Part I

Hamilton

2

Hamilton's Indicators of the Force of Selection

2.1 Introduction

To quantify the force of selection, Hamilton derived expressions for the change in fitness with respect to age-specific mutations. Hamilton's indicators are decreasing functions of age. He concluded that senescence is inevitable: survival and fertility must decline with age. I show that an alternative parametrization of mutational effects leads to indicators that can increase with age. I then consider the case of deleterious mutations with age-specific effects. In this case, it is the balance between mutation and selection pressure that determines the equilibrium number of mutations in a population. In this balance the effects of different parameterizations cancel out, but only to a linear approximation. I show that mutation accumulation has little impact at ages when this linear approximation holds. When mutation accumulation matters, nonlinear effects become important and the parameterizations of mutational effects make a difference. The results also suggest that mutation accumulation may be relatively unimportant over most of the reproductive lifespan of any species.

Senescence can be defined as an increase in mortality and/or a decrease in fertility with age. Is senescence a universal characteristic of life? It is not obvious from an evolutionary perspective why it should be. Early in life, when individuals develop and grow, mortality falls and reproductive potential increases. Why is it that these age-patterns cannot persist, in some form, with mortality continuing to decline and reproductive capacity continuing to increase? George C. Williams [212, p. 398] wrote:

"It is indeed remarkable that after a seemingly miraculous feat of morphogenesis a complex metazoan should be unable to perform the much simpler task of merely maintaining what is already formed".

William D. Hamilton's influential article on "The Moulding of Senescence by Natural Selection" [75, 76] provides a reason why senescence "cannot be avoided by any conceivable organism". Hamilton combines insights about the evolution of senescence [126, 212] with concepts and models of population dynamics [115]. Hamilton asserts that " senescence is an inevitable outcome of evolution". Did Hamilton genuinely prove that senescence is theoretically inevitable?

2.2 Hamilton's Derivations

How does a mutation that acts only at a specific age a influence the evolutionary success of an individual? Does it matter if this age is early or late in life? Hamilton [75] built on the insight of Medawar [126] that later-acting genes should be under weaker selection than earlier-acting ones due to the unavoidable decline in the number of survivors at higher and higher ages. A genetically-determined fatal disease that struck only at post-reproductive ages would be entirely out of reach of the force of selection.

2.2.1 The Framework

To quantify the force of selection Hamilton considered age-specific, mutation-induced changes in fitness. Hamilton used the most widely-accepted measure of Darwinian fitness, the intrinsic rate of population increase r, implicitly defined by the discrete version of the Lotka equation

$$\sum_{x=0}^{\infty} e^{-r\,x}\, l_x\, m_x \;=\; 1\,. \tag{2.1}$$

The function l_x gives the chance of survival to age x. The function m_x measures the amount of reproduction at that age. If the population is stable, as assumed by Hamilton, then each combination of an age-specific maternity function m_x and an age-specific survival function l_x is associated with exactly one real r that satisfies (2.1).

The survival function l_x is defined as the product of the probabilities p_a of survival from age a to $a+1$:

$$l_x \;=\; p_0\, p_1 \;\ldots\; p_{x-1}\;, \tag{2.2}$$

with

$$l_0 \;=\; 1\;.$$

The age-specific survival probabilities p_a depend on the instantaneous death rate μ_t, the force of mortality between age a and $a+1$, via

$$p_a \;=\; e^{-\int_a^{a+1} \mu_t\, dt} \;=\; e^{-\bar{\mu}_a}\;. \tag{2.3}$$

The cumulative mortality in the exponent reflects the average mortality during that time interval, denoted by $\bar{\mu}_a$.

2.2.2 Hamilton's Indicator of Survival

By taking the derivative of (2.1) with respect to $\ln p_a$ and rearranging, Hamilton derived his basic result:

$$H^\dagger \;\equiv\; \frac{d\,r}{d\,\ln p_a} \;=\; \frac{\sum_{x=a+1}^{\infty}\; e^{-r\,x}\, l_x\, m_x}{\sum_{x=0}^{\infty}\; x\, e^{-r\,x}\, l_x\, m_x}\;. \tag{2.4a}$$

Note that (2.3) implies that $H^\dagger$ can also be expressed as:

$$H^\dagger \;\equiv\; -\,\frac{d\,r}{d\,\bar{\mu}_a}\;. \tag{2.4b}$$

The value of $H^\dagger$ is a measure of the force of selection. It captures the change in fitness r induced by an increase in $\ln p_a$. An increase in $\ln p_a$ is equivalent to a reduction in average mortality $\bar{\mu}_a$ between age a and $a+1$. This sensitivity of fitness to changes in age-specific survival is captured by the ratio of remaining reproduction, the numerator in (2.4a), to generation time, the denominator. Because $H^\dagger$ declines as age increases, Hamilton concluded that the force of selection must decline with age.

2.3 Alternative Indicators

2.3.1 Different Parametrization

Hamilton's conclusion hinges on the particular parametrization he chose for the nature of the effect of a mutation. Equally reasonable, alternative forms would have been dr/dp_a, dr/dq_a, $dr/d\ln q_a$ or $dr/d\ln \bar{\mu}_a$, where q_a is the probability of dying ($q_a = 1 - p_a$) and $\bar{\mu}_a$, as noted above, equals $-\ln p_a$. The results are as follows:

$$\frac{d\,r}{d\,p_a} = \frac{1}{p_a}\,H^{\dagger}, \tag{2.5a}$$

$$\frac{d\,r}{d\,q_a} = -\frac{1}{p_a}\,H^{\dagger}, \tag{2.5b}$$

$$\frac{d\,r}{d\,\ln q_a} = -\frac{q_a}{p_a}\,H^{\dagger} \tag{2.5c}$$

and

$$\frac{d\,r}{d\,\ln \bar{\mu}_a} = -\,\bar{\mu}_a\,H^{\dagger}\,. \tag{2.5d}$$

Strikingly, the expressions in (2.5a-d) can increase in absolute value with age – in contrast to $H^{\dagger}$, which always declines.

2.3.2 When Selection Pressure Increases

Consider, for instance, (2.5d). At pre-reproductive ages the value of $dr/d\ln\bar{\mu}_a$ is entirely determined by $\bar{\mu}_a$, as $H^{\dagger}$ is constant before maturity. At reproductive ages the change in fitness with respect to mortality increases from age a to $a+1$ if

$$\left|\frac{d\,r}{d\,\ln\bar{\mu}_a}\right| < \left|\frac{d\,r}{d\,\ln\bar{\mu}_{a+1}}\right|.$$

Substituting (2.5d) and (2.4a), and using the notion of reproductive value,

$$v_a = \frac{e^{r\,a}}{l_a}\,\sum_{x=a}^{\infty} e^{-r\,x}\,l_x\,m_x\,, \tag{2.6}$$

this inequality can be rearranged to give the following condition,

$$\left(\frac{\bar{\mu}_{a+1} - \bar{\mu}_a}{\bar{\mu}_{a+1}}\right)\frac{v_{a+1}}{m_{a+1}} > 1\,. \tag{2.7}$$

Hence, the value of $dr/d\ln\bar{\mu}_a$ will increase with age if $\bar{\mu}_a < \bar{\mu}_{a+1}$ and if future reproductive value is sufficiently large compared to fertility m_{a+1}. Taking into account the fact that (2.1) must hold, the inequality in (2.7) can be rearranged as

$$\left(\frac{\bar{\mu}_{a+1} - \bar{\mu}_a}{\bar{\mu}_{a+1}}\right)\frac{e^{r(a+1)}}{l_{a+1}}\left(1 - \sum_{x=0}^{a} e^{-r\,x}\,l_x\,m_x\right) > m_{a+1}\,. \qquad (2.8)$$

This inequality determines trajectories for m_{a+1} that lead to increasing sensitivity of fitness to changes in mortality over age given a specified, increasing path for $\bar{\mu}_a$. The survival and fertility functions plotted in Fig. 2.1 and the resulting indicators $dr/d\ln\bar{\mu}_a$ and $dr/d\ln p_a$ plotted in Fig. 2.2 provide an illustrative example.

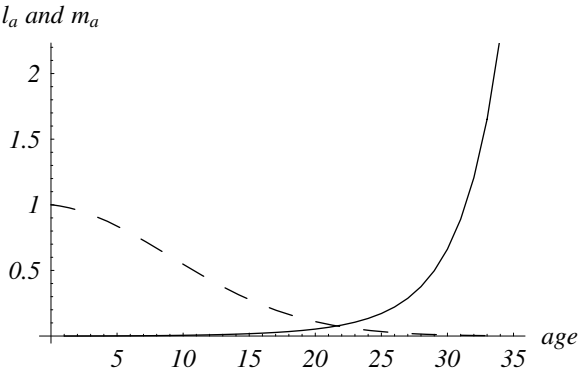

Fig. 2.1. Example of survival and maternity functions l_a and m_a (If age-specific survival probabilities p_a change according to $p_a = p_0^a$ with $p_0 < 1$, then the average force of mortality between age a and $a+1$ is given by $\bar{\mu}_a = -\ln p_0^a = -a\ln p_0$. Maternity m_{a+1} was chosen to be 0.01 units smaller than the left-hand side of the inequality in (2.8), setting $r = 0$, $p_0 = 0.99$ and $m_0 = 0$. By age 34, survival falls to 0.25%. After age 34, I fixed age-specific survival p_a at its level of $p_{35} = 0.70$ corresponding to $\bar{\mu}_{35} = 0.35$ and adjusted m_a to a constant level of 133.265 such that (2.1) is fulfilled.)

2.3.3 Fertility Indicators

The quantity Hamilton derived for the force of selection on age-specific mutations that affect fertility is

$$H^* \equiv \frac{d\,r}{d\,m_a} = \frac{e^{-r\,a}\,l_a}{\sum_{x=0}^{\infty} x\,e^{-r\,x}\,l_x\,m_x}\,. \qquad (2.9)$$

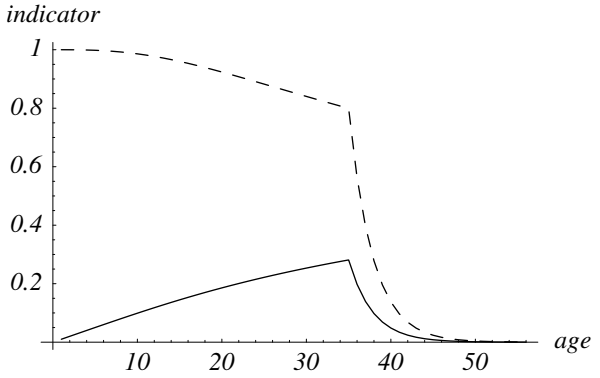

Fig. 2.2. Comparison of $H^\dagger = \frac{dr}{d \ln p_a}$ (*dashed line*) with $\frac{dr}{d \ln \bar{\mu}_a}$ (*solid line*) (While Hamilton's indicator $H^\dagger$ declines, the alternative one increases until age 34. The increase would have continued if m_{a+1} had been further determined by the inequality in (2.8). This, however, would result in a trajectory for m_a that would rise to enormous heights. Also note that Hamilton's indicator is greater than the alternative indicator, especially before age 35. This implies a considerably stronger force of selection on age-specific mutations that affect mortality.)

Hamilton considered survival effects on a log scale: He could have done the same for reproduction, calculating

$$\frac{d\,r}{d\,\ln m_a} \;=\; m_a\, H^* \;. \tag{2.10}$$

Hamilton's indicator in (2.9) necessarily declines with age but the alternative indicator in (2.10) can increase with age, depending on the trajectory of m_a.

Table 2.1 summarizes the direction of changes over age of the various indicators of the force of selection. The differences in the dynamics are due to the nonlinearity of logarithmic and exponential transformations.

2.3.4 Are Some Indicators Better?

Charlesworth [27, p.191], who reconstructed Hamilton's results, suggested that "genetic effects on survival probabilities are more likely to be additive on a log scale." His conjecture implies that mutations have additive effects on mortality. Indeed, both of Hamilton's indicators $H^\dagger = -dr/d\bar{\mu}$ and $H^* = dr/dm$ can be interpreted as assuming that mutations additively affect average mortality $\bar{\mu}$ and fertility m. This

Table 2.1. Various indicators of the force of selection in Hamilton's framework

Indicator	Change with age a
$\frac{d\,r}{d\,\ln p_a}$	$-$
$\frac{d\,r}{d\,p_a}$	$+$ or $-$*
$\frac{d\,r}{d\,q_a}$	$+$ or $-$
$\frac{d\,r}{d\,\ln q_a}$	$+$ or $-$
$\frac{d\,r}{d\,\ln \bar{\mu}_a}$	$+$ or $-$
$\frac{d\,r}{d\,m_a}$	$-$
$\frac{d\,r}{d\,\ln m_a}$	$+$ or $-$

* "$+$ or $-$" means that the change with age can be positive or negative, depending on the trajectories of m_x and l_x.

is plausible because additive risk models are widely used, most commonly in evolutionary modeling [23, 29]. The indicators $\bar{\mu}H^{\dagger}$ and mH^{*} capture the effect of a proportional change in $\bar{\mu}$ and m. Proportional-hazard models in general and Cox proportional-hazard models [45] in particular are frequently used in demographic and epidemiological research.

Deleterious mutations influence the internal condition of an organism. Internal conditions are known to interact with the environment [163, 214]. These interactions affect mortality in a non-additive manner. The idea that traits are likely to combine non-additively is also supported by recent work by Promislow [160] and Spencer and Promislow [184] which concerns the network structure of genes and epistasis respectively.

Whether age-specific mutations act proportionally or additively has been a question for empirical research. Support for the preeminence of proportional hazards comes from *Drosophila*. The study by Promislow and colleagues [161] of additive genetic variance favors proportional hazards. In the papers by Good and Tatar [68] and Mair et al. [116] change in current nutrient conditions affects mortality in a proportional manner. Furthermore, many mutants extend lifespan in *Drosophila* be-

cause they reduce mortality proportionally [87, 112, 170]). An exception is the work on the mutant chico [197]. Evidence for proportional hazards also comes from baboons [14] and mice [60] [1].

Numerous demographic and epidemiological analyses of risk factors have found that proportional effects are more common than additive effects. In particular, the impact of genetic polymorphisms, such as ApoE 2, 3 and 4, on mortality has been modeled by proportional hazards [66]. Empirical results reviewed by Promislow and Tatar [158] support the proportional-hazard assumption, suggesting that mutations act additively on log-mortality rather than log-survival. Hence, it seems plausible that the indicators $\bar{\mu}H^{\dagger}$ and mH^{*} will prove at least as valid as Hamilton's indicators.

2.3.5 Optimization vs. Mutational Burden

How mutations affect fitness is the focus of a vast literature [17, 27, 46, 54, 73, 74, 96]. Since Medawar [126] and Hamilton [75], many biologists have considered the sensitivity of fitness with respect to age-specific changes in survival or fertility [23] as an indicator of selection pressure. A key issue is whether age-patterns of mortality and fertility are molded by adaptive optimization processes or by the burden of non-adaptive mutations [2, 27, 147, 148]. Note that, in either case, an increase in mortality or a decrease in fertility is a byproduct of evolutionary processes. In the former case, senescence can arise as a side effect of an optimal balance between linked traits that effect fitness, and in the latter case senescence emerges as the weakening selection pressure is less and less successful in eradicating deleterious mutations.

Optimization models can be solved without using Hamilton's indicators [200]. If the age-patterns mainly reflect the age-specific burden of mutations, then Hamilton's indicators are not sufficient. Age-specific levels of birth and death rates depend not only on the selection pressure but also on mutation rates. In the following section I analyze this balance.

2.4 Mutation–Selection Balance

How do the alternatives of parametrization in Table 2.1 affect the equilibrium number of deleterious mutations at each age? In particular,

[1] I thank Marc Tatar for emphasizing the preeminence of proportional hazards and for pointing me to the relevant empirical evidence.

is the magnitude of mutation accumulation great enough to mold the trajectory of mortality?

The equilibrium number of mutations under mutation–selection balance can be approximated by the ratio of the total mutation rate ν (i.e., the hazard of a mutation from a set of possible mutations) and the change in fitness r:

$$\bar{n} \approx \frac{\nu}{\frac{dr}{dn}} , \tag{2.11}$$

where n denotes the number of mutations and $\bar{n}$ denotes the equilibrium number [27, pp. 125-126]. The approximation holds if ν and $\bar{n}$ are small. Using the chain rule, the derivative in (2.11) can be factored into the change in fitness with respect to survival or fertility and the effect on survival or fertility of having n mutations:

$$\frac{dr}{dn} = \frac{dr}{df}\frac{df}{dn} , \tag{2.12}$$

where f could be any of the denominators in Table 2.1.

2.4.1 Additive vs. Proportional Parametrization

Consider a mutation that has a small effect δ on mortality. Then f is equivalent to

$$\mu_a(n) = \mu_a(0) + n\,\delta \tag{2.13a}$$

in the additive case and

$$\ln \mu_a(n) = \ln \mu_a(0) + n\,\delta \tag{2.13b}$$

in the proportional case. From (2.11), (2.12) and Table 2.1 it follows that

$$\bar{n} \approx \frac{\nu}{h_a^\dagger\,\delta} \tag{2.14a}$$

in the additive case and

$$\bar{n} \approx \frac{\nu}{\mu_a(0)\,h_a^\dagger\,\delta} \tag{2.14b}$$

in the proportional case. In these ratios $h_a^\dagger$ denotes remaining reproduction at age a of an individual with no deleterious mutations. It is related to Hamilton's indicator via $h_a^\dagger = H_a^\dagger T$, where T captures generation time.

Combining (2.13) and (2.14) leads to the result

$$\mu_a(\bar{n}) \approx \mu_a(0) + \frac{\nu}{h_a^\dagger} \tag{2.15a}$$

in the additive case and

$$\mu_a(\bar{n}) \approx \mu_a(0) \exp\left(\frac{\nu}{\mu_a(0)\, h_a^\dagger}\right) \tag{2.15b}$$

in the proportional case. If mutations are rare, i.e. if $\nu/\mu_a(0)$ is small, then the formula for the proportional case can be approximated by

$$\mu_a(\bar{n}) \approx \mu_a(0)\left(1 + \frac{\nu}{\mu_a(0)\, h_a^\dagger}\right) = \mu_a(0) + \frac{\nu}{h_a^\dagger}\,. \tag{2.16}$$

Hence, if ν and $\bar{n}$ are small enough that the approximations in (2.11) and (2.16) hold, then mutation accumulation will result in about the same age-specific mortality regardless of whether mutations have additive or proportional effects.

2.4.2 A Simple Box Model

If $\bar{n}$ is large, an alternative approach is necessary. Several helpful models have been developed (e.g. [95, 127, 128, 142]); for a review see [17, 27]. A recent general model by Steinsaltz, Evans, and Wachter [187] includes earlier models as special cases.

A solution based on a simple box model similar to that of Kimura and Maruyama [95] can be readily developed. Assume a haploid, asexual population that is stationary in size. Further assume that mutations affect only one age class, to ensure that the equilibrium numbers of mutations are independent across ages. Focus on a single age a. Individuals are sorted into boxes according to their number of mutations at age a. Let $N(n)$ be the number of individuals in box n and let N be the total, constant population size at age a. In mutation–selection balance, the proportions $N(n)/N$ are fixed. Denote the lifetime reproduction of an individual in box n by $R(n)$. Let ν be the probability of passing on a new, additional mutation to the next generation. Assume that mutations occur successively, i.e. it is not possible to jump over boxes. Ignore back mutations. Mutations are deleterious, therefore $R(0) > R(1) > R(2) ... > R(K)$, K being some maximum number.

The number of individuals $N(n)$ in box n is given by the inflow of individuals minus the outflow per generation,

$$N(n) \;=\; N(n-1)\,R(n-1)\,\nu \;+\; N(n)\,R(n)\,(1-\nu)\;. \tag{2.17}$$

It follows immediately that reproduction in box zero is

$$R(0) \;=\; \frac{1}{1-\nu}\;. \tag{2.18}$$

In the case of mutations that affect mortality, the lifetime reproduction of individuals in the n'th box is given by

$$R(n) \;=\; \sum_{x=0}^{a-1} l_x\,m_x \;+\; e^{\mu_a(0)\,-\,\mu_a(n)} \sum_{x=a}^{\infty} l_x\,m_x\;. \tag{2.19}$$

This result can be expressed as

$$R(n) \;=\; R(0) \;-\; \Delta(n)\,h_a^{\dagger}\;, \tag{2.20}$$

where $\Delta(n)$ is the fraction of remaining reproduction $h_a^{\dagger}$ that is lost due to carrying n mutations. In the additive case

$$\Delta(n) \;=\; 1 \;-\; e^{-\delta\,n} \tag{2.21a}$$

and in the proportional case

$$\Delta(n) \;=\; 1 \;-\; e^{-\mu_a(0)\,(\exp[\delta\,n]\,-\,1)}\;. \tag{2.21b}$$

It follows from (2.17) and (2.20) that

$$N(n) \;=\; \frac{N(0)}{\prod_{k=1}^{n}\Delta(k)}\,R(0)^{n+1}\left(\frac{\nu}{h_a^{\dagger}}\right)^{n}\prod_{k=1}^{n-1}\left(\,R(0)\;-\;\Delta(k)\,h_a^{\dagger}\,\right). \tag{2.22}$$

The equilibrium number of mutations is the average over all boxes, i.e.

$$\bar{n} \;=\; \frac{\sum_{n=0}^{K} n\,N(n)}{\sum_{n=0}^{K} N(n)}\;. \tag{2.23}$$

Figure 2.3 plots the equilibrium number of mutations over age in the additive versus proportional case for the example presented in Fig. 2.1 and 2.2. As a second example I consider female mortality, as given in the Swedish life table for 1778-82. Results are shown in Figs. 2.4 and 2.5.

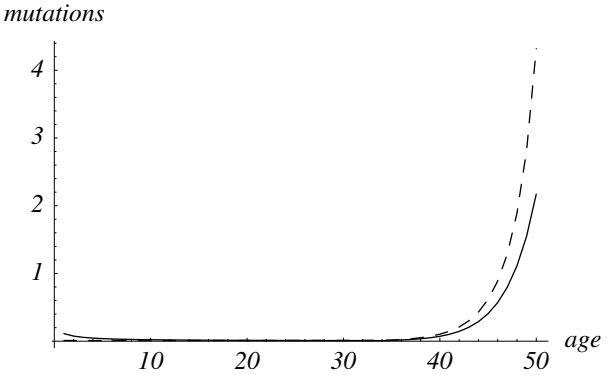

Fig. 2.3. Equilibrium number of mutations: additive (*dashed*), proportional (*solid*) (I assume that mutation pressure $\nu = 0.001$. Furthermore, I assume that a mutation at any age reduces remaining reproduction by about ten percent in both the additive and proportional case. This refers to an average reduction in the proportional case since $\Delta(n)$ depends on the level of mortality at age a, as can be seen from (2.21b). Specifically, $\delta = 0.1$ in (2.21a) and $\delta = 0.35$ in (2.21b). While in the Hamiltonian case of an additive hazard the number of mutations remains low and then increases with age, proportional effects lead to an age-specific mutational load that declines at young ages. In the example only one quarter of one percent of individuals are alive at age 34. Before this age the mutational load is close to zero. After this age, however, the equilibrium number of mutations rises sharply.)

The values of $h^\dagger$ that determine the number of mutations in Figs. 2.3 and 2.4 are calculated using specific *initial* fertility and mortality schedules. The mutations, however, will raise mortality, producing a new schedule that determines a new $h^\dagger$, as illustrated in Fig. 2.5. These dynamics are beyond the scope of this chapter. Note, however, that higher hazard rates would reduce the fitness costs of a change in age-specific mortality. Thus, more mutations would accumulate and the difference between additive and proportional parameterizations would be larger than predicted by my conservative estimate. A general treatment that takes into account interactions between ages is given by Steinsaltz, Evans, and Wachter [187].[2]

[2] I thank Kenneth W. Wachter and Brian Charlesworth for helping me considerably with this section.

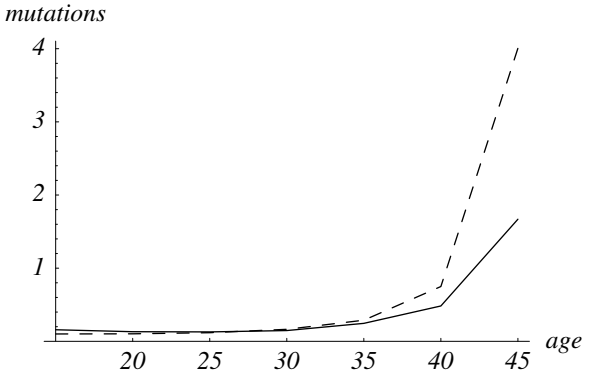

Fig. 2.4. Equilibrium number of mutations: additive (*dashed*), proportional (*solid*) (The example is based on female mortality as given in the Swedish life table for 1778-82, for seven 5-year age-groups, beginning at age 15. Since the Swedish population was growing at that time, I normalized reproduction to ensure $R = 1.00$. I consider a deleterious mutation that reduces remaining reproduction at any age by about one percent, either in an additive or in a proportional way, i.e. $\delta = 0.01$ in (2.21a) and $\delta = 0.7$ in (2.21b), and I assume a mutation pressure of $\nu = 0.001$. The difference between the additive and proportional case increases at higher ages, as levels of remaining reproduction decline. A slight decrease in the equilibrium number of mutations from the first to the second age-group can be observed.)

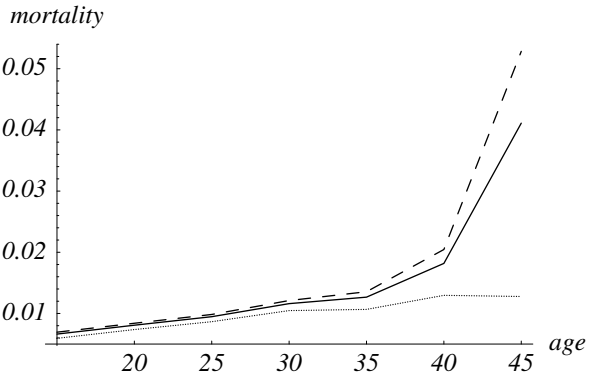

Fig. 2.5. Mortality: additive (*dashed*), proportional (*solid*), initial mortality $\mu_a(0)$(*dotted*) (Initial mortality is from the Swedish life table for 1778-82, females, for seven 5-year age-groups, beginning at age 15.)

2.5 The Importance of Mutation Accumulation

The age-trajectory of mortality can be decomposed into three parts: one component is due to the accumulation of unfavorable mutations, another fraction results from selection processes that optimize the trade-offs necessitated by resource limitations, and the remaining fraction can be attributed to unavoidable, external risks of death. How strong is the influence of mutation accumulation?

The relative impact of mutation accumulation on the molding of the mortality trajectory is crucially determined by the ratio of mutation pressure ν to remaining reproduction $h_a^\dagger$, as indicated by (2.14). The larger the value of ν, the more influential is mutation accumulation. But what is the magnitude of ν? Keightley and Charlesworth [92] point out that the rate of deleterious mutations per haploid genome in *C. elegans* in protein coding genes is about 0.5 per generation. Kimura and Maruyama [95] and Drake et al. [51] suggest mutation rates per genome per generation of about 0.1 and between $0.1 - 100$, respectively. More recent publications estimate the genomic rate of deleterious mutations in humans to be at least 1.6 [55] or even 3 [133] per generation.

If the fraction of mutations that exclusively affect mortality at a specific age is low, then these values could be consistent with a value of $\nu = 0.001$. If ν is 0.001, then Fig. 2.6 suggests that the influence of mutation accumulation is likely to be small over the major part of reproductive life. This remains speculation, however, until the magnitude of ν is estimated empirically. Abrams [2] provides suggestive evidence that the importance of mutation accumulation is likely to be small relative to the importance of optimization among trade-offs. Partridge [147] points out that little evidence can be found in favor of mutation accumulation but considerable evidence can be found to confirm the importance of trade-offs.

The conclusions drawn above and in the previous section were reached on the basis of a specific model of mutation accumulation. In general cases covered by the solutions given by Steinsaltz, Evans, and Wachter [187], the form of the mutation–selection equilibrium depends on the extent of assumed genetic recombination. At both extremes, in the absence of recombination (Equation 9 in their article) and in the presence of free recombination (Equation 27), the parametrization of the mutational effect, i.e. whether the effect is additive or proportional, influences the mutation–selection equilibrium.

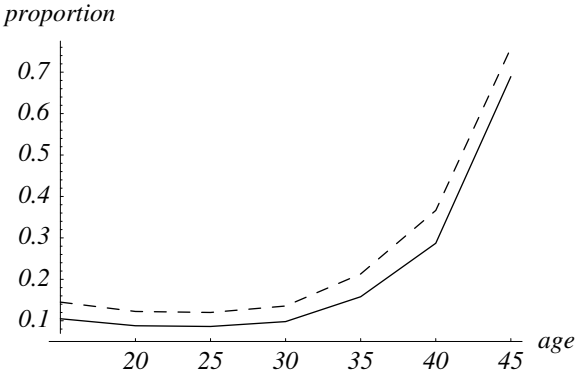

Fig. 2.6. Proportion of mortality explained by mutation accumulation: additive (*dashed*) vs. proportional (*solid*) case (The fraction $1 - \mu_a(0)/\mu_a(\bar{n})$ indicates the proportion of equilibrium mortality that can be explained by the accumulation of mutations. For the example of Swedish females, when $\nu = 0.001$, mutation accumulation explains less than a third of total mortality. At ages 45-50, however, when mortality is high and fertility is low, mutation accumulation accounts for the bulk of total mortality. Note that this illustrative example does not pertain to actual Swedish mortality but to the hypothetical outcome of one round of mutation accumulation: see Sect. 3.1 for further discussion.)

2.6 Conclusion

Hamilton stated that the force of selection inevitably has to decline with age, even "in the farthest reaches of almost any bizarre universe" [76]. He concluded that the declining selection pressure would mold the age-pattern of mortality in a way that mortality is lowest at reproductive maturity and "trails upward indefinitely at the right ... roughly asymptotic to the age of the ending of reproduction" [76, p. 119]. Hamilton's claim about the inevitability of senescence has been generally accepted, but it can be disproved, even adopting his restrictive assumptions. As shown above, alternative indicators can be derived, within Hamilton's own framework, that can result, in some circumstances and over some age ranges, in an increasing force of selection with age, thus contradicting the basis for his claim.

The results of this chapter strengthen the view that demographic schedules of mortality and fertility appear to be shaped largely by optimization of trade-offs rather than by mutation accumulation. Only at ages when remaining reproduction is low does the influence of mutation accumulation appear to become predominant. At those ages, different

parameterizations lead to different conclusions about the equilibrium number of mutations.

Some important empirical research questions are suggested by the theoretical findings of this chapter. Does the age-specific mutation rate ν change with age? If so, what is the age-trajectory of ν?