Available online at www.sciencedirect.com
SCIENCE DIRECT®
Theoretical Population Biology 65 (2004) 353–359
Theoretical Population Biology
http://www.elsevier.com/locate/ytpbi

The shape of things to come: using models with physiological structure to predict mortality trajectories

Marc Mangel[a,*] and Michael B. Bonsall[b]

[a] Department of Applied Mathematics and Statistics, Jack Baskin School of Engineering and Center for Stock Assessment Research, University of California, Santa Cruz, CA 95064, USA
[b] Department of Biological Sciences and NERC Centre for Population Biology, Imperial College at Silwood Park, Ascot, Berkshire SL5 7PY, UK

Received 14 August 2002

Abstract

If mortality rate is viewed as the outcome of processes of behavior, growth and reproduction, then it should be possible to predict mortality rate as a result of those processes. We provide two examples of how this may be done. In the first, we use the method of linear chains to treat mortality that is the result of multiple physiological processes, some of which may have delays. In the second, we assume that mortality is the result of damage associated with growth and metabolism. Both approaches lead to a rich diversity of predicted mortality trajectories. Although many of these look Gompertzian at young ages, the behavior at older ages depends upon the details of the physiological models.

1. Introduction

Mortality $\mu(t)$ for individuals of age t is perhaps the most fundamental demographic quantity (Preston et al., 2001), since it underlies calculations of population parameters via the Euler–Lotka equation and related tools. There are a number of ways of thinking about mortality rate in the context of theoretical population biology. First, mortality rate can be seen as an object of statistical analysis (Cox, 1972) and statistical prediction (Lee and Carter, 1992), with important policy implications (Fogel, 1993, 1994). Second, it can be viewed as the outcome of mutation-accumulation and other processes at the genetic level (Charlesworth and Hughes, 1996; Clarke et al., 2000; Charlesworth, 2001). Third, mortality can be viewed as the result of adaptive processes of behavior, growth and reproduction (Chicon and Kozlowski, 2000; Mangel, 2001a). Genetic and adaptationist views of mortality rate are essentially approaches based on ultimate considerations in which predictions are made by comparing a measure of genetic success in subsequent generations.

A fourth view, which is the one that we take here, is based on proximate considerations of physiological processes. That is, we view the mortality rate as both the product of natural selection acting on behavior, growth, and reproduction and of physiological realities within the life of an organism. With this viewpoint, the crucial physiological realities are that growth processes are linked and that growth comes with a (often deferred) cost, even if that cost can sometimes be fully repaid. The range of costs and consequences has recently been reviewed (Metcalfe and Monaghan, 2001; Lummaa and Clutton-Brock, 2002; Beckerman et al., 2002) and there are suggestions that costs associated with oxidative stress are intimately linked to health and fitness (Rikans and Hornbrook, 1997; von Schantz et al., 1999; Finkel and Holbrook, 2000; Ishii and Hartman, 2000; Sastre et al., 2000; Levine and Stadtman, 2001; Van Remmen and Richardson, 2001) in fundamental and immutable ways. This view is our starting point and will be an input to the evolutionary theories of development, aging and immortality (Rose and Mueller, 2000; Mangel, 2001b).

The classic model for mortality rate is due to Gompertz (1825) in which the size of a cohort declines exponentially according to $dN/dt = -\mu(t)N(t)$ and the mortality rate grows exponentially in time according to $d\mu/dt = k\mu$, so that $\mu(t) = \mu_0 \exp(kt)$. The Weibull model, for which $\mu(t) = \mu_0 + at^b$, is often proposed as an alternative, and has some useful properties because it allows one to separate initial mortality rate and the rate

*Corresponding author. Fax: +1-831-688-7017.
E-mail address: msmangel@ams.ucsc.edu (M. Mangel).

0040-5809/$ - see front matter © 2004 Elsevier Inc. All rights reserved.
doi:10.1016/j.tpb.2003.07.005

of aging (Ricklefs, 1998; Ricklefs and Scheurlein, 2001; Carey, 2003).

It is now generally agreed that there is a tendency for the mortality rate to decelerate at advanced ages (Vaupel, 1997; Rose and Mueller, 2000). That is, even after one accounts for heterogeneity in real populations (Vaupel and Yashin, 1985; Yashin and Iachine, 1995), a deceleration of mortality rate (or "mortality plateau") appears to be genuine at the largest ages. There is additional evidence that the mortality rate may, in fact, take a wide variety of patterns (Economos, 1979, 1982; Finch, 1990; Carey et al., 1992; Curtsinger et al., 1992). Two empirical tests have corroborated this hypothesis: Carey et al. (1992) showed that mortality rates in heterogeneous medfly populations decrease at older ages highlighting the possibility that mortality is not necessarily described by Gompertz's model. Curtsinger et al. (1992) showed a similar phenomenon in inbred *Drosophila melanogaster* populations: that age-specific mortality rates level off at advanced ages. Explaining these patterns at a genetic level has not been easy and generated some controversy (Mueller and Rose, 1996; Pletcher and Curstinger, 1998; Charlesworth, 2001). Models with physiological structure, such as the ones that we use in this paper, are a middle ground between those that are based on genetic mechanism and those that mix Gompertz or Weibull distributions.

In the next section, we develop a general theoretical framework for exploring changes in age-specific mortality rate as a result of multiple physiological processes. We illustrate a simple case, and in particular show that by accounting for physiological structure and lags, mortality rates can plateau in late life. We then explore how more mechanistic physiologically based models can also predict a range of age-specific mortality trajectories. Our work complements that of Sozou and Kirkwood (2001), von Zglinicki et al. (2001), and Proctor and Kirkwood (2002) on models for cellular senescence caused by oxidative and other stresses.

2. Mortality as a result of multiple physiological processes

If we view aging as the accumulation of cellular damage through molecular damage leading to functional impairment (e.g. de Boer et al., 2002), the implication is that there may be multiple mechanisms of aging and that damage accumulation is a lifelong process. We now develop a framework for exploring the hypothesis that aging is the accumulation of multiple physiological processes; similar approaches have been successfully applied to the study of development and maturation (Blythe et al., 1984).

In order to examine the consequences of different age-specific schedules, we assume that the rate of change of numbers in a cohort, $N(t)$, is determined by the accumulation of mortality over the whole lifetime. In the most general setting, mortality rate can depend upon age, population size and environment (Carey, 2003). Thus, in the most general case we write

$$\frac{dN}{dt} = -\left[\int_0^t \mu(s, N(s), E(s))ds\right] N(t), \tag{1}$$

where $\mu(s, N(s), E(s))$ is mortality rate in the interval s to $s + ds$ when the cohort size is $N(s)$ and the environment is $E(s)$. Mortality is the accumulation of multiple physiological processes, but in this framework the underlying mortality rate (μ) is fundamentally unobservable.

MacDonald (1978, 1989) introduced a technique, called the linear chain method, for dealing with such a situation. Although the method has been used before, it has not been used to explore the dynamics of mortality. It is a general method, in which no assumptions are made about underlying physiological processes (which we do in the next section) and thus allows us to explore the effects of physiological complexity on mortality rate.

The fundamental idea is to decompose the integral in Eq. (1) into a series (a chain) of linear ordinary differential equations for $N(t) = N_0(t)$ and auxiliary variables, $V_i(t)$, $i = 0, 2, \ldots, p$, where p is the order of the physiological lag and the dynamics are

$$\frac{dN}{dt} = -V_0 N, \tag{2}$$

$$\frac{dV_i}{dt} = \lambda_i(V_{i+1} - V_i), \quad i = 0, 1, 2, \ldots, p-1, \tag{3}$$

$$\frac{dV_p}{dt} = \lambda_p(\mu - V_p). \tag{4}$$

Here the λ_i are parameters that describe the overall rate of the chain. The idea is that a change in mortality rate μ has to propagate through the chain to change cohort size. In essence, this is a time-delayed process that allows physiological structure to be described in terms of a set of ordinary differential equations. By replacing Eq. (1) with $p + 1$ linear equations in which each equation links two successive members of a chain whose length is determined by the nature of the physiological lags, the accumulation of multiple modes of damage can be described. Larger values of p thus imply longer lags between a change in mortality rate and a change in cohort size. Similarly, larger values of the λ_i imply quicker responses by the cohort to changes in underlying mortality rate. Indeed, in the limit that $\lambda_i \to \infty$, we recover the standard model of exponential decay of the cohort.

It is straightforward to solve the set of equations from $t = 0$, once an appropriate set of initial values are given. Decomposing the integral of mortality (Eq. (1)) into this series of linked ODEs, allows the effects of multiple

physiological processes on mortality schedules to be defined.

Figs. 1 and 2 show the cohort survival curves and age-specific mortality trajectories for a third-, fifth- and ninth-order lagged models for all $\lambda_i = 0.1$ and $\mu = 0.1$. The model is able to describe a number of different cohort survival patterns from standard exponential decline to delayed mortality. A relative advantage of this approach is that we can describe varying patterns of cohort survival by accumulating different numbers of linear links. Moreover, age-specific mortality patterns reveal a degree of subtly in aging that cannot be captured with a standard Gompertz model (e.g. Easton, 1995). First, these physiologically lagged models allow mortality rates to plateau in late life (e.g. Mueller and Rose, 1996) and capture the principle that survival beyond a certain age is plausible: that is organisms are not necessarily programmed to die. By describing the accumulation of physiological processes as a set of linear ODEs, the model allows us to predict the deceleration of mortality rates in late life. Second, the shape of the age-specific mortality trajectory is a function of the number of distinct physiological lags that operate throughout an organism's life. Organisms with more distinct physiological structure are more likely to show protracted cohort survival and show delayed increase in age-specific mortality.

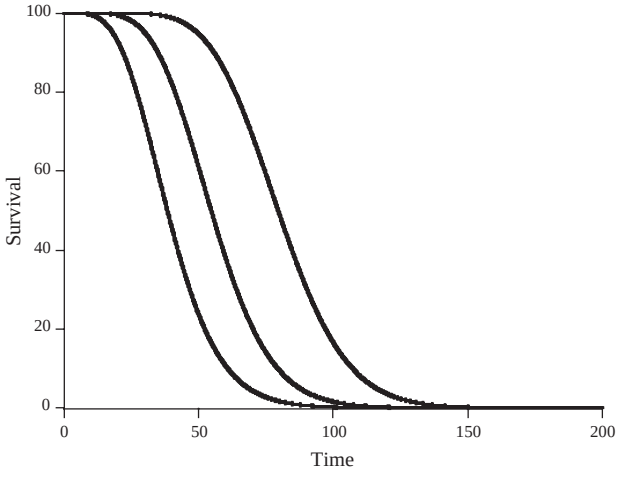

Fig. 1. Cohort survival for a third-, fifth- and ninth-order physiological lagged model. Other parameters are $\lambda_i = 0.1$, $\mu = 0.1$.

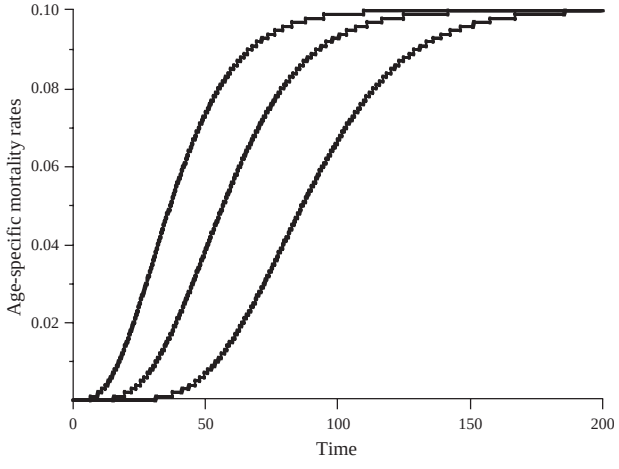

Fig. 2. Age-specific mortality rates a third-, fifth- and ninth-order physiological lagged model.

3. Mortality as a result of growth and metabolism

We now investigate a particular source of the physiological processes, oxidative damage associated with growth. As described above, oxidative stress may be a fundamental determinant of fitness (von Schantz et al., 1999; Gems, 1999); this view is consistent with the oxidative damage theory of aging (Ashok and Ali, 1999; Beckman and Ames, 1998). In particular, we assume that faster growth increases the abundance of reactive oxygen species (ROS). There is evidence that ROS can cause damage to proteins, DNA, and lipids (Tolmassof et al., 1980; Stadtman, 1992; Ames et al., 1993; Barja et al., 1994; Pollack and Leeuwenburgh, 1999; Ozawa, 1995; Shigenaga et al., 1994; van Voorhies, 2001; Van Remmen and Richardson, 2001). There is also evidence of direct associations between oxidative damage and life span (Agarwal and Sohal, 1994; Harshman and Haberer, 2000) and between longevity and low levels of free radical production in vivo (Barja et al., 1994).

We adopt the growth model of West et al. (2001) in which the fundamental state variable is weight at age t, $W(t)$, changing according to

$$\frac{dW}{dt} = aW^{3/4} - bW. \tag{5}$$

The parameters a and b can be interpreted in terms of fundamental cellular processes (West et al., 2001) such as mass of a cell, energy needed to make a single cell, add the metabolic rate of a cell. As with the von Bertalanffy description of growth, in which the exponent of the anabolic term is 2/3 rather than 3/4, Eq. (5) has an asymptotic size at which anabolic terms are exactly balanced by the catabolic ones and is given by $W_\infty = (a/b)^4$. Eq. (5) can be solved by the transformation $W = H^4$ and the exact solution is

$$W(t) = \left[W(t_0)^{1/4} \exp\left(-\frac{b}{4}(t - t_0) \right) + \frac{a}{b}\left(1 - \exp\left(-\frac{b}{4}(t - t_0) \right) \right) \right]^4 \tag{6}$$

The transformation of variables $X = W/W_\infty$ and $\tau = at/W_\infty^{1/4}$ converts Eq. (5) to the non-dimensional form

$$\frac{dX}{d\tau} = X^{3/4} - X. \quad (7)$$

Eq. (5) is based on a well-grounded theory. We are less certain about the dynamics of oxidative damage. There is evidence, however, that both metabolism (for which size is a proxy) and growth rate affect damage and that damage is repaired. Hence, if accumulated damage at age t is denoted by $D(t)$, we assume that

$$\frac{dD}{dt} = (1-\kappa)d_0 W(t)^{3/4} + \kappa d_1 \frac{1}{W(t)}\frac{dW}{dt} - \rho(W,D). \quad (8)$$

In this expression, κ is a fixed parameter measuring the relative contributions of metabolism and growth to the accumulation of damage, the d_i are appropriate scaling parameters, and $\rho(w,d)$ is the rate of repair when $W(t) = w$ and $D(t) = d$. For simplicity, we assume that $\rho(w,d) = \rho_0 wd$, with ρ_0 a fixed parameter. This is consistent, for example, with assuming that repair is conducted by antioxidant scavenger species that remove oxidatively active species (e.g. Kowald and Kirkwood, 1996; Pollack and Leeuwenburgh, 1999; Kowald and Kirkwood, 2000) and that production of antioxidants is proportional to weight; also see Cobbold et al. (2002). There is evidence that $\rho(w,d)$ may be a function of age (Zielinski and Pörtner, 2000), but for simplicity we treat it as independent of age. We also ignore the explicit treatment of oxidative stress associated with reproduction (Mangel, 2001b; Wang et al., 2001). The decline of physiological function with age, as in the classic theory of (Strehler and Mildvan, 1960), may be due to the accumulation of damage. We solved Eq. (8) numerically by converting it to a difference equation on an annual time scale, using the annualized version of Eq. (6).

We assume that annual mortality rate at age t is proportional to damage, so that if survival to age t is $S(t)$,

$$S(t) = S(t-1)\exp(-\mu_0 - d_c D(t)), \quad (9)$$

where μ_0 represents sources of mortality that are independent of the physiological processes under consideration here and d_c scales accumulated damage to survival, so that age specific mortality rate is $\mu_0 + d_c D(t)$.

For presentation, we focus on the roles of κ and ρ_0 with all other parameters fixed (values given in the caption for Fig. 3). Also, in order to focus on the shape of mortality trajectories, rather than their absolute values (which are determined by the conversion factor as well as the absolute value of the amount of oxidative damage), we report mortality rate scaled relative to that at maximum age. As κ and ρ_0 vary (Fig. 4), the predicted trajectories of mortality rate as a function of age show great variation. Their shapes range from

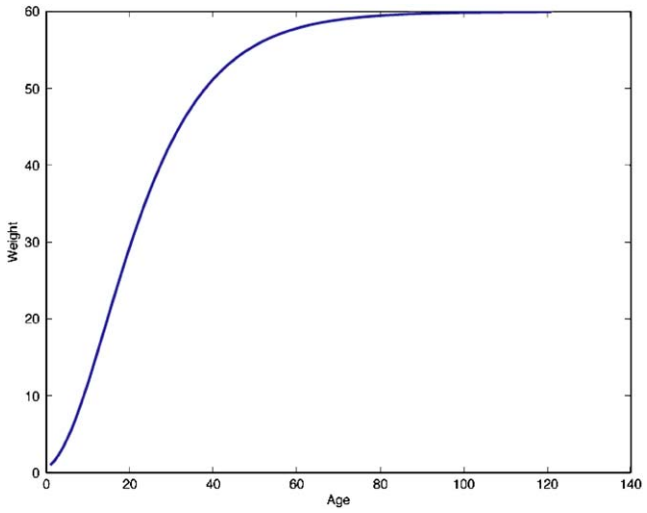

Fig. 3. Growth trajectory used to illustrate the shape of mortality trajectories when accumulated damage depends upon both size and growth rate. Parameters are $a = 0.8$, $w_0 = 1$, asymptotic mass 60 (from which b is computed), $\mu_0 = 0.005$.

"pure" Gompertzian, through intermediate ages showing a plateau of mortality rate, to a mortality plateau.

This theoretical framework allows us to understand the shape of these trajectories through the interplay between the mixture of sources of damage and repair rate. When metabolism and growth contribute equally to the development of oxidative damage, and repair rates are low, the predicted mortality trajectories are most like a Gompertzian. However, as the balance between growth-related and metabolism-related damage shifts towards the former, plateaus or even declines in predicted mortality rate may occur. Thus, we might predict, for example, that species which have a relatively short growth period (or no growth after maturity) would, all else being equal, be more likely to show patterns that deviate from Gompertzian. Increasing the rate of repair has the effect of slowing the accumulation of damage, and thus the mortality trajectory at later ages.

4. Discussion

Mortality trajectories are the output of life history evolution (Mangel, 2001a, b) and the shape of these trajectories requires consideration of life history phenomena. Previous attempts to do this are rare, and have focused on a single variable representing an "vitality" (Anderson, 1992, 2000; Weitz and Fraser, 2001), in the sense that organismal death corresponds to zero vitality. Here we have taken a different approach and tried to identify relevant physiological processes. Thus, models should incorporate physiological state and it is for this reason that these physiologically structured models are appropriate. Many different events can alter the

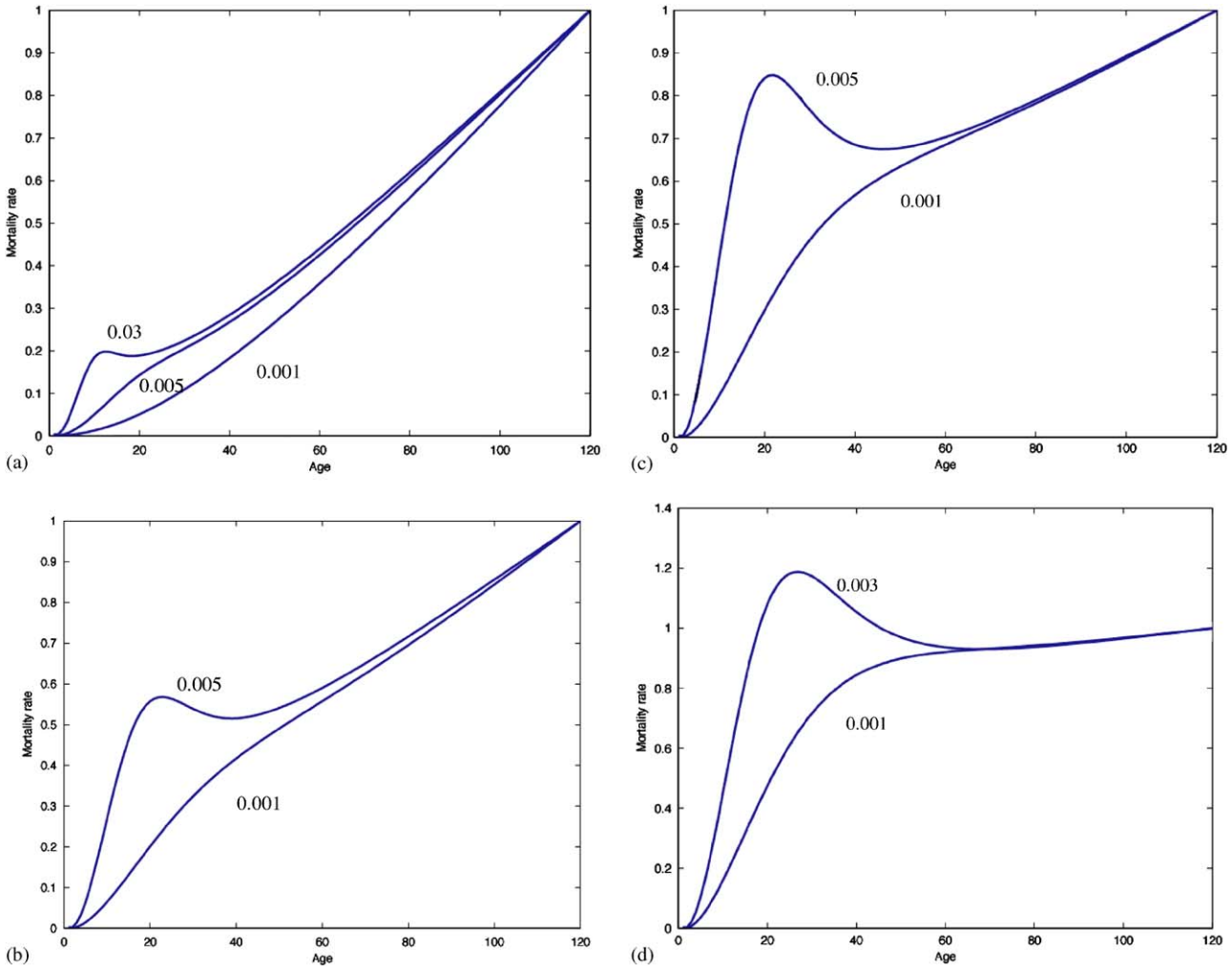

Fig. 4. The pattern of relative mortality rate (mortality at age t scaled by mortality at $t = 120$) varies considerably according to the way that growth affect the accumulation of damage (the parameter κ in Eq. (8)) and according to the level of repair (ρ_0): (a) $\kappa = 0.5$ and three values of ρ_0 are labelled on the curves; (b) $\kappa = 0.9$ and two values of ρ_0; (c) $\kappa = 0.95$ and two values of ρ_0; (d) $\kappa = 0.99$ and two values of ρ_0.

patterns of senescence but a recurrent theme emerging in the evolutionary biology of aging is that individual variability or heterogeneity is linked to the aging process and the mechanisms of mortality. All populations are heterogeneous and some individuals will suffer accumulated damage and mortality more readily than others. As frailer individuals are lost from a population, only a subset of individuals remain. Heterogeneity in physiological processes can lead to the deceleration of mortality rates in late life (Vaupel et al., 1998; Rossolini and Piantanelli, 2001). However, the issue here is not simply about mortality plateaus. In a sense, all of our organisms are clonal and the deceleration of mortality that we described is inherent in the physiological processes, of which growth is one example.

The theoretical tools that we introduced here complement each other. The linear chain makes no particular assumption about the sources of mortality and only requires that these sources be distributed across an individual's life. The models associating oxidative damage with growth and metabolism make explicit the origins of some of these physiological lags. Our results suggest that organisms that have more complicated physiological structure (and thus higher order lags) or organisms that reach asymptotic size relatively rapidly are more likely to have mortality plateaus. However, the issue here is not mortality plateaus. The main point is that we should expect the diversity of mortality trajectories to mimic the great diversity of life itself. Were we fitting data, the early portions of the predicted mortality trajectories would surely fit well as Gompertz curves, but there is no underlying reason to expect this.

Our work also emphasizes the importance of reunifying the connections between the biology of aging and demography. In a series of brilliant papers in the early part of the 20th century (reviewed by Gavrilov and Gavrilova, 1991), Raymond Pearl set out to connect mortality trajectories and biology . Pearl recognized that

"…it appears clear that there is no one universal 'law' of mortality…different species may differ in the age distribution of their dying just as characteristically as they differ in their morphology" (Pearl and Miner, 1935). However, the conceptual tools were lacking: "But what is wanted is a measure of the individual's *total* activities of all sorts, over its *whole* life; and also a numerical expression that will serve as a measure of net integrated effectiveness of *all* the environmental forces that have acted upon the individual throughout its life". In the intervening years, demography developed as a social science (e.g. Preston et al., 2001) and the biology of aging as a separate biological science (Masoro and Austad, 2001). Recent calls for the development of biodemography notwithstanding (Carey, 2001; Carey and Judge, 2001) there is much work to be done. Theoretical tools such as the ones that we describe here will become essential as cell biology develops methods for acquiring enormous amounts of data, for which a framework of analysis will be needed. Furthermore, models of age, longevity and senescence such as those presented here need to be embedded in a fuller evolutionary theory, if we are to make progress in understanding the patterns and diversity of longevity.

Acknowledgments

The work of MM was supported in part by CSTAR, the Center for Stock Assessment Research, a partnership between the National Marine Fisheries Service Santa Cruz Laboratory and the University of California Santa Cruz; and that of MBB by the Royal Society.

References

Agarwal, S., Sohal, R.S., 1994. DNA oxidative damage and life expectancy in houseflies. Proc. Natl. Acad. Sci. 91, 12332–12335.

Ames, B.N., Shigenaga, M.K., Hagen, T.M., 1993. Oxidants, antioxidants and the degenerative disease of aging. Proc. Natl. Acad. Sci. USA 90 (17), 7915–7922.

Anderson, J.J., 1992. A vitality-based stochastic model for organism survival. In: DeAngelis, D.L. (Ed.), Individual-Based Models and Approaches in Ecology. Chapman & Hall, New York, pp. 256–277.

Anderson, J.J., 2000. A vitality-based model relating stressors and environmental properties to organism survival. Ecol. Monographs 70, 445–470.

Ashok, B.T., Ali, R., 1999. The aging paradox: free radical theory of aging. Exp. Gerontol. 34, 293–303.

Barja, G., Cadenas, S., Rojas, C., Lopez-Torres, M., Perez-Campo, R., 1994. A decrease of free radical production near critical targets as a cause of maximum longevity in mammals. Comp. Biochem. Physiol. 108 B, 501–512.

Beckerman, A.P., Benton, T.G., Ranta, E., Kaitala, V., Lundberg, P., 2002. Population dynamic consequences of delayed life-history effects. Trends Ecol. Evol. 17, 263–269.

Beckman, K.B., Ames, B.N., 1998. The free radical theory of aging matures. Physiol. Rev. 78, 547–581.

Blythe, S.P., Nisbet, R.M., Gurney, W.S.C., 1984. The dynamics of population models with distributed maturation periods. Theor. Popul. Biol. 25, 289–311.

Carey, J.R., 2001. Insect biodemography. Annu. Rev. Entomol. 46, 79–110.

Carey, J.R., 2003. Longevity. Princeton University Press, Princeton, NJ.

Carey, J.R., Judge, D.S., 2001. Principles of biodemography with special reference to human longevity. Popul.: Engl. Selection 13, 9–40.

Carey, J.R., Liedo, P., Orozco, D., Vaupel, J.W., 1992. Slowing of mortality rates at older ages in large medfly cohorts. Science 258, 457–461.

Charlesworth, B., 2001. Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. J. Theor. Biol. 210, 47–65.

Charlesworth, B., Hughes, K.A., 1996. Age-specific inbreeding depression and components of genetic variance in relation to the evolution of senescence. Proc. Natl. Acad. Sci. 93, 6140–6145.

Chicon, M., Kozlowski, J., 2000. Ageing and typical survivorship curves result from optimal resource allocation. Evol. Ecol. 2, 857–870.

Clarke, G., Collins, R.A., Leavitt, B.R., Andrews, D.F., Hayden, M.R., Lumsden, C.J., McInness, R.R., 2000. A one-hit model of cell death in inherited neuronal degenerations. Nature 406, 195–199.

Cobbold, C.A., Sherratt, J.A., Maxwell, S.R.J., 2002. Lipoprotein oxidation and its significance for atherosclerosis: a mathematical approach. Bull. Math. Biol. 64, 65–95.

Cox, D.R., 1972. Regression models and life-tables. J. R. Stat. Soc. B 34, 187–220.

Curtsinger, J.W., Fukui, H., Townsend, D.R., Vaupel, J.W., 1992. Demography of genotypes: failure of the limited life-span paradigm in *Drosophila melanogaster*. Science 258, 261–263.

de Boer, J., Andressoo, J.O., de Wit, J., Hijmans, J., Beems, R.B., van Steeg, H., Weeda, G., van der Horst, G.T.J., van Leeuwen, W., Themmen, A.P.N., Meradji, M., Hoeijmakers, J.H.J., 2002. Premature ageing in mice deficient in DNA repair and transcription. Science 296, 1276–1279.

Easton, D.M., 1995. Gompertz survival kinetics: fall in number alive or growth in number dead? Theor. Popul. Biol. 48, 1–6.

Economos, A.C., 1979. A non-Gompertzian paradigm for mortality kinetics of metazoan animals and failure kinetics of manufactured products. Age 2, 74–76.

Economos, A.C., 1982. Rate of ageing, rate of dying, and the mechanism of mortality. Arch. Gerontol. Geriatr. 1, 3–27.

Finch, C.E., 1990. Longevity, Senescence, and the Genome. Chicago University Press, Chicago, USA.

Finkel, T., Holbrook, N.J., 2000. Oxidants, oxidative stress and the biology of ageing. Nature 408, 239–247.

Fogel, R.W., 1993. New sources and new techniques for the study of secular trends in nutritional status, health, mortality, and the process of aging. Hist. Methods 26, 5–41.

Fogel, R.W., 1994. Economic growth, population theory, and physiology: the bearing of long-term processes on the making of economic policy. Am. Econ. Rev. 84, 369–395.

Gavrilov, L.A., Gavrilova, N.S., 1991. The Biology of Life Span: A Quantitative Approach. Harwood Academic Publishers, London.

Gems, D., 1999. Nematode ageing: putting metabolic theories to the test. Curr. Biol. 9, R614–R616.

Gompertz, B., 1825. On the nature of the function expressive of the law of human mortality, and a new mode of determining the value of life contingencies. Philos. Trans. R. Soc. 115, 513–583.

Harshman, L.G., Haberer, B.A., 2000. Oxidative stress resistance: a robust correlated response to selection in extended longevity lines of *Drosophila melanogaster*? J. Gerontol: Biol. Sci. 55 A, B415–B417.

Ishii, N., Hartman, P.S., 2000. Oxidative stress and aging in *Caenorhabditis elegans*. Results Probl. Cell Differ. 29, 150–164.

Kowald, A., Kirkwood, T.B.L., 1996. A network theory of ageing: the interactions of defective mitochondria, aberrant proteins, free radicals and scavengers in the ageing process. Mutat. Res. 316, 209–236.

Kowald, A., Kirkwood, T.B.L., 2000. Accumulation of defective mitochondria through delayed degradation of damaged organelles and its possible role in the ageing of post-mitotic and dividing cells. J. Theor. Biol. 202, 145–160.

Lee, R.D., Carter, L.R., 1992. Modeling and forecasting US mortality. J. Amer. Stat. Assoc. 87, 659–671.

Levine, R.L., Stadtman, E.R., 2001. Oxidative modification of proteins during aging. Exp. Gerontol. 36, 1495–1502.

Lummaa, V., Clutton-Brock, T., 2002. Early development, survival and reproduction in humans. Trends Ecol. Evol. 17, 141–147.

MacDonald, N., 1978. Time Lags in Biological Models, Lecture Notes in Biomathematics, Vol. 27. Springer, Berlin, Germany.

MacDonald, N., 1989. Biological Delay Systems: Linear Stability Theory. Cambridge University Press, Cambridge, UK.

Mangel, M., 2001a. Environment and longevity: demography of growth rate. Popul. Dev. Rev. (Suppl.) 29, 57–70.

Mangel, M., 2001b. Complex adaptive systems, aging and longevity. J. Theoret. Biol. 213, 559–571.

Masoro, E.J., Austad, S.N., 2001. Handbook of the Biology of Aging. Academic Press, San Diego, CA, p. 534.

Metcalfe, N., Monaghan, P., 2001. Compensation for a bad start: grow now, pay later? Trends Ecol. Evol. 16, 254–260.

Mueller, L.D., Rose, M.R., 1996. Evolutionary theory predicts late-life mortality plateaus. Proc. Natl. Acad. Sci. USA 93, 15249–15253.

Ozawa, T., 1995. Mitochondrial DNA mutations associated with aging and degenerative diseases. Exp. Gerontol. 30, 269–290.

Pearl, R., Miner, J.R., 1935. Experimental studies on the duration of life. XIV. The comparative mortality of certain lower organisms. Q. Rev. Biol. 10, 60–79.

Pletcher, S.D., Curstinger, J.W., 1998. Mortality plateaus and the evolution of senescence: why are old-age mortality rates so low? Evolution 52, 454–464.

Pollack, M., Leeuwenburgh, C., 1999. Molecular mechanisms of oxidative stress in aging: free radicals, aging, antioxidants and disease. In: Sen, C.K., Packer, L., Hanninen, O. (Eds.), Handbook of Oxidants and Antioxidants in Exercise. Elsevier, Amsterdam.

Preston, S.H., Heuveline, P., Guillot, M., 2001. Demography. Measuring and Modeling Population Processes. Blackwell, Oxford.

Proctor, C.J., Kirkwood, T.B.L., 2002. Modelling telomere shortening and the role of oxidative stress. Mech. Ageing Dev. 123, 351–363.

Ricklefs, R.E., 1998. Evolutionary theories of aging: confirmation of a fundamental prediction, with implications for the genetic basis and evolution of life span. Am. Nat. 152, 24–44.

Ricklefs, R.E., Scheurlein, A., 2001. Comparison of aging-related mortality among birds and mammals. Exp. Gerontol. 36, 845–857.

Rikans, L.E., Hornbrook, K.R., 1997. Lipid peroxidation, antioxidant protection and aging. Biochim. Biophys. Acta 1362, 116–127.

Rose, M.R., Mueller, L.D., 2000. Ageing and immortality. Philos. Trans. R Soc. 355, 1657–1662.

Rossolini, G., Piantanelli, L., 2001. Mathematical modeling of the ageing processes and the mechanisms of mortality: paramount role of heterogeneity. Exp. Gerontol. 36, 1277–1288.

Sastre, J., Pallardo', F.V., Vina, J., 2000. Mitochondrial oxidative stress plays a key role in aging and apoptosis. IUBMB Life 49, 427–435.

Shigenaga, M.K., Hagen, T.M., Ames, B.N., 1994. Oxidative damage and mitochondrial decay in aging. Proc. Natl. Acad. Sci. USA 91 (23), 10771–10778.

Sozou, P., Kirkwood, T.B.L., 2001. A stochastic model of cell replicative senescence based on telomere shortening, oxidative stress, and somatic mutations in nuclear and mitochondrial DNA. J. Theor. Biol. 213, 573–586.

Stadtman, E.R., 1992. Protein oxidation and aging. Science 257, 1220–1224.

Strehler, B.L., Mildvan, A.S., 1960. General theory of mortality and aging. Science 132, 14–21.

Tolmassof, J.M., Ono, T., Cutler, R.G., 1980. Superoxide dismutase: correlation with life-span and specific metabolic rate in primate species. Proc. Natl. Acad. Sci. USA 77 (5), 2777–2781.

Van Remmen, H., Richardson, A., 2001. Oxidative damage to mitochondria and aging. Exp. Gerontol. 36, 957–968.

van Voorhies, W.A., 2001. Metabolism and life span. Exp. Gerontol. 36, 55–64.

Vaupel, J.W., 1997. Trajectories of mortality at advanced ages. In: Wachter, K.W., Finch, C.E. (Eds.), Between Zeus and the Salmon. National Academy Press, Washington, DC, pp. 17–37.

Vaupel, J.W., Yashin, A.I., 1985. Some surprising effects of selection on population dynamics. Am. Stat. 39, 176–185.

Vaupel, J.W., Carey, J.R., Christensen, K., Johnson, T.E., Yashin, A.I., Holm, N.V., Iachine, I.A., Kannisto, V., Khazaeli, A.A., Liedo, P., Longo, V.D., Zeng, Y., Manton, K.G., Curtsinger, J.W., 1998. Biodemographic trajectories of longevity. Science 280, 855–860.

von Schantz, T., Bensch, S., Graham, M., Hasselquist, D., Wittzel, H., 1999. Good genes, oxidative stress and condition-dependent signals. Proc. R. Soc. London Ser. B 266, 1–2.

von Zglinicki, T., Bürkle, A., Kirkwood, T.B.L., 2001. Stress, DNA damage and ageing—an integrative approach. Exp. Gerontol. 36, 1049–1062.

Wang, Y., Salmon, A.B., Harshman, L.G., 2001. A cost of reproduction: oxidative stress susceptibility is associated with increased egg production in *Drosophila melanogaster*. Exp. Gerontol. 36, 1349–1359.

Weitz, J.S., Fraser, H.B., 2001. Explaining mortality plateaus. Proc. Natl. Acad. Sci. 98, 15383–15386.

West, G.B., Brown, J.H., Enquist, B.J., 2001. A general model for ontogenetic growth. Nature 413, 628–631.

Yashin, A.I., Iachine, I.A., 1995. Survival of related individuals: an extension of some fundamental results of heterogeneity analysis. Math. Popul. Stud. 5, 321–339.

Zielinski, S., Pörtner, H.-O., 2000. Oxidative stress and antioxidative defense in cephalopods: a function of metabolic rate or age? Comp. Biochem. Physiol. Part B 125, 147–160.