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The evolution of senescence through decelerating selection for system reliability

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Abstract

Senescence is a universal phenomenon in organisms, characterized by increasing mortality and decreasing fecundity with advancing chronological age. Most proximate agents of senescence, such as reactive oxygen species and UV radiation, are thought to operate by causing a gradual build-up of bodily damage. Yet most current evolutionary theories of senescence emphasize the deleterious effects of functioning genes in late life, leaving a gap between proximate and ultimate explanations. Here, we present an evolutionary model of senescence based on reliability theory, in which beneficial genes or gene products gradually get damaged and thereby fail, rather than actively cause harm. Specifically, the model allows organisms to evolve multiple redundant copies of a gene product (or gene) that performs a vital function, assuming that organisms can avoid condition-dependent death so long as at least one copy remains undamaged. We show that organisms with low levels of extrinsic mortality, and high levels of genetic damage, tend to evolve high levels of redundancy, and that mutation–selection balance results in a stable population distribution of the number of redundant elements. In contrast to previous evolutionary models of senescence, the mortality curves that emerge from such populations match empirical senescence patterns in three key respects: they exhibit: (1) an initially low, but rapidly increasing mortality rate at young ages, (2) a plateau in mortality at advanced ages and (3) 'mortality compensation', whereby the height of the mortality plateau is independent of the environmental conditions under which different populations evolved.

Introduction

Senescence is a universal phenomenon in organisms, characterized by increasing mortality and decreasing fecundity with advancing chronological age (e.g. Bonduriansky & Brassil, 2002; see Hughes & Reynolds, 2005; Bonsall, 2006; Williams *et al.*, 2006; Ackermann & Pletcher, 2007; Monaghan *et al.*, 2008 for recent general reviews). The ubiquity of senescence is a puzzle in evolutionary biology, because all else being equal, individuals that forgo senescence should have a selective advantage over those that senesce. Traditionally, senescence has been thought to arise as a consequence of genes with late-acting deleterious effects, which persist over generations in organisms' genomes because there is little selection to purge them ('mutation accumulation' theory; Medawar, 1946, 1952), and/or because they have earlier acting benefits ('antagonistic pleiotropy' theory; Williams, 1957). These theories now have a firm theoretical foundation (Hamilton, 1966; Charlesworth, 1994), and many of their underlying assumptions have found widespread support. For example, laboratory selection experiments on fruit flies (*Drosophila* spp.) have repeatedly shown negative genetic correlations between early and late fecundity (Rose, 1991). Likewise, in an intensively studied population of wild mute swans (*Cygnus olor*) individuals that started their reproductive lives early also tended to end their reproductive lives early and such traits were heritable, indicating that genetic trade-offs can help shape reproductive senescence (Charmantier *et al.*, 2006).

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Nevertheless, in general, attempts to identify specific genes with temporal antagonistic pleiotropic effects have met with mixed success (Kirkwood, 2005; Leroi *et al.*, 2005; Flatt & Promislow, 2007). Furthermore, through their emphasis on the deleterious effects of functioning genes, the above theories place genetics, rather than environmental damage, as the primary driver of senescence. Here we quantitatively examine the implications of an alternative perspective, arguing that the age dependency of gene action can arise not only because genes themselves produce deleterious effects, but also because they or their products can get damaged, and therefore eventually fail to act in an advantageous way. Gerontologists have identified a host of candidate agents capable of generating such damage, ranging from intrinsically generated metabolic by-products, such as reactive oxygen species, to extrinsic agents such as solar radiation (Arking, 1998; Pletcher *et al.*, 2007). We therefore investigate the possibility that senescence can arise because accumulated damage becomes so great that it eventually impairs the transcription of beneficial genes (or destroys their beneficial products), rather than as a simple consequence of functioning genes with late-acting deleterious effects.

Nevertheless, one might wonder why organisms do not evolve genetic systems that are less vulnerable (or indeed invulnerable) to environmental damage. One possibility is that the underlying vulnerability is an unavoidable consequence of an optimal resource allocation strategy, reflecting the price an organism is prepared to pay to enhance its reproduction ('disposable soma' theory; Kirkwood, 1977, 1997; Kirkwood & Holliday, 1979; see also Abrams & Ludwig, 1995; Mangel, 2001). Here we argue that adaptations to reduce the vulnerability of the soma to damage will only be as good as they need to be, such that there will be little selection to allow organisms to respond to the types of damage that would occur far beyond their typical lifetimes, even if such a response were entirely cost free. Therefore, a trade-off between repair and reproduction is not necessary for senescence, even if such trade-offs occur.

One of the most natural ways to reduce genomic vulnerability is to evolve multiple copies of the same essential gene (or gene product) that can act as back-ups should any one of them fail or become damaged (Clark, 1994; Nowak *et al.*, 1997; Conant & Wagner, 2003; Kafri *et al.*, 2006). The work of Gavrilov & Gavrilova (2001, 2006), falling under the general heading of 'reliability theory' (Barlow *et al.*, 1965) has adopted this perspective by taking an engineering approach to understand how biological systems with irreplaceable redundant components can exhibit increased failure rates, i.e. actuarial senescence, as they age. However, the built in redundancy in their models provides a starting point for their theory rather than an end point, and it has been criticized for not being evolutionarily based (Pletcher & Curtsinger, 1998; Pletcher & Neuhauser, 2000). Using a quasispecies model of evolution, we show how a degree of redundancy (and more broadly an ability to deal with damage to system components) can evolve by natural selection, and that the resulting population equilibrium is sufficiently diverse to generate mortality trajectories with attributes that are observed in natural populations, but are not as readily understood by the late-acting deleterious effects of functioning genes.

The model

Following Gavrilov & Gavrilova (2001), we assume that a particular vital function of an organism can be represented as a system of elements that are redundant, mutually substitutable and irreplaceable when damaged (i.e. they are in 'parallel'). We envision these redundant elements as gene products whose number is heritable at a single locus, although our model could also be applied (with appropriate modifications) to a multi-locus system treating the elements as genes themselves. The elements are subject to random failure due to damage at a constant, independent rate k, and organisms can only avoid condition-dependent death so long as they have at least one remaining undamaged element. In addition to 'intrinsic' condition-dependent mortality caused by the extinction of undamaged elements, we also assume a constant 'extrinsic' age- and condition-independent mortality rate of q, such that the expected cumulative survivorship at time t for a monotypic population of individuals with n redundant elements is

$$l(t) = (e^{-qt})(1 - (1 - e^{-kt})^n). \quad (1)$$

The expected survivorship of a mixed-n population is the average of these survival probabilities weighted by the relative abundances of the genotypes that determine individuals' n values.

Greater redundancy leads to greater survivorship, and, assuming a constant birth rate, individuals with greater n have greater lifetime reproductive output (Fig. 1). Thus, insofar as lifetime reproductive output (R) is related to fitness, (i.e. in populations with discrete generations), there is directional selection for redundancy (an analysis demonstrating that our results are analogous when generations continuously overlap, and fitness is measured by the intrinsic rate of natural increase, is provided in Appendix S1). However, this directional selection operates in a decelerating fashion: the marginal increase in R of adding an additional element is greater in individuals with low n compared with individuals with high n (Fig. 1). Therefore, under the realistic assumption that most non-neutral mutations are deleterious (Eyre-Walker & Keightley, 2007), we hypothesize that selection will eventually be balanced by mutation, resulting in populations that evolve towards an equilibrium distribution of genotypes. Given that R is dependent not only on n, but also on the failure and extrinsic mortality rates (Fig. 1), exactly where the mutation–selection balance is

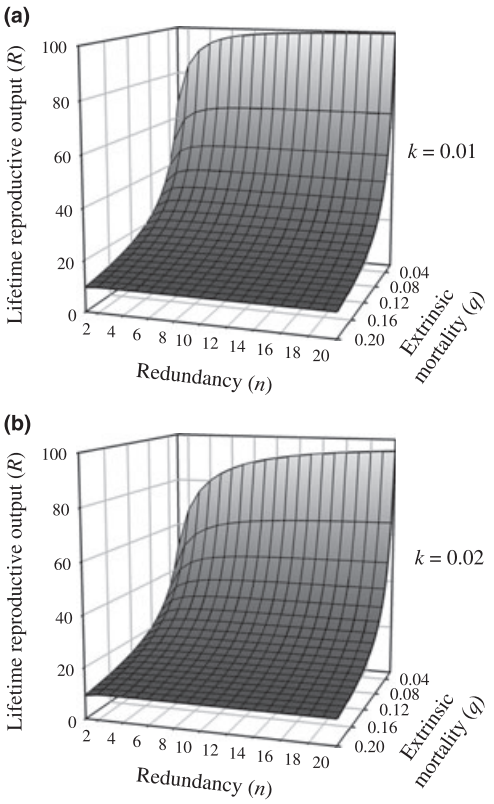

Fig. 1 Diminishing value of redundancy in parallel systems. In systems whose elements are redundant, irreplaceable and heritable, there is positive, directional, yet decelerating selection for redundancy (n), whether fitness is measured in terms of R, lifetime reproductive output (a,b) or r, intrinsic rate of natural increase (see Appendix S1). The asymptotic relationship between R and n is influenced by both k, the failure rate of each element, and q, the condition- and age-independent (extrinsic) mortality rate. (a) $k = 0.01$; (b) $k = 0.02$. In both cases we assumed a constant age-independent birth rate of $b = 2$, although this simply acts as a scalar. Although birth rate often trades off with survivorship, we avoided such complexities so that senescence would not be built into our model through pleiotropy.

struck should depend critically on k and q, as well as on the relative rates of mutations that increase and decrease redundancy.

We modelled the evolution of redundancy using a discrete-generation version of the quasispecies equation (Nowak, 2006), which tracks the relative abundances of N different genotypes over many generations. 'Genotype 1' corresponds to individuals with $n = 1$ element, and so on. The discrete quasispecies is characterized by a system of simultaneous recursion equations given by:

$$x_i' = \frac{\sum_{j=1}^{N} x_j f_j \mu_{ji}}{\sum_{i=1}^{N} \sum_{j=1}^{N} x_j f_j \mu_{ji}}, \quad i = 1, 2, \ldots, N \qquad (2)$$

where x_i' is the relative abundance of genotype i in the next generation, x_j is the relative abundance of genotype j in the current generation, f_j is the reproductive success of genotype j and μ_{ji} is the transition rate between genotype j and genotype i (i.e. the mutation rate when $i \neq j$). Befitting populations with discrete generations, we used lifetime reproductive output ($R = \int_0^\tau b(t)l(t)\mathrm{d}t$) as a proxy for f, assuming a constant birth rate of $b(t) = b$, which acts simply as a scalar. We set τ to 10^6 to ensure that the maximum length of the reproductive season is finite, but in reality the vast majority of individuals will have died long before this time is reached. In our model, mutant offspring that inherit a different element number than their parents only differ by one element (e.g. an individual with three elements can potentially have offspring with three, two or four redundant elements). We also assume that all 'up-mutations' (mutations that increase n by one) are equally likely and occur at the rate α, and similarly, that all 'down-mutations' (mutations that decrease n by one) are equally likely and occur at the rate β ($\beta > \alpha$). Thus, the transition rate (μ) in equation 2 is given by α when $i = j + 1$, β when $i = j - 1$, $1 - \alpha$ when $i = j = 1$, $1 - \beta$ when $i = j = N$, $1 - \alpha - \beta$ when $1 < i = j < N$ and 0 otherwise ($\alpha + \beta \leq 1$). Aside from rare mutations, offspring begin life with the same n value as their parent; only the genotype specifying redundancy is inherited, not damage itself.

Results and discussion

To investigate the evolution of redundancy under different levels of k and q, we started with populations with no redundancy ($n = 1$) and modelled the evolution of the relative abundance distribution of genotypes using the quasispecies equation. Figure 2 shows two example evolutionary outcomes of this analysis at two levels of extrinsic mortality q. Early on, there is a fast turnover of genotypes (Fig. 2a–d) as the mean level of redundancy evolves (Fig. 2e and f). However, over successive generations, this turnover slows and eventually ceases, whereupon the relative abundance distribution of the genotypes remains constant (Fig. 2g and h). Eigenvector analysis allows us to identify this equilibrium distribution and confirms that the equilibrium is stable (Appendix S2). Thus, redundancy evolves but only to a point; there is no selection for intrinsic immortality through infinite n. Note that this is true even if redundancy is cost-free, as in our model; however, including costs would clearly limit the evolution of redundancy even further.

Environmental conditions can greatly affect the equilibrium distribution and the mean evolved value of n (Fig. 3a). For example, far greater redundancy evolves under relatively low extrinsic mortality ($q = 0.02$; Fig. 2a, c, e and g) than under relatively high extrinsic mortality ($q = 0.20$; Fig. 2b, d, f and h). Likewise, greater levels of redundancy evolve when elements are intrinsically likely to get damaged (high k). In general therefore, individuals only inherit the level of

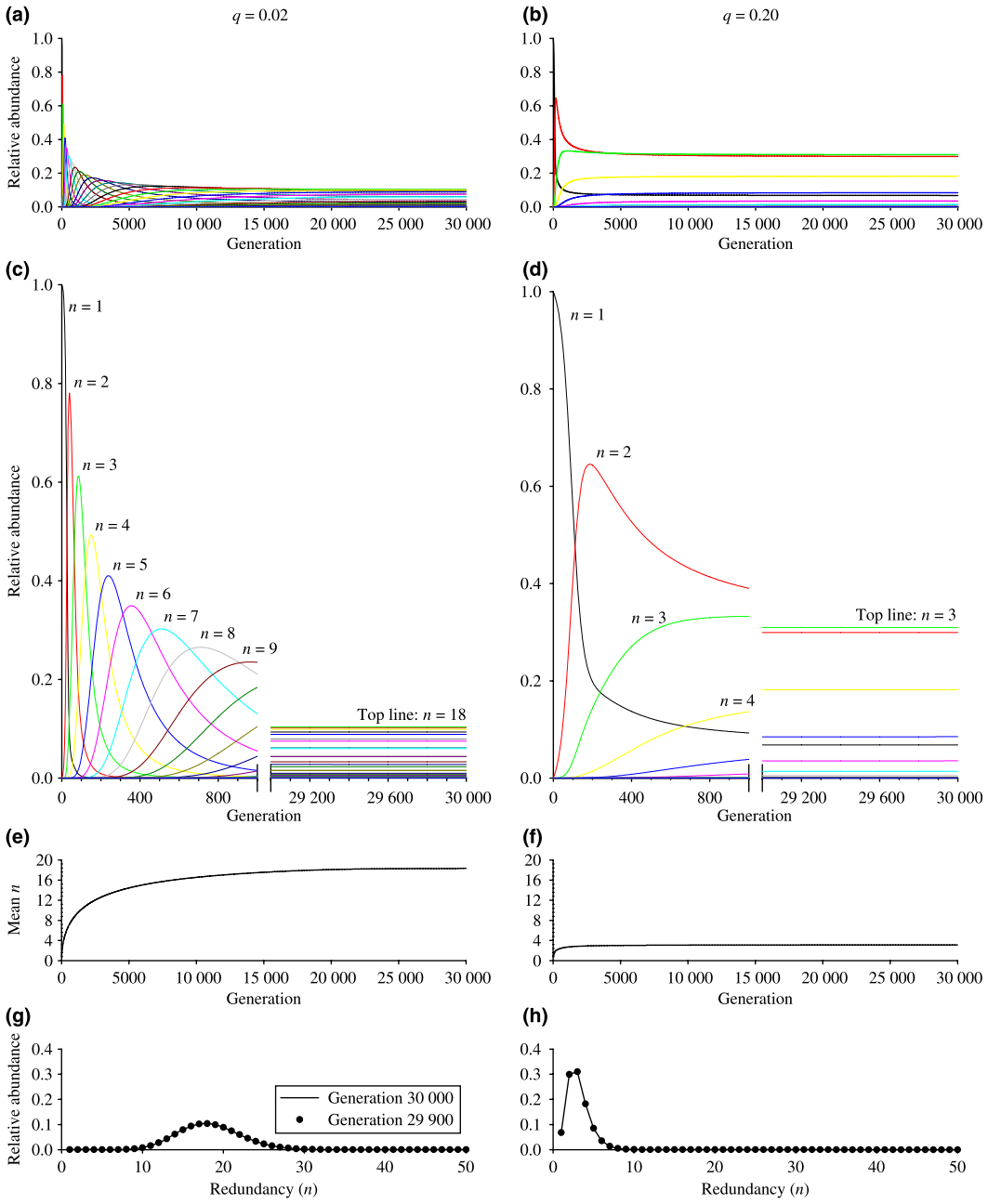

Fig. 2 Quasispecies evolution. (a,b) Example evolutionary trajectories of the relative abundances over 30 000 generations of 50 different genotypes (levels of redundancy) in a large population where lines correspond to individuals with different numbers of parallel elements (n = 1–50). Here our maximum of N = 50 elements was set sufficiently high to allow the distribution of n at equilibrium to be effectively independent of N. A failure rate of k = 0.01 and a birth rate of b = 2 was assumed in all cases. Trajectories under two different extrinsic mortality regimes are shown: (a) q = 0.02 and (b) q = 0.20 (all panels in the same column have these same parameter values and represent the output from the same numerical analysis). Panels (c) and (d) show details (i.e. the first and last 1000 generations) of (a) and (b) respectively; the identities of several genotypes are given. To help distinguish between lines in (a–d), a colour version of this figure is available online. At the start (generation 0), all individuals have n = 1 element. Evolution then proceeds according to the discrete quasispecies equation, using lifetime reproductive output (R) as a measure of fitness, and mutation parameters of α = 0.001 (up-mutation rate) and β = 0.01 (down-mutation rate). (e,f) The evolutionary trajectories of mean n in the population. Eventually, the decelerating fitness functions results in mean n reaching an asymptote that is strongly dependent on q. This equilibrium value is independent of initial genotype relative abundances (confirmed by analyses starting with monocultures of n = 50, not shown – see also Appendix S2). (g,h) At equilibrium, there is a stable distribution of relative abundances (relative abundances shown for generations 29 900 and 30 000).

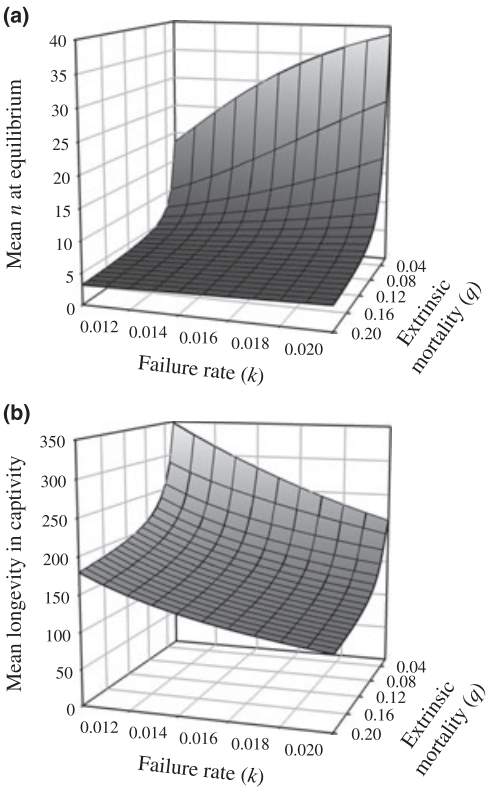

Fig. 3 Redundancy and longevity in different environments. (a) The mean number of elements at equilibrium (mean n) as a function of element failure rate (k) and extrinsic mortality (q). (b) The mean longevity in captivity (i.e. when there is no extrinsic mortality) for populations that originally evolved under different combinations of k and q. Other parameter values: $\alpha = 0.001$, $\beta = 0.01$, $b = 2$.

redundancy that is likely to be positively advantageous in their lifetimes under the prevailing environmental conditions.

This environmental dependence of evolved redundancy leads to differences in the average longevity of individuals from populations that evolve under different values of k and q. These differences remain even when the population, previously subject to selection, is placed into 'captivity', with zero extrinsic mortality, thereby matching patterns that are frequently observed in natural and experimental populations (e.g. Keller & Genoud, 1997; Stearns *et al.*, 2000; Carlson *et al.*, 2007 and papers cited therein; but see Abrams, 1993; Williams & Day, 2003; Reznick *et al.*, 2004). Thus, individuals from populations that originally evolved under relatively high extrinsic mortality have a shorter mean longevity in captivity compared with individuals from populations that evolved under relatively low extrinsic mortality (Williams, 1957; Fig. 3b). Although increasing k results in the evolution of greater redundancy (Fig. 3a), individuals from high-k populations still have a shorter mean longevity than individuals from low-k populations due to under-compensation for the direct effect of damage (Fig. 3b).

In our model, senescence evolves from nonsenescing ancestral populations. At the start of the evolutionary process, when populations are composed of individuals with no redundancy, cumulative survivorship is described by a simple exponential decay (Fig. 4a and b), and mortality is constant with age (Fig. 4c and d). However, the stable mixed-n populations that evolve due to decelerating selection for reliability show increasing mortality with age, i.e. actuarial senescence. More specifically, the senescence patterns exhibited by our model populations match those of natural populations in three key respects (Gavrilov & Gavrilova, 2001): First, they have an initially low, but near-exponentially increasing mortality rate. Second, like natural and experimental populations (Carey *et al.*, 1992; Curtsinger *et al.*, 1992; Pletcher & Curtsinger, 1998), our model populations exhibit a waning mortality rate at old ages, culminating in a mortality plateau in the 'oldest old' (Fig. 4c and d). This plateau is not directly predicted by the classical evolutionary theories (i.e. the 'mutation accumulation' and 'antagonistic pleiotropy' theories) and can only be recovered (e.g. Mueller & Rose, 1996) with difficulty (Pletcher & Curtsinger, 1998; Wachter, 1999). Third, our model populations show 'compensatory mortality', in which the height of the mortality plateau is related only to the failure rate, and not to the extrinsic mortality under which the population evolved (Fig. 4c and d). This matches data from real populations whose mortality rates converge in the oldest age classes (Gavrilov & Gavrilova, 1991) and is a feature in common with related Markov mortality models (Steinsaltz & Evans, 2004). Finally, Gavrilov & Gavrilova (2001) argued that realistic early-life (Gompertzian) mortality was only possible in populations of organisms with redundant components if there was a distribution of values of n, rather than a monoculture (see Appendix S3 for further discussion and analysis). In the absence of an evolutionary framework, it was suggested that the variation could arise if organisms are born with varying levels of realized n due to a high incidence of initial defects (Gavrilov & Gavrilova, 2001), an idea that has met with resistance (Pletcher & Neuhauser, 2000). Here, we show that this initial defects hypothesis is not needed to have variation in n; rather, the necessary variation can be maintained at the population level by mutation–selection balance.

Our model assumes random damage to redundant gene products and one could readily apply the same type of model to consider damage to genes themselves; indeed many previous models of ageing have assumed random damage to genes (e.g. Szilard, 1959). Pletcher *et al.* (2002) found no support for global (whole organism) increases in gene disregulation with advancing age in *Drosophila* and neither did Rogina *et al.* (1998) when screening a more limited array of genes. However, as

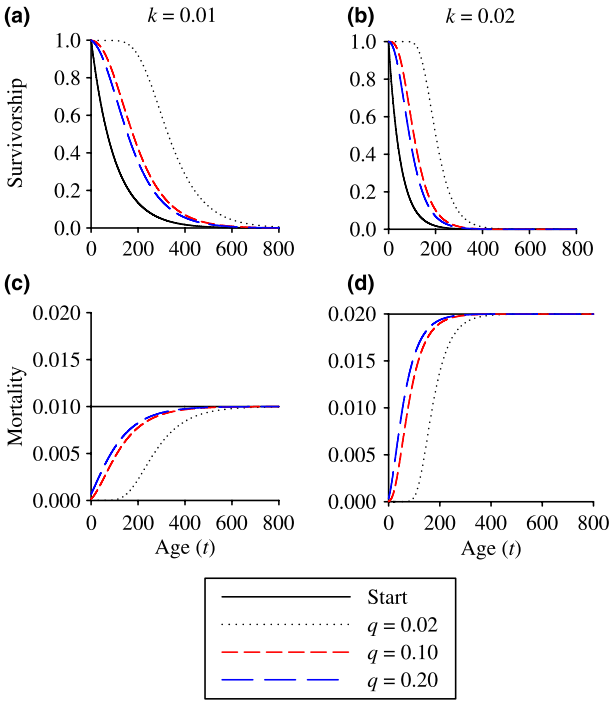

Fig. 4 Evolution of senescence. (a,b) Examples of cumulative population survivorship and (c,d) instantaneous mortality curves based on relative abundance distributions of the number of elements (n) before quasispecies evolution (when all individuals had $n = 1$; solid lines) and after quasispecies evolution (broken lines). All curves represent survivorship and mortality 'in captivity'; i.e. when there is no extrinsic mortality. However, the broken lines represent the extrinsic mortality conditions in which the populations originally evolved for 30 000 generations: dotted line (black), $q = 0.02$; short-dashed line (red), $q = 0.10$; long-dashed line (blue), $q = 0.20$; a colour version of this figure is available online. In (a) and (c), there was a failure rate of $k = 0.01$; in (b) and (d), $k = 0.02$; in both cases, the birth rate was $b = 2$.

Pletcher *et al.* (2002) note, if stochastic disregulation occurs differently in different cells, then it would be difficult to detect such changes through a whole-organism analysis (in other words, if different cells fail to express *different* genes due to damage, then one would be less likely to find consistent increases in the variance of expression of any given gene over the whole organism). Direct evidence for increased cell-to-cell variation in gene expression was recently provided by Bahar *et al.* (2006) who reported increased heterogeneity in gene expression among cells in ageing mouse hearts. Moreover, recent work by Somel *et al.* (2006) has reported an age-correlated increase in heterogeneity of gene expression (ACHE) in both rats and humans. Both of these studies highlight the plausibility of age-dependent failure of gene function arising through stochastic damage (see also de Grey, 2007).

The idea that there is little selection to allow organisms to respond to damage far beyond their typical lifetimes has had a long history in evolutionary thought (Comfort, 1979). Likewise, it has long been appreciated that genetic redundancy will evolve to make somatic genomes more robust to environmental damage (Nowak *et al.*, 1997; Wagner, 1999). Redundancy may also play a role in 'canalization' (Waddington, 1942), that is, the buffering of developmental pathways against mutational or environmental perturbations (Kitano, 2004; Hansen, 2006). Here we have explicitly linked these phenomena, by developing and exploring a formal evolutionary model for senescence using a quasispecies model of redundancy. As Bonsall (2006, p. 130) recently noted, 'developing a population genetic framework to explore how genome size and gene duplications might affect the patterns and predictions on longevity evolution will refine the evolutionary theory of ageing'.

Our general result can be made by analogy: homeowners who have experienced blackouts may have a back-up generator in case the electricity fails. However, almost no homeowner would consider having a 'back-up for the back-up' because such bad luck rarely arises. In this way, only a finite number of contingencies evolve in natural organisms to sustain it simply because the likelihood of additional back-ups being needed is increasingly remote. Multi-stage cancers acting late life can arise for much the same reason, when a series of checks and balances preventing cell proliferation within a typical lifespan can by chance all eventually become damaged, and the disease spreads (Armitage & Doll, 1954; Nunney, 1999, 2003; Campisi, 2003; Frank, 2004, 2007). Indeed, there are now a number of biological examples of death or severe impairment arising as part of a stochastic multi-stage process in which key genes become damaged by somatic mutation. For example, Frank (2005) compared the age-specific incidences of inherited and sporadic forms of retinoblastoma and showed how the dynamics of these cancers were consistent with a simple multi-stage process of somatic mutations. In bilateral retinoblastomas, tumours develop in both eyes as a result of an inherited predisposition to tumour formation. By contrast, unilateral cases arise in one eye and are thought to occur sporadically. Both patterns of age onset can be readily understood if one assumes that these particular cancers arise as a two stage process, with the first mutation inherited in bilateral retinoblastoma subjects.

Note that in our model for the evolution of senescence, the time-dependent deleterious effects arise not through the late-life action of functioning genes as typically assumed (see Penna, 1995 for a rather extreme example of a model with time dependency built into the genes themselves) but through damage-based late-life inaction of beneficial genes/gene products. As any evolved protective mechanisms are always subject to some form of damage themselves, such damage is logically inevitable. Interestingly, Ackermann *et al.* (2007) also developed a 'damage-centric' evolutionary model of senescence. Although both models demonstrate how environmental

damage can lead to senescence arising from nonsenescing ancestral populations, there are several key differences between their model and ours. Ackermann *et al.*'s (2007) contribution was intended to explain the evolutionary origin of senescence in single celled organisms such as prokaryotes. Appropriately in this single celled context, there is no separation of soma and germ line; so, environmental damage accrued by a cell is passed on during cell division. In this case, senescence can readily arise due to the evolved asymmetric partitioning of damage between the products of cell division, effectively leading to an increasingly damaged and death-prone 'parent' and a pristine 'offspring'. By contrast, in our model only the genotype governing redundancy is inherited (subject to mutation), not damage itself. Therefore, our model is more appropriate in multicellular organisms where damage to somatic cells need not be inherited.

Through its emphasis on damage, our model also shares many assumptions with the disposable soma theory (Kirkwood, 1977; Kirkwood & Holliday, 1979), one of the key recent advances in the development of an evolutionary understanding of senescence. However, the disposable soma theory assumes a trade-off between reproduction and repair. In the system we have modelled, senescence readily evolves without the need to invoke such a trade-off. The disposable soma model has been characterized as an example of pleiotropy which emphasizes damage, such that a gene diverting energy to reproduction has the antagonistic pleiotropic effect of reducing damage repair (Kirkwood & Austad, 2000). By the same token our model might be taken to represent an example of the mutation accumulation theory, this time emphasizing accumulated damage to vital elements rather than the late-acting deleterious effects of functioning genes. Of course in both cases, selection to counter late-life gene activity or inactivity will be relatively weak, but the underlying mechanism giving rise to senescence (failure to do good vs. active harm) is fundamentally different, as is the evolutionary response. As noted earlier, there may well be selection against redundancy (anti-redundancy) if redundant elements are costly (Krakauer & Plotkin, 2002). Whether or not measures to protect the soma from environmental damage incur a cost, and whether or not these costs are traded against reproduction, it is clear that senescence will still arise due to the eventual degeneration of redundant systems that perform vital functions.

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References

Abrams, P.A. 1993. Does increased mortality favor the evolution of more rapid senescence? *Evolution* **47**: 877–887.

Abrams, P.A. & Ludwig, D. 1995. Optimality theory, Gompertz' law, and the disposable soma theory of senescence. *Evolution* **49**: 1055–1066.

Ackermann, M. & Pletcher, S.D. 2007. Evolutionary biology as a foundation for studying aging and aging-related disease. In: *Evolution in Health and Disease Second Edition* (S.C. Stearns & J.C. Koella, eds), pp. 241–252. Oxford University Press, Oxford.

Ackermann, M., Chao, L., Bergstrom, C.T. & Doebeli, M. 2007. On the evolutionary origin of aging. *Aging Cell* **6**: 235–244.

Arking, R. 1998. *Biology of Aging: Observations and Principles*. Sinauer Associates, Sunderland, MA.

Armitage, P. & Doll, R. 1954. The age distribution of cancer and a multi-stage theory of carcinogenesis. *Br. J. Cancer* **8**: 1–12 (Reprinted in ***Int. J. Epidemiol.* 33**: 1174–1179).

Bahar, R., Hartmann, C.H., Rodriguez, K.A., Denny, A.D., Busuttil, R.A., Dollé, M.E.T., Calder, R.B., Chisolm, G.B., Pollock, B.H., Klein, C.A. & Vijg, J. 2006. Increased cell-to-cell variation in gene expression in ageing mouse heart. *Nature* **441**: 1011–1015.

Barlow, R.E., Proschan, F. & Hunter, L.C. 1965. *Mathematical Theory of Reliability*. John Wiley & Sons, New York.

Bonduriansky, R. & Brassil, C.E. 2002. Rapid and costly ageing in wild male flies. *Nature* **420**: 377.

Bonsall, M.B. 2006. Longevity and ageing: appraising the evolutionary consequences of growing old. *Philos. Trans. R. Soc. B* **361**: 119–135.

Campisi, J. 2003. Cancer and ageing: rival demons? *Nat. Rev. Cancer* **3**: 339–349.

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

Carlson, S.M., Hilborn, R., Hendry, A.P. & Quinn, T.P. 2007. Predation by bears drives senescence in natural populations of salmon. *PLoS ONE* **2**: e1286.

Charlesworth, B. 1994. *Evolution in Age-structured Populations*. Cambridge University Press, London.

Charmantier, A., Perrins, C., McCleery, R.H. & Sheldon, B.C. 2006. Quantitative genetics of age at reproduction in wild swans: support for antagonistic pleiotropy models of senescence. *Proc. Natl Acad. Sci. USA* **103**: 6587–6592.

Clark, A.G. 1994. Invasion and maintenance of a gene duplication. *Proc. Natl Acad. Sci. USA* **91**: 2950–2954.

Comfort, A. 1979. *The Biology of Senescence*. Churchill Livingstone, London.

Conant, G.C. & Wagner, A. 2003. Duplicate genes and robustness to transient gene knock-downs in *Caenorhabditis elegans*. *Proc. R. Soc. Lond. B* **271**: 89–96.

Curtsinger, J.W., Fukui, H.H., Townsend, D.R. & Vaupel, J.W. 1992. Demography of genotypes: failure of the limited life-span paradigm in *Drosophila melanogaster*. *Science* **258**: 461–463.

Eyre-Walker, A. & Keightley, P.D. 2007. The distribution of fitness effects of new mutations. *Nat. Rev. Genet.* **8**: 610–618.

Flatt, T. & Promislow, D.E.L. 2007. Still pondering an age-old question. *Science* **318**: 1255–1256.

Frank, S.A. 2004. Genetic variation in cancer predisposition: mutational decay of a robust genetic control network. *Proc. Natl Acad. Sci. USA* **101**: 8061–8065.

Frank, S.A. 2005. Age-specific incidence of inherited versus sporadic cancers: a test of the multistage theory of carcinogenesis. *Proc. Natl Acad. Sci. USA* **102**: 1071–1075.

Frank, S.A. 2007. *Dynamics of Cancer: Incidence, Inheritance, and Evolution*. Princeton University Press, Princeton, NJ.

Gavrilov, L.A. & Gavrilova, N.S. 1991. *The Biology of Life Span: A Quantitative Approach*. Harwood Academic Publisher, New York.

Gavrilov, L.A. & Gavrilova, N.S. 2001. The reliability theory of aging and longevity. *J. Theor. Biol.* **213**: 527–545.

Gavrilov, L.A. & Gavrilova, N.S. 2006. Reliability theory of aging and longevity. In: *Handbook of the Biology of Aging*, 6th edn (E.J. Masoro & S.N. Austad, eds), pp. 4–42. Academic Press, San Diego, CA.

de Grey, A.D.N.J. 2007. Protagonistic pleiotropy: why cancer may be the only pathogenic effect of accumulating nuclear mutations and epimutations in aging. *Mech. Ageing Dev.* **128**: 456–459.

Hamilton, W.D. 1966. The moulding of senescence by natural selection. *J. Theor. Biol.* **12**: 12–45.

Hansen, T.F. 2006. The evolution of genetic architecture. *Annu. Rev. Ecol. Evol. Syst.* **37**: 123–157.

Hughes, K.A. & Reynolds, R.M. 2005. Evolutionary and mechanistic theories of aging. *Annu. Rev. Entomol.* **50**: 421–445.

Kafri, R., Levy, M. & Pilpel, Y. 2006. The regulatory utilization of genetic redundancy through responsive backup circuits. *Proc. Natl Acad. Sci. USA* **103**: 11653–11658.

Keller, L. & Genoud, M. 1997. Extraordinary lifespans in ants: a test of evolutionary theories of ageing. *Nature* **389**: 958–960.

Kirkwood, T.B.L. 1977. Evolution of ageing. *Nature* **270**: 301–304.

Kirkwood, T.B.L. 1997. The origins of human ageing. *Philos. Trans. R. Soc. Lond. B* **352**: 1765–1772.

Kirkwood, T.B.L. 2005. Understanding the odd science of aging. *Cell* **120**: 437–447.

Kirkwood, T.B.L. & Austad, S.N. 2000. Why do we age? *Nature* **408**: 233–238.

Kirkwood, T.B.L. & Holliday, R. 1979. The evolution of ageing and longevity. *Proc. R. Soc. Lond. B* **205**: 531–546.

Kitano, H. 2004. Biological robustness. *Nat. Rev. Genet.* **5**: 826–837.

Krakauer, D.C. & Plotkin, J.B. 2002. Redundancy, antiredundancy, and the robustness of genomes. *Proc. Natl Acad. Sci. USA* **99**: 1405–1409.

Leroi, A.M., Bartke, A., De Benedictis, G., Franceschi, C., Gartner, A., Gonos, E., Feder, M.E., Kivisild, T., Lee, S., Kartal-Özer, N., Schumacher, M., Sikora, E., Slagboom, E., Tatar, M., Yashin, A.I., Vijg, J. & Zwaan, B. 2005. What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? *Mech. Ageing Dev.* **126**: 421–429.

Mangel, M. 2001. Complex adaptive systems, aging and longevity. *J. Theor. Biol.* **213**: 559–571.

Medawar, P.B. 1946. Old age and natural death. *Mod. Q.* **1**: 30–56.

Medawar, P.B. 1952. *An Unsolved Problem of Biology*. Western Printing Systems, Bristol.

Monaghan, P., Charmantier, A., Nussey, D.H. & Ricklefs, R.E. 2008. The evolutionary ecology of senescence. *Funct. Ecol.* **22**: 371–378.

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

Nowak, M.A. 2006. *Evolutionary Dynamics: Exploring the Equations of Life*. Harvard University Press, Cambridge, MA.

Nowak, M.A., Boerlijst, M.C., Cooke, J. & Maynard Smith, J. 1997. Evolution of genetic redundancy. *Nature* **388**: 167–171.

Nunney, L. 1999. Lineage selection and the evolution of multistage carcinogenesis. *Proc. R. Soc. Lond. B* **266**: 493–498.

Nunney, L. 2003. The population genetics of multistage carcinogenesis. *Proc. R. Soc. Lond. B* **270**: 1183–1191.

Penna, T.J.P. 1995. A bit-string model for biological aging. *J. Stat. Phys.* **78**: 1629–1633.

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

Pletcher, S.D. & Neuhauser, C. 2000. Biological aging – criteria for modeling and a new mechanistic model. *Int. J. Mod. Phys. C* **11**: 525–546.

Pletcher, S.D., Macdonald, S.J., Marguerie, R., Certa, U., Stearns, S.C., Goldstein, D.B. & Partridge, L. 2002. Genome-wide transcript profiles in aging and calorically restricted *Drosophila melanogaster*. *Curr. Biol.* **12**: 712–723.

Pletcher, S.D., Kabil, H. & Partridge, L. 2007. Chemical complexity and the genetics of aging. *Annu. Rev. Ecol. Evol. Syst.* **38**: 299–326.

Reznick, D.N., Bryant, M.J., Roff, D., Ghalambor, C.K. & Ghalambor, D.E. 2004. Effect of extrinsic mortality on the evolution of senescence in guppies. *Nature* **431**: 1095–1099.

Rogina, B., Vaupel, J.W., Partridge, L. & Helfand, S.L. 1998. Regulation of gene expression is preserved in aging *Drosophila melanogaster*. *Curr. Biol.* **8**: 475.

Rose, M.R. 1991. *Evolutionary Biology of Aging*. Oxford University Press, Oxford.

Somel, M., Khaitovich, P., Bahn, S., Pääbo, S. & Lachmann, M. 2006. Gene expression becomes heterogeneous with age. *Curr. Biol.* **16**: R359–R360.

Stearns, S.C., Ackermann, M., Doebeli, M. & Kaiser, M. 2000. Experimental evolution of aging, growth, and reproduction in fruitflies. *Proc. Natl Acad. Sci. USA* **97**: 3309–3313.

Steinsaltz, D. & Evans, S.N. 2004. Markov mortality models: Implications of quasistationarity and varying initial distributions. *Theor. Popul. Biol.* **65**: 319–337.

Szilard, L. 1959. On the nature of the aging process. *Proc. Natl Acad. Sci. USA* **45**: 30–45.

Wachter, K.W. 1999. Evolutionary demographic models for mortality plateaus. *Proc. Natl Acad. Sci. USA* **96**: 10544–10547.

Waddington, C.H. 1942. Canalization of development and the inheritance of acquired characters. *Nature* **150**: 563–565.

Wagner, A. 1999. Redundant gene functions and natural selection. *J. Evol. Biol.* **12**: 1–16.

Williams, G.C. 1957. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* **11**: 398–411.

Williams, P.D. & Day, T. 2003. Antagonistic pleiotropy, mortality source interactions, and the evolutionary theory of senescence. *Evolution* **57**: 1478–1488.

Williams, P.D., Day, T., Fletcher, Q. & Rowe, L. 2006. The shaping of senescence in the wild. *Trends Ecol. Evol.* **21**: 458–463.

Supporting information

Additional Supporting Information may be found in the online version of this article:

Appendix S1 Discussion of a continuously overlapping-generation version of the model.

Appendix S2 Eigenvector analysis of the nature and stability of the equilibrium.

Appendix S3 Discussion of the importance of distributions of *n*.

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