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Complex Adaptive Systems, Aging and Longevity

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Mortality and reproduction are intimately entwined in the study of aging and longevity. I apply the modern theory of complex adaptive systems (nonlinear, stochastic, dynamic methods) to questions of aging and longevity. I begin by highlighting major questions that must be answered in order to obtain a deeper understanding of aging. These are: (i) What should (in an evolutionary sense) mortality trajectories look like? (ii) Why does caloric restriction slow aging? (iii) Why does reproduction cause delayed mortality? (iv) Why does compensatory growth cause delayed mortality? I show how dynamic state variable models based on stochastic dynamic programming (Clark & Mangel, 2000) can be used to embed genetic theories of senescence (either mutation accumulation or antagonistic pleiotropy) in the somatic environment, as George Williams called for in 1957, and how they make the disposable soma theory of aging operational. Such models will allow unification of genetic and phenotypic theories of aging.

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1. Introduction

Lewis Thomas (1979, p. 101) recognized that understanding the complexity of living systems may be essential to understanding the nature of disease and aging when he wrote

> It may turn out, however, when we have learned more about pathogenesis in general, that *most of the events that underlie tissue damage in these diseases are host mechanisms, under host control. We are vulnerable because of our very intricacy and complexity*. We are systems of mechanisms, subject to all the small disturbances, tiny monkey wrenches, that can, in the end, produce the wracking and unhinging of interminable chains of coordinate, meticulously timed interaction.

More recently, the physician Nuland (1993, p. 73) noted that "The major question is not *whether* aging leads to debility, the inability to overcome disease, and then death, but *why* individuals age in the first place." Similarly, Kirkwood (1999a) emphasizes that the most important questions concerning aging are now evolutionary (that is, "why") ones.

I will approach questions concerning the evolutionary ecology of aging and longevity from the perspective of the modern theory of complex adaptive systems. General introductions can be found in Gleick (1988), Lewin (1999), Kellert (1993), Slobodkin (1992), and Waldrop (1992). More technical ones are Anonymous (1999), Belew & Mitchell (1996), Fox (1988), Glass & Mackey (1988), Kauffman (1993), Nijhout *et al.* (1997), Smith (1998), or Stein (1989). By a complex adaptive system, I understand a system that is composed of a diversity of components, interacting with and mutually affecting each other and by doing this leading to novel emergent behavior.

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I intend this not as a metaphor, but in the same spirit in which Lewin & Regine (2000, p. 18) write about complex adaptive systems in the business world: "… when we speak of businesses as complex adaptive systems we are not speaking of a metaphor or a technique; rather, we are saying that by understanding the characteristics of complex adaptive systems in general, we can find a way to understand and work with the deep nature of organizations". Similarly, understanding the nature of aging and longevity will require understanding the characteristics of complex adaptive systems. The tools for this study will be nonlinear, dynamic stochastic processes and optimization methods.

Our current conceptual understanding of aging and longevity was created by the great theoretical biologists R.A. Fisher ([1930], 2000), G.C. Williams (1957) and W.D. Hamilton (1966). The framework laid by Fisher, Williams and Hamilton has served well (Charlesworth, 1990, 1994), but is based on the Euler–Lotka equation that characterizes the growth rate of a population according to an age-dependent schedule of survival and fecundity. The Euler–Lotka equation is a typological approach that assumes that organisms are all the same, and that life history decisions are taken once and for an average environment. Surely none of this happens in nature (Vaupel *et al*., 1998): organisms and environments vary and there is phenotypic plasticity; the Euler–Lotka equation cannot account for these. Indeed, the Euler–Lotka equation treats the schedule of survival and fecundity as inputs, whereas they are also outputs of evolution of the life history. The Euler–Lotka equation was already a standard tool in the 1950s when Peter Medawar described aging as an unsolved problem of biology.

A life history theory without physiological state is like a population model without density dependence: one can learn something from it (and indeed we have), but it is very limited. A conceptual foundation for understanding different modes of aging requires accounting for physiological state as well as genes and the environment. The theory of condition-based life histories (Mangel & Clark, 1988; Clark & Mangel, 2000; Houston & McNamara, 1999) provides the conceptual foundation for doing this; the Euler–Lotka equation is a special case of this theory (Mangel, 1987).

In the next section, I introduce various definitions of aging and describe four questions which are of relevance today. In the third section, I develop a dynamic state variable model to show how mortality trajectories can be predicted from basic physiological processes and an evolutionary approach. I close the paper with an assessment for the future on the unification of genetic and phenotypic models of aging.

2. Defining Aging and the Four Questions

There are at least three definitions of aging in current use:

Physiological definition: Aging is a decline of state or repair with increasing age.

Actuarial definition: Aging is an increase of mortality rate with increasing age.

Evolutionary definition: Aging is the persistent decline in components of fitness (rates of survival and reproduction) with increasing age.

Thus, aging is a decline in physiological repair, an increase in probability of death and a decline in fertility with advancing adult age. Only a small proportion of individuals survive to become aged in nature, and the effects of aging are very much more obvious in captive populations living in benign conditions and in many human groups (Partridge & Mangel, 1999). It has long been recognized that aging is, in itself, maladaptive but that its rate can still evolve. Since the seminal work of Williams and Hamilton, two general genetic theories of aging have developed. Even where there is no aging, death will occur from extrinsic causes, such as disease, predation and accidents. Any new, harmful, mutation that affects the survival or fertility of the young will be expressed in most individuals that carry it, and thus will be subject to strong selection. In contrast, a mutation that affects only the old will be expressed solely in the few initial carriers that survive to old age; before then, the carriers die or become less fertile at a rate no different from non-carriers. Selection will therefore be weaker. The intensity of the natural selection maintaining viability and fertility therefore declines at later ages (Hamilton, 1966). Growth and learning can both lead to a decrease in mortality rate over at

least part of the adult period, but the intensity of selection maintaining survival and fertility must sooner or later decline with age. Selection will therefore be less able to eliminate new mutations with effects at later ages and they will rise to higher frequency under mutation-selection balance; this is called the mutation accumulation theory of aging (Hamilton, 1966; Partridge & Barton, 1993).

Aging can also evolve as a side-effect of the limited combinations of survival and fertility that organisms can achieve at different ages, because of their own biology and because of the ecological conditions that they encounter. If a new mutation arises that increases fitness at young ages (e.g. because it increases fertility then) but at the expense of lowered fitness later in life (e.g. because survival or fertility is reduced), natural selection can incorporate the mutation into the population despite its adverse effects later in life because selection will be stronger on the early, beneficial effect. This is called the antagonistic pleiotropy theory of aging (Williams, 1957; Partridge & Barton, 1993). Experimental support for either the mutation accumulation theory or the antagonistic pleiotropy theory of aging is mixed (Pletcher & Curstinger, 1998).

The antagonistic pleiotropy theory of aging requires that the same gene act in different ways at different ages. Furthermore, it is intimately connected to the soma; Williams noted that these must be pleiotropic genes of a special sort: "It is necessary to postulate genes that have opposite effects on fitness at different ages, or, more accurately, in different *somatic environments*" (p. 401; italics in original). For example, Lipman *et al.* (1999a) note that diet and sex both effect the prevalence of age-related lesions in rats with different genotypes. The genes cannot escape the soma.

A life history optimization theory of aging based in physiological ecology that converges with antagonistic pleiotropy is the notion of disposable soma (Kirkwood, 1977; Kirkwood & Rose, 1991). The disposable soma theory of aging is based on observations: (i) that most mortality in natural populations is due to extrinsic mortality, (ii) that somatic maintenance is costly, and (iii) that it is, in a Darwinian sense, disadvantageous to maintain the soma past the natural expectation of life. However, the disposable soma theory does not postulate an explicit genetic mechanism.

All three evolutionary theories of aging predict that the intrinsic rate of aging will evolve in response to the rate at which the intensity of selection on survival and fertility declines with age as a result of the impact of extrinsic hazards. Aging is caused by physiological wear and tear, but the extent to which damage is avoided, prevented or repaired evolves. These theories lead to the strong qualitative prediction that the rate of aging should increase for organisms that have evolved in situations where extrinsic mortality of young adults is higher and this prediction has been confirmed [e.g. Ricklefs (1998) and references therein].

Four important questions for which we have an incomplete understanding are given below.

What should (in an evolutionary sense) mortality trajectories look like? Since Medawar's classic work (see the 1952 essay in Medawar [1957] 1981), or even before that (Dublin *et al.* [1936] 1949), aging has often been interpreted synonymously with increasing mortality rates. Mortality rate at age t, $m(t)$, is fundamentally a population concept, since it is defined by relating cohort population size at age t, $N(t)$ and at age $t + \mathrm{d}t$ by

$$N(t + \mathrm{d}t) = N(t)\exp(-m(t)\,\mathrm{d}t). \tag{1}$$

If aging is interpreted as $m(t)$ increasing with t, then there are an infinite number of ways that this can happen. Two common models for the increase in mortality rate with age are the Gompertz model for which $m(t) = m_0 \mathrm{e}^{kt}$ and the Weibull model for which

$$m(t) = m_0 + at^b.$$

It is possible to characterize aging via a pair of differential equations. For example, for Gompertz aging these equations are (Easton, 1995)

$$\begin{aligned} \frac{\mathrm{d}N}{\mathrm{d}t} &= -m(t)N(\mathrm{t}), \\ \frac{\mathrm{d}m}{\mathrm{d}t} &= km(t), \end{aligned} \tag{2}$$

in which cohort size declines exponentially with age and mortality rate rises exponentially with age.

A variety of studies over the last 20 years show that mortality trajectories do not necessarily increase with age, but may level off or even decline with age (e.g. Vaupel *et al*., 1979; Hougaard, 1984; Vaupel & Yashin, 1985; Vaupel, 1990; Carey *et al*., 1992; Kowald & Kirkwood, 1993; Vaupel & Carey, 1993; Charlesworth & Partridge, 1997; Vaupel, 1997; Horiuchi & Wilmoth, 1998; Pletcher & Curtsinger, 1998; Horiuchi, 2000; Service, 2000; Tuljapurkar *et al*., 2000). We now understand that various kinds of heterogeneity can lead to the leveling of mortality trajectories. How mortality trajectories rise is of more than academic interest; it clearly underlies one of the most important social policy questions that the developed nations face in the 21st century (Lee & Tuljapurkar, 1997; Tuljapurkar & Boe, 1998; Bloom, 1999).

These studies show that we need to be able to predict the shapes of mortality trajectories, moving beyond curve fitting. Some recent attempts have been made. Mueller & Rose (1996) proposed a genetic (including both mutation accumulation and antagonistic pleiotropy) model for the prediction of the shape of mortality trajectories. However, there have been challenges to their claims (Charlesworth & Partridge, 1997; Pletcher & Curtsinger, 1998; Wachter, 1999; Kirkwood, 1999c). For example, Pletcher & Curtsinger (1998) and Wachter (1999) showed that the absorbing state of the Markov chain associated with the Mueller–Rose model does not have mortality plateaus, but that transient states, which correspond to populations that are not in genetic equilibrium, do. It may also be possible to apply genetic algorithms to the analysis of this problem (Oliveira *et al*., 1995; Penna & de Oliveira, 1995; Ito, 1996). Regardless of how one evaluates these claims and challenges, a purely genetic model still leaves the phenotype and soma out of the picture.

Why does caloric restriction slow aging? It was first observed in the 1930s and often confirmed since then (especially in laboratory studies) that caloric restriction (often called undernutrition without malnutrition) in the adult phase of life slows aging (Harrison & Archer, 1988; Weindruch *et al*., 1995; Weindruch & Sohal, 1997; Lipman *et al*., 1999b). Masoro & Austad (1996) noted

> Fitness, in the form of increased survival during unpredictable food shortages, will be enhanced in individuals with genomes that direct resources away from reproduction, thereby providing additional resources for successfully coping with environmental challenges (stressors). Thus, individuals with genomes of this sort are more likely to survive a period of food shortage and reproduce when food is once again abundant—clearly a selective advantage—than individuals with less plastic genomes" (p. B387).

Finch (1990) provides examples of natural situations where caloric restriction increases longevity. The reason for caloric restriction slowing aging is not fully known, but it may be related to oxidative damage or other costs of metabolism or growth (e.g. Holehan & Merry, 1986; Graves, 1993; Wolf *et al*., 1995; Sohal & Weindruch, 1996; Tatar & Promislow, 1997; Wolf & Pendergrass, 1999) and cell expression (Pendergrass *et al*., 1995; Lee *et al*., 1999).

Why does reproduction cause (*delayed*) *mortality?* It is also generally observed that reproduction causes an increase in mortality (Carey *et al*., 1986; Roitberg, 1989; Ernsting *et al*., 1993; Newton & Rothery, 1997; Westendorp & Kirkwood, 1998), but this may not always be the case (Le Bourg *et al*., 1993). Recent evidence suggests that the increase in mortality may be delayed to considerably later in life (Sgrò & Partridge, 1999) and that signals from the reproductive system regulate lifespan (Hsin & Kenyon, 1999; Walker *et al*. (2000)).

To illustrate this point, I reanalysed the data presented in Roitberg (1989), concerning survival and longevity of the tephritid fly *Rhagoletis basiola*. Briefly, Roitberg's results were that the survival curves of reproducing flies differed from that of non-reproducing but mated individuals (Fig. 1(a)); furthermore, through day 40 or 45, the survival curve of non-reproducing but mated individuals was statistically identical to that of unmated individuals (not shown here, but Fig. 1 of Roitberg 1989). The data are noisy, but show the pattern of increasing mortality with age (Fig. 1(b)). These data suggest that the process of reproduction itself leads to additional mortality

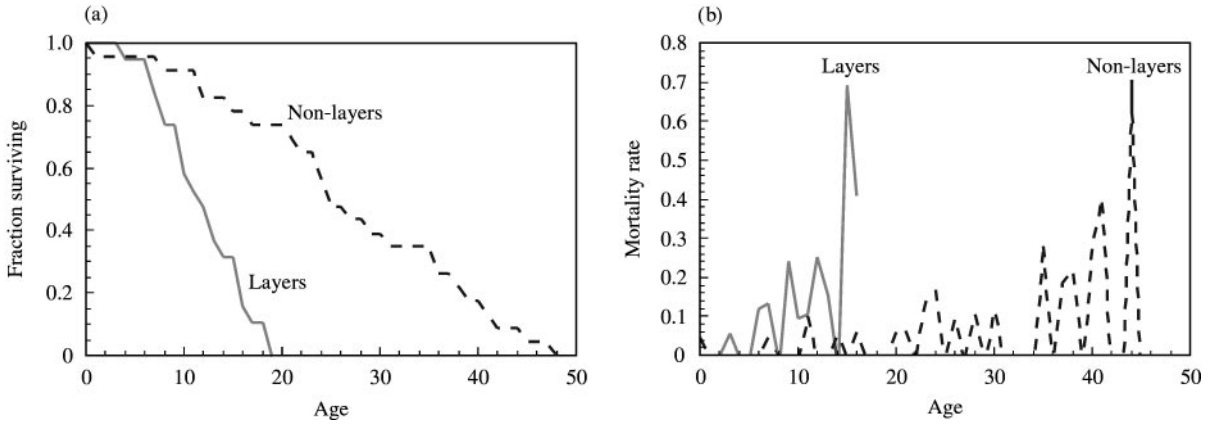

FIG. 1. (a) Roitberg (1989) discovered that female *Rhagoletis basiola* who laid eggs (solid line) had lower survival rates than those who did not lay eggs (dashed line). (b) Although the data are noisy, both layers and non-layers show the pattern of increasing mortality rate with increasing age.

and that non-reproductive individuals can still have a delayed but "classic" (Medawarian) pattern of aging; Westendorp & Kirkwood (1998) report similar patterns in British aristocratic women. On the other hand, Tatar & Promislow (1997) conclude that in *Drosophila melanogaster* there is a fitness cost to mating but not to egg production.

Why does compensatory growth cause delayed mortality? Compensatory growth occurs if organisms (usually juveniles) catch up from a period of resource shortage during which growth is slowed or stopped with rapid growth once resources become available again. Evidence is accumulating that such catch-up growth can have a variety of costs and that the costs may be deferred until much later in life (Hales *et al*., 1996 and references therein, Desai & Hales, 1997; Metcalfe & Monaghan, 2000). For example, Desai & Hales (1997) demonstrate that mice which had a compensatory growth period in the first three weeks of life had substantially higher mortality rates at ages 8–12 months. The detailed reasons for a longevity cost of compensatory growth are unknown, although they may involve a perturbation of normal development that is not fully recovered in later refeeding and thus leads to a more vulnerable adult phenotype, differential gene expression (Hill *et al*., 2000), telomere shortening (Jennings *et al*., 1999) or differential repair, as measured by protein turnover (Ricklefs *et al*., 1994; Conceicao *et al*., 1997; Morgan *et al*., 2000).

3. Dynamic State Variable Methods Make the Disposable Soma Theory Operational

Promislow & Tatar (1998) have called for more biologically realistic genetic models for the evolution of aging. Pletcher & Curtsinger (1998) agree; they propose that progress in understanding the nature of senescence can be made by developing models that incorporate pleiotropy and/or mechanistic constraints on mortality rate, classic demographic notions of heterogeneity and redundancy, optimality and quantitative genetics. Part of this realism must be to embed genes within organisms, i.e. to deal with the somatic environment that Williams identified in his 1957 paper. To be sure, we also need to make the connection work in the other direction (de Haan & van Zant, 1999). As described above, the Euler–Lotka equation cannot be used to predict the shape of mortality trajectories, since mortality trajectories are inputs to the Euler–Lotka equation. However, mortality trajectories are also outputs of life history evolution and thus to predict the shape of mortality trajectories one requires a life history model. Such a model must incorporate physiological state, because physiological state is clearly implicated in age-related mortality tradeoffs (Tatar & Carey, 1995) and because one of the fundamental definitions of aging is a decline of state with age. It is for this reason that dynamic state variable models (Mangel & Clark, 1988; Houston & McNamara,

1999; Clark & Mangel, 2000) are appropriate. Such models make the disposable soma theory of aging (Kirkwood, 1977, 1990, 199b; Kirkwood & Rose, 1991) operational (also see Abrams & Ludwig, 1995; Cichon & Kozlowski, 2000; Shanley & Kirkwood, 2000) and will ultimately allow us to link genetic models for mutation accumulation or antagonistic pleiotropy and life history optimization models. Here, I choose a particularly simple example, and focus on the conceptual framework, rather than develop a model of a particular system. Shanley & Kirkwood (2000) show, for example, how the details of functional form and parameters can be estimated when one is applying the approach to a particular system.

Models such as the one described in this section, and those of Abrams & Ludwig (1995), Houston & McNamara (1999), Cichon & Kozlowski (2000) or Shanley & Kirkwood (2000), can be used to investigate the effect of antagonistic pleiotropy or mutation accumulation. In doing this, it is important to recognize that Williams's view of antagonistic pleiotropy leads to senescence only if the genes that are favored in the young are the same genes that cause problems in the elderly. Thus, it is more than a life history tradeoff. To see the difference, imagine an insect that at pupation has total amount of resources R available for oviposition and somatic maintenance. This resource can be partitioned into a maximum number of eggs αR and resources available for somatic repair $(1-\alpha)R$. This is the life history tradeoff and can be analysed by a number of methods (Mangel & Clark, 1988; Clark & Mangel, 2000). Antagonistic pleiotropy arises in the allocation of repair over the life of the organism. That is, if $\rho(a)$ denotes the repair rate at age a, repair is now constrained by the condition that $(1-\alpha)R = \sum_a \rho(a)$ and it is clear that genes that increase repair at a young age perforce lower it at later ages. To be sure, it is likely that major components of the history (such as feeding and reproduction) may simultaneously have current and delayed effects on mortality; Tatar & Carey (1995) provide an example of this in the beetle *Callosobruchus maculatus*. Houston & McNamara (1999, p. 260) review an example of "apparent aging" which is also a result of a life history tradeoff, rather than bona fide aging.

One should not expect one dynamic state variable model to fit all biological situations (also see Chapter 4 in Clark & Mangel (2000) where this point is elaborated for the case of insect oviposition). Here I investigate a model in which repair rates are constant but damage accumulates. The model involves two state variables. The first, $X(t)$, characterizes resources available for living life and reproduction at age t. The second, $D(t)$, characterizes the accumulated damage to age t. Such damage is caused, for example, by metabolic by-products (Beckman & Ames, 1998), activity (Hayes *et al.*, 1992), or reproduction (Berube *et al.*, 1994). Death from one age to the next may be caused by external mortality, m_0, starvation, or damage. For simplicity, I treat them as independent effects (clearly, this need not be so, but again it is a simpler starting point), so that survival from age t to $t+1$, given that $X(t)=x$ and $D(t)=d$, is $\exp(-m_0)\sigma_x(x)\sigma_d(d)$, where

$$\sigma_x(x) = \min\left(1, \left(\frac{x}{x_c}\right)^4\right),$$
$$\sigma_d(d) = \max\left(0, 1-\left(\frac{d}{d_c}\right)^2\right). \tag{3}$$

Here x_c and d_c and the exponents are parameters; their values are given in Table 1. Sallee (1982) proved a general result that cellular senescence cannot be accounted for by linear damage; hence, I assume a nonlinear relationship between damage and survival. There are, of course, an infinite number of nonlinear relationships between damage or reserves and survival and eqn (3) is intended as an example. Shanley & Kirkwood (2000) show how such models can be fit to a particular situation.

State dynamics connect one age and the next. It is easiest to begin by considering the dynamics for a sterile individual. In this case, the dynamics are

$$X(t+1) = X(t) - \alpha X(t)^\beta + Y(t),$$
$$D(t+1) = D(t) + d_b + d_0\alpha X(t)^\beta - \rho. \tag{4}$$

TABLE 1
Parameters in the Dynamic State Variable Model

d_{max}	Maximum value of damage	50
d_c	Parameter in survival function	$0.7d_{max}$
x_{max}	Maximum value of state	37
x_c	Parameter in the survival function	$0.1x_{max}$
α	Metabolic coefficient	0.1
β	Metabolic exponent	0.75
Y_1	Energetic content of food, measured in units of the state variable	1.5
T	Maximum age	90
p_{00}	Probability an age with no food is followed by one with no food	0.5
p_{11}	Probability an age with food is followed by one with food	0.8
d_0	Metabolic-related damage parameters	0.05
d_b	Metabolic-independent damage parameters	0.25
ρ	Damage repair rate	$0.8d_b$
d_r	Damage due to reproduction	$0.6d_0$

In this equation, $\alpha X(t)^{\beta}$ characterizes metabolic costs and $Y(t)$ is the food available at age t and follows the generally well-known nonlinear allometric relationship between metabolic costs and reserves (Calder, 1984; Reiss, 1989; Zuev, 2000). Masoro & Austad (1996) consider that variations in food availability are crucial for understanding the evolution of plasticity in allocations between maintenance and reproduction. The simplest model for food availability is a two-state Markov process $Y(t) = Y_0 = 0$ (state 0) or $Y(t) = Y_1$ (state 1), where the latter is a fixed quantity. The transitions are characterized by $p_{ij} = Pr\{Y(t+1) = j \mid Y(t) = i\}$. The parameters d_b and d_0 characterize the way that damage accumulates independent of metabolism and dependent on metabolism respectively and ρ characterizes the repair of damage. I assume that repair is constant, but it could change with age. Clearly, one can combine d_b and ρ to work with the difference $d_b - \rho$; I separate them here to help identify the relevant physiological processes. I assume, as in Fig. 1, that although sterile or non-reproductive individuals tend to live longer than reproductive ones, they still age and ultimately show physiological senescence and may show actuarial senescence, as in the non-reproductive individuals in Fig. 1. This observation constrains the choice of parameters so that non-reproductive individuals ultimately age with increasing mortality rates.

Equations (4) can be iterated forward directly, once an initial condition is specified. For purposes of illustration, I assume that $X(0) = 0.4x_{\max} + 0.08x_{\max}Z$, where Z is normally distributed with mean 0 and standard deviation 1, $D(0) = 0.05d_c\exp(Z_{0.2} - 0.04)$ where $Z_{0.2}$ is normally distributed with mean 0 and standard deviation 0.2, no external mortality, and constant food. The latter conditions might apply to a "laboratory" setting for an organism that evolved under conditions of external mortality and fluctuating food supplies. I also consider "ad libitum" food (Y_0) or "caloric restriction" ($0.6Y_0$). It is then a simple matter, using eqns (3) and (4), to estimate survival to age and from that, mortality rate as a function of age. The results (Fig. 2) capture two key features of aging. Mortality rates rise with age and caloric restriction slows the rise of mortality because it reduces the state, which reduces the damage caused by metabolism. The slightly higher mortality rate for calorically restricted individuals at young age is due to starvation of individuals whose randomly chosen initial state is too small (cf. Mueller *et al*., 1997). Most importantly, the method provides a means to predict how much caloric restriction will slow aging. That is, given a set of parameters, a precise prediction about the nature of the mortality curve emerges.

The situation with non-sterile individuals is more complicated because the level of reproductive activity at each age must be characterized. For simplicity of illustrating the method, I consider univoltine organisms, so that a natural measure of Darwinian fitness is lifetime expected

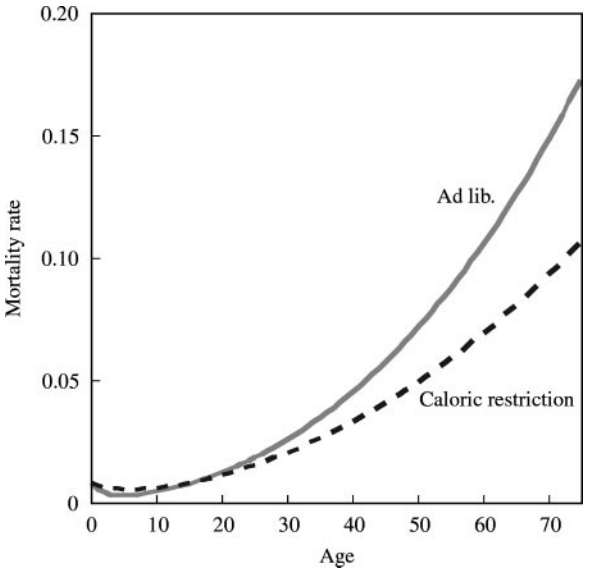

FIG. 2. The mortality rate as a function of age for sterile individuals in the dynamic state variable model under conditions of ad libitum food (solid line) or caloric restriction (dashed line), as described in the text.

reproduction; otherwise the conceptual framework does not change but the implementation details become much more complicated (see below). Univoltine organisms age, as the data in Fig. 1 show. Thus, the assumption of a univoltine lifestyle both simplifies the analysis and applies to at least some organisms of interest [indeed, aging could well be implicated in potential sympatric speciation in *Rhagoletis* spp. (Filchak *et al.*, 2000)].

To begin characterizing reproduction, assume that there is an age-dependent measure of the quality of $q(t)$ of offspring produced at age t

$$q(t) = \frac{t}{t + 0.2T}. \tag{5}$$

Qualitatively similar results are obtained if $q(t)$ is peaked rather than asymptotic. The choice of this function is to characterize improving egg quality as the individual ages [eqn (5)] or maximum egg quality at an intermediate age [peak $q(t)$]. I also assume that there is a minimum level of reserves x_r required for reproduction. If reserves are below the minimum, the state dynamics are given by eqn (4). If reserves are above the minimum and the reproductive effort is $C(t)$, the state dynamics are

$$\begin{aligned} X(t+1) &= X(t) - \alpha X(t)^{\beta} - C(t) + Y(t), \\ D(t+1) &= D(t) + d_b + d_0 \alpha X(t)^{\beta} + d_r C(t) - \rho \end{aligned} \tag{6}$$

so that reproduction decreases the state by $C(t)$ and increases damage by $d_r C(t)$, with the obvious interpretation of d_r. It is the connection between reproduction at age t and accumulated damage, which may lead to higher mortality rates later in life because of the nonlinear relationship between damage and survival, that makes this a model of antagonistic pleiotropy, rather than simply a model of a tradeoff between immediate survival and reproduction (see Mangel & Clark, 1988; Clark & Mangel, 2000 for examples of the latter).

To characterize the optimal level of reproduction define

$$\begin{aligned} F(x,d,i,t) = {} & \text{Maximum expected accumulated} \\ & \text{reproduction between age } t \text{ and age} \\ & T, \text{ given that } X(t) = x,\ D(t) = d, \\ & Y(t) = I. \end{aligned} \tag{7}$$

This function satisfies the end-of-life condition (Mangel & Clark, 1988; Clark & Mangel, 2000) $F(x,d,i,T) = 0$ for all x, d, and i.

For previous ages, $F(x,d,i,t)$ satisfies the equations of stochastic dynamic programming derived as follows. First, if $x < x_r$, $X(t) = x$ and $D(t) = d$, the states at the next age will be

$$\begin{aligned} x' &= x - \alpha x^{\beta} + Y_i, \\ d' &= d + d_b + d_0 \alpha x^{\beta} - \rho. \end{aligned} \tag{8}$$

Given these new states and the transition probabilities for food, the expected value of future reproduction is

$$\begin{aligned} F(x,d,i,t) = {} & \exp(-m_0)\sigma_x(x)\sigma_d(d) \\ & \times \sum_j p_{ij} F(x', d', j, t+1). \end{aligned} \tag{9}$$

If the state exceeds the minimum level needed for reproduction and reproductive effort is $C(t) = c$,

then the new states are

$$x'' = x - \alpha x^{\beta} - c + Y_i,$$

$$d'' = d + d_b + d_0 \alpha x^{\beta} + d_r c - \rho. \qquad (10)$$

It is the second line in eqn (10) that embeds antagonistic pleiotropy in a somatic context. If reserves x are constant, then the same level of reproduction early in life, when d will typically be small, will have a different effect on survival than later in life when d is larger. Furthermore, these models tend towards larger clutches later in life at the same level of reserves [see Chapter 4 of Clark & Mangel (2000) and references therein] so that one might expect an even bigger effect on survival of reproductive genes acting early or late in life.

Thus, if reproductive effort $C(t) = c$ increments lifetime reproductive success by an amount $f(c)q(t)$, the optimal level of reproductive effort is found as the solution of

$$F(x,d,i,t) = \max_c \left\{ f(c)q(t) + \exp(-m_0)\sigma_x(x)\sigma_d(d) \times \sum_j p_{ij} F(x'', d'', j, t+1) \right\}. \qquad (11)$$

For simplicity, I set $f(c) = c$; in more complicated cases (e.g. in which there is density dependence in offspring survival due to limited resources, Clark & Mangel (2000), reproductive accumulation could be a nonlinear function of reproductive effort. The solution of eqn (11) generates the optimal level of reproductive effort $C^*(x,d,t,i)$ for each state, age and food situation. Once this is determined, it is possible to conduct computer experiments similar to those done for the sterile individuals by forward iteration and Monte Carlo simulation (Clark & Mangel, 2000). That is, one follows the forward dynamics of equations analogous to eqns (4) (but taking into account the level of reproduction), in the absence of external mortality and with constant food. Using the same initial conditions as for the sterile individuals leads to the prediction of lower survival of reproductive individuals (Fig. 3(a)). Furthermore, mortality rates rise rapidly only after nearly 50% of cumulative reproduction has occurred (Fig. 3(b)). We thus predict a rise in mortality rates long after reproduction has begun.

A full sensitivity analysis is beyond the scope of the present paper. However, as with the mortality

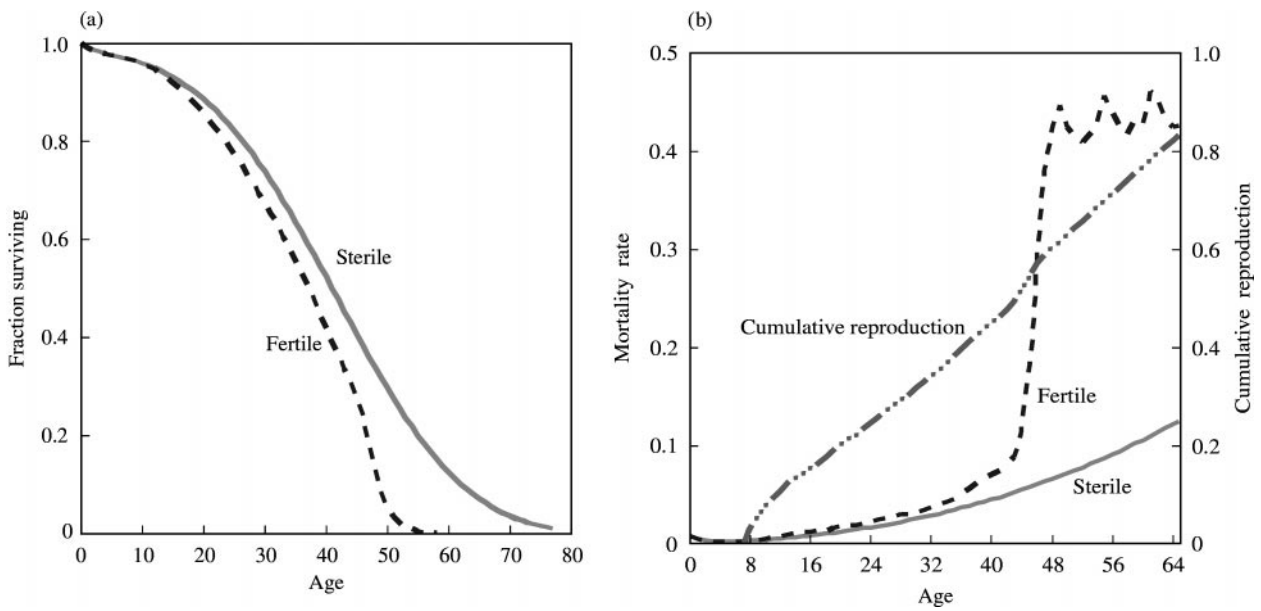

FIG. 3. (a) Survival of reproductive (fertile, dashed line) and sterile individuals (solid line). (b) Mortality rates of reproductive (fertile, dashed line) and sterile individuals and cumulative reproduction (dashed-dotted line) of the fertile individuals. Note that about 40% of the reproduction has occurred before mortality rates begin to rise.

rates of sterile individuals, the theory described here allows one to predict the shape of mortality curves based on fundamental physiological and ecological measurements. For example, with these methods we are able to predict how quickly mortality rates will rise and when and if they will plateau and how parameters and functional forms drive these behaviors of the solutions. Shanley & Kirkwood (2000) show how to parametrize a model in the same spirit as this one.

For the case of overlapping generations, reproduction needs to be discounted by the growth rate r of the population. However, the value of r used in the dynamic programming equations must be the same as that in the Euler–Lotka equation characterizing the growth rate of the population; this can be found by iteratively solving the two sets of equations (Mangel *et al*., 1994; Houston & McNamara, 1999; Clark & Mangel, 2000). That is, r is an ESS: the optimal individual response to a population growing at rate r must be the pattern of development, behavior and reproduction that generates this growth rate.

4. Discussion

Williams (1957) emphasized the importance of placing the genetic context within the somatic environment and Kirkwood (1999c, p. 387) that "gene effects will be modulated though continuous changes in the physiological status of the organism in a state-dependent manner. We need more evolutionary models which take this into account". This need is true for both mutation accumulation and antagonistic pleiotropy: both genotype and phenotype matter. The evolutionary models used here are phenotypic and there are no variables tracking alternative alleles at the genes which affect the life history attributes. The relationship between genetic and phenotypic models has received considerable attention over the years (e.g. Charlesworth, 1990; Grafen, 1991; Roff, 1992, 1997; Stearns, 1992) and will not be reviewed in detail here. Charlesworth (1990) investigated conditions under which life history optimization (based on the Euler–Lotka equation) and quantitative genetic models lead to the same conclusion, but as described above, the Euler–Lotka equation is insufficient for the task at hand. Whether or not a quantitative genetic model represents genetics, in the context of mutation accumulation or antagonistic pleiotropy, or more honestly phenotype can be debated too (Stearns & Hoekstra, 2000). Aging is both polygenic and multifactorial (Partridge & Barton, 1993; Schächter *et al*., 1993; Lee *et al*., 1999; Pletcher *et al*., 2000); for example Lee *et al*. (1999) monitored the expression of more than 6000 genes associated with aspects of aging and caloric restriction. My argument here is that there is a need for a plurality of approaches and for connecting the genetic and somatic aspects of aging and longevity.

Nearly 50 years after his classic paper, Williams (1992, p. 150) called once again for this kind of linkage:

> The problem of the evolution of senescence is solved, and in a general and qualitative way ... no recent work has improved on that of Hamilton (1966). Improvement is long overdue. We need an explicit theorem of the form
>
> $$y_x = f(\hat{y}, x, u, v, w \ \ldots),$$
>
> where y_x is a measure of adaptive performance at age x, like fleetness, visual acuity, or the ability to avoid death. The constant $\hat{y}$ would be the maximum value of y. The independent variables would include age (x) and perhaps age-specific survivals, fertilities, and other factors. The equation needs to be derived logically from a fitness-maximization model with realistic genetic, developmental, and demographic constraints. It must then be shown to predict successfully the effects of age on measures of adaptive performance in a diversity of populations subject to senescence.

Organisms are complex and variable, but much of that complexity and variability can be understood by application of modern conceptual tools that focus on nonlinear, stochastic and dynamic systems within a Darwinian framework that links physiological state, genes and the environment. Application of these methods will allow us to learn much about aging, longevity and senescence.

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