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Environment and longevity: emergence without interaction, multiple steady states and stochastic clocks

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ABSTRACT

Because they are non-linear, biological systems are often characterized by emergent properties, multiple steady states, and thresholds. These are now well understood and appreciated in ecology; they are also important components for understanding life span, at both the level of the population and the level of the individual, and allow novel insights into the biology of ageing and longevity. The deceleration of mortality rate at later ages can be understood as an emergent property, in the sense of a macroscopic phenomenon (population mortality rate) arising (in this case, without interaction) from different microscopic ones (individual mortality). Models of individual ageing based on the autocatalysis and inhibition of replicating units lead to multiple stable steady states separated by thresholds. These systems respond to environmental challenges and this response leads to individual ontogeny of ageing; the environment thus sets a stochastic clock. Recognition of the implicit non-linearity of biological systems will be essential for advances in the theoretical formulation of life span and ageing.

Keywords: ageing, free radicals, life span, longevity, oxidative damage.

INTRODUCTION

Understanding the determinants of life span has important biological and social implications. It is generally understood that ageing, as with many other processes of life history (Thorpe *et al.*, 1998), is controlled by the interplay of genetics and environment (Ishii and Hartman, 2000). Here, I explore aspects of the relationship between environment and life span from the perspective of non-linear dynamics of biological systems. This perspective allows novel insights into both individual and population phenomena. I adopt the following definitions (Goldwasser, 2001): For an individual, the term *life span* refers to the duration of life, typically defined as the period of time from birth until death. *Mean life span* is the average age at death; it can apply to either a real cohort or to a hypothetical one derived from a life table. *Maximum potential life span* is the theoretical highest attainable age. *Maximum observed life span* refers, in general, to the highest known age at death for a species or a population. With the exception of the first, the definitions are population-based quantities.

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Two aspects of non-linear dynamics of relevance to understanding life span and individual ageing are emergent properties (in which a macroscopic characteristic, such as population level mortality rate, arises from microscopic characteristics, such as individual mortality, with different behaviours) and the existence of thresholds in systems with multiple steady states (Levin, 1999; Solé and Goodwin, 2000). Such non-linear properties of biological systems are now generally appreciated in the ecological sciences (Levin, 1999; Scheffer *et al.*, 2001; Dong *et al.*, 2002) and this paper shows that these properties are also important for the study of age and longevity. There have been calls to link new kinds of mathematical models to the study of ageing and longevity (McClearn, 1997; Jazwinski *et al.*, 1998; Piantanelli *et al.*, 2001); this is one such contribution.

MORTALITY DECELERATION AS AN EMERGENT PROPERTY

Perhaps the most fundamental quantity associated with life span and ageing (Carey and Judge, 2001; Preston *et al.*, 2001) is the cohort mortality rate at age t, $m(t)$, defined as follows. If $N(t)$ is the number of individuals of a cohort alive at age t, then

$$\frac{\mathrm{d}N}{\mathrm{d}t} = -m(t)N(t) \tag{1}$$

The foundational model for demography is due to Gompertz. In it, $m(t)$ increases at an exponential rate [so that log ($m(t)$) is linear with age]:

$$\frac{\mathrm{d}m}{\mathrm{d}t} = km(t) \tag{2}$$

Consequently,

$$N(t) = N(0)\exp\left[-\frac{m(0)}{k}(\mathrm{e}^{kt}-1)\right] \tag{3}$$

Mortality rate, $m(t)$, is an increasing function of age for the Gompertz model. It is now generally understood that heterogeneity – for example, variation in the values of the rate of ageing, k – can lead to a deceleration of the estimated mortality trajectory for a population (Vaupel *et al.*, 1979; Yashin *et al.*, 1995; Rossolini and Piantanelli, 2001) at later ages. Indeed, simple models show that the composite mortality trajectory in a population composed of just two types can have virtually any shape (Vaupel and Yashin, 1985).

What is less appreciated is that the deceleration of mortality trajectories is an emergent property. Emergence is generally understood (Holland, 1998; Johnson, 2001) to mean that a population property differs in fundamental ways from the properties of its individual constitutive members and that generally interactions between the individual members shape the emergent property. To explore emergence in the context of the trajectory of mortality, rewrite equation (3) as

$$N(t) = N(0)\exp\left[-m(0)g(t)\right] \tag{4}$$

and assume that $m(0)$ has a gamma distribution with parameters ν and α. Variation of $m(0)$ might occur, for example, because individuals achieve adulthood with different levels of accumulated damage to tissues. An experimental verification of the case of individual

variation in initial mortality rate but a common rate of ageing has recently been described (Linnen *et al.*, 2001).

The frequency distribution of $m(0)$ is

$$f(m(0)) = \mathrm{e}^{-\alpha m(0)} m(0)^{v-1} \frac{\alpha^v}{\Gamma(v)} \tag{5}$$

The mean value of $m(0)$, $\overline{m(0)} = v/\alpha$, and the coefficient of variation of $m(0)$ is $1/\sqrt{v}$. The expected value of $N(t)$ is

$$E\{N(t)\} = N(0)\left[\frac{\alpha}{\alpha + g(t)}\right]^v = N(0)\left[\frac{v}{v + \overline{m(0)}g(t)}\right]^v \tag{6}$$

For a cohort, mortality rate is estimated according to

$$\hat{m}(t) = \frac{-1}{E\{N(t)\}} \frac{\mathrm{d}}{\mathrm{d}t} E\{N(t)\} \tag{7}$$

If there is sufficient variation in the initial value of mortality rate and the Gompertz parameter is sufficiently small, then the estimated mortality rate will decelerate with increasing age, but this depends upon the initial variation in mortality rate (Fig. 1a) and the Gompertz rate of ageing (Fig. 1b). Since the mortality rate for individuals is rising with age (Fig. 1c), levelling of the mortality rate is an emergent property without interaction between members of the population, each of whom experiences mortality according to a different Gompertzian curve.

We may thus ask if this outcome is automatically foreseen? The answer is 'no'. Whether mortality trajectories decelerate or not depends upon the inherent rate of ageing in the Gompertz parameter and the amount of heterogeneity in the population. For the model described here, the estimated rate of mortality is

$$\hat{m}(t) = \frac{v\,\overline{m(0)}g'(t)}{v + \overline{m(0)}g(t)} \tag{8}$$

The general condition for deceleration of mortality trajectories is that $\hat{m}'(0) > 0$, $\hat{m}''(0) > 0$ and that there is an age t_s at which convexity switches – that is, that $\hat{m}''(t_s) = 0$. Differentiation of equation (8) gives

$$\hat{m}''(t) = \frac{\overline{m}_0 v \mathrm{g}'''(t)}{(v + \overline{m}_0 g(t))} - 3\frac{(\overline{m}_0)^2 v \mathrm{g}''(t) g'(t)}{(v + \overline{m}_0 g(t))^2} + 2\frac{(\overline{m}_0)^3 v (g'(t))^3}{(v + \overline{m}_0 g(t))^3} \tag{9}$$

Equation (9) is a transcendental equation that must be solved numerically for the age at which convexity switches. The most important characteristic of this equation, however, is that all parameters – average initial mortality rate, coefficient of variation of initial mortality rate and Gompertz growth parameter – appear. It is this interaction of the parameters that is responsible for the emergent property of the mortality trajectory.

THRESHOLDS FOR REPLICATORS WITH MULTIPLE STEADY STATES AND THE ONTOGENY OF AGEING

In the most general sense, biological systems consist of replicating units that interact through autocatalysis and inhibition of competing replicators (Maynard Smith and

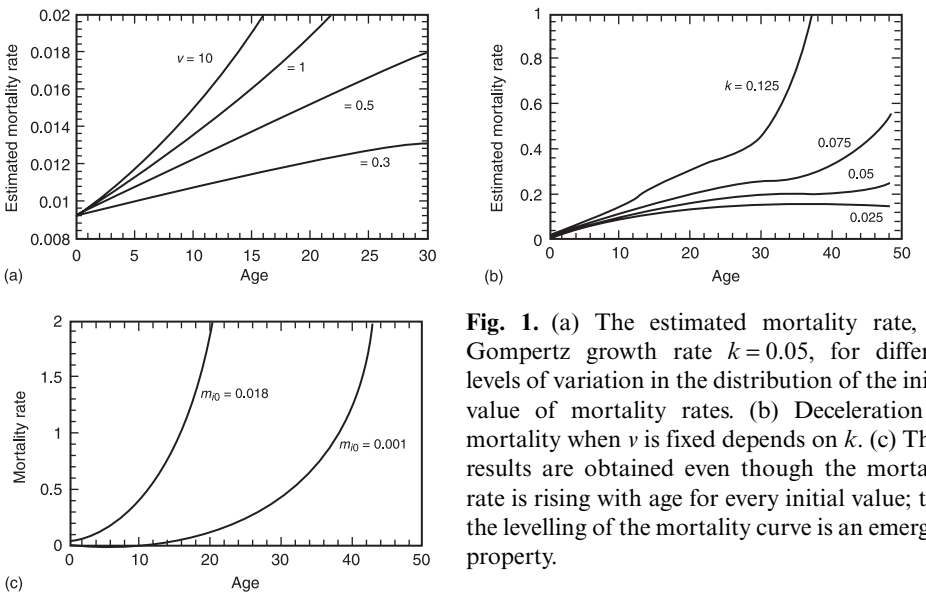

Fig. 1. (a) The estimated mortality rate, for Gompertz growth rate $k = 0.05$, for different levels of variation in the distribution of the initial value of mortality rates. (b) Deceleration of mortality when v is fixed depends on k. (c) These results are obtained even though the mortality rate is rising with age for every initial value; thus the levelling of the mortality curve is an emergent property.

Szathmary, 1995; Gerhart and Kirschner, 1997; Lifson and Lifson 1999; Scheuring and Szathmary, 2001). One of the classic replicator models, originating with Hoffman (1974) and extended by Kirkwood and Holliday (1975) to ageing, focuses on a set of polypeptide adaptors that combine all of the functions of protein synthesis. The key variable in this model is the fraction $q(t)$ of adaptors at age t that have not yet lost specificity because they have no errors at the sites crucial for operation of the synthetic machinery. The dynamics of $q(t)$ (Kowald and Kirkwood, 1993) are:

$$q(t+1) = q(t) + \varepsilon \frac{q(t)^n\,[AS - (S + A - 1)R] + (S + A - 1)R}{q(t)^n A(S + A - 1)(1 - R) + A(S + A - 1)R} - q(t) = q(t) + \varepsilon F(q(t)) \qquad (10)$$

where n is the number of non-overlapping residues that are important for specificity, A is the number of different amino acids, S is the specificity of a properly functioning adaptor, R is the relative specificity of an improperly functioning adaptor, ε scales biological and calendar time, and $F(q)$ is defined by the middle expression in equation (9). For appropriate values of these parameters, the dynamical system $q(t+1) = q(t) + \varepsilon F(q(t))$ can have multiple stable steady states, $\overline{q}_s$, for which $F(\overline{q}_s) = 0$ separated by a threshold unstable steady state (Fig. 2a). When there are multiple steady states, we may consider the one with a high fraction of functioning replicators to be young or non-senescent and the one with a low fraction of functioning replicators to be old or senescent.

If there is no mechanism for transitions between the two stable steady states, an individual starting with a high fraction of functional replicators will remain there forever and thus the model cannot be used for ageing. However, environmental challenges can be added to the dynamics of the replicators by assuming that, with probability $1 - \lambda_e$, the dynamics given by equation (9) apply and that, with probability λ_e, an environmental challenge occurs and that this reduces the fraction of functional replicators so that the dynamics are now

$$q(t+1) = q(t) + \varepsilon[F(q) - q_e] \qquad (11)$$

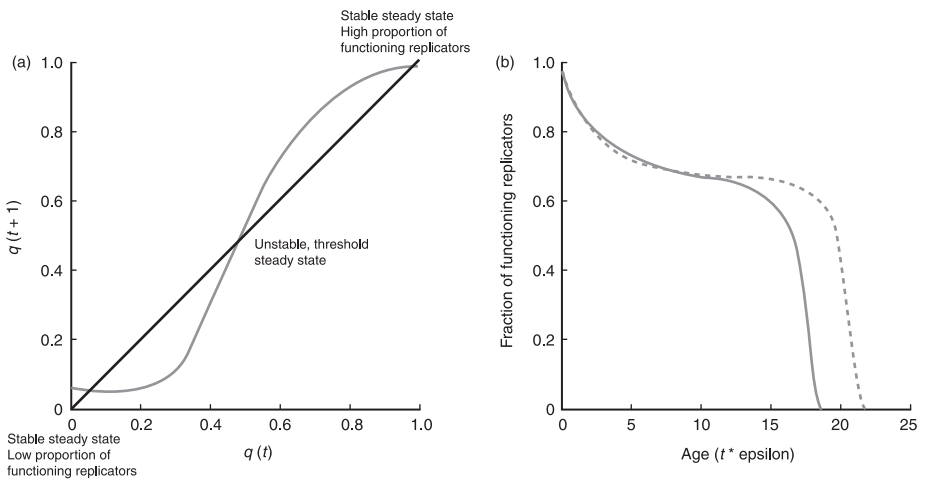

Fig. 2. (a) The Hoffman-Kirkwood-Holliday (HKH) model for replicators leads to multiple steady states and thresholds. This panel (based on 20 amino acids, $n = 5$, $S = 1000$ and $R = 0.03$) shows the non-linear relationship between the $q(t)$ and $q(t + 1)$ and the 1 : 1 line. Steady states are at the intersection of the curve and the line. (b) Ontogenies for two individual HKH models in which environmental insults reduce the fraction of functional replicators (additional parameters are $\varepsilon = 0.01$, $\lambda_e = 0.85$ and $q_e = 0.2$). The trajectories show a slow decline in middle age, followed by rapid senescence and individual variation in the rate of ageing. Life span can be inferred from the age at which the fraction of functioning replicators drops to a value so low that the organism cannot function properly.

where εq_e is the fraction of replicators lost due to environmental challenge. The consequence of this interaction between the environment and the organism is a (gradual) decline in $q(t)$ until the unstable steady state is crossed, at which point there is a more rapid transition to the other stable steady state (Fig. 2b).

Life span can be understood as the time to transition between the two stable steady states. The mean life span satisfies (Mangel, 1985)

$$T(q) = 1 + (1 - \lambda_e)T(q + \varepsilon F(q)) + \lambda_e T(q + \varepsilon(F(q) - q_e)) \tag{12}$$

which can be solved by methods that exploit the smallness of the parameter ε (Mangel and Tier, 1993).

The competitive phase plane of reactive oxygen species and antioxidants

The replicator model is especially attractive because it is one-dimensional, which allows rapid and easy analysis of the steady states and resulting dynamics. More elaborate models focus on the network theory of ageing (Kowald and Kirkwood, 1994, 2000; Kirkwood and Kowald, 1997), in which the component elements are mitochondria, aberrant proteins, radicals and scavengers. The formulations of this idea vary; for example, Kowald and Kirkwood (2000) use a system of nine non-linear differential equations characterizing genetically intact and defective mitochondria with different levels of membrane damage, antioxidants, radicals and ATP.

Regardless of the particular formulation, the key observation is that antioxidants and radicals are a competitive dynamical system, much as F.C. Frank envisioned 50 years ago (Frank, 1953). Accepting the principle that biological systems work via autocatalysis and inhibition (Gerhart and Kirschner, 1997), the projection of such competitive systems into the phase plane of reactive oxygen species (ROS) and antioxidants can be summarized in principle by a pair of deterministic differential equations for the dynamics of ROS, $R(t)$, and antioxidants, $A(t)$:

$$\frac{\mathrm{d}R}{\mathrm{d}t} = g_1(R, A)$$

$$\frac{\mathrm{d}A}{\mathrm{d}t} = g_2(R, A) \tag{13}$$

where the functions $g_1(R, A)$ and $g_2(R, A)$ are such that the R–A phase plane has multiple stable steady states (Fig. 3a), one of which can be interpreted as young/non-senescent and the other as old/senescent. As with the simpler one-dimensional system, in the absence of environmental challenges, such a system will remain in the vicinity of the stable steady state corresponding to non-senescence if it starts in that vicinity.

The effect of environmental challenges is an increase in the level of radicals and an appropriate stochastic version of equation (13) is

$$\mathrm{d}R = g_1(R, A)\mathrm{d}t + \omega \mathrm{d}\Pi$$

$$\mathrm{d}A = g_2(R, A)\mathrm{d}t \tag{14}$$

where ω measures the increase in radicals from an environmental challenge and $\mathrm{d}\Pi$ is the increment in the Poisson process, which is 1 with probability $\lambda \mathrm{d}t + o(\mathrm{d}t)$ and 0 with probability $1 - \lambda \mathrm{d}t + o(\mathrm{d}t)$. This extension exhibits a similar ontogeny of ageing as the one-dimensional replicator model did (Fig. 3b). Life span can be defined as the age at which a point in the phase plane close to the senescent steady state is reached, given starting values near the non-senescent state.

DISCUSSION

The determinants of life span are generally polygenic and multifactorial (Schächter *et al.*, 1993; Miller, 1999) and we should expect epistasis and pleiotropy to occur (Williams, 1957). These properties will each enhance the non-linear aspects of the biological system. Here, I have explored the implications of some aspects of non-linearity for understanding ageing and longevity using mathematical models. Indeed, theories of ageing and senescence are all, in some sense, non-linear, and many biomarkers of ageing show non-linear dynamics (Arking, 1998). The approach used in this paper makes explicit the nature and role of non-linearity. To be sure, the evidence associated with the suite of ideas developed here is still mixed. There is a negative relationship between motor coordination and oxidative damage to the brain (Sastre *et al.*, 2000). There is conflicting evidence, however, about the pattern of antioxidants as a function of age (Rikans and Hornbrook, 1997; Hauck and Bartke, 2001; Sukhotin *et al.*, 2002), although there are plenty of examples of oxidative damage increasing with the age of an organism (van Voorhies, 2001). Elsewhere it has been suggested that the declining levels of antioxidants with age might contribute to a short life span in cephalo-

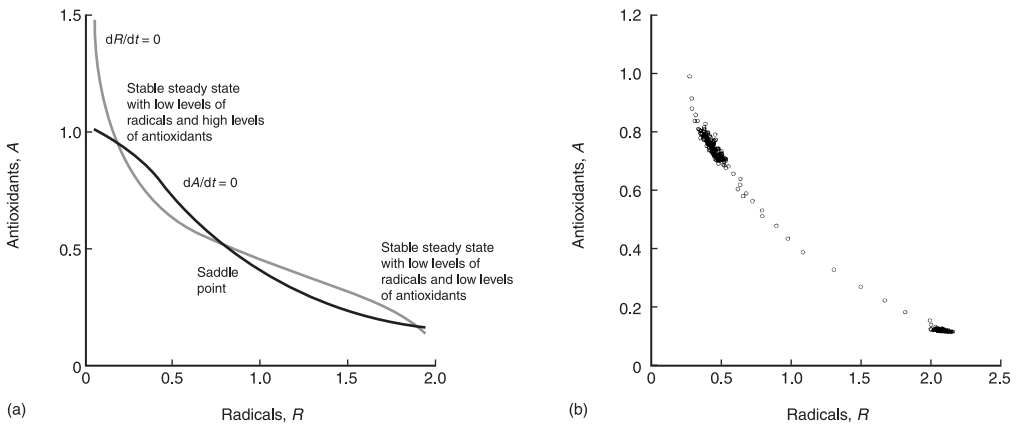

Fig. 3. (a) The phase plane for a competitive system of reactive oxygen species and antioxidants leading to multiple steady states that include a non-senescent stable state (low radicals, high antioxidants), a senescent stable state (high radicals, low antioxidants) and a threshold saddle point separating them. For computational purposes, I used a variant of the model of Gardner *et al*. (2000), in which

$$g_1(R, A) = \frac{\alpha}{1 + \rho_1 A^{\beta}} - R \quad \text{and} \quad g_2(R, A) = \frac{1}{1 + \rho_2 R^{\gamma}} - A$$

with cooperativity parameters $\alpha = 2$, $\beta = 3$; other parameters are $\rho_1 = 12$, $\rho_2 = 1.5$. (b) Numerical iteration of equations (14) shows an individual ontogeny of ageing. Additional parameters are $dt = 0.1$, $\lambda = 0.1$ and $\omega = 0.014$. Each dot represents the position of the system (R, A) after 100 time steps, with an initial position randomly chosen around the non-senescent steady state. The clouds of points indicate long residence times in those regions of the phase space before relatively rapid transition across the threshold separatrix.

pods (Zielinski and Pörtner, 2000). Life span shows correlations with both the generation (negative: Sohal and Weindruch, 1996) and repair (positive: Hart and Setlow, 1974) of reactive oxygen species (ROS). In addition, the theory developed here suggests – even for the heuristic phase plane analysis – that animals of the same age may be expected to have widely different values of ROS and antioxidants.

The true contribution of mathematics to biology lies in a precise qualitative framework of reasoning (Bangham and Asquith, 2001). The models developed here are conceptual tools (*sensu* Mangel *et al.*, 2001) for understanding the broader question of the relationships between stress resistance and longevity, an emerging theme in research on ageing (Lithgow, 2000) The models discussed here are also public mechanisms in the sense of Martin *et al.* (1996) and thus should be generally operational over a wide range of species.

Perhaps the most important conclusion to be drawn from emergent properties is that scaling from individuals to populations needs to be done with caution. In addition, we must recognize that mortality rate, one of the fundamental demographic quantities, is itself the result of patterns of behaviour, growth and reproduction.

Other recent work (Cobbold *et al.*, 2002) suggests hysteresis in the dynamics of oxidized lipids or proteins and their antioxidants. Thresholds become especially important when

one recognizes the role that non-genetic factors play in longevity (Finch, 1997; Finch and Kirkwood, 2000). In particular, recognition of thresholds allows an explicit and clear way for chance events to interact with the biological system. Indeed, when thresholds exist in the biological system, chance is no longer noise but is central to understanding the nature of ageing (Jazwinski, 2001). Organisms deal with ROS damage by either reducing the production of ROS or increasing the defences (van Voorhies, 2001); there appear to be differences in the way long-lived and short-lived organisms approach the problem of oxidative damage, with long-lived organisms generally taking the former approach. Such empirical information provides clues about the shape of the separatrix. This is important because the geometry around the threshold (unstable) steady state or separatix tells us something about the rate of senescence (Finch, 1998), because the dynamics around the threshold tell us how rapidly the organism will age. In this context, Voskoboynik *et al*. (2001) recently proposed the existence of an ageing clock set by the environment; this is likely to be a stochastic clock.

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