lande [105] emphasizes that the change in a phenotype is determined by selection pressure (i.e. the indicator) together with the response matrix (the so called G-matrix), which includes variances and covariances for all fitness-relevant traits. The matrix not only takes into account "genetical variation" but also trade-offs among traits. Hamilton ignored these trade-offs.

The indicator of selection pressure together with the response matrix yields information about *short* term evolutionary processes. The implications for the long term, however, cannot be readily assessed because

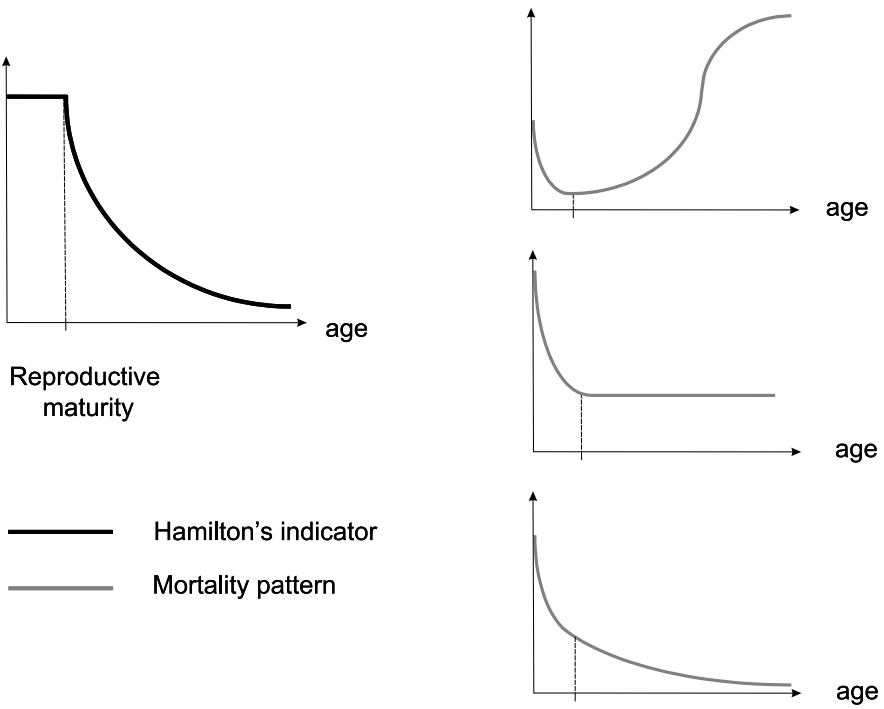

Fig. 3.1. The relation between Hamilton's declining indicator of selection pressure (*left side, in black*) and three possible age-patterns of mortality (*right side, in grey*)

the selection pressure is determined by what it shapes. The calculation of the indicator of selection pressure is based on the age-trajectories of mortality and fertility, and these trajectories depend on current levels of fitness-relevant traits. The entries in the G-matrix correspond to the variances and covariances at current levels of traits. But if, say, n traits are involved, then the indicator as well as the matrix take different values in an n-dimensional space. Evolution moves a species in this space at the speed and in the direction specifically determined by its position in that space. As position changes, speed and direction change.

In other words, as traits are shaped by evolution, they re-shape the selection pressure and possibly the G-matrix. It is not clear whether this process will ultimately converge and, if it does, to what evolutionary equilibrium. Since the force of selection is essential for evolutionary demographic theory, the implications of this feedback loop have to be understood. This requires modeling.

In sum, the quantities in Table 2.1 are *indicators* of the force of selection. They can provide an impression of the short-term direction and magnitude of the force of selection on age-specific survival and reproduction. But they are only one aspect of a multi-faceted story.

3.2 Theoretical Arguments

3.2.1 Mutation–Selection Balance

If mutation accumulation were the main explanation for senescence, which Hamilton assumes is a trait that is common to all individuals in a population, then each individual must be affected. For any particular deleterious mutation, mutation–selection balance implies that at least some individuals do not carry that mutation, namely those individuals in the zero-box. As long as selection pressure significantly exceeds mutation pressure, most individuals will be in the zero-box. Therefore, each individual would have to have his or her own set of deleterious mutations, being non-mutant for some genes and mutant for others. If genes had large and/or epistatic (non-linear) effects, a small set of genes could be sufficient. A population however, would then be highly heterogeneous, with some individuals suffering a rapid increase in mortality and others enjoying slow or postponed senescence. This does not appear to be the case, at least not for humans. Low variance in the age of senescent death requires the existence of many genes that have negative effects towards the end of reproductive life but no effects before that. Hamilton's theory assumes then that many genes have small effects that act additively. I will review the empirical evidence for age-specific, late-acting mutations in a subsequent section.

If there are few genes that have age-specific effects, then for mutation accumulation to be the main cause of senescence, these genes must be fixed in the population to lead to the phenomenon of senescence, which Hamilton claims to be universal. Fixation of a mutation implies that every individual in the population carries the same mutant allele for the gene in question. In this theoretical model this means that no individual is left in the zero box. The fixation of deleterious mutations at advanced ages poses a further challenge: unraveling.

3.2.2 Unraveling

Human mortality rises much more slowly than suggested by the results in Fig. 2.5, consistent with an earlier, similar observation by Abrams

[2, p. 357f]. This leads to a problem we have not yet touched on. All the indicators in Table 2.1 imply that the force of selection drops to zero when reproduction ceases. Several authors have argued that recurrent, deleterious mutations that only effect post-reproductive ages would become fixed, yielding a black hole of death at the age when reproduction ends [32, 146, 198, 208]. This could have been shown in all the figures above if the curves were drawn to higher ages. As $h_a^\dagger$ approaches ν, the equilibrium number of mutations steeply rises.

However, remaining reproduction $h_a^\dagger$ is calculated on the basis of a non-mutant life-history schedule. As $h_a^\dagger$ approaches zero, the equilibrium number of mutations rises to its maximum number at the age when $0 < h_a^\dagger << \nu$, even though a small fraction of reproduction is left. Hence, all bad genes after that age are fixed in the population and no individual is left with the non-mutant schedule. The disadvantage of carrying the mutation disappears, since every individual carries it. The fitness differential with respect to that mutation is gone. Therefore, a new $h_a^\dagger$ that falls more quickly near the end of reproductive life determines the selection pressure. Consequently, the point at which all mutations become fixed moves forward to a younger age. This process of unraveling would move the wall of death to younger and younger ages until it ultimately reaches maturity. Semelparity would be the only life-history strategy possible, which clearly is not the case.

Unraveling crucially depends on the age-trajectory of the mutation pressure. The age–window at the end of reproductive life, when selection pressure is weak and mutation pressure is strong, might be small. Let a be the first age when remaining reproduction is much smaller in magnitude compared to the mutation pressure, i.e. $0 < h_a^\dagger << \nu$, and A the age from which onwards remaining reproduction is zero, i.e. $h_A^\dagger = 0$. Unraveling will occur only if there are mutations whose effects become apparent inside but not before the age interval $[a, A]$. On the other hand, mutation accumulation will shape the age-pattern of mortality only if there are mutations that increase mortality at older ages, including within the interval $[a, A]$. Furthermore, such mutations cannot have major effects at ages where selection pressure is high.

In sum, there are many restrictions on the nature of the mutations that could permit mutation accumulation to shape aging, as discussed in this section and in the previous section. We will see in Sect. 3.3.1 below, that it is not clear that enough such mutations exist.

3.2.3 Variable Environments

Hamilton assumes a constant environment but environments are – in fact – variable. Accounting for changing environments can weaken mutation accumulation considerably. As the environment switches between good and bad times, it becomes essential during bad periods (during droughts, for example) to survive a long time in order to reproduce at all. Such a period would create a bottleneck. Only those individuals that were able to switch to a "survival mode", having no or very few bad mutations at higher ages, would constitute the gene-pool for all following generations, cleaning out any mutation accumulation.

Many species are able to switch between different life-history strategies depending on environmental conditions [7, 20, 63]. The same genome allows for strategies that can substantially differ in life expectancy. Given the short-lived strategy that might be optimal under average environmental conditions, mutations are predicted to accumulate at ages beyond the corresponding expected end of life. These mutations would raise mortality, preventing a substantial extension of lifespan, i.e. switching to the long-lived strategy. For species with alternative short and long-lived strategies, an increase in mortality with age in the short-lived strategy cannot be explained by mutation accumulation.

This reasoning only holds if mutations are assumed to be age-specific, i.e. time counting. Probably, however, gene expression is state-specific rather than age-specific. In this case a deleterious mutation could hide in the genome if the respective gene is not expressed in survival mode.

State– or condition-specific mutations could also explain results from an experiment conducted in Linda Partridge's laboratory. Mair et al. [116] show that dietary shifts can lead to switching between two different trajectories of mortality, one for the line on a restricted diet and one for the unrestricted line. The possibility of immediate shifts between a higher and a lower mortality curve in both directions, up and down, cannot be explained by simple mutation accumulation, especially since the shifts can occur at both younger and older ages. Such shifts and other kinds of plasticity in the age-pattern of mortality can, however, be explained by optimization models, as I discuss in Chap. 6.

Let me also note that the influence of unpredictable, stochastic environments (and in this regard also finite population sizes, finite time, and neutral theory) cannot be neglected when explaining the evolution of senescence [143, 199]. I will return to these points in Chap. 6.

3.2.4 Other Mechanisms

Variable environments are one counter–mechanism against mutation accumulation. Other mechanisms that can reduce the amount of mutations accumulating are synergistic epistasis and the occurrence of beneficial mutations [177, 211]. In the former case, the force of selection prevents the accumulation of mutations more strongly, because mutational effects magnify each other. In the latter case, the beneficial effect of some mutations offsets the deleterious effect of other mutations and therefore prevents an increase in mortality. Note that optimization of age-patterns of mortality, fertility and other traits results from the selection of beneficial mutations.

Hamilton pointed out that his results cannot explain the decline in mortality during development nor the existence of a post-reproductive period. Hamilton hypothesized that parental care is a missing piece in his framework that could account for both decreasing juvenile mortality as well as life after the end of reproduction. Parental care is a special form of resource transfer from parents to offspring. Lee, [109], Chu and Lee [36] and Robson and Kaplan [168] argue that intergenerational transfers that are made before, at and after birth can significantly influence the evolution of life-history schedules and, in particular, could explain the U-shaped trajectory of mortality in humans.

3.3 Empirical Evidence

3.3.1 Testing Preconditions for Mutation Accumulation

Three important preconditions for Hamilton's approach are:

- The existence of genes with effects confined to particular ages, especially to later ages.
- Mutations in these genes have small, deleterious effects.
- Effects of mutations do not interact with each other.

These preconditions have been tested empirically with an emphasis on the first condition.

To test the first precondition for the theory of mutation accumulation two large demographic studies in *Drosophila* have been conducted. Pletcher et al. [155] used inbred lines and found only weak evidence for the existence of mutations with deleterious effects confined to higher ages. The mutational load at later ages of their lines, however, might have been effectively saturated because of inbreeding depression (Yampolsky et al. [216], see also Sgrò and Partridge [178]). Negative epistasis

at such a high mutational load could explain the results of Pletcher and colleagues [155]. Yampolsky and colleagues [216] conducted experiments with outbred lines of *Drosophila* and found clear evidence for age-specific effects after 10 and 20 generations. This evidence, however, decreased after 30 generations.

Evidence from Pletcher et al. [156] (for *Drosophila*) and Golden and Melov [67] (for *C. elegans*), who tested age-specific gene-expression levels, supports the existence of genes with age-specific effects, whereas Landis et al. [106] found a small tendency towards down-regulation of energy metabolism genes in *Drosophila* over adult ages. As a general pattern for both *Drosophila* and *C. elegans*, McCarroll et al. [124] found gene expression levels to be higher at younger ages than at later ages.

The second precondition of mutation accumulation is that mutations have small effects. Some mutations may, however, have major effects. It has been shown that the lifespan can be strongly effected by single mutations in *C.elegans* [89, 113] and *Drosophila* [40, 112, 145, 190].

Hamilton's third precondition is that aging-related genes should effect mortality in a linear, i.e. non-epistatic, manner. It has been shown, however, that genes effecting the lifespan of flies and worms interact [110, 180] and their expression depends on their genetic background [185]. Recently, Spencer and Promislow [184] showed for *Drosophila* that gene $\times$ genetic background interactions not only affect lifespan as a whole, but they also affect mortality in an age-specific manner. They conclude that aging-related traits could, to a significant extent, be shaped by age-specific epistasis. This possibility has not been considered so far in the evolutionary theories of senescence. The epistatic action of aging-related genes is further supported by Promislow [160], who shows that proteins associated with senescence interact more strongly than would be expected by chance.

If mutation accumulation were the main cause of senescence, the empirical evidence should be abundant and clear. The evidence, however, suggests that two out of three preconditions may be violated and evidence for the first precondition is not unambiguous.

3.3.2 Checking Predictions from Mutation Accumulation

If mutation accumulation were at work, then a main prediction is that there will be an increase in genetic variation and inbreeding effects with age. The evidence for an increase in genetic variation is mixed. Some evidence supports such an increase [82, 83] whereas others report an increase in genetic variance early in life followed by a decline in later life

[161, 191]. The strongest support for the mutation accumulation theory is given by Hughes et al. [84], who show a marked increase in both genetic variation and inbreeding effects in *Drosophila* with age. The authors emphasize that the increase in inbreeding effects is expected only under mutation accumulation, not under antagonistic pleiotrophy [30]. Caution should be exercised regarding evidence of increasing inbreeding depression with age because old flies may just be more enfeebled and hence susceptible to the effects of inbreeding.

On the basis of his results, Hamilton made predictions about the age-pattern of mortality. He inferred that mortality should be lowest at reproductive maturity and "trails upward indefinitely at the right ... roughly asymptotic to the age of the ending of reproduction" [76, p. 119], i.e. the theory of mutation accumulation would rule out the existence of a post-reproductive period. Mortality trajectories at older ages, however, have been found to level off and, in some studies, to decline for humans and various species kept in protected environments [21, 32, 47, 151, 201]. Several species studied in the laboratory have been shown to enjoy an extended period of post-reproductive life.

The level of extrinsic mortality determines the age beyond which remaining reproduction ($h_a^\dagger$) becomes negligible in the wild. This is the age at which Hamilton predicts a steep increase in mortality. The higher the extrinsic risk of death, the earlier the age at which mutations could accumulate. Hence, animals kept in laboratories, zoos, or other protected environments should suffer senescence at ages few of them would reach in the wild. Their lifespans should not exceed maximum lifespan in the wild. Many lab and zoo animals, however, live much longer than in the wild [19, 21]).

Furthermore, when kept protected from extrinsic hazards, a steeper rise in mortality with age is predicted for populations from high risk environments than for populations from lower risk environments. However, guppies from high risk pools showed a slower pace of senescence than guppies from lower risk pools when brought into the laboratory [163], contrary to the prediction of mutation accumulation theory. Differences in phenotypic development under high and low density conditions is one explanation for this phenomenon. Abrams [4] discusses this and several other explanations for the guppy puzzle. To explain long lives in protected environments, alternatives to the theory of mutation accumulation, e.g., alternatives based on optimization approaches, have to be found.

3.3.3 Empirical Evidence for Non-senescence

According to Hamilton senescence should be a ubiquitous characteristic of life histories, and mortality should start rising when reproductive maturity is reached. Three well-known gerontologists [43, 56, 188] emphasized, however, that "certain animals and plants do not manifest increases of mortality rate or other signs of senescence" [56, p. 221]. In particular, Finch [56, 57], Finch and Austad [58] and Ottinger et al. [144] have prepared the way for studies of non-senescence by focusing research on species with " negligible senescence", i.e., species for which death rates rise very slowly, if at all, with age. Caswell [23, p. 39] discusses increases in fertility as well as decreases in mortality with size (and therefore with age) and provides numerous examples and references.

The strongest evidence for non-senescence in animal species comes from studies of corals. Babcook [10] shows in three coral species (*Goniastrea aspera, G. favulus, and Platygyra sinensis*) that mortality is inversely related to colony size and age. Furthermore, the total fecundity of the three species increases steeply with size and age, "due to a combination of increased polyp fecundity and increased surface area"[10]. Grigg [70] presents comparable results for two other corals, *Muricea californica* and *Muricea fruticosa*.

Like the massive reef-building corals, some plants develop into large clonal clusters [56, Table 4.2, p. 229]. The quaking aspen (*Populus tremuloides*) grove studied by Kemperman and Barnes [93] covered 81,000 square meters and was estimated to be at least 10,000 years old. It seems likely that the bigger such a clonal cluster is, the lower is its chance of death.

Other species that are candidates for non-senescence include the wild leek *Allium tricocum* [136], brown algae *Ascophyllum nodosum* [1], the forest tree *Garcinia lucida* [71], the neotropical tree *Cecropia obtusifolia* [6] and the cushion plant *Limonium delicatulum* [78].

Strong evidence for a period of parallel increase in age-specific survival and fertility in non-modular animals can be found for some species of molluscs. Fertility often increases by ten-fold or so as individuals grow following reproductive maturity, and mortality decreases sharply (e.g., for the marine gastropods *Umbonium costatum* [139, 140] and *Littorina rudis* [85] and the bivalve *Yoldia notabilis* [134, 135]). There is also evidence of non-senescence for echinoderms such as sea urchins [53]. Hydra species [123] are likely candidates as well.

Some vertebrates may possibly enjoy non-senescence. Finch [56] summarizes suggestive data on rockfish, hagfish and various other

species. For some reptiles, death rates decline somewhat after the age of reproductive maturity is reached, e.g., for *Sceloporus graciosus* [195], some populations of *Sceloporus undulatus* [194] and some populations of *Lacerta vivipara* [80][1].

Kohler et al. [100] analyze data sets for various species living in zoos and aquaria worldwide. They state that "there are several groups for which the age-pattern of mortality is nearly level". Comparing survival probabilities from the first decade of life (age 1 to 10, i.e. excluding juvenile death) with the second decade of life the evidence shows that raptors and crocodiles enjoy better survival in the second decade of their lives than in the first decade. Ratites show no signs of decrease in survival probability from their first to their second decade of life.

Non-senescent life histories cannot be explained by mutation accumulation.

3.4 Conclusion

The empirical evidence together with the theoretical arguments presented in this chapter indicate that mutation accumulation theory does not provide the fundamental explanation for the evolution of age-patterns of mortality. Together with my results from Chap. 2 they cast doubt on the assertion that senescence is inevitable.

It seems likely that the variety of possible age-trajectories of mortality is broad. Figure 3.2 summarizes various possibilities. During the first phase of life, development, mortality declines. During the second phase, mortality may increase, it may remain roughly constant, or it may decline. Then late in life, when most adults are dead, mortality may increase, level off or decline.

The age that marks the start and end of the different phases might be influenced strongly by growth patterns. For some species, growth ceases at reproductive maturity and marks the age when mortality starts rising. As noted above, however, individuals from many species continue to grow after the onset of reproduction and mortality may continue to fall until the age when growth stops. Models are needed to study which of these hypothetical age-patterns are theoretically possible. I will derive such models in the following two chapters.

[1] I thank my colleague Martin Dölling for his substantial help in gathering the references regarding evidence of non-senescent species.

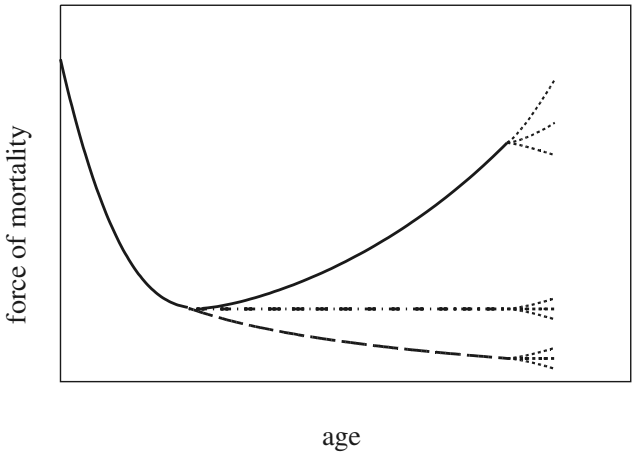

Fig. 3.2. Different hypothetical mortality trajectories

Note that the age-pattern of mortality reflects the average mortality in the population. The frail tend to die first. Hence, as individuals die, average mortality successively approaches the individual mortality trajectory of the most robust ones. The more heterogeneous a population is, the stronger is this effect. Therefore the age-pattern of mortality might exhibit a leveling and even a decline in mortality although the underlying individual age-pattern is still increasing [32, 151, 204, 206, 207].

The evidence suggests that mortality and fertility over the bulk of reproductive life are shaped by mechanisms other than mutation accumulation. Theories based on trade-offs might explain the existence of non-senescent life-history strategies [147, 148, 150]. It is not clear whether mutation accumulation plays a significant role in the evolution of senescence. If it turns out that mutation accumulation is an important mechanism for some species at older ages, then models of mutation accumulation need to be combined with trade-off models of the evolution of senescence to clarify the dynamics of demographic schedules [2, 200]. In the following two chapters, I develop trade-off models and explore their implications for the evolution of the age-patterns of mortality.