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The vitality model: A way to understand population survival and demographic heterogeneity

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ABSTRACT

A four-parameter model describing mortality as the first passage of an abstract measure of survival capacity, vitality, is developed and used to explore four classic problems in demography: (1) medfly demographic paradox, (2) effect of diet restriction on longevity, (3) cross-life stage effects on survival curves and (4) mortality plateaus. The model quantifies the sources of mortality in these classical problems into vitality-dependent and independent parts, and characterizes the vitality-dependent part in terms of initial and evolving heterogeneities. Three temporal scales express the balance of these factors: a time scale of death from senescence, a time scale of accidental mortality and a crossover time between evolving vs. initial heterogeneity. The examples demonstrate how the first-passage approach provides a unique and informative perspective into the processes that shape the survival curves of populations.

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1. Introduction

Since Gompertz (1825) first proposed that mortality rates increase exponentially with age, population survival has predominantly been modeled in terms of the instantaneous rate of mortality. The approach is so ubiquitous that the rate is typically referred to as the hazard rate or force of mortality, which inadvertently suggests a physics-like tangibility. However, the concept of an instantaneous mortality rate is elusive and biologically tenuous. In particular, except in the case of accidents, the moment of death is the result of the accumulation of age-related degradation or disease prior to the event. An alternative approach, sometimes called first passage or Markov mortality models, describes the stochastic rate of loss of survival capacity, or vitality, to a killing boundary at zero vitality. The difference between approaches is subtle but significant. In force of mortality models, the organisms that die at a specific age are randomly selected from those alive at the previous increment of time and attribute. In first passage models, the organisms that die at a specific age had, in the previous increment, vitalities near zero. Thus, who lives and who dies at a specific age depends on the individuals' vitality trajectories up to that age.

First passage approaches, and specifically the vitality model, assume that death from disease or old age is the result of the accumulation of damage to the point that the homeostatic ability of an organism's biochemical system fails. Expressing the process in terms of the loss of vitality instead of the accumulation of damage, the model characterizes the stochastic rate of vitality loss by a Wiener process in which the time to death is determined by the first passage time of vitality to the zero boundary. In the process, the stochastic rate is described with a mean and variance, and the probability distribution of age at death from the loss of vitality is described by an inverse Gaussian distribution. The mathematical properties of this model have been studied in detail by Chhikara and Folks (1989), Anderson (2000), Aalen and Gjessing (2001), Steinsaltz and Evans (2004, 2007), Anderson et al. (2008) and others. The model has been used to describe equipment failure (Whitmore, 1986), survival curves in a range of species (Anderson, 1992), the effects of natural and xenobiotic stressors on survival (Anderson, 2000; Hamel, 2001; Springman et al., 2005; Anderson et al., 2008), and the deceleration of mortality rate in old age, i.e. mortality plateau (Weitz and Fraser, 2001).

While first passage models, and specifically the Wiener diffusion model, have been informative, they generally assume that a cohort is initially homogeneous, i.e. individuals start with unit amount of vitality. However, such models are overly simplistic because the first passage time of vitality to the killing boundary depends on both its initial distribution and rate of loss (Aalen and Gjessing, 2001; Steinsaltz and Evans, 2004). Consequently, such models implicitly explain heterogeneity in cohort survival

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entirely in terms of the stochastic rate of vitality loss, a form of evolving heterogeneity in survival capacity. They do not address the heterogeneity endowed in a cohort at birth, a form of initial heterogeneity in survival capacity. In this paper, we extend the first passage model by including initial heterogeneity into the previous model that contained evolving heterogeneity as well as mean senescence and accidental mortality processes. We explore the characteristics of the model and illustrate its application to four classical problems in demography.

Before we proceed with the details of the model, it is worth briefly noting the differences and similarities of our work to frailty models, which have similar goals in characterizing the effects of heterogeneity on survival curves. The frailty model, first proposed by Vaupel et al. (1979) and developed by Vaupel et al. (1998), Yashin and Iachine (1995, 1999), Yashin et al. (2000) and others, expresses an individual's survival capacity in terms of the deviation of its mortality rate from a cohort baseline. While individual frailties remain fixed from birth, the distribution of frailty in the cohort evolves over time because the more frail individuals are preferentially culled from the population. In contrast to a focus on mortality rates, the vitality approach expresses the stochastic trajectory of an individual's vitality at birth, to a zero boundary representing death. Both approaches contain an initial heterogeneity expressed as a distribution of fixed frailty, or initial vitality, and in both approaches the cohort heterogeneity evolves as weak individuals are culled from the population. However, in the vitality approach, the heterogeneity also evolves because of the experiences of individuals, whereas, in the original frailty approach, experience does not change the individual's frailty. Furthermore, as we develop below, in the vitality framework, heterogeneity and mortality emerge from a single three-parameter equation that has a biological basis. In contrast, in the frailty framework, heterogeneity and baseline mortality equations are independent, require more parameters and arguably are biologically more abstract.

2. Model

2.1. Background

We build our model on the vitality model of Anderson (2000) where population survival depends on two components: l_v a vitality-dependent killing process that occurs at the zero boundary and l_a a vitality-independent killing process, which is an extrinsic or accidental mortality. Combining processes, the survival curve is

$$l(t) = l_a(t)\, l_v(t). \tag{1}$$

We characterize the extrinsic killing process with a Poisson process such that every member of the population, independent of its vitality, is equally susceptible to accidental mortality at a rate k:

$$l_a(t) = \exp(-kt). \tag{2}$$

The vitality-dependent boundary killing process is defined

$$l_v(t) = 1 - \int_0^t \int_0^\infty f(t\,|v_0)\, p(v_0)\, \mathrm{d}v_0 \mathrm{d}t \tag{3}$$

where $p(v_0)$ is the distribution of initial vitality, v_0, on the interval $(0, \infty)$ and $f(t|v_0)$ is the distribution of the first arrival time to the zero vitality boundary conditional on having vitality v_0 at time zero. Note that $p(v_0)$ sets the population's "initial heterogeneity". It is similar to the lifelong heterogeneity sometimes included in force of mortality models (e.g. Curtsinger et al. (2005) and Rose et al. (2007)). The change in vitality with age characterized by $f(t\,|v_0)$ is the "evolving heterogeneity", which was coined by Steinsaltz and Evans (2004) and used by Weitz and Fraser (2001) as an explanation of mortality plateaus.

We represent evolving heterogeneity through a Wiener process which describes the rate of change of vitality according to the stochastic differential equation

$$\frac{\mathrm{d}v}{\mathrm{d}t} = -\rho + \sigma\varepsilon_t. \tag{4}$$

The two parameters characterize evolving heterogeneity in survival capacity in terms of a mean rate of loss of vitality (drift) ρ and a variability in the rate (spread) σ. The term ε_t is a white noise function that characterizes the stochastic variability in the rate. These spread and drift terms are constant over the integration interval that typically represents the entire lifespan or some left-truncated portion of it. Additionally, the model can be used piecewise where the coefficients are set constant in each interval. Fig. 1 illustrates random paths of vitality starting at $v_0 = 1$ and absorbing into the killing boundary at $v = 0$. The probability distribution for the first passage time of the Wiener process to the absorbing boundary, $v = 0$, is given by the inverse Gaussian distribution as (Cox and Miller, 1965)

$$f(t\,|v_0) = \frac{v_0}{\sigma\sqrt{2\pi}} t^{-2/3} \exp\left(\frac{(v_0 - \rho t)^2}{2\sigma^2 t}\right). \tag{5}$$

The initial distribution, or initial heterogeneity in a population's survival capacity, strongly affects the shape of the survival curve. In fact, Steinsaltz and Evans (2004) showed that, in general, a survival curve of any shape can be produced from an arbitrary initial distribution. Thus, in selecting an initial distribution, we seek one that is biologically realistic and analytically tractable. A natural choice is a Gaussian distribution such that a population has a mean survival capacity, $\bar{v}_0$ and the initial heterogeneity is expressed as

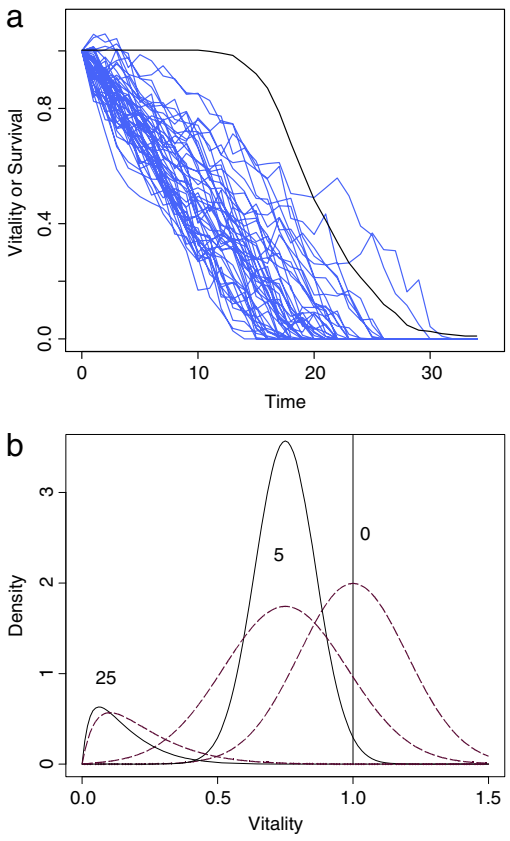

Fig. 1. (a) Depicts individual vitality trajectories (Eq. (4)) and survival (Eq. (8)) with $\bar{v}_0 = 1$ and $\tau = 0$. (b) Solid line: vitality density starts from a Dirac distribution at day 0 (Eq. (14)). Dash line: vitality density starts from a Gaussian distribution with $sd = 0.1$ (Eq. (15)). At day 5, both distributions are Gaussian, and at day 25 they are evolving in a quasi-stationary gamma-like distribution. Over time, the area under the curve declines by loss of vitality into zero-boundary and the effect of initial variation diminishes as the densities of the two distributions converge.

the distribution's standard deviation τ:

$$p(v_0) = \frac{1}{\sqrt{2\pi\tau^2}} \exp\left(\frac{(v_0-\bar{v}_0)^2}{2\tau^2}\right). \quad (6)$$

Using Eqs. (5) and (6) in (3), we approximate the marginal distribution of first arrival time with

$$f(t) = \int_{-\infty}^{\infty} f(t|v_0)\, p(v_0)\, dv_0 = \frac{\rho\tau^2 + \bar{v}_0\sigma^2}{\sqrt{2\pi\left(\tau^2+\sigma^2 t\right)^3}} \exp\left(\frac{(\bar{v}_0-\rho t)^2}{2\left(\tau^2+\sigma^2 t\right)}\right). \quad (7)$$

Note that in Eq. (7), we integrate over the range$(-\infty, \infty)$, which violates the allowable range of vitality $v \geq 0$. For negative vitalities not to become an issue, some restrictions on $\bar{v}_0$ and τ are required, which will be discussed later. The survival, dependent on vitality, becomes

$$l_v(t) = 1 - \int_0^t f(t)\, dt = \Phi\left(\frac{\bar{v}_0-\rho t}{\sqrt{\tau^2+\sigma^2 t}}\right) - \exp\left(\frac{2\tau^2\rho^2}{\sigma^4} + \frac{2\bar{v}_0\rho}{\sigma^2}\right)\Phi\left(-\frac{\frac{2\tau^2\rho}{\sigma^2}+\bar{v}_0+\rho t}{\sqrt{\tau^2+\sigma^2 t}}\right) \quad (8)$$

where Φ is a cumulative normal distribution. Finally, using Eqs. (2) and (8) in (1), the curve of total survival with age is expressed in terms of four coefficients as

$$l(t) = \left(\Phi\left(\frac{1-rt}{\sqrt{u^2+s^2 t}}\right) - \exp\left(\frac{2u^2r^2}{s^4} + \frac{2r}{s^2}\right) \times \Phi\left(-\frac{\frac{2u^2r}{s^2}+1+rt}{\sqrt{u^2+s^2 t}}\right)\right)\exp(-kt) \quad (9)$$

where

$$r = \rho/\bar{v}_0 \quad (10)$$

is the normalized mean rate of vitality loss, or drift rate,

$$s = \sigma/\bar{v}_0 \quad (11)$$

is the normalized variability in the rate of loss of vitality, or spread rate,

$$u = \tau/\bar{v}_0 \quad (12)$$

is the coefficient of variation of the initial vitality distribution and k is the accidental or extrinsic mortality rate. Under this normalization, the initial heterogeneity is a Gaussian distribution with a unit mean and variance, u^2.

The survival function hazard rate is

$$h(t) = \frac{f(t)}{l(t)} + k. \quad (13)$$

2.2. Initial condition and vitality distribution

The Gaussian distribution is a simple, but biologically plausible, choice for initial population heterogeneity, not only because it is one of the most common distributions in nature, but also because it yields an analytical approximation for the distribution of vitality in the population with age. To develop this distribution, we note that when $\tau \to 0$, Eq. (6) approaches a Dirac delta function with a zero variance and unit area. With this limit, the evolution of vitality density in the surviving population at age t is (Cox and Miller, 1965)

$$p_v(v, t|v_0, 0) = \frac{1}{\sqrt{2\pi\sigma^2 t}}\left(\exp\left(-\frac{(v-\bar{v}_0+\sigma t)^2}{2\sigma^2 t}\right) - \exp\left(\frac{2\rho v_0}{\sigma^2} - \frac{(v+\bar{v}_0+\sigma t)^2}{2\sigma^2 t}\right)\right). \quad (14)$$

The density evolves with time from a Dirac delta function spike into a Gaussian-like shape and then into a quasi-stationary gamma-like distribution, which is proportional to $\rho^2 t \exp(-\rho t)$ if $\sigma = 1$ (Aalen and Gjessing, 2001). The area of the quasi-stationary distribution is eventually absorbed into the zero-vitality boundary (Fig. 1b). The evolving vitality density in a population with an initial Gaussian distribution can be approximated by integrating the evolving density described by Eq. (14) with the initial distribution of Eq. (6) giving

$$p_v(v, t) = \int_{-\infty}^{\infty} p_v(v, t|v_0, 0)\, p(v_0)\, dv_0 = \frac{1}{\sqrt{2\pi\left(\tau^2+\sigma^2 t\right)}}\left(\exp\left(-\frac{(v-\bar{v}_0+\sigma t)^2}{2\left(\tau^2+\sigma^2 t\right)}\right) \times \left(1 - \exp\left(-\frac{2v\bar{v}_0\left(\rho\tau^2+\sigma^2\right)}{\sigma^2\left(\tau^2+\sigma^2 t\right)}\right)\right)\right). \quad (15)$$

Fig. 1b illustrates Eq. (15). It begins as a Gaussian distribution and evolves into a gamma-like distribution that is essentially equivalent to Eq. (14). This convergence from the initial distribution to the quasi-stationary distribution is a property of the Wiener process with an absorbing boundary. Under certain values of the drift and spread terms, the final distribution is independent of the initial condition (Aalen and Gjessing, 2001).

Note that survival defined by Eq. (9) and the probability density defined by Eq. (15) are only approximations of our process because, by specifying an initial Gaussian distribution, we admit negative vitalities into the population which, in essence, implies that a portion of the population is initially dead. However, the error is insignificant if $\tau/\bar{v}_0 < 0.35$. Then $p_v(v, 0)$ is Gaussian-like and the distribution evolves into a gamma-like distribution with age, as illustrated by the dashed lines in Fig. 1b. Aalen and Gjessing (2001) noted that initiating the process with a gamma-like distribution proportional to $t^c \exp(-\rho t)$ yields a quasi-stationary gamma distribution. However, we do not believe this is generally biologically realistic because it implies that the initial heterogeneity is right skewed, with the dominant portion of the population having initial low vitality. Li (2007), using AIC criteria, compared the maximum likelihood fits from gamma and Gaussian initial distributions for a survival curve that was left-truncated at different times. Generally, with small left-truncation intervals, a model with the Gaussian initial distribution fits the survival data best, while with a large left-truncation interval the gamma initial distribution provided a better fit to the data. This result is expected because, when left-truncating a survival curve with spreading vitality distribution similar to Fig. 1b, we see that a Gaussian distribution is a better representation of the initial distribution early on, while a skewed gamma-like distribution is a better representation of the initial distribution for greater left-truncation times.

2.3. Parameter estimation

To estimate the model parameters r, s, k and u in Eq. (9) from survival data, we cast the estimation problem as a maximal likelihood optimization similar to the one developed by Salinger et al. (2003). The approach deals with interval-censored data in which mortalities are counted at the end of each time interval, rather than continuously. Standard errors are obtained by taking the square root of the diagonal elements in the inverse of the Hessian of the negative log-likelihood, evaluated at the parameter estimates (Kendall and Stuart, 1979). More details about the fitting routine are available in the on-line supplemental information.

3. Model characteristics

Eq. (9), with its four model parameters, defines the interactions of senescence, accidental mortality, and evolving and initial heterogeneities on population survival curves. Below, we describe the parameters and graphically illustrate how they affect a survival curve.

3.1. Average senescence

The most important term in the model is the mean rate of loss of vitality, r. It quantifies the average rate at which survival capacity declines with age and is the mean rate of senescence, or aging, without heterogeneity or accidental mortality. Several mechanisms have been proposed for aging including accumulation of faulty cells due to the mistranscription of messenger RNA (Wiegel et al., 1973), free radicals that produce oxidative damage (Beckman and Ames, 1998; Ashok and Ali, 1999; Bokov et al., 2004; Muller et al., 2007), minute impairments to the immune and neuronal endocrine systems (Yin and Chen, 2005), shortening of telomeres important for chromosome replication and protection (Passos and von Zglinicki, 2005), and activation of a gene controlling proliferation of stem cells involved with tissue repair and regeneration (Janzen et al., 2006; Krishnamurthy et al., 2006). In addition, several studies have connected growth to increased oxidative damage and reduced life span (Olson and Shine, 2002; Ruel and Whitham, 2002; Munch and Conover, 2003). Recent studies in mice indicate a progressive and random accumulation of mtDNA point mutations. Importantly, for our assumption of a linear decline in vitality, the accumulations were linear, suggesting no involvement of a vicious circle of accumulations (Kukat and Trifunovic, 2009). However, acceleration of age related degradation in function is observed in numerous animal systems (Muller et al., 2007). Whether the rate of damage accumulation is generally linear or accelerative is not especially germane to our level of model since, by characterizing the rate over the lifespan, we can represent the mean rate of both linear and nonlinear damage accumulations.

In our scenario, average vitality in the absence of variations declines linearly from a unit initial value and reaches zero at age T_s. We designate this as the senescence time scale,

$$T_s = 1/r. \tag{16}$$

In effect, T_s is the deterministic time to mortality from senescence. It also has an approximate relationship with body mass, M, as $r \sim M^b$ where $b \sim -0.25$ (Anderson, 2000). Fig. 2a illustrates how variations in r change the survival curve in the absence of other factors.

3.2. Accidental mortality

Age-independent, accidental or extrinsic mortality is an important element in force of mortality models starting with the Gompertz–Makeham model (Makeham, 1867). First passage models have, for the most part, ignored the process, but it was first included in the vitality model by Anderson (1992). In the current model, age or vitality-independent mortality is characterized by the Poisson rate, k. In the absence of other factors, it produces an exponential survival curve, as is typically found in many survival models in ecology (Fig. 2b). The mean time (i.e. extrinsic time scale) to accidental mortality we designate

$$T_a = 1/k. \tag{17}$$

As an aside, accidental mortality can also be expressed through an age-dependent process similar to the one formulated in the Gompertz model. The result is a mixed model with both force of mortality and first passage mortality processes. This form and others will be explored in a forthcoming manuscript.

3.3. Evolving heterogeneity

Evolving heterogeneity, characterized by s, stochastically modifies the deterministic senescence rate, see Eq. (4). The body of evidence noted above indicates that aging results from random accumulation of damage at the molecular level. The random rate term of the Wiener process, σ, in its dimensional form and s in its nondimensional form, readily captures this randomness. Because the variance of the Wiener process increases linearly with time, we define the temporal evolution of evolving heterogeneity as $E = s^2 t$. However, evolving heterogeneity only has a small effect on life expectancy because, as s increases, it decreases early life survival and increases late life survival. This pattern is evident as a change in the survival curve slope at the mean senescence time, i.e. $\mathrm{d}l/\mathrm{d}t$ at T_s (Fig. 2c). Note that curves with differing s are not symmetrical because evolving heterogeneity increases with age.

3.4. Initial heterogeneity

The initial heterogeneity is the variance in the initial vitality distribution, which we designate $I = u^2$. Initial heterogeneity is similar to lifelong heterogeneity in the traditional frailty models (Vaupel et al., 1979). It likely has genetic factors but also may be produced by plastic processes influenced by environmental and stochastic phenomenon (Rea et al., 2005). When the model is fit to left-truncation data, the estimated initial heterogeneity includes evolving heterogeneity up to the truncation point. Irrespective of the source, in a vitality construct, initial heterogeneity does not evolve with time. We specify the initial heterogeneity with a Gaussian distribution and require $u < 0.35$ to ensure that the initial distribution effectively does not include negative vitalities. Gaussian distributed initial heterogeneity acting on the average senescence produces a survival curve characteristic of a cumulative normal distribution (Fig. 2d). Since the contribution of I is constant in time, curves produced by varying u^2 are symmetrical around T_s, and intersect at the median survival time.

3.5. Characteristic time scales

Together, these four factors produce the survival curve illustrated in Fig. 2e. A salient point is that the effect of evolving and initial heterogeneities cannot be disentangled unless the underlying processes are specified. We propose that the Wiener process with its linear evolving heterogeneity, combined with a Gaussian initial heterogeneity makes for a biologically realistic and mathematically tractable model and, therefore, a parsimonious approach in which to disentangle population heterogeneity. Because evolving heterogeneity increases with time and initial heterogeneity is constant, we can define a heterogeneity crossover time at which the two are equal as

$$T_h = u^2/s^2. \tag{18}$$

At ages less than T_h, initial heterogeneity mainly controls the slope of the survival curve, and at greater ages evolving heterogeneity controls curve slope. This feature is a property of the quasi-stationary distribution produced by the Wiener process (Aalen and Gjessing, 2001).

Comparing the heterogeneity crossover and senescence times indicates whether a survival curve approaches a mortality plateau at which the hazard rate levels off with age. In Fig. 2e, $T_h = 0.09$ and $T_s = 1$ such that, at the average senescence age, the evolving heterogeneity dominates the initial heterogeneity and the survival curve has a mortality plateau at old age (Fig. 2f). In some situations, $T_h > T_s$ such that, at the senescence age, the initial heterogeneity dominates and the curve will not have a mortality plateau. In the same manner, the ratio of the accidental and senescence time scales indicates the relative importance of extrinsic and intrinsic factors on the survival curve.

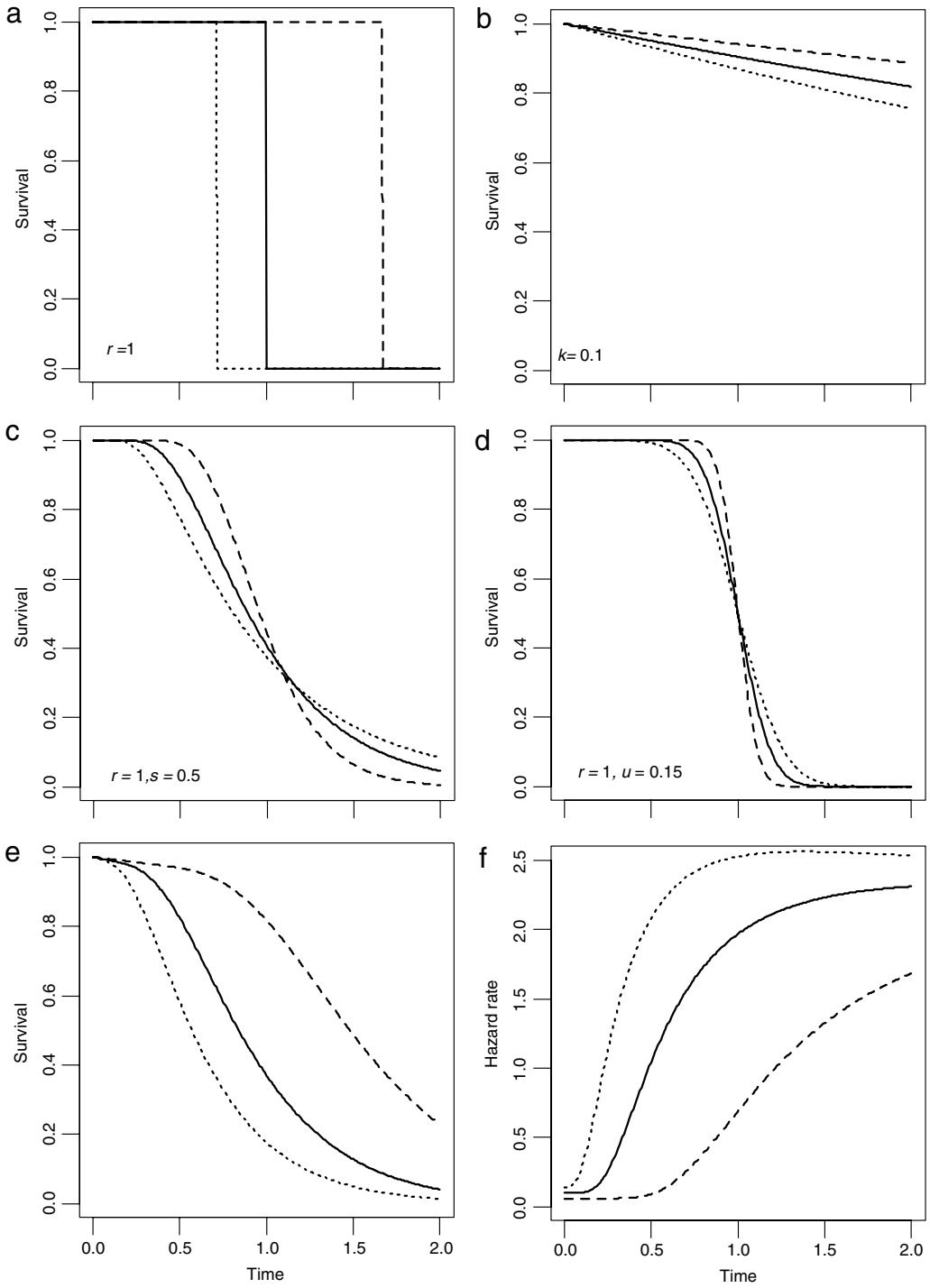

Fig. 2. Effect of Eq. (9) parameters on survival. (a) Mean senescence effect from r with $s, k, u = 0$. (b) Accidental mortality effect from k with $r, s, u = 0$. (c) Evolving heterogeneity effect from s with $u, k = 0$. (d) Initial heterogeneity effect from u with $s, k = 0$. (e) Total survival. (f) Hazard rate. Base parameters are $r = 1, s = 0.5, k = 0.1$, $u = 0.15$ and variations shown in dashed lines vary parameters by a factor of 0.6 (– – –) and 1.4 (- - -).

3.6. Mean and variance of vitality

The distribution of vitality of the population alive at a specific age depends mostly on the interplay between evolving heterogeneity, which set by s increases variability with age, and mortality, which set by r decreases variability with age by removing population members. Fig. 1 illustrates this balance. The vitality paths initially spread because of the stochastic rate and, as paths are absorbed into the boundary (starting ∼ day 12 in Fig. 1a), the variability amongst the surviving paths decreases. The vitality distribution mean and variance are defined

$$E\left[v_{alive}\right] = \int_0^\infty v f_{alive}\left(v, t\right) \mathrm{d}v \tag{19}$$

and

$$\mathrm{Var}\left[v_{alive}\right] = \int_0^\infty v^2 f_{alive}\left(v, t\right) \mathrm{d}v - E\left[v_{alive}\right]^2 \tag{20}$$

where the probability density of vitality of the remaining population is

$$f_{alive}\left(v, t\right) = \frac{p_v\left(v, t\right)}{l_v\left(t\right)}. \tag{21}$$

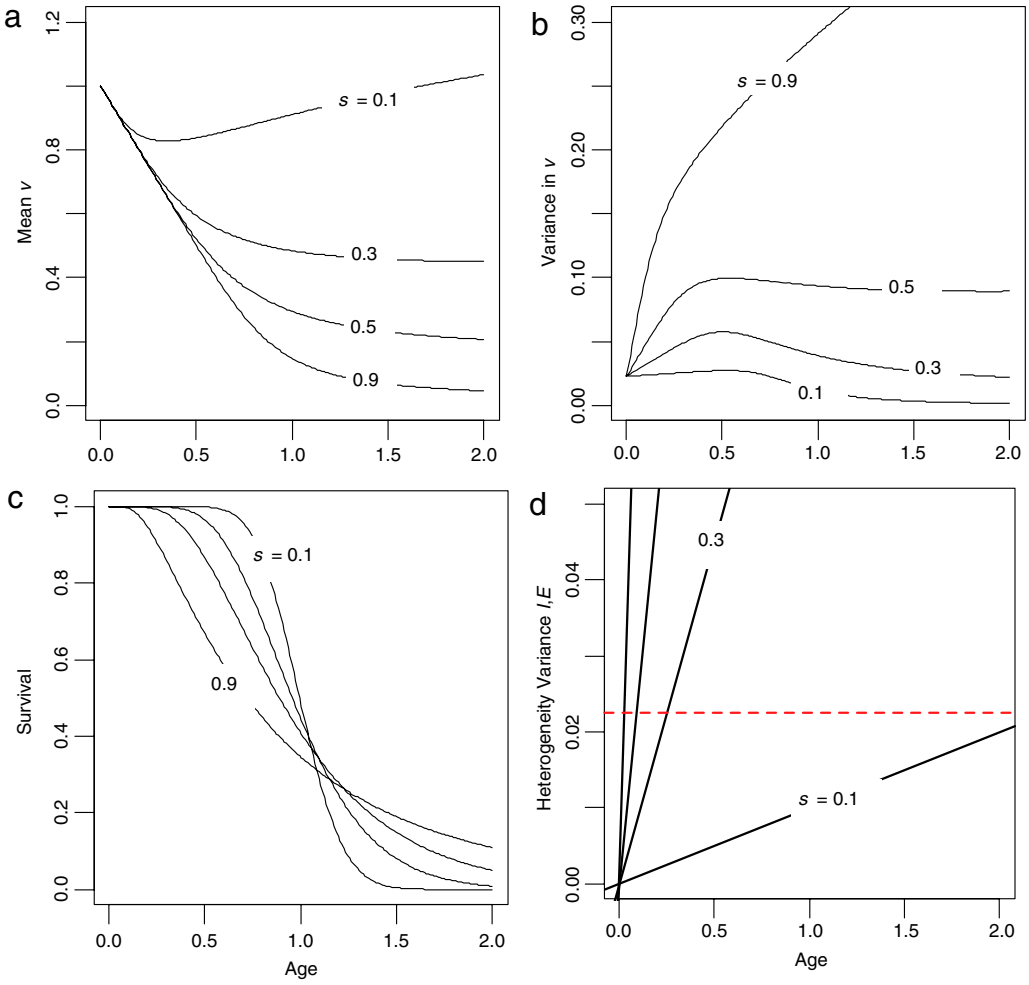

Fig. 3. Survival and vitality statistics with age for $s = 0.1, 0.3, 0.5, 0.9$ and $r = 1, u = 0.15, k = 0$. (a) Effect of evolving heterogeneity on vitality mean. (b) Effect of evolving heterogeneity on vitality variance survival. (c) Effect of evolving heterogeneity on survival. (d) Variance in initial I (– – –) and evolving E (—) heterogeneity with age.

The temporal patterns of the mean and variance of the vitality distribution are primarily determined by the ratio of s to r, which reflects the interaction between an increase in variance from evolving heterogeneity and a decrease from death (Fig. 3). Because the parameters are normalized, the mean initial vitality always begins at one (Fig. 3a) and as age increases, it approaches the mean value of the quasi-stationary distribution, $\bar{v}_*$. When $\bar{v}_* < 1$, the mean vitality asymptotically decreases to $\bar{v}_*$ (Fig. 3a, with $s > 0.3$), but when $\bar{v}_* > 1$, the mean vitality may first pass through an intermediate minimum and then rise to $\bar{v}_*$ (Fig. 3a, $s = 0.1$). In effect, when s is sufficiently large, a fraction of the population randomly gains vitality and the individuals that survive to old age are generally from this fraction. The variance in vitality from Eq. (20) again depends on s relative to r. At age zero, the variance is set by the initial variance u^2. It then evolves to the variance of the quasi-stationary distribution, which is set by s and r (Fig. 3b). Fig. 3c illustrates the survival curves corresponding to the mean and variance curves. Note as s increases, the slope decreases at the median survival. Fig. 3d graphically illustrates that the variance of the evolving heterogeneity increases linearly with age while the initial heterogeneity is constant.

3.7. Hazard rate

In the model, the shape of the hazard rate given by Eq. (13) depends principally on the ratio of the heterogeneity and senescence time scales. In particular, we focus on the character of the hazard rate at advanced age since it is important to many issues in demography. Note T_h characterizes the crossover point where evolving heterogeneity dominates initial heterogeneity and T_s is the mean time to mortality from senescence. If $T_h/T_s > 1$, then at advanced age the shape of hazard rate is determined by the initial heterogeneity distribution and when $T_h/T_s < 1$, evolving heterogeneity determines the character of the hazard rate at advanced age. In particular, the hazard rate approaches slope of the quasi-stationary distribution at $v = 0$ (Aalen and Gjessing, 2001). Fig. 4 illustrates the effect of initial and evolving heterogeneities on the hazard rate using $r = 1$ and $k = 0$. When s is small, e.g. $s = 0.1$ in Fig. 4a, then T_h is very big and $T_h/T_s > 1$. Then at advanced age the hazard rate increases in an approximate linear manner, but when s is sufficiently large $T_h/T_s < 1$ and the hazard rate may either rise to its asymptote, e.g. $s = 0.5$ in Fig. 4a, or reach an intermediate maximum and then decrease, e.g. $s = 0.9$ in Fig. 4a. Because the model is limited to values of initial heterogeneity with $u < 0.35$, the effect of initial heterogeneity has less pronounced effect. Increasing u causes the asymptotic rate to decrease (Fig. 4b). The accidental mortality, k, simply shifts the hazard rate curve up or down uniformly.

4. Examples

We now illustrate how the vitality model provides insights into several classical patterns in demography. In particular, we illustrate how changes in survival curves are quantified by model parameters and how, in turn, these provide hypotheses on the relative importance of biological processes acting on the

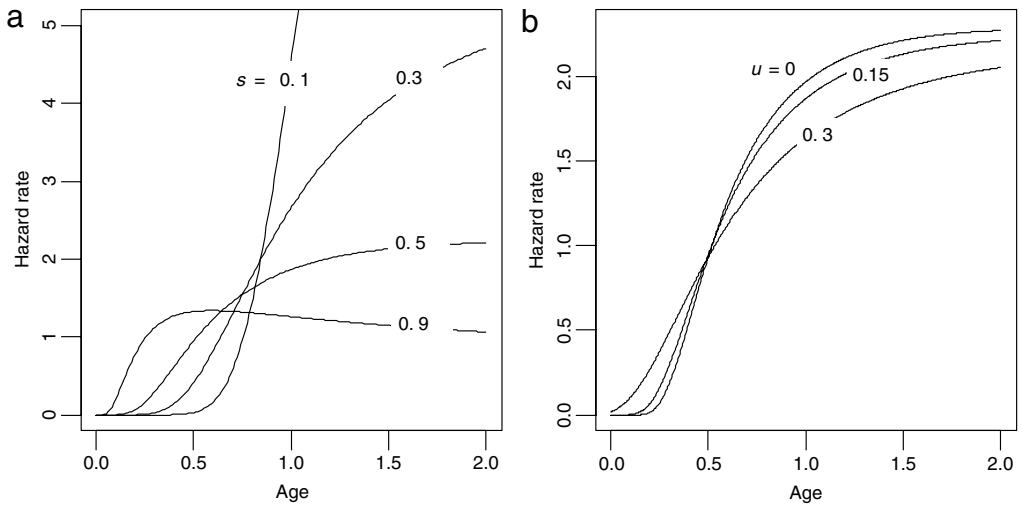

Fig. 4. Hazard rate as a function of age for different ranges of model parameters. (a) Effect of evolving heterogeneity s on hazard rate. With $r = 1$, $u = 0.15$ and $k = 0$ the s values of 0.1, 0.3, 0.5 and 0.9 correspond to $T_h/T_s = 2.25$, 0.25, 0.09 and 0.028. (b) Effect of initial heterogeneity, u, on the hazard rate. With $r = 1$, $s = 0.5$ and $k = 0$ the u values correspond to $T_h/T_s = 0$, 0.09 and 0.36. Survivals curves corresponding to Fig. 4a are illustrated in Fig. 3c.

Table 1
Parameter estimation for Medfly survival paradox (time scale: day).

Groups		r[a]	s[a]	k[a]	u[a]	T_s[a]	T_a[a]	T_h[a]	ELS
Male	Value	0.044	0.059	0.002	0.266	22.73	558.4	20.33	22.62
	s.e.	2E−05	7E−06	3E−05	4E−05	0.010	8.3	0.01	
Female	Value	0.049	0.098	0.003	0	20.41	286	0	20.08
	s.e.	3E−05	1E−04	3E−05	3E−06	0.011	2.6	7E−10	

[a] The parameter with significantly different values at 5% level for the both groups. The definition of two significantly different values is that their 95% confidence intervals do not overlap each other.

populations. In the first example initial and evolving heterogeneities produce a demographic paradox in which male medflies exhibit higher mean life expectancy, but females are usually the last to die. In the second example diet restriction affects the mean senescence age but not heterogeneity. In the third example, the effect of left-truncated data on parameter estimates is evaluated and the implication to cross life stage effects is discussed. In the fourth example, a hypothesis is developed for when mortality plateaus are observable.

4.1. Initial and evolving heterogeneities and the medfly survival paradox

Across numerous species, females have greater life expectancies than males, but Carey et al. (1995) identified a demographic paradox in which male medflies (*Ceratitis capitata*) exhibited a greater life expectancy than females, but the females were usually the last to die. A consequence of this paradox is a mortality crossover where males have lower mortality rates when young, but after the crossover age, the female rate is lower. This crossover is significant because it was generally believed that sex ratio is biased towards one sex over the entire lifespan such that if females had a longer expected lifespan, they would also have lower mortality rates at all ages. The Carey et al. study indicated that age dependent mortalities were more complicated than previously realized. We explore the paradox through the vitality model to gain additional insights into the pattern and its possible causes.

Carey et al. sorted approximately 7200 medflies (both sexes) into five size classes maintained in each of 167 cages. The separation of sizes removed size dimorphism as a potential source of mortality differences between males and females. We fit the vitality model to the male and female survivorship data and found all parameters were significantly different ($p < 0.01$) (Table 1). Fig. 5a and b illustrate the model fit. The model underestimates male survival after day 60 when, on average, less than 3 males were still alive in each cage. The same condition occurred for the females at day 68 (Fig. 5b). The males had slightly lower mean vitality rates, corresponding to their greater expected lifespans. However, the old age females had a higher vitality rate variance and therefore greater evolving heterogeneity. The initial heterogeneity in the male cohort was large but was essentially zero in the female population (Fig. 5c). Carey et al., using a 7-day running geometric mean of the data, reported the hazard rates crossed over about day 20. From the vitality model the crossover was also at day 20 (Fig. 5d).

Carey proposed that three interrelated categories of factors were in play in producing the crossover. The first category, constitutional endowment, is a general measure of overall fitness to resist disease stress, physical challenge and deterioration, and originates from the effects of chromosomal differenced between males and females. They suggested that females at emergence were on the average frailer (their qualitative measure of survival capacity) than males but females had more variance in frailty. The second category, reproductive biology, concerns processes associated with the cost of reproduction. Of particular note here, are studies showing virgin insects typically exhibit lower mortality rates than females that mate and reproduce. The third category, behavioral predispositions, evolves maintaining territories and other high risk-high stake strategies. Carey et al. commented that these categories interact in complex ways. We use the vitality parameters (Table 1) to quantify the possible contributions of these three categories of processes.

The Carey et al. hypothesis that females were frailer than males is supported by the difference in r in the two sexes. Noting that $1/r$ is the senescence time, T_s, we see that, on average, the time to senescence in females was 10% less than in males, which is essentially the difference in the expected lifespan of males and females.

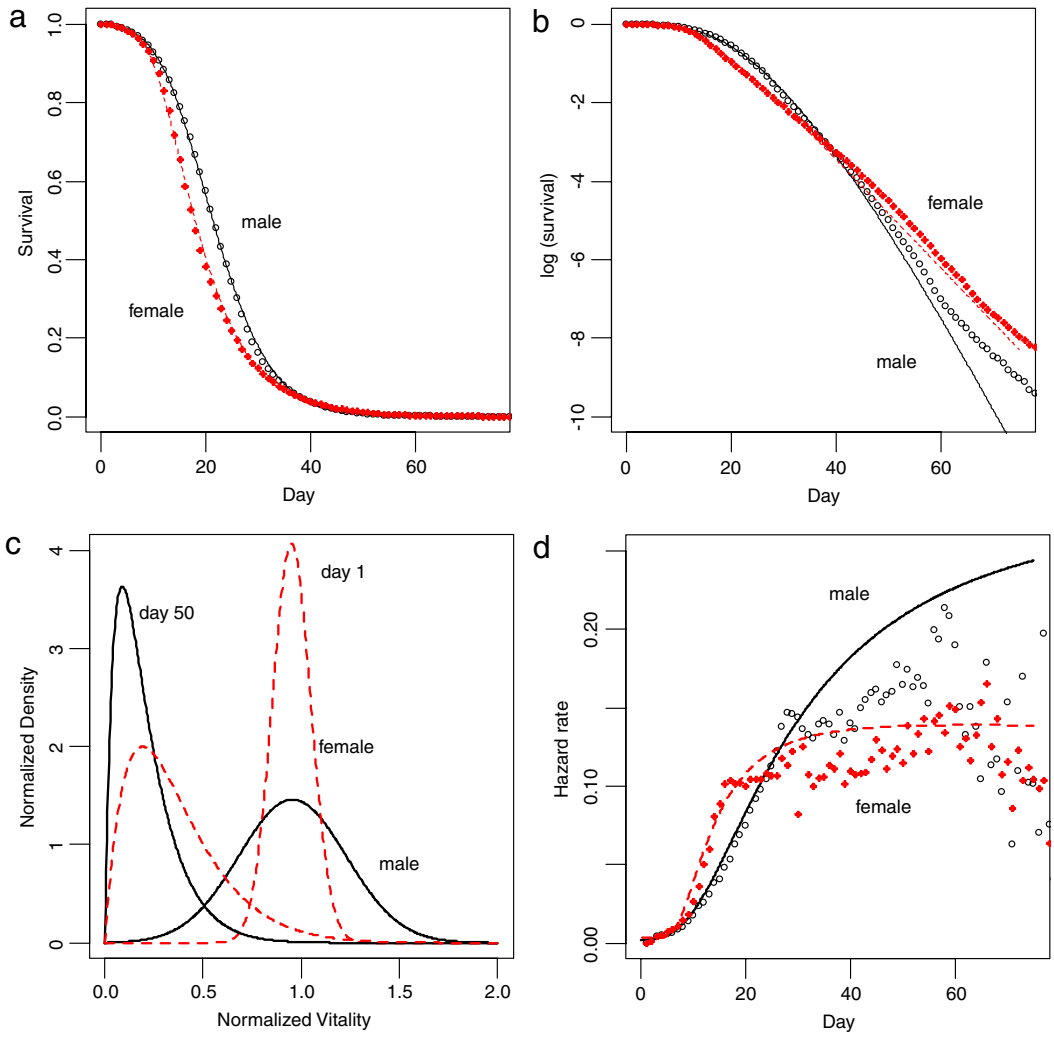

Fig. 5. Medfly mortality paradox. (a) Model fitting to male (○) and female (●) survival data. (b) log (survival). (c) Normalized vitality distribution at day 1 (early life stage) and day 50 (late life stage). (d) Hazard rate. The vitality distributions are normalized to unit area for each time.

Carey et al. suggested that variance in frailty was greater in females than in males. However, the vitality model gives a different result. Variance in the initial vitality distribution was large in males and zero in females at age zero. At day 1 the variability in male vitality was much larger than in the females (Fig. 5c). To reconcile this difference, we note that frailty as used by Carey does not distinguish between initial and evolving factors and therefore we propose frailty is not a sufficiently precise term. Furthermore, we suggest that the reproductive difference between males and females, the second category of their factors, is quantified by evolving heterogeneity and indicated greater variability in the females; the ratio of s in females to males is 1.66. We suggest that the large s in the female group resulted from variability in fecundity coupled with the fact that virgins have demonstrated longer lifespans. In this hypothesis, the major difference in male–female variability involves reproduction, not initial heterogeneity or frailty.

The male–female difference in initial vitality is striking and requires further consideration. One possibility might involve covariability in the estimation of s and u. Because both parameters quantify variability in survival, it is possible that if s is biased high then u is biased low. Because the male cohort had a high u and low s and the female cohort had a low u and high s, is it possible that the parameter estimates are sufficiently biased to reverse the values of u? Furthermore, if this were the case, then we expect s values would also be biased in the opposite manner and males would have greater evolving heterogeneity. However, the female cohort clearly had greater late life variability and, because the effect of initial heterogeneity diminishes with age, an extreme bias in model estimates is not sufficient to explain the differences in initial heterogeneity. We also explored the possibility of bias with numerical simulations and found it was not important (Appendix). Alternatively, we consider "biological" factors. Carey et al. noted that females have two X chromosomes compared to the one X chromosome in males. The X chromosome is three times larger than the Y chromosome and contains far more genetic information, most of which is unrelated to the female genotype. Thus, higher initial heterogeneity in the males might be attributed to the lack redundancy of genetic material in the male. However, this explanation begs the question of how the chromosome difference might relate to the mean vitality of males and females.

Finally, consider the extrinsic factor k which is 50% larger in the female cohort than in the male cohort: 0.003 vs. 0.002. This difference is not large because this accidental mortality is small compared to the vitality-based mortality. The accidental mortality time scale is approximately 20 times longer than the senescence time scale. However, the male–female accidental mortality differences are statistically significant and suggest that the female cohort experiences slightly higher rates of vitality-independent mortality. Note also that for male medflies, initial heterogeneity dominates evolving heterogeneity up to the senescence time since $T_h \sim T_s$. In contrast, for the females, since

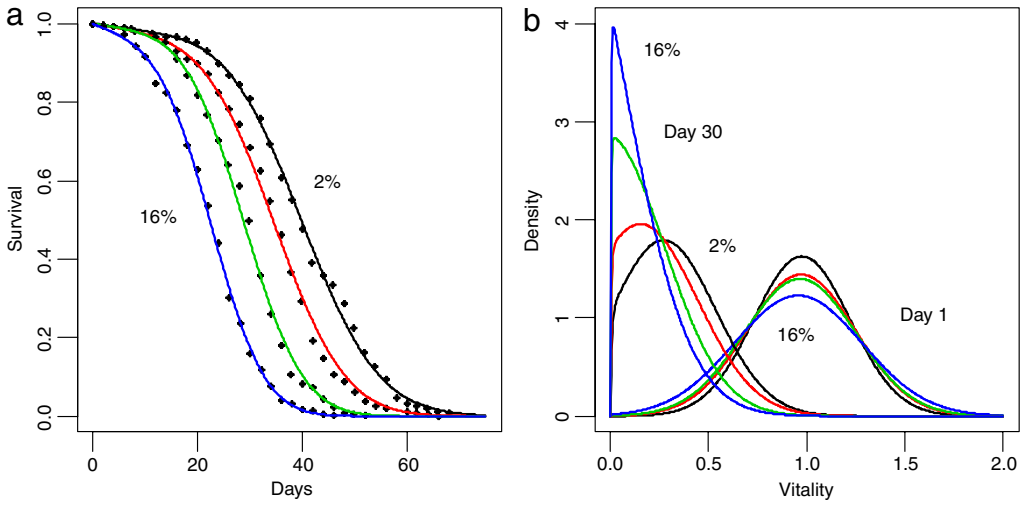

Fig. 6. (a) Model fitting to survival data for drosophila with diets with 2%, 4%, 8% or 16% yeast. (b) Normalized vitality distributions at day 1 (early life stage) and day 30 (late life stage). The vitality distributions are normalized to unit area for each time.

Table 2
Parameter estimation for female *Drosophila* diet restriction (time scale: day), ELS is the observed expected lifespan.

Yeast concentration (%)		r[a]	s	k	u	T_s[a]	T_a	T_h	ELS
2	Value	0.024	0.019	0.002	0.244	40.89	585.9	221.8	38.51
	s.e.	0.001	0.006	0.001	0.023	0.95	301.7	189.5	
4	Value	0.028	0.017	0.002	0.276	35.42	459.8	263.8	32.92
	s.e.	0.001	0.008	0.001	0.027	0.88	256.4	244.3	
8	Value	0.034	0.015	0.002	0.285	29.3	570.4	360.9	27.48
	s.e.	0.001	0.010	0.001	0.024	0.72	407.3	488.9	
16	Value	0.043	0.016	0.005	0.325	23.39	221	400.1	21.12
	s.e.	0.001	0.019	0.002	0.028	0.67	111.5	954.2	

[a] The parameter with significantly different values for all the groups at 5% level. The definition of two significantly different values is that their 95% confidence intervals do not overlap each other.

$T_h = 0$, the survival curve shape is determined by evolving heterogeneity, which we suggest is associated with stress in reproduction.

In general, the shape of the vitality distribution with age (Fig. 5c) provides a plausible quantification of the factors Carey et al. hypothesized are responsible for the mortality paradox. In early life, males have a larger spread in vitality, which we assume is of genetic origin, but at older ages the females have a larger spread in vitality as a result of greater evolving heterogeneity associated with variable fecundities within the female cohort. The model results support the point Carey et al. made that sex-differences in survival curves are complex and general conclusions on sex-differences are risky. However, with the vitality model, we have plausible links between model parameters and biological mechanisms that produce the mortality paradox.

Finally, as a cautionary but speculative note, the medfly data exhibited a significant change in the hazard rate at about day 35 (Fig. 5d). Carey et al. noted that after this date, male mating activity was reduced and female egg production was low to nil. A link between the matting activity and the vitality rate r might explain this abrupt shift in hazard rate. It would also imply a violation of the constant parameters assumption of the model which illustrates the limitations of explaining survival curves with four parameters.

4.2. Effect of diet restriction

Dietary restriction (DR) increases longevity in numerous populations and involves fundamental changes in cellular aging (Mair et al., 2005; Yin and Chen, 2005). Characteristically, increases in longevity are reported as mean survival times or simply illustrated by the survival curves. With the vitality model, we can explore in greater detail the effects of DR. To illustrate we pose the question, "does DR act uniformly across all members of the population or does it increase heterogeneity; affecting some members of the population positively and others negatively?" The question is relevant to population ecology because if DR induces heterogeneity in survival and the effect is heritable, then we might expect DR to increase the rate of natural selection.

In terms of the model parameters, if DR acts uniformly across a population, then only r should change with DR, while if the effect is reflected in evolving heterogeneity, we expect s to change; therefore, T_h should change with DR. In either case u should not change if the study draws the groups from the same initial population. For our example, we use data from an experiment of drosophila food restriction (Min and Tatar, 2006) in which adult *Drosophila melanogaster* were fed a diet with 11% sugar, 5.2% cornmeal and inactive-yeast concentrations of 1%, 2%, 4%, 8% or 16% (w/v). Mortality was significantly reduced on restricted diets with adult mean survival time declining monotonically from 38.5 days to 21.2 days with diets varying between 2% and 16% yeast. The survival curves and data fits are shown in Fig. 6a and parameter estimates are listed in Table 2. Fig. 6b illustrates the effect of DR on the vitality distributions over time. All distributions are similar at day 1. With DR affecting r, the distributions are driven to the absorbing boundary at different speeds so that at late life (day 30) the vitality profile is closer to zero for the group fed 16% yeast than for the group fed 2% yeast.

The model gives a clear relationship between DR and the mean rate of vitality loss which can be expressed $\log r = -3.75 + 3.99x$, $r^2 = 0.96$, $p < 0.02$, where x is percent of yeast and r is in $1/d$. Increasing r corresponds to decreasing T_s and the remarkable drop

in expected lifespan. Also note a similar regression with *ELS* since $ELS \sim 1/r : \log ELS = 3.74 - 3.83x$, $r^2 = 0.96$, $p < 0.02$. However, the model fit also indicates that DR does not affect population heterogeneity; neither s nor u^2 change significantly with x (Table 2) and regressions of log s or log u against x are not significant: $p > 0.40$ and $p > 0.79$, respectively. This result occurs because $T_s \ll T_h$ such that initial heterogeneity dominates and it is not be affected by diet. Correspondingly, in species in which evolving heterogeneity dominates, we may expect DR to affect population heterogeneity. Finally, the model indicates that vitality-independent mortality, expressed by k, is not affected by DR.

Thus, we suggest that in drosophila DR decreased the rate of damage accumulation in an exponential manner $r = 0.023 \exp(4x)$. Furthermore, because the evolving heterogeneity was low relative to the initial heterogeneity, DR had little effect on heterogeneity in the populations. However, the lack of a relationship between DR and heterogeneity may in part be a consequence of the experimental design. Because DR was produced by dilution of the yeast content in the food, not restricted food availability, there was no obvious mechanism to induce heterogeneity in the amount of food received. In contrast, Anderson (2000) found that in a study where rotifers were put under DR by extending the time between feeding intervals (Verdone-Smith and Enesco, 1982) s increased significantly with longer durations between feeding. In fact, the group with greater DR had a larger fraction of high vitality members than did the group with less DR. Anderson postulated that under increased stress, the stronger individuals had less competition from weaker individuals than they would have experienced in a situation with greater amounts of food. He hypothesized that when mortality depends on acquisition of resources through foraging contests, limitation of the resource might decrease the ability of weaker individuals to compete, resulting in the stronger individuals winning more contests and becoming stronger still. Thus, when DR is induced by contest competition for resources, we might expect increased heterogeneity in a population. However, as was the case in the drosophila study, when DR is induced without competition it may have less impact on heterogeneity. We explore this hypothesis further and provide evidence for the effects of contest competition in the next example below. Note also that while contests for resources may induce heterogeneity, this does not resolve the issue of whether DR might affect the rate of natural selection.

4.3. Effects across life stages

The experience of a cohort in one life stage can affect the survival pattern in later life stages, e.g. spring growth rate in juvenile salmon affects adult return rate (Beckman et al., 1998), early life growth rate affects resistance to starvation in yellow perch (Letcher et al., 1996) and mild stress in early stages increases longevity (hormetic effect) in invertebrate species (Le Bourg, 2009). Anderson et al. (2008) considered such cross stage effects in a treatment-challenge framework in which groups from different treatments were then subjected to the same stressor, i.e. challenge. In a vitality framework, if the groups only differ in the treatment, then differences in their survival patterns in the challenge should reflect the effect of the treatments on the initial vitality distribution in the challenge stage. Furthermore, relating patterns in the challenge-stage vitality parameters to the treatment-stage conditions it is possible to quantify the effect of the treatments on evolving heterogeneity in the treatment stage. Thus, the cross-life stage effects noted above can be set in a treatment-challenge framework in which the link between stages is expresses by how the treatment stage affects the initial heterogeneity of the challenge stage. The effect is also relevant to the interpretation of left-truncated survival curves. Importantly, in a vitality framework the initial heterogeneity estimated for left-truncated survival data depends on the nature and length of the left truncation period as well as the initial heterogeneity of the cohort at birth.

Thus, all the above-mentioned scenarios can be put in a vitality framework in which the treatment-challenge transition point or the left-truncation point is designated age, t_0, and the vitality distribution at t_0 is determined by the initial heterogeneity at birth, $t = 0$, and the evolving heterogeneity between 0 and t_0. Furthermore, because vitality parameters for the period, $t > t_0$ depend on the mean initial vitality, all parameters except k. depend on the nature of the truncation period.

To illustrate this cross-life stage effect we use a study by Letcher et al. (1996) that characterized the effects of early life history growth on the time to starvation of yellow perch (*Perca flavescens*). In the experiment groups of fish were removed from a common brood stock tank at different ages and subjected to a starvation challenge. For our illustration we consider one group removed at age 25 d (∼15 mm length) and second removed at age 39 d (∼20 mm length). Fish in the blood stock increased weight exponentially up through day 30 and thereafter exhibited little growth, which Letcher et al. suggested was because the fish did not receive sufficient food as their body size increased. However, no mortality occurred over the period and so the two groups were in different bioenergetic states as well as sizes at the time of their respective starvation challenges.

The 25-d group had a higher median survival time in the starvation challenge than the 39-d age group (10 d vs. 7 d), but the older fish exhibited greater heterogeneity as evidenced by the shallower slope of the survival curve about the median survival date (Fig. 7a). The model indicates that these differences in heterogeneity were primarily a result of different initial heterogeneities in the challenge stage; other terms were not significantly different (Table 3). In both groups, evolving heterogeneity was small; however initial heterogeneity was small in the 25-d group and large in the 39-d group. In the 39-d group $T_h \gg T_s$, so the effects of initial heterogeneity dominated the effects of evolving heterogeneity. Finally, because the two groups were taken from the same brood stock, their initial heterogeneities at birth were equal and we conclude that the initial heterogeneity of the survival curve, left-truncated at day 39, was the result of a greater rate of evolving heterogeneity in the brood stock between day 25 and 39. Thus, in this example the differences in the patterns of starvation can be attributed to initial heterogeneity resulting from the conditions and duration during the left-truncation period. Furthermore, because the 39-d group was food limited, the individuals were subjected to contest competition for food, which Anderson's (2000) hypothesized would increased evolving heterogeneity. In contrast, in example 2 the drosophila diet was limited through food quality, not amount, and the groups exhibited no increase in evolving heterogeneity.

The fact that events prior to the left-truncation age affect survival presents both problems and opportunities. It suggests that juvenile conditions are important for understanding adult survival and that cross-life stage effects are important in fixing the patterns of life time survival. However, cross-life stage effects present an opportunity when put in the context of treatment-challenge experiments (Anderson et al., 2008). When similar groups, drawn from different treatments, are exposed to a uniform stressor challenge, their survivals over the challenge should be the result of the cumulative effects of the treatments. In this sense, a standardized challenge effectively becomes a probe in which to quantify the effects of past conditions or treatments on future survival capacity.

4.4. Mortality plateaus

The leveling off, or decline, in the mortality rate at advanced age is observed in populations as wide ranging as fruitflies (Carey et al.,

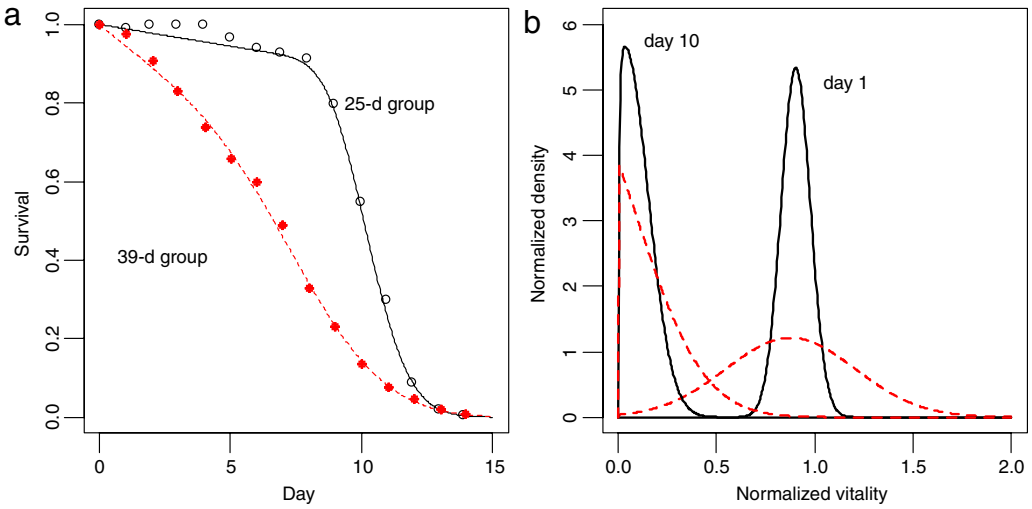

Fig. 7. Yellow perch study. (a) Model fitting to survival fraction data. (b) Normalized vitality distribution at day 1 (early life stage) and day 10 (late life stage) for 25-d group (—) and 39-d group (– – –) population separately. The vitality distributions are normalized to unit area for each time.

Table 3
Parameter estimation for yellow perch study (time scale: day).

Truncation age (d)		r	s	k	u^a	T_s	T_a	T_h
25	Value	0.097	0.031	0.011	0.068	10.3	87.4	4.7
	s.e.	0.003	0.010	0.011	0.007	0.20	53.5	12.1
39	Value	0.123	0.012	0.053	0.330	8.1	19.0	752.9
	s.e.	0.020	0.270	0.040	0.041	0.58	7.6	109.3

[a] The parameter with significantly different values at 5% level. The definition of two significantly different values is that their 95% confidence intervals do not overlap each other.

1992) to humans (Vaupel et al., 1998). Because of the ubiquity of the feature, a vigorous discussion in the biogemographic literature has ensued on how it can be explained through the effects of heterogeneity on the force of mortality (Curtsinger et al., 2005). A predominant theory generates plateaus with heterogeneity in a cohort expressed as a lifetime, or fixed frailty property. In this theory individuals that are born frail die first such that the mortality plateau is produced by simple culling (Vaupel et al., 1979). Numerous forms of this model have been explored with differing distributions of fixed heterogeneity (Steinsaltz and Wachter, 2006). Frailty models have also been developed to express acquired heterogeneity or variable frailty (Yashin et al., 2000). In these models variable frailty is similar to our evolving heterogeneity but it acts on the mortality rate directly and so its dynamics are different and it does not explicitly adjust variability as individuals are removed by mortality; whereas the vitality model does. Along a separate line, Gavrilov and Gavrilova (1991, 2001) developed models based on reliability theory in which a system contains redundant components such that the system fails only when all redundant components fail. Importantly, the reliability models increase heterogeneity with age, which is also a form of evolving heterogeneity or variable frailty (Curtsinger et al., 2005). Mueller and Rose (1996) explored mortality plateaus with a numerical simulation of a simple form of antagonistic pleiotropy in which mutations that increase fecundity have negative impacts on longevity. The model produced mortality plateaus through a form of evolving heterogeneity. However, the biological meaning of the algorithm has been questioned (Curtsinger et al., 2005). We note that these models are all similar in that they seek to explain mortality plateaus in terms of some form of heterogeneity acting directly on the force of mortality.

First passage time models provided a different and largely understudied perspective from which to explore mortality plateaus. A notable exception is Weitz and Fraser (2001) who demonstrated that a vitality model with a homogeneous initial condition produces a mortality plateau. Steinsaltz and Evans (2004) explored mathematical details of mortality plateaus in terms of first passage models, which they classified as "Markov mortality models". They pointed out that the first passage time depends on the initial distribution and concluded that the Weitz and Fraser model is most valuable in illustrating that mortality plateaus exist under certain conditions. Horvitz and Tuljapurkar (2008) developed a parallel approach using a discrete-space discrete time Markov chain model with a set of transient states and one absorbing state representing mortality and found age-specific mortality always reaches a plateau at advanced age. In our context, the Weitz–Fraser model is the case where $T_h/T_s = 0$ and therefore it is guaranteed to produce mortality plateaus. Aalen and Gjessing (2001) also explored the effects of initial distributions on the mortality plateau by casting the problem in terms of the effect of the initial distribution on the quasi-stationary distribution at old age. In our notation, with $\sigma = 1$ and $k = 0$ they found that a gamma function initial distribution proportional to $v^c \exp(-\rho v)$ gives a quasistationary distribution proportional to $v^{(c-1)/2} \exp\left(-v\rho^2/2\right)$. They noted that when $c < 1$, the hazard rate decreases at advanced age and if $c > 1$, it increases with advanced age. However, the choice of a gamma initial distribution generally is not biologically realistic because the population mode is less than the mean, which implies that the population begins life close to the death boundary. As we noted earlier, a Gaussian function is a better representation, e.g. gene distributions related to longevity are known to have Gaussian distributions (e.g., Rea et al., 2005). However, the salient point Aalen and Gjessing made is that, under general initial conditions, leaving out the early age, one can achieve a unimodal or decreasing hazard rate, i.e. a mortality plateau. In our model, these patterns depend on the ratio of the heterogeneity crossover time to the senescence time, T_h/T_s. Smaller values produce more pronounced mortality plateaus (Fig. 4a).

When first passage approaches have been referenced in the literature, they often have been misunderstood. For example, Mueller et al. (2003) characterized the Weitz and Fraser (2001)

model as "a model that assumes individual mortality rates are random variables" and concluded that such a mortality rate resulting from uncorrelated Gaussian noise has no biological motivation. As we note, the Weitz and Fraser model, which is a vitality model, is not formulated in terms of the mortality rate. The variability is in the vitality loss rate, which has a strong biological motivation in variable rates of degradation of cellular processes through mechanisms such as reactive oxidative species (Yin and Chen, 2005). Mueller et al. also incorrectly concluded that the instantaneous mortality rate in the Weitz and Fraser model increases linearly with age, which is not the case (see Fig. 4).

While Mueller et al. misinterpreted the vitality concept, the model does support their contention that demographic or fixed heterogeneity models require biologically implausible levels of variations to produce mortality plateaus. To illustrate this claim, we can represent the fixed frailty/heterogeneity conditions referred to by Mueller et al. (2003) in terms of initial heterogeneity in vitality. If this dominates evolving heterogeneity and $T_h/T_s > 1$ then the hazard rate increases in a linear manner and does not produce a mortality plateau (see Fig. 4a line with $s = 0.1$). Thus, as Mueller et al. suggest, a mortality plateau is unlikely to be observed if initial heterogeneity, i.e. lifetime or fixed frailty, is the major source of heterogeneity.

Finally, we consider how the vitality model might further contribute to understanding of mortality plateaus. Firstly, the model presents a straightforward classification of initial and evolving heterogeneities in a mathematically tractable and rigorous way and combines concepts from fixed and variable frailty models into a single closed-form equation. Secondly, the two sources of heterogeneity are biologically plausible: initial heterogeneity can, in part, be attributed to genetic heterogeneity in a population and evolving heterogeneity is a general representation of variability in aging at the cellular level (Yin and Chen, 2005). Thirdly, the model provides an alternative perspective in which to understand the effect of mutations and environmental factors on variations in lifespans amongst individuals of the same genotype or ancestral line. The classical approaches often compare hazard rates and express the variations through stochastic terms in the Gompertz model (e.g. Pletcher et al., 1998; Mueller et al., 2003), which results in largely unrecognized biases (Zens and Peart, 2003). We suggest that first passage, vitality-type, models provide a way to deal with such problems arising from individual variation and age-dependent patterns in the hazard rate.

5. Discussion

In this paper, we have extended the 3-parameter vitality model (a Markov mortality model in which the time to death is the first passage time of survival capacity to a killing boundary) by characterizing initial heterogeneity as a Gaussian distribution of vitality. The 4-parameter model formulates survival curves in terms of an accidental, or extrinsic mortality rate k, a mean rate of loss of vitality r, and the effects of initial u, and evolving s, heterogeneities on the trajectory of vitality to the killing boundary. The survival process is characterized by three fundamental time scales: the mean time to accidental or extrinsic mortality, $T_a = 1/k$, the mean time to mortality by senescence, $T_s = 1/r$, and a heterogeneity crossover time at which evolving heterogeneity exceeds initial heterogeneity, $T_h = u^2/s^2$. The ratio T_h/T_s characterizes the relative influence of initial and evolving heterogeneity over the lifespan, which should be of interest to demographers concerned with mortality plateaus, heterogeneity theory and similar concepts (Curtsinger et al., 2005; Rose et al., 2007). In a similar manner, T_a/T_s characterizes the relative effects of vitality-independent and vitality-dependent factors on survival and as such is a measure of relative effects of intrinsic and extrinsic survival processes.

Expressing mortality as a first passage process is fundamentally different from classical models that treat the mortality event as the process of interest; the first passage perspective focuses on the processes leading up to the mortality event (Aalen and Gjessing, 2001). The difference is subtle and has been unappreciated because the term vitality has also been used in classical mortality rate models (Strehler and Mildvan, 1960; Zuev et al., 2000; Curtsinger et al., 2005) and interchangeably with frailty (Curtsinger et al., 2005). We surmise this mixed usage has lead to confusion and a general misunderstanding of the first passage approach.

The vitality model has similarities, but also important differences to state-dependent models of mortality. Like in the vitality model, state-dependent models such as those of Cichoń and Kozlowski (2000) and Mangel and Bonsall (2004) assume mortality is the result of damage associated with specific physiological processes such as growth and metabolism. The vitality approach abstracts results of these processes into the single measure, vitality. As with frailty models, the most significant difference between the two approaches is in how mortality is represented. Stage-dependent models express the rate of mortality as a function of the cumulative damage while in the vitality model mortality occurs when the cumulative damage reaches a threshold.

In demography, first passage models have mostly focused on explaining mortality plateaus in terms of quasi-stationary distributions (Weitz and Fraser, 2001; Aalen and Gjessing, 2001) and as Steinsaltz and Evans (2007) noted "translating quasi-stationary distributions into demographic reality offers a novel account of the mortality plateaus, distinct from the standard dyad of population heterogeneity (mortality rates stop rising because the few survivors at extreme ages are an intrinsically healthier subset of the initial population) and temporal heterogeneity (the aging process itself slows down in time)". Thus, first passage approaches and vitality in particular, have been viewed more as a useful convention to obtain mortality plateaus (Mueller et al., 2003; Steinsaltz and Evans, 2004; Curtsinger et al., 2005) rather than as an index with a biological basis. It has not, as Rose et al. (2007) noted, been applied to empirical research in demography. However, we note that vitality has been applied in ecology. In particular, dose–response survival curves can be explained in terms of the effects of dose exposures on the vitality parameters (Anderson, 2000; Hamel, 2001; Springman et al., 2005; Anderson et al., 2008).

In our examples, we illustrated how the model provides a useful and insightful framework in which to view the effects of variability in the processes that shape survival patterns. In the demographic paradox we posited that male medflies had greater initial heterogeneity because of lower genetic redundancy while females had greater evolving heterogeneity through variability in female fecundity. In the diet restriction example, we found that DR affected the mean senescence rate in an exponential manner but had no effect on heterogeneity because the diet quality, not quantity, was restricted. In counterpoint, in yellow perch an inadvertent diet restriction through quantity but not quality induced contest competition and increased evolving heterogeneity. The yellow perch study also illustrated that the duration and conditions of a left-truncation period has quantifiable effects on survival in the post-truncation period. Finally, we demonstrated that mortality plateaus depend largely on the ratio of the heterogeneity crossover time to the senescence time.

In summary, vitality as a first passage process, defined by four biologically intuitive parameters, provides an explicit and tractable hypothesis of the processes shaping survival curves. It offers a unique measure missing from force of mortality models:

Table A.1
Simulation results with actual and estimated parameters and standard error.

Parameter	r	k	s	u
Actual	0.05	0.002	0.1	0.0
Estimate	0.04781	0.00210	0.09766	0.00005
(s.e.)	(0.00024)	(0.00020)	(0.00080)	(0.00134)
Actual	0.05	0.002	0.1	0.05
Estimate	0.04741	0.00209	0.09520	0.05192
(s.e.)	(0.00024)	(0.00022)	(0.00125)	(0.02987)
Actual	0.05	0.002	0.1	0.1
Estimate	0.04744	0.00201	0.09616	0.09234
(s.e.)	(0.00024)	(0.00022)	(0.00127)	(0.01682)
Actual	0.05	0.002	0.1	0.2
Estimate	0.04769	0.00219	0.09368	0.20165
(s.e.)	(0.00029)	(0. 00031)	(0. 00139)	(0. 01007)
Actual	0.05	0.002	0.1	0.3
Estimate	0.04700	0.00273	0.09739	0.27275
(s.e.)	(0.00040)	(0.00051)	(0.00150)	(0.00867)
Actual	0.05	0.002	0.001	0.1
Estimate	0.05001	0.00192	0.00034	0.10054
(s.e.)	(0.00005)	(0.00012)	(0.00776)	(0.00083)
Actual	0.05	0.002	0.005	0.1
Estimate	0.04996	0.00199	0.00675	0.09852
(s.e.)	(0.00006)	(0.00012)	(0.00163)	(0.00217)
Actual	0.05	0.002	0.01	0.1
Estimate	0.04994	0.00200	0.01040	0.09908
(s.e.)	(0.00006)	(0.00012)	(0.00118)	(0.00240)
Actual	0.05	0.002	0.05	0.1
Estimate	0.04898	0.00195	0.04812	0.10898
(s.e.)	(0.00013)	(0.00015)	(0.00098)	(0.00756)

the distribution of the survival capacity within the population over age. As with any model, it is a simplified construct of a biologically complex system and so an important and unresolved question is how far can the first passage construct be extended into the biology of mortality? Ample evidence supports vitality as a reasonable facsimile for the degradation of cellular processes. But can a Wiener model of cellular degradation account for natural selection of senescence? In particular, is the partition between initial and evolving heterogeneity sufficient to encompass the competing theories of senescence: mutation accumulation and antagonistic pleiotropy? Furthermore, because natural selection acts both on mortality and reproduction, is it possible to link these with a vitality-like process? These issues are beyond our immediate scope, but we suggest that the first passage construct of mortality offers a biologically reasonable way from which to approach difficult topics in demography and ecology.

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Appendix A

To the explore the possible covariance and bias in estimates of the initial and evolving heterogeneities we simulated survival curves based on a numerical equivalent of Eq. (4). The distribution of initial vitalities for each survival curve followed a Gaussian distribution. The vitality trajectory of each individual was calculated in single time steps with $v_t = v_{t+1} - r_a + s_a W$ where in each step W is a random number drawn from a normal distribution, $N(0, 1)$. Death time, t^*, was recorded as the first passage time to $v_t \leq 0$ or when accidental mortality occurred with a probability of $\exp(-kt^*)$.

Survival curves were generated from t^* for populations with 10,000 members. The value of r and k were similar to the values estimated for the medfly example (Table 2). To explore the effect of variations in s and u we first fixed s and varied u and then fixed u and varied s. We then estimated the model coefficients using the algorithm in the supplemental online material. Table A.1 compares the actual and estimated parameters along with the standard error in the estimates.

The estimation algorithm reliably distinguishes the two sources of heterogeneity. The small differences between the true and estimated values are probably due to the statistical bias (binomial error) introduced by the simulation. However, when u approaches 0.3, the algorithm tends to underestimate u. This is because at values of $u > 0.3$ the lower tail of the initial vitality distribution violates the assumption that $v_0 \geq 0$. In general, the estimation procedure provides an effective way to disentangle the two forms of heterogeneity.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tpb.2009.05.004.

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