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The relationship of mammal survivorship and body mass modeled by metabolic and vitality theories

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Abstract

A model describes the relationship between mammal body mass and survivorship by combining replicative senescence theory postulating a cellular basis of aging, metabolic theory relating metabolism to body mass, and vitality theory relating survival to vitality loss and extrinsic mortality. In the combined framework, intrinsic mortality results from replicative senescence of the hematopoietic stem cells and extrinsic mortality results from environmental challenges. Because the model expresses the intrinsic and extrinsic rates with different powers of body mass, across the spectrum of mammals, survivorship changes from Type I to Type II curve shapes with decreasing body mass. Fitting the model to body mass and maximum lifespan data of 494 nonvolant mammals yields allometric relationships of body mass to the vitality parameters, from which full survivorship profiles were generated from body mass alone. Because maximum lifespan data is predominantly derived from captive populations, the generated survivorship curves were dominated by intrinsic mortality. Comparison of the mass-derived and observed survivorship curves provides insights into how specific populations deviate from the aggregate of populations observed under captivity.

Keywords

AnAge database; Hematopoiesis; Macroecology theory; Maximum lifespan; Replicative senescence

Introduction

The relationships of body size to animal physiology, metabolism, life history and ecology (Blueweiss et al. 1978; Lindstedt and Calder 1981; Calder 1984) convey important information on the processes shaping the evolution and functioning of the biosphere. Most important of these is the quarter-power scaling of metabolism B to body size in mass M , $B = aM^{3/4}$ (Kleiber 1947), known as the WBE theory or simply metabolic theory (West et al. 1997; Brown et al. 2004; Banavar et al. 2010). The $3/4$ exponent emerges by the limitation on metabolism by the rate that materials move through the branching network of a mammal's

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circulation system. The theory has also been extended to life history (Brown et al. 2004) and a metabolic theory of ecology (Humphries and McCann 2014). The relationship of body size to metabolism also plays a central role in the study of evolution and life histories of extinct species. In particular, Cope's rule (Cope 1904), in which over evolutionary time the body size of clades increased by orders of magnitude (Alroy 1998; Smith et al. 2010; Evans et al. 2012; Benson et al. 2014), is thought to be driven by interactions of ecological process and abiotic forcing (Raia et al. 2012; Saarinen et al. 2014; Segura et al. 2016). However, the body size increase also may be controlled by intrinsic biological factors (Sookias et al. 2012) that are limited by the allometric relationships of mass to metabolism and generation time, which in turn set the rate of gene mutation (Okie et al. 2013).

Thus, critical to extending the relationships of body size to life history and evolution is the relationship of body size to mammal lifespan and survivorship. While an approximate quarter-power relationship of body size to maximum lifespan is well-established (Blueweiss et al. 1978; Lindstedt and Calder 1981; de Magalhães et al. 2007; de Magalhães and Costa 2009), a mechanistic model underlying the relationship has not been elaborated and the shape of survivorship curves with body size has not been addressed. Part of the difficulty involves the fact that mortality results from both intrinsic aging processes and environmental challenges. Intrinsic factors that involve cellular-level aging should be implicitly connected to body size through metabolism. Extrinsic factors may also involve body size through the ability of larger mammals to avoid injury. Additionally, mode-of-life effects the rate of mortality, with ability to fly being of particular importance in explaining the longer lifespan of birds relative to mammals (Healy et al. 2014).

The goal of this paper is to develop a mathematical model linking body size to longevity through cellular level processes. The framework combines metabolic theory (West et al. 1997; Brown et al. 2004), processes of cell aging (López-Otín et al. 2013) and vitality theory (Anderson 2000; Li and Anderson 2013; Anderson et al. 2017).

Methods

Model framework

For modelling the relationship between mammal maximum lifespan MLS and body mass M , four distinct theories are linked in a multistep process. Generalizing the process, in the first step survivorship, I_x as a function of age x , is expressed by linking a theory of hematopoietic control of longevity with the vitality theory of survivorship. The resulting equation describes hematopoietic system degradation in terms of vitality loss rate characterized by a parameter set Q . In the second step, the vitality loss parameters Q are related to mammal body mass through a parameter set P using metabolic and macro-ecological theories. Generalized, the equation $I_x = f_1(Q, x)$ is derived from hematopoietic and vitality theories and $Q = f_2(P, M)$ is derived from metabolic and macro-ecological theories. Because the MLS is taken as the age of the last individual in a cohort, it depends on the initial cohort size. Thus, define MLS as the cohort age at which $I_x = I_{MLS}$. The body mass and maximum lifespan relationship is then $MLS = f_3(P, M)$ where f_3 is derived numerically from combining f_1 and f_2 and P depends on the selection of I_{MLS} .

To describe the details of this model begin by reviewing metabolic theory because of its centrality to the overall model. Next hematopoiesis is discussed and the dimensional scaling connections to longevity are reviewed. Finally, the vitality-based survivorship, as a model of hematopoiesis, is described.

Metabolic theory

Metabolic theory characterizes Kleiber's law in terms of the constraints on the distribution rate of resources to cells. The law expresses a power-law relationship between metabolism and body size as

$$B \sim M^b \quad (1)$$

where b is approximately $3/4$ ¹. The relationship emerges from the assumption of the minimization of energy dissipation in a fractal network of branching tubes, i.e., the circulatory system that distributes blood from the heart to cells through the vascular network (West et al. 1997; Brown et al. 2004). A further extension of the theory invokes a cascade of power-relationships between body size and metabolism that result in the observed power-law. The processes, which together control oxygen supply to mitochondria for the synthesis of ATP, thus work on scales of molecules to organs (Darveau et al. 2002).

These allometric models predict that the amount of blood servicing a metabolic site increases with body size. To set the foundation of the model first consider the unique allometric properties of physiological systems involved with oxygen transport. Ninety percent of the oxygen transported is used in muscle work (Darveau et al. 2002). The systems directly involved, i.e., muscle, blood, spleen, and skeleton, scale with body size at powers greater than one while the systems not directly involved, the digestive, renal, integumentary, endocrine and nervous systems, scale with powers less than one (Calder 1984). As a consequence, the rate at which a blood cell supplies oxygen to a metabolic site declines with body size as $M^{-1/4}$ while, the cell's cycle time (Banavar et al. 2010) and lifespan (Gillooly et al. 2012) both increase with body size as $M^{1/4}$. Taken together, these allometric relationships indicate that the demand on the individual cells of the circulatory system decline with increasing body size with the $-1/4$ power. Specifically this allometric scaling applies to the erythrocytes (red blood cells) (Wiegel and Perelson 2004) and the leukocytes (white blood cells) that protect somatic cells from pathogens and damage. In particular, leukocytes play a key role in regulating aging².

¹A body of literature discusses where the coefficient is between $2/3$ and $3/4$ (Dodds et al. 2001; da Silva et al. 2006; Banavar et al. 2010; Lee 2015). For the model, the value of the exponent is not germane.

²Leukocytes, the central actors of the immune system, are produced from hematopoietic stem cells in the bone marrow and the lymph system. The leukocytes circulate as a component of blood to detect and remove pathogens from the body and repair damaged tissue. The gradual reduction of immune system function with age involves essentially all the aging hallmarks but of particular importance are the loss of proteostasis and the reduction in the number of naïve T cells and stem cells with age (Ponnappan and Ponnappan 2011). Collectively these processes are known as immunosenescence (Weiskopf et al. 2009) and result in inflammaging, both of which are hallmarks of aging leading to death (Franceschi et al. 2007). While immune system function is an index of aging, degradation of other processes working across the molecular, cellular and system levels are also important (López-Otín et al. 2013).

Hematopoiesis

Background—A number of findings illuminate the link between hematopoiesis and longevity. First, in the bone marrow, adult blood cells are constantly regenerated by self-renewal and hierarchical differentiation of hematopoietic stem cells (HSC) that through a series of progenitor stages result in the production of erythrocyte (red cells) and a wide variety of leukocytes (white cells) (Rieger and Schroeder 2012; Jagannathan-Bogdan and Zon 2013). In the process, a dividing stem cell produces a daughter cell to replace itself and a progenitor cell that in further divisions differentiates into red and white blood cells.

The link between hematopoiesis and longevity involves HSC aging. While aging and lifespan involve multiple physiological pathways (Kirkwood and Austad 2000; Warren and Rossi 2009) from molecular to intercellular (López-Otín et al. 2013), hematopoiesis in its position at the top of the immune system, plays a central role in immune system aging (Geiger et al. 2013), immunosenescence and of somatic tissue deregulation (Henry et al. 2011; Kovtonyuk et al. 2016; Park 2017). Aging in these systems can lead to proximal causes of mortality such as cancer (Rozhok et al. 2014; Rozhok and DeGregori 2016) and chronic stress that feed back to increase leukocyte production resulting in atherosclerosis, inflammation and cardiovascular disease (Hanna and Hedrick 2014; Heidt et al. 2014; Elias et al. 2017). Also, the sympathetic nervous system regulates the HSC self-renewal rate, pool size and the rate blood cells egress to the circulation system (Bellinger and Lorton 2014). Thus, the replication rate of HSC is affected by body status as tracked by the sympathetic nervous system and therefore is tuned to the mammal's interaction with its environment.

Body size regulation of metabolic rate—Evidence indicates aging at the cellular level is regulated by body size. Specifically, the metabolic rate of mammalian cells increase in isolation, becoming essentially indistinguishable from the metabolism rate of a unicelled organism (West et al. 2002). In essence, cell metabolism is regulated by the rate of resource delivery. Studies support the centrality of body size in regulating the efficiency of the hematopoietic system and immune system efficiency. At the cellular level, lymphocyte numbers scale with body size such that larger mammals have more immune system protection than smaller mammals (Wiegel and Perelson 2004; Perelson and Wiegel 2009). Additionally, a study of blood of 85 bird species revealed large-brained birds exhibit lower oxidative damage to lipids and had higher antioxidant capacity leading to a hypothesis of “oxidative avoidance” with large body size (Vágási et al. 2016).

Replicative senescence—Thus, lifespan has cellular level controls through, what has been termed, the replicative senescence” hypotheses (de Magalhães and Faragher 2008). This hypothesis draws on aging research showing that interventions that induce premature aging and shortened longevity involve increased cell apoptosis and accelerated senescence, while interventions that increased longevity reduced apoptosis and delay senescence. These correlations between the rate of apoptosis and senescence and changes in lifespan suggest that an organism's lifespan is linked to the number of times a cell divides.

Three findings support the hypotheses that replication of HSC is central to senescence. First, in humans, HSC resides in an active pool of approximately 400 cells and a quiescent reserve

of approximately 10^4 cells (Dingli and Pacheco 2010). A HSC divides about every year in a human (Gordon et al. 2002) and through self-renewal the HSC pool appears sufficient to maintain the blood supply through life, which is on the order of 10^{11} blood cells per day for humans. In contrast, a mouse maintains its blood regeneration rate with HSC divisions every few weeks (Gordon et al. 2002). Second, the rate of division of HSC decreases with increasing body size as $r_{HSC} \sim M^{-1/4}$ (Dingli and Pacheco 2006; Dingli et al. 2008). Third, and central to the theory, studies suggest the total HSC population in adult mammals is independent of body size (Abkowitz et al. 2002; Dingli et al. 2008).

Based on these findings Dingli et al. (2008) proposed that the total number of HSC replications over a lifespan should be independent of body size. Noting that lifespan scales with body mass as approximately $M^{1/4}$ and using the mass scaling of the replication rate r_{HSC} , then the total number of replications is $T \sim M^{1/4} M^{-1/4} \sim M^0$, and therefore can be independent of body mass. Also of importance, T is approximately the Hayflick limit³. However, while T is essentially the same across the six orders of body size magnitude, e.g., African pygmy mouse (10 g) to elephant (5000 kg), there was no clear evidence that HSC replicative senescence limits the production of blood or directly contributes to blood aging. However, a number of molecular mechanisms contribute to a HSC replication limit. In their slow replication, HSC accrue DNA damage through reactive oxidative species (Weiss and Ito 2015), alternation of epigenetic profiles of the DNA (Warren and Rossi 2009; Beerman and Rossi 2014) and erosion of telomere end caps (Zimmermann and Martens 2008). Additionally, in the multiple replications involved in the HSC progenitor cell transformations to the terminal blood lineages, damage accumulates leading to reduction in the capacity of the hematopoietic system. Importantly, the damage can propagate through self-renewal of the stem cells (Beerman 2017).

In short, the three findings that across the body-mass spectrum mammals have equivalent HSC populations, cell replication rate is a power function of body mass, and the total number of replications is fixed, together suggest a possible mechanism for the body mass to longevity relationship that works at both cellular and system levels.

Linking hematopoiesis to survivorship with vitality theory

The replicative senescence theory described above provides a foundation for developing a theory of hematopoiesis regulation of survivorship, generically expressed in the introduction to the model as $I_x = f_1(Q, x)$. First define an age-dependent survival capacity V_x at age x , as an index of the capacity of the hematopoietic system to maintain the immune system. Take the initial survival capacity V_0 as an index of the initial number of HSC. Therefore, the initial survival capacity is a constant across all mammal body sizes. Define a normalized survival capacity, designated vitality, as $v_x = V_x/V_0$ where v_0 is the initial vitality and like the initial survival capacity, is independent of body size. Vitality declines with age from the gradual accumulation of damage in the hematopoietic system through DNA mutation,

³This is an upper limit of cell replication, determined by the attrition of the protective telomeres end caps on chromosomes (Hayflick and Moorhead 1961). Once the telomere reaches a critical length, cell replication stops. However, telomerase can maintain TL (Blackburn et al. 2015). Evidence suggests that TL declines with lifespan in some species but not others. Telomerase varies with body size but not life span (Monaghan 2010).

epigenetic alterations and telomere attrition as discussed above. The rate of decline is characterized by a Wiener process defined by an average rate of decline and a stochastic variability in the rate as

$$\frac{dv_x}{dx} = -\rho + \sigma W_x \quad (2)$$

Where W_x is a noise process with zero mean and unit variance, ρ is the mean rate of loss of vitality and σ scales the level of stochastic variability in the rate (Anderson 2000; Li and Anderson 2013; Anderson et al. 2017). Equation 2 characterizes an ensemble of random vitality trajectories that begin at $v_0=1$ and drift towards a zero boundary where they are absorbed (Fig. 1). Each path is then assumed to represent a probabilistic realization of an individual's immune system function from initial to end states.

In the vitality framework, mortality results from the loss of vitality either from the stochastic degradation of vitality according to Eq. 2 or from the loss of vitality from an environmental challenge to the remaining vitality (Fig. 1) (Li and Anderson 2013). Equation 2 is a simple representation of a stochastic process, whether it is too simple is worth consideration. An important property of the Wiener process is its linear increase in variance with time. The choice rests on the assumed nature of the processes that determine the limits of HSC replication. If the limit is due to telomere attrition then vitality is a measure of telomere length and a Wiener process is a reasonable choice in that the process step size represents an incremental loss of telomere length with each cell division and the stochastic time interval between steps represents the interval between HSC divisions. Importantly, the Wiener process first passage time to a boundary naturally captures the onset of HSC senescence when telomere length reaches the Hayflick limit (Hayflick and Moorhead 1961) as proposed by Dingli et al. (2008). Furthermore, Steenstrup et al. (2017) proposed telomere length plausibly establishes a biological limit to longevity. Accumulation of DNA mutations and epigenetic alterations should have similar properties in that once sufficient damage has accumulated DNA replication becomes unstable. Finally, the ability of the Wiener process to explain survivorship curve mechanisms and shapes is well-established (Woodbury and Manton 1977; Whitmore 1983, 1986; Anderson 2000; Weitz and Fraser 2001; Steinsaltz and Evans 2004; Li and Anderson 2009; Li et al. 2013; Li and Anderson 2015; Sharrow and Anderson 2016; Anderson et al. 2017).

Intrinsic survival—The rate of mortality is defined by the probability distribution of arrival time of random vitality paths defined by Eq. 2 to the zero boundary. Ignoring the preferential removal of lower vitality paths by extrinsic challenges, survival through intrinsic processes only is

$$l_x^{\text{In}} = \Phi\left(\frac{1-\rho x}{\sqrt{\sigma^2 x}}\right) - \exp\left(\frac{2\rho}{\sigma^2}\right) \Phi\left(-\frac{1+\rho x}{\sqrt{\sigma^2 x}}\right) \quad (3)$$

Where $\Phi(x) = (1/\sqrt{2\pi}) \int_{-\infty}^x \exp(-x^2/2)dx$ is the cumulative standard normal distribution (Li and Anderson 2013).

Extrinsic survival—In the vitality framework extrinsic mortality results when an environmental challenge such as disease, predation or physical injury exceeds the age-specific survival capacity of the organism (Fig. 1). With stochastically stable challenges, if challenges have varying magnitudes the frequency of extrinsic mortality events increases with age (Li and Anderson 2013). However, when extrinsic events are always fatal the frequency of extrinsic challenges to vitality can be represented as a Poisson frequency distribution with mean λ and the extrinsic survival equation becomes

$$l_x^{\text{Ex}} = \exp(-\lambda x) \quad (4)$$

As an aside, a juvenile extrinsic mortality rate, involving challenges to a developing juvenile immune system can be expressed in a similar manner (Anderson et al. 2017). Here juvenile extrinsic mortality is not considered and is assumed to have a minimum impact on *MLS*.

Total survival, ELS, MLS—The final equation, characterizing the effects of intrinsic and extrinsic mortality processes on survival is

$$l_x = l_x^{\text{In}} l_x^{\text{Ex}} = \left[\Phi\left(\frac{1-\rho x}{\sqrt{\sigma^2 x}}\right) - \exp\left(\frac{2\rho}{\sigma^2}\right) \Phi\left(-\frac{1+\rho x}{\sqrt{\sigma^2 x}}\right) \right] \exp(-\lambda x). \quad (5)$$

From this equation, the vitality rate parameters are defined $Q = [\rho, \sigma, \lambda]$ Interpreted in terms of hematopoiesis dynamics, ρ is the mean rate of HSC degradation, σ is the stochastic variability in the rate and λ is the rate of mortality when extrinsic challenges exceed the self-repair capacity of the immune system.

$$\text{The expected lifespan(ELS) is defined } ELS = \int_0^{\infty} l_x dx.$$

The maximum lifespan (*MLS*) in the AnAge database represents the highest reported value for a species. For nonflying mammal species, the data tend to come from animals in captivity (de Magalhães and Costa 2009). *MLS* is also a function of cohort size. For the model, it is defined as the age at which a fixed fraction of the population remains. Additionally the model considers only adults, so early life mortality is removed. For the analysis, the *MLS* is defined as the age at which $l_{x=MLS} = 0.01$. The analysis, repeated for $l_{x=MLS} = 0.03$ and $l_{x=MLS} = 0.09$, does not significantly change the features of the model.

Linking vitality rate parameters to body size

The next step formulates $Q = f(P, M)$ relating vitality parameters and body mass.

Mass-intrinsic rate relationship based on metabolic theory—Equation 2 expresses the rate of decline of vitality ρ based on the relationship of hematopoiesis to aging and metabolism discussed above. Applying metabolic theory and replicative senescence the rate of degradation of HSC is assumed to follow a power function of adult body mass as $\rho \sim M^{-h}$ where the metabolic exponent h is a free parameter, which from metabolic theory is approximately 0.25. The stochastic variation in the rate is assumed to follow the same relationship, giving $\sigma \sim M^{-h}$.

Mass-extrinsic rate relationship based macroecology theory—The extrinsic mortality rate, λ in Eq. 5 characterizes acute environmental challenges to the remaining vitality. The mechanisms for these challenges plausibly include disease, physical injury and predation (Carnes and Olshansky 1997). However, a specific classification is not forthcoming because an accepted partition between intrinsic and extrinsic mortalities does not exist (Koopman et al. 2015). In the vitality-based partition, the magnitude and frequency of the challenges involve the state of the environment and mortality results when the challenge magnitude exceeds the vitality level, which depends on body size and age. Thus, λ is intended to capture a complex of extrinsic processes that induce mortality. In the simple model in which any challenge exceeds the available vitality, intrinsic mortality only depends on challenge frequency and is independent of age. This assumption reasonably captures the effects of extrinsic mortality in animals (Anderson 2000; Li and Anderson 2009). However, the magnitude of challenges is of particular importance in human populations in which the cause of death has changed over history (Anderson et al. 2017).

Because extrinsic mortality has been traditionally inferred from human cause of death data, there has been little consideration of the effect of species body mass on the rate of extrinsic mortality. It seems that extrinsic mortality resulting from physical injury should decrease with increasing body mass but relating mass to the susceptibility to disease is problematic and may be confounded with intrinsic processes as has been suggested in (Koopman et al. 2015; Anderson et al. 2017). However, some insight on the possible mass-dependence of challenge frequency comes from consideration of predator-prey encounters in macroecology theory (Hatton et al. 2015).

Consider the relationship of challenge frequency to body mass in terms of (Hatton et al. 2015) in which the predator-prey encounter frequency is related to the ratio of population densities (N number/area) as $\lambda \sim N_{\text{pred}}/N_{\text{prey}}$. Predator-prey studies indicate that the predation rate declines as a power of increasing prey population biomass. Across a range of large mammal ecosystems, predator and prey biomass densities (D total biomass/area) exhibited the relationship $D_{\text{pred}} \sim D_{\text{prey}}^{3/4}$ where $D_i = M_i N_i$. Furthermore, the size structure of predator and prey communities was found nearly constant across biomass gradients. That is, mean body mass of predators M_{pred} and M_{prey} were approximately invariant across ranges of prey densities D_{prey} . Thus, to a first order, predator and prey body masses have a proportional relationship $M_{\text{pred}} \propto M_{\text{prey}}$. Then the predation rate on the prey in a trophic

structure can be expressed $\lambda \sim M_{\text{prey}}^{-1/4} N_{\text{prey}}^{-1/4}$ which suggests that predation rate decreases as a negative one-quarter power of increasing prey body mass and population density. However, because population density is also determined by ecological factors and not directly linked to prey or predator body masses, for this model N_{prey} is assumed constant. Finally, including both the effects of predator-prey encounters and mass-dependent susceptibility to physical injury and disease, assume the extrinsic mortality rate declines as a power of body mass $\lambda \sim M^{-k}$ where k is a free parameter.

Summary of body size to model parameters relationship—From the discussion above the relationships of body size to vitality parameters $Q = f(P, M)$ where $P = [c_\rho, c_\sigma, c_\lambda, h, k]$ are defined

$$\rho = c_\rho M^{-h} \quad \sigma = c_\sigma M^{-h} \quad \lambda = c_\lambda M^{-k} \quad (6)$$

Model fitting

The parameter set P defines the model relating log MLS to log M . In estimating P different parameters are fit while others are set by biological criteria, resulting in individual models designated P_i . The parameter set for specific model i estimated by fitting maximum lifespan and mass data across a range of species with the regression $P_i = f_i^{-1}(MLS, M | l_{MLS})$. Healy et al. (2014) demonstrated a log-log relationship between MLS and M and therefore fitting the five parameters in P results in an over-fitted model, i.e., the general log-log relationship can be achieved with a range of different model parameters. However, it is possible to reduce the dimensionality of P by fixing specific parameters based on biological arguments. First, the parameter h has a theoretical value based on metabolic theory. Second, from Eq. 5 Q can be estimated for survivorship curves for individual species s as $Q_{L,s} = g(I_{x,s})$ and therefore the relationship of Q across different species provides information in which to constrain the parameter space of P_i . Furthermore, values of Q estimated from Eq. 6 with P models and a species mass, i.e., $Q_{M,s} = f(P_i, M_s)$, can be compared to $Q_{L,s}$ estimates from survivorship curves giving comparisons of Q derived independently.

Estimating $\hat{P}$ —The model predicts a relationship between body size and maximum lifespan, in terms of Eq. 5 with parameters P_i defined by Eq. 6. These were estimated by fitting the model log MLS to log M data using the R[®] language nls2 nonlinear fitting package exploring a user-defined parameter space with a brute-force algorithm (R Core Team 2016). A biologically plausible range of parameters is partitioned into 10,000 grid points κ , each yielding a trial parameter set $P_{i,\kappa}$. For each κ point log MLE is calculated using the bisection method that incrementally shrinks the interval between the boundaries x_{lower} and x_{upper} . The process stops, defining MLE , when $|I_x - I_{MLS}| < 0.0001$. Residual sum of squares between the observed log MLS_j and model predicted log $MLS_j(P_i, \kappa)$ for each grid point is defined

$$RSS_{i,\kappa} = \sum_j \left(\log MLS_j - \log MLS_j(P_{i,\kappa}) \right)^2 \quad (7)$$

where j is species. The optimal set for Model i is $\min(RSS_{i,\kappa})$.

The fitting routines and estimates of model parameters have a number of caveats. First, the estimation of MLS incorporates the bisection iteration method, which, resulting in singularities in the fitting algorithm, necessitates searching the parameter space with the brute-force method. As a result, the algorithm calculates the RSS for each starting grid point but does not converge to a better set of parameters. Second, P depends on the selected target survival, I_{MLS} . Third, the relationship $\log MLS$ to $\log M$ is essentially linear and therefore estimating the relationship with a five-parameter set over fits the data. Therefore, parameter sets with 3, 4, and 5 free parameters were explored.

The full and reduced sets of P are given in Table 1. Sets 5 and 6 have five free parameters. Sets P_1 to P_4 fixed $h = 0.25$ as postulated from metabolic theory. Sets 1 and 2 also defined c_σ proportional to c_ρ based on the relationship $\sigma = 0.65\rho$ observed in $Q_{L,I}$ derived from fitting survivorship curves. Sets, 1, 3, 5 use $I_{MLS} = 0.01$ and Sets, 2, 4, 6 use $I_{MLS} = 0.03$. In essence, the relationships of the intrinsic parameters are defined independent of mass.

Estimating Q—The Q parameters were estimated in two ways. The $Q_{L,i}$ was estimated from survivorship curves with a maximum-likelihood routine that fits Eq. 5 to survival data (Salinger et al. 2003). The algorithm “vitality.k” is available in R code at www.CRAN.R-project.org/package=vitality. The $Q_{M,i}$ was generated with the P Sets and species body mass.

Data

Maximum lifespan data—To estimate the P sets the model was fit to maximum lifespan and body weight data drawn from data in Appendix 2 of (Healy et al. 2014). The data which originated from the AnAge database (de Magalhães and Costa 2009), consisted of 494 nonvolant terrestrial mammal species, each constructed using over 100 maximum lifespan records. Most species had between 100 and 1000 records with a few species over 1000 records. Over 92% of the mammal species in the AnAge database were captive.

Survivorship data—Survivorship data was extracted from six published studies representing captive and wild species, different life history strategies and body sizes. Data for field vole (*Microtus agrestis*) (Selman et al. 2013), pigtail macaque (*Macaca nemestrina*) (Ha et al. 2000) and Asian elephant (*Elephas maximus*) (Sukumar et al. 1997) were collected from captive populations. Data for female mountain gorilla (*Gorilla beringei beringei*) (Robbins et al. 2011), Yellowstone grizzly bear (*Ursus arctos horribilis*) (Knight and Eberhardt 1985) and Namibian cheetah (*Acinonyx jubatus jubatus*) (Marker et al. 2003) were collected from wild habitats. The effects of juvenile mortality was removed by linearly projecting the survivorship slope from the onset of adulthood back to zero age.

Results

Fit of log M to log MLS

Table 1 shows the parameter sets for the six P Sets. All fits are similar with Sets 3 and 5 having the lowest RSS and Set 2 the highest. RSS in Sets 3–6 are similar to the linear regression RSS (69.65). Accounting for model dimensionality, Sets 1 and 2 have the lowest AIC and Sets 3–6 have $AIC > 4$. In general, fits to the log MLS vs. log M data are similar for all models. Across the spectrum, Sets 1 and 3 represent the two extremes in properties. Figure 2 illustrates Sets 1 and 3 are similar to the linear regression fit. Set 1 curves convex upward and Set 3 curves convex downward relative to the linear regression line, which has a slope of 0.19. While all models have similar fits in Fig. 2 the survivorship curves generated are significantly different and this difference provides valuable information on which to judge the biological feasibility of the Sets.

Survivorship patterns based on mass

Figure 3 illustrates survivorship curves generated from $Q_{Ms} = f(P_i, M_s)$ for P_1 (Fig. 3a) and P_3 (Fig. 3b). In both figures, the survivorship curves switch from Type I in large-mass mammals to Type II in small-mass mammals. The curves in Fig. 3b are Type II at all masses.

Figure 4 illustrates that differences between Sets 1 and 3 involve differing contributions of mass to the vitality parameters ρ , σ , and λ . First, note that the stochastic contribution to intrinsic mortality, characterized by c_σ , is larger for Set 3 than Set 1 (Table 1). This results in greater Type II survivorship character in Set 3 than Set 1. Note that both Sets generate the same MLS , depicted by the intersection of the black survival survivorship curves with the dashed line depicting $\log(I_{MLS})$. Set 3 also has greater extrinsic mortality, characterized by large c_λ (Table 1).

Figure 4 depicts the contribution of extrinsic mortality in terms of the difference in the black solid lines (survivorship from both intrinsic and extrinsic processes) and dashed red lines (survivorship from intrinsic processes only). Greater deviations between the black and red lines indicated greater contributions of extrinsic mortality.

These different intrinsic and extrinsic contributions to survivorship are illustrated by the ratio of ELS and MLS as a function of body mass for Sets 1 and 3 (Fig. 5). The ratio depicts the degree of rectangularization of the survivorship curve and quantifies the shift between Type I and Type II curves with mass. Lower ratios indicate more rectangularization and Type I character and higher ratios indicate less rectangularization, which is characteristic of Type II curves. Set 1 (Fig. 5a) shows the dominance of Type I character with higher body masses. Set 3 (Fig. 5b) shows strong Type II character and an extreme shift to Type II character with decreasing body mass.

The relationships between Q and a survivorship curve shape is detailed in (Li and Anderson 2009). In essence, increasing ρ decreases ELS while leaving the general curve shape largely unchanged. Increasing σ decreases the slope of the survivorship curve about the ELS causing the curve to become less rectangular, i.e., assume more Type II shape. Increasing λ

increases the overall curve slope with the greatest effect in early life prior to the onset of intrinsic mortality.

Survivorship patterns based on fitting survival data

Figure 6 illustrates the fit of Eq. 5 to observed survivorship data representing captive and wild species, different life history strategies and body sizes. For each example, survivorship curves were generated from the fitted Q_L parameters. Table 2 gives the Q_L and Q_M generated from Set 1 for each example. Figure 6 also depicts survivorship curves derived from Q_M , which were generated from Eq. 6 using species mass and P_L . Figure 7 shows the relationship of σ to ρ across the six species. This relationship was then used to fix σ in Sets 1 and 2.

Comparison of mass-based and observation-based survivorship curves

Comparison of survivorship curves generated with Q_L and Q_M parameters are illustrated in Fig. 6. These are therefore estimates based on the cross-species properties inferred by the model. The ratios Q_L/Q_M (Table 3) provide information on the deviations of the mass-based estimates of survival. In general, the Q_M parameters underestimate survival in the macaque and gorilla, closely estimate the elephant, and over predict survival for cheetah, bear and vole data. Possible reasons for these patterns are noted in the Discussion.

Discussion

This paper extends the theory of replicative senescence using vitality theory to describe the stochastic rate of degradation of the HSC pool and its transition into senescence and organism death. Relating the rate of vitality decline to body mass with metabolic theory yields a model for the pattern of survivorship from intrinsic mortality processes associated with aging. Additionally, relationships between predator-prey interactions and body size suggest a possible functional form for extrinsic mortality processes independent of aging. Combining the two rates, a base effect of body size on intrinsic and extrinsic survivorship patterns is characterized by five parameters: h and k allometrically scale body size effects and c_p , c_σ and c_λ proportionally scale rescaled body size to characterize intrinsic and extrinsic mortality rates. Setting h to 0.25 based on metabolic theory and expressing a relationship between the stochastic parameters c_p and c_σ based on survivorship curve relationships reduces the parameter space. The properties of the model with 3 and 4 free parameters are explored and found to reasonably fit observed mammal survivorship curves and the relationship of mass to maximum life span across mammal species. Importantly, the model partitions mortality into intrinsic and extrinsic elements that depend on different powers of body mass.

Relationship between mass, maximum lifespan and survivorship

The fitting algorithm determines parameters for each model with the minimum RSS based on the assumption that the observation of the oldest individual of a cohort represents 1% of the initial cohort. All six versions of P reasonably fit the data of log mass vs log mass maximum survivorship (Fig. 2). Note that in the P Sets 5 and 6 and other fitting runs k is

approximately 0.26 ± 0.02 . This suggests that k is approximately 0.25, and as inferred from metabolic theory, is a factor shaping the slope of the log M vs log MLS relationship.

However, the regression lines in Fig. 2 are generated by vastly different survivorship curves as illustrated in Figs. 3 and 4, which treat c_σ as proportional to c_ρ according to survivorship curve relationships or treat it as a free parameter respectively. As Fig. 4 illustrates both P Sets 1 and 3 give similar MLS for $I_{MLS} = 0.01$ but the respective survivorship curves are significantly different. Which one if either Set is realistic? To answer this question note that inferring survivorship curve shapes based on only mass and lifespan of the oldest individual in a cohort is highly problematic. However, the vitality theory provides some insight because ρ is approximately inverse to ELS (Anderson 2000). Furthermore, the relationship of ELS and MLS is a function of mass (Fig. 5). Thus, M - MLS patterns have some information on which to infer survivorship mass-patterns. However, while ELS is constrained by ρ , the shape of the survivorship curve about ELS depends mostly on σ and λ (Li and Anderson 2009). Thus, because Set 1 constraints c_ρ with information from observed survivorship curves (Fig. 7) it incorporates more information than Set 3. Therefore, Set 1 provides a more information rich representation of the M vs. MLS and survivorship curve relationships. Additional support for Set 1 comes from the fact that the data in Fig. 2 consists of 92% captive species and therefore the cohorts experienced little extrinsic mortality associated with predation, injury and disease. Thus, the associated survivorship curves should exhibit little influence of extrinsic mortality. As an aside, the model disregards juvenile mortality under the assumption that juvenile mortality processes do not affect old age mortality.

Limits of mass-estimated survivorship

In fitting the model to MLS data across a wide range of body masses, the model partitions intrinsic and extrinsic processes shaping survivorship. To explore cohort-level differences in the partition, the vitality model was fit to survivorship profiles from six species from field voles to elephants collected from captive and wild populations. A comparison of the parameters derived using only mass to those derived from survivorship data reveals the high variability of extrinsic mortality between environments and illustrates the limitations of inferring survivorship from mass information only.

Field Vole—For the field vole (Fig. 6a), Q_M fits the shape of the observed survivorship curve but right-shifts the curve by about one year. It thus over predicts the MLS by a year. The model attributes this shift to the mass-derived vitality loss rate ρ_M , which is half that estimated from the survivorship data ρ_L (Table 3). One possibility for an increased vitality loss in the observed cohort involves the voles being individually weaned and held in single cages with occasional handling and testing (Selman et al. 2008). Voles are highly social animals so these conditions might have increased stress, which is revealed in higher ρ_L .

Pigtail Macaque—For the pigtail macaque (Fig. 6b), the survival data was derived from the males in the Washington Regional Primate Research Center Pigtail Macaque Colony (Ha et al. 2000). The vitality loss rate was lower for the observed population than that predicted by mass, while the intrinsic mortality rate in the observed population λ_L was considerably larger than that predicted by mass (Table 3). Notably, the infant mortality in the population

was high and therefore the surviving population may reflect a selection of stronger individuals. Additionally, the population was under sophisticated veterinary and husbandry care. These factors together could account for lower ρ_L . However, the significantly higher extrinsic mortality rate, which is reflected by the Type II shape of the survivorship curve, is unexplained and may represent adverse conditions for this experimental population.

Namibian Cheetah—The significantly different cheetah survivorship curves derived from Q_L and Q_M (Fig. 6c) resulted from differences in both intrinsic and extrinsic mortality rates (Table 3). Note the cheetah population was wild while the Q_M coefficients were derived from 92% captive populations. Thus, the wild population may have been overstressed compared to captive populations. Additionally, the high λ_L may be the result of the 90% overlap of the cheetah habitat with commercial farms in Namibia. Over the period of the study (1991–2000) between 100 and 300 individuals were removed by farmers yearly (Marker et al. 2003).

Mountain Gorilla—The survivorship data for female mountain gorilla (Fig. 6d) represents a population in the Virunga Volcano region of Rwanda, Uganda, and Democratic Republic of Congo. Comparing Q_L to Q_M the observed wild population exhibited lower vitality loss and extrinsic mortality than predicted (Table 3). The biological reasons for these differences are unclear but a number of caveats are worth noting. The population had experienced significant poaching in the past but during the study the level was low (Robbins et al. 2011). The high longevity of the gorilla population relative to the mass-based prediction reflects a similar pattern for the pigtail macaque population. One possible explanation involves lower stress levels in primates compared to other species in the AnAge database. For example, studies with baboons indicated that the level of early adversity could affect lifespan by a factor of two. Under high stress, baboon MLS was < 15 years, while under low stress conditions, MLS was >25 years (Tung et al. 2016). Notably, for both the macaque and gorilla, MLS based on Q_L about a decade higher than MLS predicted by Q_M .

Grizzly bear—The survivorship curve (Fig. 6e) for grizzly bear was extracted from Fig. 7 in (Knight and Eberhardt 1985) depicting the grizzly bear population in Yellowstone National Park in the 1970s. During this time, the population was under significant hunting pressures within the park and its boundaries. Compared to Q_M , the Q_L parameters had higher rates of extrinsic mortality and vitality loss (Table 3). Thus, the mass based predictions did not capture the actual population's higher rate of aging ($\rho_L > \rho_M$) or higher rate of extrinsic mortality ($\lambda_L > \lambda_M$). These differences likely reflect the stressed conditions of the wild population from which Q_L was derived.

Asian elephant—The survivorship for Asian elephants (Fig. 6f) was derived from males in a captive breeding population in the Mudumalai and Anamalai Wildlife Sanctuaries of India (Sukumar et al. 1997). The ρ_L and ρ_M estimates were essentially equal while the variance in the observed population was higher than in the mass-based projection. The higher extrinsic mortality rate in the observed population may reflect poaching activity in the same way that the higher λ_L in the cheetah and bear populations might reflect hunting.

Shifting between type I and II survivorship curves

The model provides an explanation for the shift from Type I and Type II survivorship curves with decreasing body mass in terms of mass-specific shifts in the intrinsic and extrinsic mortality rates. The extrinsic component of the shift simply involves the inverse relationship of the extrinsic rate with body mass, i.e., as mass increases the extrinsic mortality rate declines in the model, $\lambda \sim M^{-k}$.

The possible contribution of mass on the intrinsic factors in shifting survivorship curve form is more complex and involves the stochastic nature of vitality loss expressed by Eq. 2 and by hypothesis, the stochastic nature of hematopoiesis aging. To illustrate, note that variance in vitality defined by Eq. 2 accumulates with age x as $\text{Var}[v_x] \sim \sigma^2 x$ and to a first order the *ELS* is $x \sim 1/\rho$. Then variance in vitality at the *ELS* is $\text{Var}[v_{ELS}] \sim \sigma^2/\rho$. Next, the assumed mass relationships of Eq. 6 indicate $\text{Var}[v_{ELS}] \sim M^{-2k}/M^{-k} = M^{-k}$ where k is approximately $1/4$. Thus, based on the assumption that Eqs. 2 and 6 represent the stochastic changes in HSC population or function with age then small species should experience greater variance in vitality over their lifespan than do large species. Thus, both intrinsic and extrinsic factors have mechanisms to shift survivorship curves from Type I to Type II form as body mass decreases. Importantly, variations in the extrinsic mortality rate between factors of 0.01 to 10 have small effects on the ratio of maximum to expected lifespans (Fig. 5a). This suggests that, to a first order, survivorship patterns might be inferred from body size with the environmental effects being secondary except under conditions of high extrinsic mortality.

General discussion

The model developed in this paper is an extension of previous models hypothesizing that the replicative limit of cells in critical metabolic systems determines the maximum lifespan of mammals. In these models lifespan decreases with body mass because the rate of replication of cells increases with decreasing mass. These models suggest the hematopoietic system is central because daily it produces a vast number of blood cells for oxygen transport, waste removal and immune maintenance. Thus, the underlying hypotheses of the model presented here is that replicative senescence of HSCs strongly shapes survivorship. The model reasonably fits the relationship between M and MLS ; however, it is limited because the fits do not uniquely identify the survivorship curve shape underlying the relationship. By fitting the model independently to survivorship curves, a unique set of model parameters emerges, reconciling some dependencies of the relationship of mass to both maximum lifespan and survivorship.

An interesting prospect for evaluating population wellbeing possibly emerges by comparing the ratios of vitality loss rates ρ and extrinsic mortality rates λ derived from mass and from survivorship data. The ratio $\rho_M/\rho_L > 1$ suggests abnormally high levels of chronic stress while $\lambda_M/\lambda_L > 1$ suggests abnormally high extrinsic mortality such as from hunting.

The underlying principle of the model is that large-scale survival patterns are shaped by identifiable interactions of cellular and macroecological processes. While such interactions are invariably complex, the model developed here links these processes with highly simplified theories of senescence, metabolism, mortality and macroecology. The value of

this framework will depend on whether it can describe survivorship patterns of populations in different foraging environments, levels of fossarality and across breeds. Finally, an important step in the development of the framework will be to seek connections to evolutionary theory.

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Fig. 1.

Illustration of survival curve (dashed red line) generated from extrinsic and intrinsic mortality processes defined by Eqs. 3, 4. Extrinsic mortality results when a challenge event occurs (vertical dashed lines). Adult intrinsic mortality results (triangles) when stochastic vitality paths (dashed black lines) reach the zero boundary

Fig. 2.

Depicts model fit of mass-longevity relationship of terrestrial mammals using parameter Set P_1 (solid red line) and Set P_3 (broken blue line). The resulting models are nearly linear as evident by the linear fit (dashed blue line)

Fig. 3.
Survivorship curves from Eq. 5 for P_1 (a) and P_3 (b) for mass 0.01, 1 100 and 1000 kg

Fig. 4. Examples of survivorship with both intrinsic and extrinsic processes (solid black line) and survivorship with intrinsic processes only (broken red line) for masses 0.001, 0.01, 1 and 10 kg. (a) is generated with parameter Set P_1 and (b) from P_3

Fig. 5.

Ratio of maximum lifespan to expected lifespan as a function of the log mass of mammal for the parameter Set P_1 (a) and Set P_3 (b). The broken red, solid black and broken blue lines depicted frequency of challenges 0.3λ , λ and 30λ

Fig. 6. Survivorship data (circle) for example species. The solid black lines were generated with the Q_M parameter sets. The dashed blue lines passing through the observations were generated with the Q_L parameter sets (Table 2). The dotted red lines depicts survival of 0.01 so the intersection of a survivorship curve with the line depicts the MLS

Fig. 7.
Relationship of vitality parameters ρ and σ derived by fitting the vitality model Eq. 5 to survivorship curves for species given in Table 2

Table 1

Parameter Sets P defined by Eq. 6 generated by fitting models to log M vs log MLS data. Survival at MLS is defined I_{MLS} . RSS is minimum residual sum of squares, Eq. 7, n is the number of fitting parameters for each Set and AIC is the difference in the Akaike information criterion between Sets

Set	I_{MLS}	c_p	c_σ	c_λ	h	k	RSS	n	AIC^c
1	0.01	0.1705	0.1108 ^a	0.0096	0.25 ^b	0.534	70.40	3	0
2	0.03	0.1502	0.0976 ^a	0.00156	0.25 ^b	0.216	71.26	3	0.04
3	0.01	0.3740	1.0780	0.1470	0.25 ^b	0.196	69.52	4	4.20
4	0.03	0.2304	0.36	0.045	0.25 ^b	0.280	69.76	4	4.20
5	0.01	0.64	1.62	0.068	0.29	0.208	69.53	5	8.45
6	0.03	0.2304	0.3580	0.0443	0.24	0.299	69.71	5	8.46

^aFixed parameters $c_\sigma = 0.65$ c_p

^bFixed parameters based on metabolic theory

^c $AIC_j = n_l \log(RSS_j) - n_l \log(RSS_1)$

Parameter sets $Q_{\bullet} = [\rho_{\bullet}, \sigma_{\bullet}, \lambda_{\bullet}]$ to generate survivorship curves in Fig. 6 using Eq. 5. Q_L is estimated by fitting Eq. 5 to published survival data. Q_M is derived from Eq. 6 using mammal mass and fitting parameters P from Set 1. Early life mortality was removed from the survival data by linearly projecting survival to zero age using the survivorship curve slope at onset of adult age

Table 2

Example species	Mass kg	Adult age (year)	Parameter sets		ρ (year ⁻¹)	σ (year ⁻¹)	λ (year ⁻¹)
Field Vole	0.03	0.17	Q_M		0.410	0.266	0.062
			Q_L		0.81	0.52	0
Pigtail Macaque	10	2	Q_M		0.096	0.062	0.003
			Q_L		0.060	0.065	0.048
Namibian Cheetah	50	0	Q_M		0.064	0.042	0.001
			Q_L		0.14	0.10	0.220
Mountain Gorilla	100	8	Q_M		0.054	0.035	0.001
			Q_L		0.032	0.044	0
Grizzly Bear	275	5	Q_M		0.042	0.027	0.005
			Q_L		0.078	0.065	0.036
Asian Elephant	4000	5	Q_M		0.020	0.013	0
			Q_L		0.019	0.027	0.003

Table 3Ratios of model parameter sets Q_L to Q_M

Species	ρ_L/ρ_M	σ_L/σ_M	λ_L/λ_M
Field Vole	2.0	2.0	0
Pigtail Macaque	0.6	1.0	17
Namibian Cheetah	2.1	2.4	184
Mountain Gorilla	0.6	1.3	0
Grizzly Bear	1.8	2.4	76
Asian Elephant	0.9	2.1	31