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The evolution of senescence in multi-component systems

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ABSTRACT

Actuarial senescence is characterized by an increase in mortality rate with increasing chronological age. The reliability theory of senescence proposes that organisms' vital functions can be modelled as a suite of damageable, irreplaceable elements (typically genes or their products) that protect their bearer from condition-dependent death so long as at least one of the elements remains intact. Current incarnations of the reliability theory of senescence are continuous-time models with no explicit evolutionary component. Here, we use elementary probability theory and evolutionary dynamics analysis to derive a discrete-time version of the reliability theory of senescence. We include three variations on this theme: the 'Series' model in which damage to any of n elements results in death, the 'Parallel' model, in which damage accumulates in random order and damage to all n elements results in death, and the 'Cascade' (multi-stage) model, which is like the Parallel model, except the irreparable damage necessarily follows a strict sequence. For simplicity, we refer to the state of having multiple elements as 'redundancy', but this does not imply that the elements are necessarily identical. We show that redundancy leads to actuarial senescence in the Parallel and Cascade models but not in the Series model. We further demonstrate that in the Parallel and Cascade models, lifetime reproductive output (a potential proxy for fitness in populations with discrete generations) is a positive but decelerating function of redundancy. The positive nature of the fitness function leads to the prediction that redundancy and senescence should evolve from non-redundant, non-senescing ancestral populations; however, the deceleration of the fitness function leads to the prediction that this evolution towards increased redundancy will eventually be limited by mutation-selection balance. Using evolutionary dynamics analysis involving the discrete-generation quasispecies equation, we confirm these two predictions. Finally, we show that a population's equilibrium redundancy is sensitive to the environmental conditions that prevailed during its evolution, such as the rate of extrinsic mortality.

1. Introduction

Actuarial senescence is characterized by an increase in mortality rate with increasing chronological age, reflecting general bodily deterioration (Kirkwood and Austad, 2000). Since "ageing is a deleterious trait" (Bonsall, 2006, p. 131), and extremely widespread in the tree of life, the questions of how senescence evolved, and why it has not been purged from populations, are of perennial interest to evolutionary biologists.

Early evolutionary theories of senescence (Wallace, *ca.* 1865; Weismann, 1889) were group-selectionist in nature, proposing that individuals senesce and eventually die in order to make space and resources available for future generations composed of younger, more vigorous individuals. However, such arguments are circular because, if ageing is one of the reasons why individuals must be replaced, they presuppose that individuals must deteriorate over time. Moreover, they fail to explain how a population of altruistically senescing individuals would not be subject to invasion by more slowly senescing or even non-senescing invaders. Recent studies have placed group-selectionist arguments on a stronger theoretical foundation by emphasizing instances where senescence appears to be "selected for its own sake" (Mitteldorf, 2004; Longo et al., 2005) as a result of kin- or group-level benefits including payoffs to close relatives, and reduced local extinction risk due to communicable diseases or chaotic population dynamics (Mitteldorf, 2006, 2009).

Nevertheless, individual-based theories of the evolution of senescence have come to the fore. Chief among these are the 'mutation accumulation' theory ('MA'; Medawar, 1946, 1952), and the 'antagonistic pleiotropy' theory ('AP'; Williams, 1957). These related theories argue that senescence occurs due to the deleterious late-life action of specific genes that remain unpurged in organisms' genomes because the force of selection is very weak in old

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age-classes (MA), or because they have beneficial effects earlier in life (AP; also see Charlesworth, 1994; Hamilton, 1966).

Despite the cogency of these arguments, and clear evidence for tradeoffs (e.g., Charmantier et al., 2006), the current evidence for specific genes with late-acting deleterious effects is mixed at best (Flatt and Promislow, 2007; Kirkwood, 2005; Leroi et al., 2005; Shostak, 2006). Additionally, these theories do not account for already well-established proximate mechanisms of senescence, in particular those that are linked to the buildup of somatic damage. Damaging agents include intrinsically generated metabolic byproducts, such as reactive oxygen species, and extrinsic factors, such as ultraviolet radiation, among other agents (Arking, 1998).

A third important evolutionary theory, the 'disposable soma' theory ('DS'; Kirkwood, 1977; Kirkwood and Holliday, 1979), argues that senescence arises as a consequence of organisms optimizing resource allocation when there is a tradeoff between somatic maintenance and reproduction. Encouragingly, unlike MA and AP, DS sees damage rather than actively deleterious genes as the direct source of senescence, and therefore helps to forge an important link with established proximate causes of general bodily deterioration. Moreover, the theory makes a clear distinction between damage to the germ line (inherited) and damage to the soma (not inherited). However, at its simplest, DS assumes that the structures and processes needed to maintain the soma have already evolved, so that dealing with the problem of somatic damage is mainly a matter of diverting more or fewer resources to repair. Certainly, allocation tradeoffs are likely to play a role in determining within-generation senescence patterns, but the question remains of how such tradeoffs evolved in the first place. For example, one might ask if repair were cost free, then do any other factors limit the efficiency of somatic maintenance. Of equal importance, DS also makes no provision for these maintenance structures to become damaged themselves. Finally, most variants of DS would appear to predict that increased energy input should mitigate the maintenance–reproduction tradeoff, which is at odds with important work on caloric restriction (reviewed in Mitteldorf, 2001; but see Shanley and Kirkwood, 2001).

A wholly different approach to understand the evolution of senescence is one based on reliability theory. Reliability theory is a branch of applied statistics that deals with the prediction of survivorship, failure rates, senescence, and longevity (Barlow et al., 1965), typically in machines. Gavrilov and Gavrilova (2001) have adapted reliability theory to help understand senescence in biological systems. In their theory, organisms' vital functions can be modelled as suites of parallel, redundant elements that are subject to random damage (e.g., genes or gene products). Here, 'redundancy' simply refers to the condition of having multiple elements, and does not necessarily imply that the elements are identical (although this is the convention we adopt; see below). As long as one of the elements of a vital function remains undamaged, that function is preserved and the organism lives. However, once all the elements of a vital function are damaged, that function ceases to work and the organism dies. Thus, in reliability theory, harm arises from accumulated damage to beneficial genes or gene products, rather than from late-acting actively deleterious genes as in MA and AP. In this theory senescence – that is, an increase in mortality rate with age – can occur only when a vital function has more than one element associated with it (Gavrilov and Gavrilova, 2001). Following criticisms that reliability theory was non-evolutionary (e.g., see Pletcher and Curtsinger, 1998), we have recently showed that such redundancy readily evolves from ancestral populations with no redundancy (Laird and Sherratt, 2009).

Evolutionarily based models of reliability theory have several features that recommend them over previous theories of senescence: (1) They generate mortality curves that exhibit (i) rapidly increasing mortality early in life, (ii) asymptotic mortality late in life (i.e., mortality 'plateaus'; but also see Coe et al., 2002), and (iii) 'mortality compensation', in which the mortality plateaus of populations from different environments level off at the same asymptote (Gavrilov and Gavrilova, 2001; Laird and Sherratt, 2009). (2) They envision accumulated damage to genes or gene products, rather than time-specific deleterious effects of functioning genes, as the primary driver of physiological decay and condition-dependent death (Szilard, 1959), which is more in line with established proximate causes of ageing (see above). (3) They see somatic reliability as a function of redundancy, which is a well-known feature of biological systems in general and genetic architecture in particular (Conant and Wagner, 2003; Nowak et al., 1997). And (4) evolutionary models of the reliability theory of senescence explain how these traits can evolve to a polymorphic equilibrium from a non-senescing ancestral population (Laird and Sherratt, 2009). (Note that point (4) does not imply that shorter-lived varieties evolved from longer-lived varieties, but rather that the relationship between mortality risk and age evolved from being constant to monotonically increasing.)

Previous incarnations of reliability theory have considered continuous-time models. In Gavrilov and Gavrilova's (2001) formulation [Eq. (1)] for example, a particular vital function is composed of n irreplaceable, redundant elements, each of which has a continuous failure rate of k. Their model does not explicitly treat repair or regeneration of elements. However, even mechanisms of repair and regeneration are subject to damage. It follows that there must be some rate of irreparable damage that may be somewhat less than the rate of repairable damage. The realized damage rate k can be envisioned as the former, with no loss of generality. As long as at least one of an individual's elements remains undamaged, the individual survives. When they are all damaged, the vital function stops working and the individual dies. In this particular case, the expected survivorship of a particular element is given by simple exponential decay, e^{-kt}. Therefore, the probability that the element *is* damaged by time t is simply $1 - e^{-kt}$, and the probability that all of the elements are damaged is $(1 - e^{-kt})^n$. From this, it is clear that the expected intrinsic survivorship of individuals with n elements, as a function of time is

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

This paper makes two main contributions to the development of the reliability theory of senescence:

First, we extend the approach of Gavrilov and Gavrilova (2001) and Laird and Sherratt (2009) by considering three alternative types of element/genetic architecture. Appealing to the standard analogy of an electrical circuit, Eq. (1) describes a system in which the elements are effectively in parallel. It therefore seems natural to ask what happens when elements are in series, i.e., when damage to a single element causes the vital function to fail and the individual to die. Thus, in addition to the 'Parallel' model, we also present a 'Series' model (also see Gavrilov and Gavrilova, 2001). Along with the Series and Parallel models, we consider a third type of model [a 'Cascade' model, analogous to the multi-stage model of disease progression (Armitage and Doll, 1954; Frank, 2004a,b,c)] in which irreparable damage occurs in a strict sequence. For example, one way that damage can occur in a sequence is if 'higher order' elements can be repaired by 'lower-order' elements in a cascading fashion, such that deterioration follows a strict progression of stages. Fig. 1 shows schematic diagrams for all three models. Note that the concept of 'redundancy' has a subtly different application to the Series model, as compared to the Parallel and Cascade models: in the Parallel and Cascade models, redundant elements are held 'in reserve', whereas in the Series model, they are superfluous. Although we discuss both continuous- and discrete-time versions of the three models, here we focus on the latter, which have not been described previously.

Second, we build on our earlier work that used an evolutionary dynamics approach (specifically, the quasispecies equation) to demonstrate that redundancy, and hence senescence, can evolve from non-redundant, non-senescing ancestral populations (Laird and Sherratt, 2009). Thus, we show that redundancy and senescence evolve in the Parallel and Cascade models, but not in the Series model.

2. Derivation of discrete-time senescence models, and comparison with continuous-time counterparts

2.1. Features common to all three models

We modelled three possible systems of irreplaceable elements, the Series, Parallel, and Cascade models (Fig. 1). In all three models, individuals have n elements. 'Elements' are abstractions of genes or gene products, broadly representing the checks and balances that buffer biological systems against failure and allow individual organisms to stay alive. Depending on the context they can be profitably thought of as representing, for example, multiple biochemical pathways to the same final product, stages in multi-stage cancers or other diseases, or even morphological entities such as sets of teeth. The elements are subject to damage, but the consequences of this damage, and an individual's ability to deal with it, differ among the three models.

For each individual at each time step, each element is damaged with probability d, the discrete-time analogue to the failure rate k in Gavrilov and Gavrilova's (2001) continuous-time model. In the Series and Parallel models, each element can be thought of as a copy, so it is natural to assume that all copies should have the same rate/probability of breakdown. It is somewhat less obvious why this should be true in the Cascade model, but we assumed as such for consistency, analytical tractability, and simplicity (i.e., to start with a minimum-assumption model); future work could relax this assumption for all three models. Also note that previously damaged elements can be re-damaged, but this has no additional effect on the individual since 'undamaged' and 'damaged' are the only possible states of an element.

Before proceeding with detailed descriptions of the three models, it is important to distinguish our work from an influential class of models that has arisen over the last 15 years, based on the influential 'Penna bit-string model' of senescence (see the original paper by Penna, 1995, and its intellectual progeny, e.g., Coe et al., 2002; Coe and Mao, 2003). In these models, individuals' genomes are represented by bit-strings (or continuous equivalents) in which each bit represents a particular age at which harmful deleterious mutations can arise. Thus, Penna-type models are a formalized version of traditional MA theory (Coe et al., 2002): harm arises due to actively deleterious genes with time-dependent effects. By contrast, in our model, harm arises due to accumulated damage to beneficial genes or gene products, and time-dependency is an emergent property of this damage, rather than explicitly built in.

2.2. Series model

Individuals have n elements. These elements are subject to damage, and the vital function ceases to work once any of the n elements is damaged (i.e., each element is vital, as opposed to redundant). When an element is damaged the individual dies (Fig. 1a).

We would like to know the probability l_t^{int} that an individual is still alive at time t in the absence of extrinsic mortality (i.e., the expected 'intrinsic survivorship'). (Throughout this paper, we will use $l^{\text{int}}(t)$ to denote survivorship as a continuous function of time and l_t^{int} to denote survivorship at discrete time-steps.) This is equivalent to the probability that none of the n elements has been damaged, t time steps in a row. Thus, the expected intrinsic survivorship is given by

$$l_t^{\text{int}} = (1-d)^{tn}. \tag{2}$$

The derivation of the continuous-time Series model is similarly straightforward. The expected survivorship of a particular element is given by simple exponential decay, e^{-kt}. Since all n elements must remain undamaged in order that an individual survives, the expected intrinsic survivorship is given by

$$l^{\text{int}}(t) = e^{-ktn}. \tag{3}$$

Note that Gavrilov and Gavrilova (2001) examined the similar yet distinct scenario of multiple series-connected blocks that were themselves composed of parallel elements, but not in the evolutionary context considered here.

2.3. Parallel model

Individuals have n redundant elements. These elements are subject to damage, but so long as at least one of an individual's elements is undamaged, the corresponding vital function works and the individual does not die due to bodily deterioration (Fig. 1b).

The probability that any given element is not damaged in t time steps is $(1-d)^t$. Therefore, the probability that that element *is* damaged in t time steps is $1-(1-d)^t$. The probability that all of the elements are damaged is $(1-(1-d)^t)^n$, and hence, the probability that at least one of the elements remains undamaged is equal to the expected intrinsic survivorship and is given by

$$l_t^{\text{int}} = 1-(1-(1-d)^t)^n. \tag{4}$$

As shown by Gavrilov and Gavrilova (2001), and as derived in Section 1, in continuous time, intrinsic survivorship is given by Eq. (1).

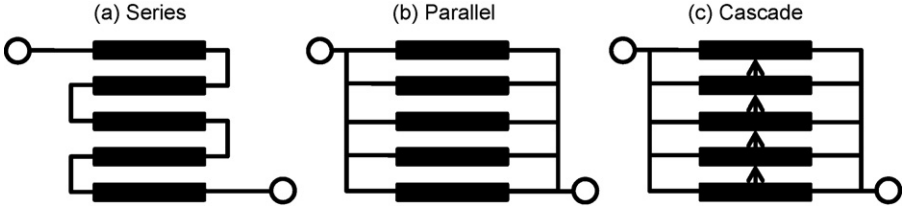

Fig. 1. Schematic representation of the three models. Irreplaceable elements are indicated by the black rectangles (here, $n=5$ elements). In the discrete-time models, the elements are subject to random damage at a probability of d per time step. This damage breaks the path on which the element is situated. So long as there is at least one continuous path between the circles, the vital function continues to work and the individual survives. (a) In the Series model, the individual dies as soon as one element is damaged. (b) In the Parallel model, the individual survives until all the elements are damaged. (c) The Cascade model is like the Parallel model, with one additional wrinkle: accumulated damage must proceed in order from the lowest to the highest element, with the direction of damage indicated by arrows. One reason why a strict damage sequence may arise is that higher-order elements are repaired by lower-order elements (so long as they themselves are not damaged). Alternatively, the Cascade model can be considered a multi-stage model, with a series of checks and balances preventing disease progression, as envisioned by Frank (2004a,b,c) and drawing on the classic model of Armitage and Doll (1954).

2.4. Cascade model

As with the Parallel model, the elements are subject to damage, and a single undamaged element is sufficient to prevent death due to bodily deterioration. However, in contrast to the Parallel model in which the elements work redundantly, here they work redundantly *and* sequentially (Fig. 1c): Element 2 cannot get damaged without prior damage to Element 1 (Element 1 being the start of the linear sequence), Element 3 cannot get damaged without prior damage to Element 2, and so on. This means that Element i can only get damaged if $i = 1$, or if $i > 1$ and all elements $1, \ldots, i-1$ have already been permanently damaged (or are currently in the process of becoming permanently damaged within the same time step). Thus, elements are permanently damaged in a cascading fashion. Such a situation could arise if, for example, Element 1 repairs Element 2, Element 2 repairs Element 3, and so on (nothing repairs Element 1 and Element n repairs no other element). In this interpretation, we must assume that the time scale of repair is much shorter that the time scale of deterioration, such that if Element n is damaged, it can be repaired by Element $n-1$ (if it is still functioning) sufficiently quickly to prevent death. Alternatively, the Cascade model can be considered as an analogue of the 'multi-stage model' of disease progression where individuals must pass through particular disease stages before eventually succumbing to the disease when they reach stage n (see below).

Let E_1 represent the event that after t time steps Element 1 remains undamaged, E_2 represent the event that Element 2 remains undamaged, and, generically, E_i represent the event that Element i remains undamaged, where i is an integer between 1 and n. The probability that Element 1 is not damaged in t time steps is

$$\mathbb{P}(E_1) = (1-d)^t. \tag{5}$$

The probability that Element 2 is not damaged in t time steps is equal to the probability Element 1 is not damaged in t time steps plus the probability that Element 1 *is* damaged at some time t_1, yet Element 2 is not damaged between t_1 and t, inclusive. Because t_1 can be any time step between 1 and t, this means that

$$\mathbb{P}(E_2) = \mathbb{P}(E_1) + \sum_{t_1=1}^{t} (1-d)^{t_1-1} d (1-d)^{t-t_1+1} = \mathbb{P}(E_1) + td(1-d)^t. \tag{6}$$

In general, for $i > 1$ the probability that Element i is not damaged in t time steps is equal to the probability that Element $i-1$ is not damaged in t time steps plus the probability that Elements 1 through $i-1$ *are* damaged in that interval, yet Element i is not damaged at the same time as Element $i-1$ or thereafter [for $i = 1$, the probability that Element i is not damaged in t time steps is simply given by Eq. (5)]. While there are t ways that exactly one element can be damaged in t time steps [Eq. (6)], the number of ways that exactly $i-1$ elements can be damaged in t time steps is $\binom{i+t-2}{i-1}$. (This is a classic 'M marbles in B boxes' combinatorics problem where the M marbles are analogous to the $i-1$ damaged elements and the B boxes are analogous to the t time steps.) The probability of each of the ways that exactly $i-1$ elements can be damaged is $d^{i-1}(1-d)^t$. Thus, the probability that Element i is not damaged in t time steps is given by the recursion equation:

$$\mathbb{P}(E_i) = \mathbb{P}(E_{i-1}) + \binom{i+t-2}{i-1} d^{i-1}(1-d)^t, \tag{7}$$

where $\mathbb{P}(E_0)$ is defined as 0, and keeping in mind that $\binom{-1}{0} = 1$, and $\binom{w}{v} = 0$ if $w < v$ and both w and v are non-negative integers.

If Element n is permanently damaged, this means that all the elements must be damaged, and the individual dies. Similarly, if Element n is not damaged, then by definition not all the elements are damaged, and the individual does not die due to bodily deterioration. Thus, the expected intrinsic survivorship in the Cascade model is equal to the probability that Element n is not damaged at time t and is given by the recursion equation

$$l_t^{\text{int}} = \mathbb{P}(E_n) = \mathbb{P}(E_{n-1}) + \binom{n+t-2}{n-1} d^{n-1}(1-d)^t, \tag{8}$$

which can be expressed non-recursively as

$$l_t^{\text{int}} = \sum_{i=1}^{n} \binom{i+t-2}{i-1} d^{i-1}(1-d)^t = (1-d)^t \sum_{i=1}^{n} \binom{i+t-2}{i-1} d^{i-1}. \tag{9}$$

The continuous-time Cascade model's survivorship equation can be found by noting the similarity of the Cascade model to the multi-stage model of disease progression (Armitage and Doll, 1954; Frank, 2004a,b,c). In this model, individuals start in stage 0, and must pass through multiple successive stages $1, \ldots, n-1$ before dying when they reach stage n. Frank (2004a) modelled this process as a system of differential equations:

$$\begin{aligned} \frac{dx_0}{dt} &= -u_0(t)x_0(t) - d_0(t)x_0(t), \\ \frac{dx_i}{dt} &= u_{i-1}(t)x_{i-1}(t) - u_i(t)x_i(t) - d_i(t)x_i(t), \\ \frac{dx_n}{dt} &= u_{n-1}(t)x_{n-1}(t), \end{aligned} \tag{10}$$

where i is an integer between 1 and $n-1$, $x_j(t)$ is the proportion of individuals in stage j at time t, $u_j(t)$ is the rate at which individuals advance one stage, and $d_j(t)$ is the 'extrinsic' death rate from other causes for individuals in stage j [note that in Eq. (10), the symbol d is used in a different context than in our discrete-time models]. By setting all $u_j(t)$ to the constant continuous failure rate of k, and setting all $d_j(t) = 0$ (since we would like to know the *intrinsic* survivorship), we are left with a continuous version of the Cascade model:

$$\begin{aligned} \frac{dx_0}{dt} &= -kx_0(t), \\ \frac{dx_i}{dt} &= kx_{i-1}(t) - kx_i(t), \\ \frac{dx_n}{dt} &= kx_{n-1}(t). \end{aligned} \tag{11}$$

Following Frank (2004a), the general solution for this model is the Poisson relationship $x_i(t) = e^{-kt}(kt)^i/i!$ for $i = 0, \ldots, n-1$, and the initial condition that $x_0(0) = 1$ and $x_i(0) = 0$ for $i > 0$. Because individuals survive as long as they are in stage $n-1$ or lower, intrinsic survivorship for the continuous-time cascade model is given by

$$l^{\text{int}}(t) = \sum_{i=0}^{n-1} \frac{e^{-kt}(kt)^i}{i!} = e^{-kt} \sum_{i=0}^{n-1} \frac{(kt)^i}{i!} \tag{12}$$

Table 1 provides a summary of the discrete- and continuous-time survivorship equations for the Series, Parallel, and Cascade models.

Table 1
Summary of intrinsic survivorship equations for continuous- and discrete-time versions of the Series, Parallel and Cascade models. $l^{\text{int}}(t)$ and l_t^{int} represent expected intrinsic survivorship as a function of time, t, in the continuous- and discrete-time models, respectively. n represents the number of elements that compose the vital function. k and d represent the continuous damage rate and the discrete damage probability, respectively. Note that for the continuous-time Cascade model, the limits on the index i have been changed from how they appear in Eq. (12) to match the corresponding discrete-time model.

Model type	Continuous time	Discrete time
Series	$l_{\text{int}}(t) = e^{-ktn}$	$l_t^{\text{int}} = (1-d)^{tn}$
Parallel	$l^{\text{int}}(t) = 1-(1-e^{-kt})^n$	$l_t^{\text{int}} = 1-(1-(1-d)^t)^n$
Cascade	$l^{\text{int}}(t) = e^{-kt}\sum_{i=1}^{n}\frac{(kt)^{i-1}}{(i-1)!}$	$l_t^{\text{int}} = (1-d)^t\sum_{i=1}^{n}\binom{i+t-2}{i-1}d^{i-1}$

2.5. Calculating survivorship, mortality, longevity, and lifetime reproductive output in discrete-time models

Intrinsic survivorship l_t^{int} represents the mean survivorship to age t, provided that there are no extrinsic sources of mortality. This allowed us to double check the outputs of Eqs. (2), (4), and (9) by comparing predicted survivorship curves with the mean survivorship curves derived from 100 computer-simulated cohorts of 100 individuals. For each of the three models, we examined four levels of n (n = 1, 5, 10, and 50). In all twelve cases, the simulations and the corresponding analytical solutions were congruent (see Appendix A in the supplementary material).

The intrinsic mortality probability as a function of age is

$$q_t^{\text{int}} = \frac{(l_t^{\text{int}} - l_{t+1}^{\text{int}})}{(l_t^{\text{int}})}. \tag{13}$$

For a constant extrinsic mortality probability of q^{ext}, and assuming that extrinsic and intrinsic mortality are independent, the overall mortality probability at age t is

$$q_t = q^{\text{ext}} + q_t^{\text{int}} - q^{\text{ext}}q_t^{\text{int}}, \tag{14}$$

and the overall survivorship at age t is

$$l_t = l_t^{\text{int}}(1-q^{\text{ext}})^t. \tag{15}$$

Under this overall age-dependent mortality and survivorship, the mean longevity is

$$\varphi = \sum_{t=1}^{\infty} tq_t\prod_{u=0}^{t-1}(1-q_u) = \sum_{t=1}^{\infty} l_t, \tag{16}$$

which can be calculated to an arbitrary level of precision using either mortality or survivorship data.

Lifetime reproductive output is given by the equation:

$$R = \sum_{t=1}^{\infty} l_t b_t, \tag{17}$$

where b_t is the birthrate at age t (Williams and Day, 2003). For model-exploration purposes it is useful to assume a constant age- and condition-independent birthrate of b (Laird and Sherratt, 2009). In this case, therefore, $R = b\varphi$. Of course, in real biological systems birthrates are not constant, but treating them as such avoids having senescence automatically built into the model.

3. Patterns of intrinsic survivorship and mortality in discrete-time models

In the Series model, redundancy decreases intrinsic survivorship (Fig. 2a) and increases intrinsic mortality (Fig. 3a) as a consequence

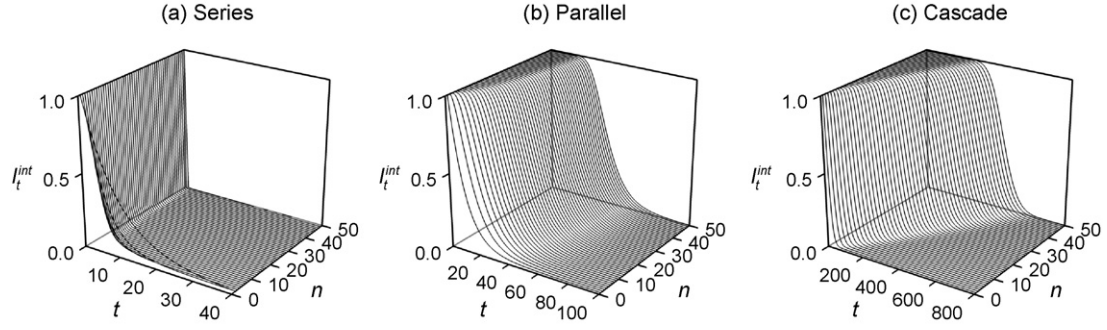

Fig. 2. Expected intrinsic survivorship (l_t^{int}) as a function of age (t; discrete-time) and redundancy (n) under an extrinsic mortality rate of $q^{\text{ext}} = 0$ and a damage rate of $d = 0.1$. (a) Series model, (b) Parallel model, (c) Cascade model. Survivorship curves represent analytical solutions based on Eqs. (2), (4), and (9), for panels (a), (b), and (c), respectively.

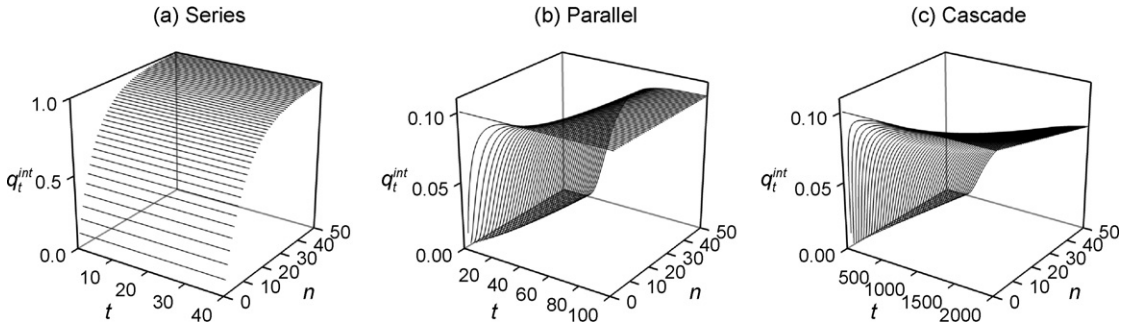

Fig. 3. Expected intrinsic mortality (q_t^{int}) as a function of age (t; discrete-time) and redundancy (n) under an extrinsic mortality rate of $q^{ext} = 0$ and a damage rate of $d = 0.1$. (a) Series model, (b) Parallel model, (c) Cascade model. Mortality curves represent analytical solutions based on Eq. (13). Note that the t-axis in panel (c) extends further than the corresponding t-axis in Fig. 2c. This was done to show more of the approach to the mortality plateau. Actuarial senescence occurs in the Parallel and Cascade models, but not in the Series model.

of more links in the chain. Senescence does not occur for any level of redundancy; rather mortality rates remain constant at all ages (Fig. 3a).

In contrast, in the Parallel and Cascade models, redundancy increases intrinsic survivorship (Fig. 2b,c) and decreases intrinsic mortality (Fig. 3b,c). In these two models, senescence occurs in cases where $n > 1$, i.e., when redundancy exists (Fig. 3b,c), and the shape of the mortality curves resembles real curves in that risk rapidly increases early in life before reaching a 'plateau' late in life. The height of the plateau is determined solely by – and is equal to – the damage rate d, the probability of the last element failing after all the others have already failed (Gavrilov and Gavrilova, 2001). This means that populations that evolved under different levels of extrinsic mortality (but similar levels of damage) will undergo a convergence in their mortality rates late in life ('mortality compensation'; Gavrilov and Gavrilova, 1991). Thus, along with the plateau itself, the reliability theory of senescence readily generates aspects of late-life mortality that are difficult to explain with other (non-reliability-based) evolutionary theories of senescence (Demetrius, 2001; Pletcher and Curtsinger, 1998; Wachter, 1999).

4. Relationship between redundancy and lifetime reproductive output

In the Series model, redundancy reduces lifetime reproductive output (Fig. 4a). Thus, insofar as lifetime reproductive output can be taken as a proxy for fitness [e.g., in the case of discrete generations, assuming that there are sufficiently many time steps per generation (τ) that $l_\tau \approx 0$], there is strong selection to reduce the number of elements in series-connected systems. In reality, however, organisms have multiple vital functions, all of which must be functioning in order for the individual to survive. Therefore, while one might expect natural selection to reduce the number of elements in series within a particular vital function, one should not expect natural selection to eliminate series-connected elements altogether, especially across multiple vital functions.

In the Parallel and Cascade models, redundancy increases lifetime reproductive output (Fig. 4b,c). Thus, natural selection should result in an increased number of parallel and cascading elements in vital functions (once again insofar as R represents fitness). However, this directional selection cannot operate indefinitely for three reasons. The first reason is that increased redundancy might come at a metabolic and ultimately reproductive cost (Frank, 2008), leading to an optimization of redundancy (i.e., as in the DS model). The second reason is that there may be a negative relationship over evolutionary time between element quantity and quality ('the paradox of robustness'; Frank, 2004b, 2007). The third reason is the one we examine here, and is related to the fact that the increase in lifetime reproductive success decelerates at high redundancy (with the exception of the Cascade model in the case of zero extrinsic mortality; Fig. 4c). Under the reasonable assumption of biased mutation rates, wherein the probability that offspring have fewer elements than their parents exceeds the probability that offspring have more elements than their parents (i.e., deleterious mutations are more common than beneficial ones; Eyre-Walker and Keightley, 2007), decelerating directional selection for redundancy should eventually face a mutation-selection balance. Previously, we have demonstrated this for the continuous-time version of the Parallel model (Laird and Sherratt, 2009). In the next section, we explore the evolution of redundancy in the discrete-time versions of the Series, Parallel, and Cascade models.

Unsurprisingly, in all three models, increased extrinsic mortality decreases lifetime reproductive output (Fig. 4), and also decreases the benefit of having fewer elements in the Series model, or more elements in the Parallel and Cascade models.

5. The (limited) evolution of redundancy and its consequences

Here we assumed that the number of elements n was heritable, and for simplicity we viewed this redundancy trait as if it were controlled by a single gene. We modelled the evolution of redundancy using the discrete-generation quasispecies equation, which tracks the relative abundance of N genotypes (corresponding to different levels of n) through evolutionary time (see Nowak (2006) for an in-depth explanation of the quasispecies equation with continuously overlapping generations). The discrete-generation quasispecies equation is a system of recursion equations given by

$$x_i' = \frac{\sum_{j=1}^{N} x_j f_j \mu_{ij}}{\sum_{h=1}^{N}\sum_{j=1}^{N} x_j f_j \mu_{hj}}, \qquad i = 1, \ldots, N, \tag{18}$$

where x_j is the relative abundance of genotype j in the current generation, f_j is the fitness (reproductive success) of genotype j, and μ_{ij} is the transition probability from genotype j to genotype i (i.e., the mutation rate when $j \neq i$). Using lifetime reproductive output (R) as a proxy for fitness, as is appropriate for a discrete-generation analysis, the numerator of Eq. (18) is the number of genotype i offspring produced per individual in the current generation and the denominator is the total number of offspring produced per individual in the current generation. Therefore, the quotient x_i' is the relative abundance of genotype i in the next generation. For the transition rate, we assumed that mutations could only increase n by one (at a rate of $\mu_{ij} = \alpha$ when $i = j + 1$) or decrease n by one (at a rate $\mu_{ij} = \beta$ when $i = j - 1$; $\alpha + \beta < 1$). For example, the transition

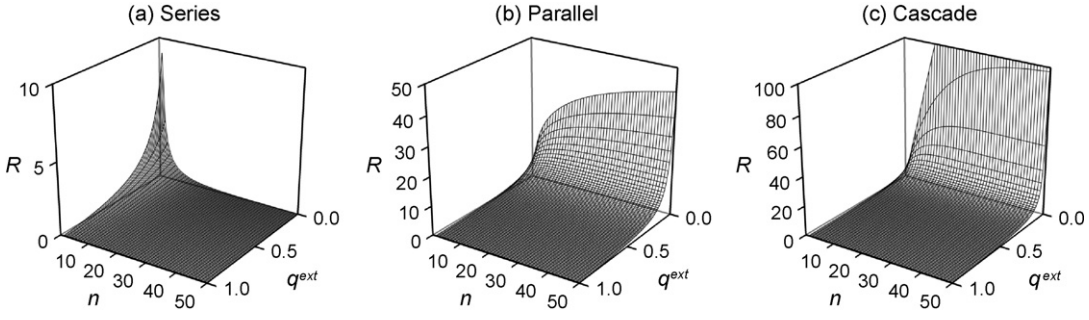

Fig. 4. Expected lifetime reproductive output (R) in the discrete-time models as a function of redundancy (n) and extrinsic mortality (q^{ext}), under a damage rate of $d = 0.1$, and a constant birth rate of $b = 1$ (hence, R is directly proportional to mean longevity). (a) Series model, (b) Parallel model, (c) Cascade model. Surfaces are based on Eq. (17). Lifetime reproductive output increases linearly with n only in the Cascade model, and only if $q^{ext} = 0$; otherwise it decelerates (and even decreases in the Series model).

probability matrix for $N = 5$ is

$$\mu = [\mu_{ij}] = \text{“Offspring}\,(i)\text{”} \quad \begin{matrix} \\ \alpha \\ \alpha \\ 0 \\ 0 \\ 0 \end{matrix} \begin{matrix} \text{“Parent}\,(j)\text{”} \\ 1-\alpha & \beta & 0 & 0 & 0 \\ \alpha & 1-\alpha-\beta & \beta & 0 & 0 \\ 0 & \alpha & 1-\alpha-\beta & \beta & 0 \\ 0 & 0 & \alpha & 1-\alpha-\beta & \beta \\ 0 & 0 & 0 & \alpha & 1-\beta \end{matrix} \tag{19}$$

Reflecting the fact that deleterious mutations are more common than beneficial ones (Eyre-Walker and Keightley, 2007), we further assumed that $\beta > \alpha$.

Multi-gene (as opposed to single-gene) control of vital functions is another possibility, and is perhaps particularly relevant for the Cascade model. However, with multi-gene control, the μ matrix becomes extremely large because there are many more possible genotypes (2^N instead of N). For instance when $N = 50$, the μ matrix has $(2^{50})^2 > 10^{30}$ entries—far too large for the models to be analytically tractable. Therefore, we opted to stay with single-gene control, which we argue below would make only small, quantitative differences to our results. See Frank (2004b) for a computer simulation (i.e., non-analytical approach) in which stages, and transitions between stages, are mediated by separate genes.

Fig. 5 (top row) and Appendix B in the supplementary material show 30,000 generations of discrete-generation quasispecies evolution for the discrete-time Series, Parallel, and Cascade models for example parameter values of $d = 0.01$, $b = 1$, $q^{\text{ext}} = 0.02$, $\alpha = 0.001$, and $\beta = 0.01$. As many as $N = 50$ elements were *allowed* to evolve [N must be specified to allow the application Eq. (18)]; however, this was greater than the number of elements that actually *did* evolve. This represents conditions under which the evolved distribution of n was independent of N, and was the motivation behind the parameter values chosen for these examples.

In all three cases, at generation 0 every individual had $n = 1$ element (i.e., no redundancy). In the Series model, there was negligible deviation from the starting conditions over evolutionary time (stable mean $n = 1.004$; Fig. 5a). This reflects the fact that for the Series model, individuals with only one element have the greatest lifetime reproductive output (Fig. 4a), and confirms our prediction that selection should favour a reduction (or at least resist an increase) in the number of series-connected elements.

On the other hand, in the Parallel and Cascade models, the average number of elements increased over evolutionary time before settling on stable values (approximately 18 and 6 elements, respectively, in Fig. 5b,c). This reflects the facts that lifetime reproductive output increases with n in the Parallel and Cascade models, but that this relationship is a decelerating one (Fig. 4b,c). Hence, these results confirm our prediction that selection should favour an increase in the number of parallel- or cascade-connected elements, but only until a mutation-selection balance is reached. Nunney (1999, 2003) used an altogether different analysis to reach a similar conclusion about the number

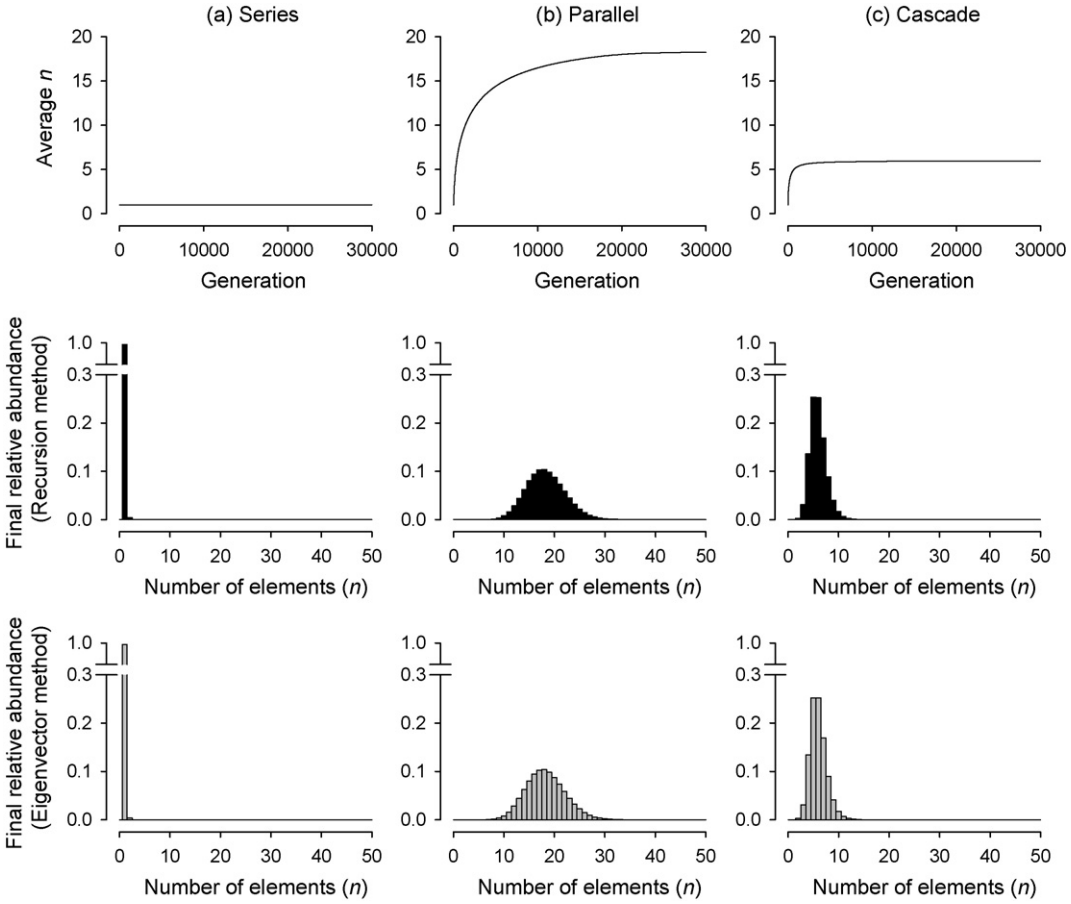

Fig. 5. Top row: example of discrete-generation quasispecies evolution for the discrete-time version of the (a) Series, (b) Parallel, and (c) Cascade models. The panels show the evolutionary trajectory of the average number of elements (n) over 30,000 generations. The damage rate was $d = 0.01$, the birth rate was $b = 1$, the extrinsic mortality rate was $q^{\text{ext}} = 0.02$, and the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively. At the start, every individual had $n = 1$ element. See Appendix B in the supplementary material for the evolutionary trajectories of the relative abundances of the 50 individual genotypes for the same model conditions shown here. Middle row: the corresponding stable relative abundance distributions of the 50 genotypes (corresponding to 1–50 elements; black bars) after 30,000 recursions of Eq. (18). Bottom row: the corresponding stable relative abundance distributions of the fifty genotypes (grey bars) as determined by eigenvector analysis.

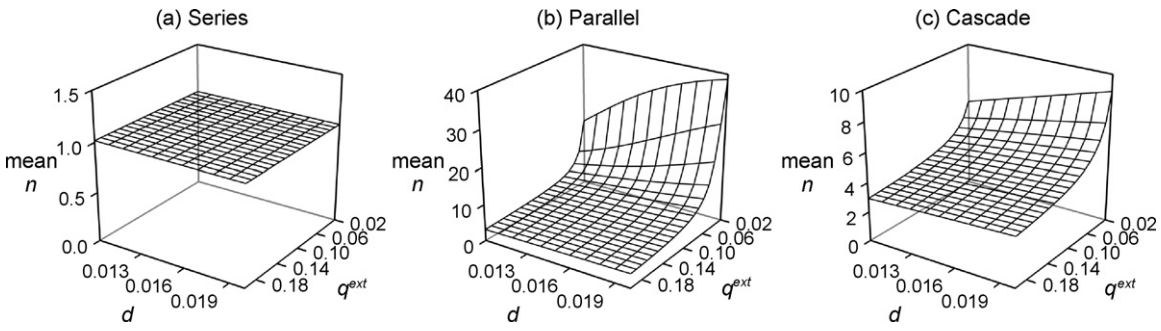

Fig. 6. The equilibrium mean number of elements (mean n, as calculated by eigenvector analysis) for various combinations of damage rate (d) and extrinsic mortality (q^{ext}) for the discrete-time version of the (a) Series, (b) Parallel, and (c) Cascade models. In all cases, the birth rate was $b = 1$, the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively, and at the start, every individual had $n = 1$ element.

of tumour-suppressor loci that should evolve for multi-stage cancers.

We have showed that for certain types of element architecture, redundancy – and, following from Section 3, senescence – can evolve from non-redundant, non-senescing ancestral populations. (Again we stress that this does not mean that longevity decreased over evolutionary time; indeed the opposite was true in the Parallel and Cascade models.) Moreover, *distributions* of n (*middle row*, Fig. 5b,c), which can occur due to a high incidence of initial defects, or which, as described here, can be maintained at the population level via mutation-selection balance, may lead to more biologically realistic population mortality curves compared to monocultures (Gavrilov and Gavrilova, 2001; Laird and Sherratt, 2009). In this example quasispecies analysis, the mean number of elements that evolved in the Parallel model was roughly three times the number that evolved in the Cascade model (compare Fig. 5b,c). Given equal parameter values, fewer elements evolve in the Cascade model because, with the necessary ordering, it takes far longer before all elements are damaged.

Importantly, the distributions of n that emerge from the discrete quasispecies analysis are formal mathematical equilibria, and they are stable. To see why this is so, consider a modified version of Eq. (18) that operates on absolute abundances (a_i) rather than relative abundances (x_i):

$$a_i' = \sum_{j=1}^{N} a_j f_j \mu_{ij}, \qquad i = 1, \ldots, n. \tag{20}$$

This can be converted into matrix form:

$$\vec{a'} = M\vec{a}, \tag{21}$$

where $\vec{a_i} = [a_i']$ and $\vec{a} = [a_i]$ are column vectors representing the abundances of each genotype i in the next and current generation, respectively, and $M = [f_j \mu_{ij}]$ is the transition matrix incorporating fitness and mutation. Because this is a linear model, the long-term relative abundances of its variables are stable, even though the absolute abundances typically are not (Nowak, 2006; Otto and Day, 2006). Additionally, this stable equilibrium relative abundance distribution is given by the leading eigenvector of M, whose length is scaled so that its elements sum to one (Nowak, 2006; Otto and Day, 2006). Indeed, eigenvector analysis gave the same long-term relative abundance distribution of genotypes as 30,000 generations of discrete quasispecies evolution (e.g., compare Fig. 5, middle and bottom rows).

Naturally, precisely how much redundancy evolves depends on the parameter values chosen. Fig. 6 shows the equilibrium mean number of elements that evolve for various combinations of damage rate and extrinsic mortality (d: [0.01, 0.02]; q^{ext}: [0.02, 0.2]; other parameter values: $b = 1$, $\alpha = 0.001$ and $\beta = 0.01$). In the Series model, d and q^{ext} have very little effect on the mean n that evolves; mean n was always approximately 1 (Fig. 6a). Regardless of the environmental conditions, redundancy is so deleterious in the Series model that it effectively never evolves.

In contrast, in the Parallel and Cascade models, d has a positive effect and q^{ext} has a negative effect on the evolved mean redundancy (Fig. 6b,c). The explanations for both of these results are closely linked. Damage rate has a positive effect on the evolution of redundancy because as damage rate increases, individuals are more likely to require "backup" elements within their expected lifespan as partially determined by the extrinsic mortality rate. Similarly, extrinsic mortality has a negative effect on the evolution of redundancy because as extrinsic mortality increases, individuals require fewer backups because they will probably not live long enough to use very many of them. Thus, we predict natural selection to mold redundancy, and by extension senescence, to the environmental conditions experienced by an evolving population.

Note that in Fig. 6, the maximum value of d and the minimum value of q^{ext} were chosen to ensure that the maximum number of elements that were allowed to evolve (50) had a minimal influence on mean n (e.g., in the Parallel model, when $d = 0.02$ and $q^{ext} = 0.02$, mean n at equilibrium was the highest of any of the conditions examined at 38.7; however, the relative abundance of individuals with $n = N = 50$ elements was only 0.000243). Greater values of d or smaller values of q^{ext} simply lead to a greater mean equilibrium number of elements in the Parallel and Cascade models; our qualitative results still hold. Note also that the equilibrium mean n was the same whether it was calculated after applying 30,000 recursions of the discrete quasispecies equation [Eq. (18)] or by eigenvector analysis (see Appendix C in the supplementary material).

Would the results be qualitatively different if we used multi-gene versus single-gene control? We argue no. Given low and downwardly biased mutation rates, the probability of offspring with increased redundancy relative to their parents would decline very slightly with increasing n, and the probability of offspring with decreased redundancy would increase very slightly with increasing n, because there are more opportunities for damage to occur at higher n in multi-gene versus single-gene control. Thus, quantitatively, the mutation-selection balance would be shifted slightly to the left. But qualitatively, there would still be a non-trivial equilibrium solution, and there would still be the evolution of redundancy and senescence from non-redundant, non-senescing populations, at least in the Parallel and Cascade models.

The differences in average n mean that even when populations that evolved under different d and q^{ext} are brought into captivity and relieved of extrinsic mortality (i.e., q^{ext} is set to 0, but d stays the same), they still exhibit differences in mean longevity (Fig. 7). In the Series model, there is essentially no variation in average n for different values of d and q^{ext} – all parameter combinations lead to the evolution of no redundancy (Fig. 6a). Therefore, when populations

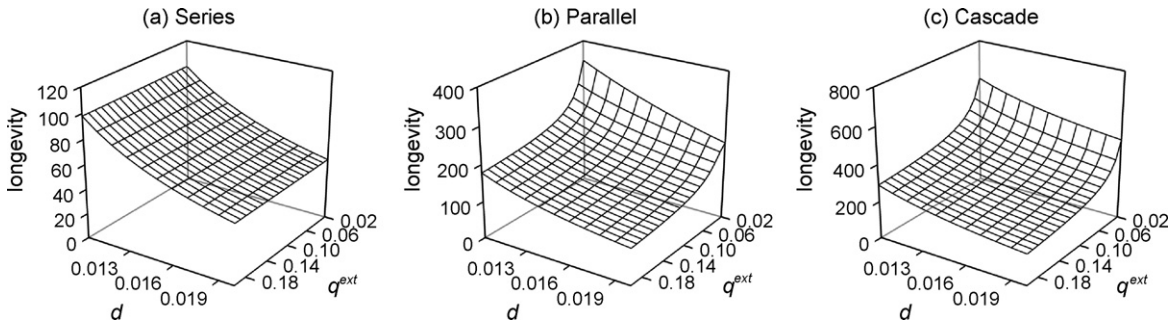

Fig. 7. The mean longevity in captivity (i.e., $q^{ext} = 0$) for mixed-n equilibrium populations (as calculated by eigenvector analysis) for various combinations of damage rate (d) and extrinsic mortality (q^{ext}) for the discrete-time version of the (a) Series, (b) Parallel, and (c) Cascade models. In all cases, the birth rate was $b = 1$, the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively, and at the start, every individual had $n = 1$ element.

whose individuals have series-connected elements are brought into captivity, there is no effect of q^{ext} on mean longevity (Fig. 7a). Conversely, there is a negative effect of damage on mean longevity in captivity in the Series model (Fig. 7a). However, this is simply a direct effect of damage – when essentially all individuals have one and only one element, those whose elements are damaged more readily are likely to die sooner.

Unlike in the Series model, in the Parallel and Cascade models there is a negative effect of extrinsic mortality on the evolved mean n (Fig. 6b,c). Thus, when populations whose individuals have parallel- or cascade-connected elements are brought into captivity, those that originally evolved under relatively high extrinsic mortality have a shorter mean longevity than those that originally evolved under relatively low extrinsic mortality (Fig. 7b,c).

The effect of damage rate on mean longevity in captivity is also more subtle in the Parallel and Cascade models. As with the Series model, in the Parallel and Cascade models there is a negative effect of damage rate on mean longevity in captivity (Fig. 7b,c). But, unlike in the Series model, the direct action of damage is only a partial explanation. After all, populations have the potential to 'compensate' for increased damage rates by evolving extra elements (Fig. 6b,c). However, because the position of the mutation-selection balance with respect to n in high- versus low-damage populations, such compensation does not fully occur; rather, individuals in populations that evolved under high-d conditions live shorter than individuals that evolved under low-d conditions, even after long-term, cost-free selection to ameliorate the damage (Fig. 7b,c). For further discussion of the environmental dependence of the evolution of senescence and longevity see, for example, Abrams (1993), Carlson et al. (2007), Keller and Genoud (1997), Reznick et al. (2004), Stearns et al. (2000), Williams and Day (2003).

6. Conclusion

Reliability theory is a powerful approach for understanding the evolution of senescence. In this approach, various elements accumulate damage, ultimately resulting in their bearer's death. Here, we derived three discrete-time models, one in which the elements of a vital function are in series, one in which they are in parallel, and one in which they become damaged in a cascading fashion. We showed that redundancy leads to senescence in the Parallel and Cascade models, but not in the Series model. Further, in the Parallel and Cascade models, lifetime reproductive output is related to redundancy in a positive but decelerating fashion, a situation that leads to a mutation-selection balance and the evolution of a stable equilibrium population distribution of redundancy. The arrangements of elements in the Parallel and Cascade models are simplified to be sure; however, in a general sense, they represent the way collections of checks and balances maintain life in real systems. Thus, broadly, senescence may arise because the systems that have evolved to allow robust physiological functioning ultimately get damaged, and there is little selection to do anything to improve their reliability beyond a certain point. In this manner, harm arises from the inactivity of elements (genes or their products) that accumulate damage over time and ultimately fail to do the organism good, rather than as a consequence of late-acting actively deleterious genes.

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Appendices A–C. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.biosystems.2009.10.008.

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Appendix A. Comparison of analytical and simulated survivorship curves

The evolution of senescence in multi-component systems

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Survivorship curves derived from the analytical solutions are the same as the curves generated by following the survivorship of simulated cohorts (Fig. A.1).

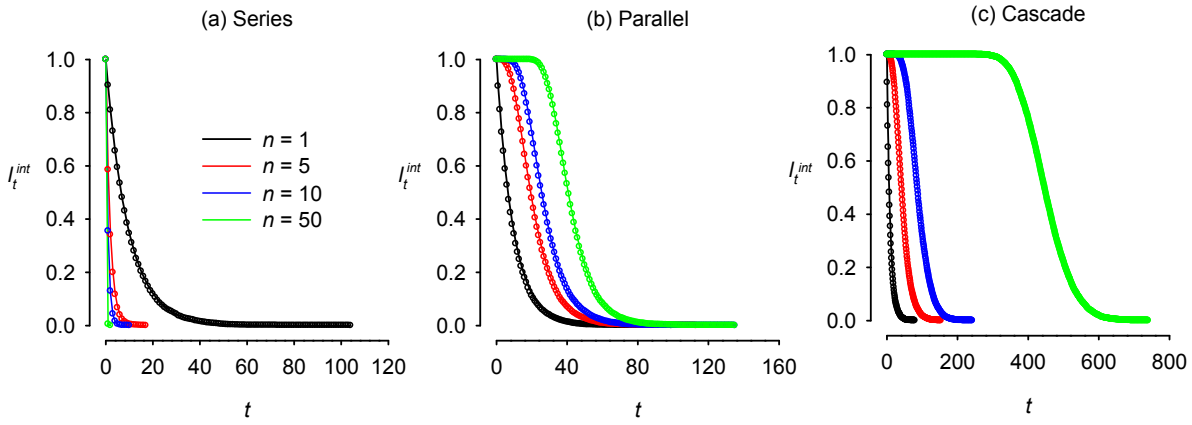

Fig. A.1. Intrinsic survivorship curves (l_t^{int} versus t) for monoculture populations with four different levels of redundancy (black, n = 1; red, n = 5; blue, n = 10; green, n = 50), under an extrinsic mortality rate of q^{ext} = 0 and a damage rate of d = 0.1. Lines represent analytical solutions based on Eqs. (2), (4), and (9), for panels (a), (b), and (c), respectively (i.e., the Series, Parallel, and Cascade models). Circles represent the mean survivorship curves derived from 100 simulated cohorts of 100 individuals (maximum t for each line is the age-at-death of the longest-lived of 10,000 individuals in each simulation). There was a good fit between the analytical solutions and the numerical simulations (all $r > 0.9999$).

Appendix B. Discrete-generation quasispecies evolution of genotype relative abundance

The evolution of senescence in multi-component systems

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Figures B.1, B.2, and B.3 show examples of the discrete-generation quasispecies evolution for the Series, Parallel, and Cascade models, respectively.

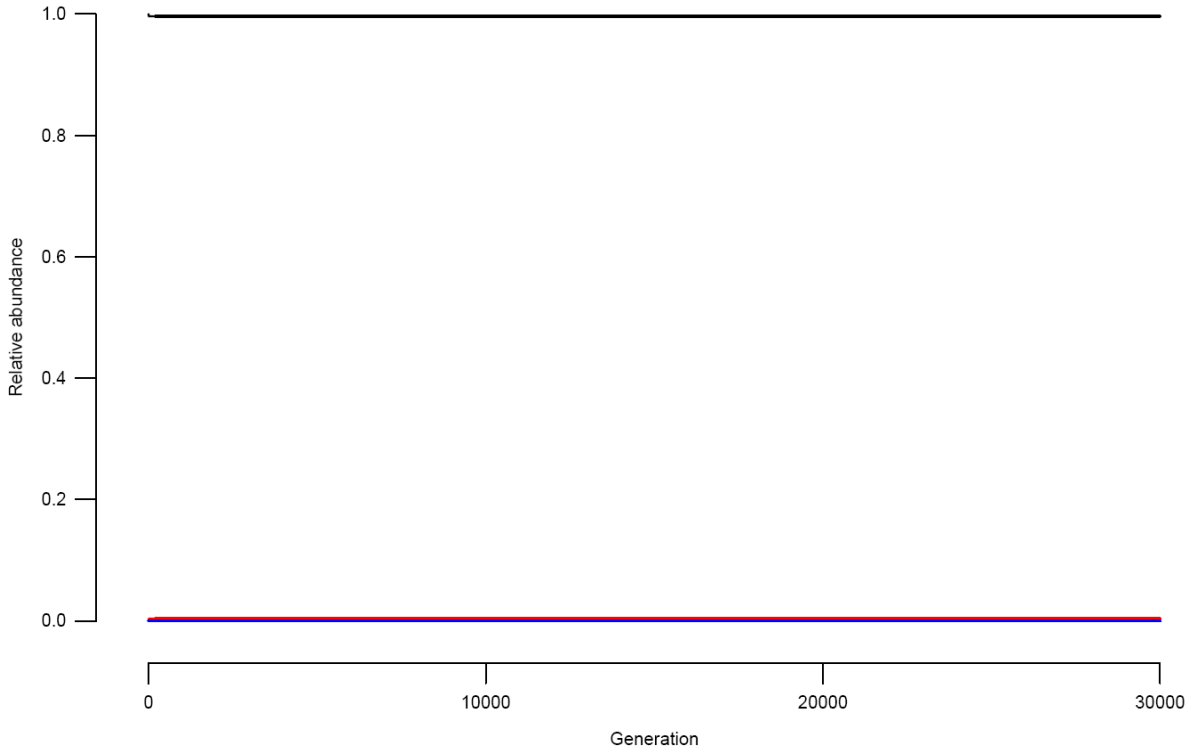
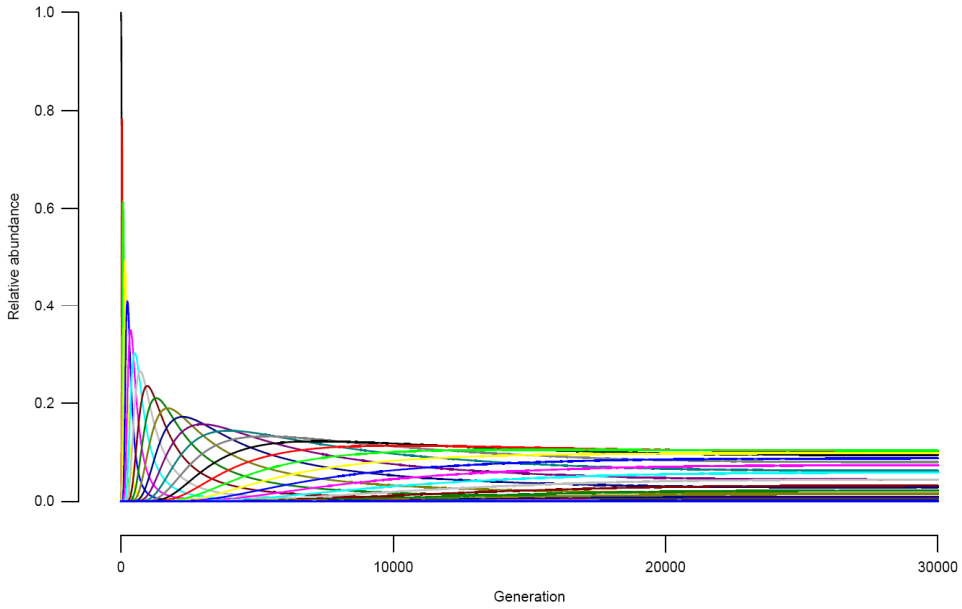


Fig. B.1. Example of discrete-generation quasispecies evolution for the discrete-time version of the Series model. The figure shows the evolutionary trajectories of the relative abundances of 50 genotypes (colours, corresponding to individuals with $n = 1$ to 50 series elements) over 30,000 generations. The damage rate was $d = 0.01$, the birth rate was $b = 1$, the extrinsic mortality rate was $q^{ext} = 0.02$, and the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively. At the start, every individual had $n = 1$ element and very little changed over 30,000 generations: the line with a relative abundance close to 1 represents the $n = 1$ genotype; all other lines (genotypes) overlapped with relative abundances close to 0. The stable equilibrium distribution of genotypes is shown in the bottom panel of Fig. 5a in the main text.

(a)



(b)

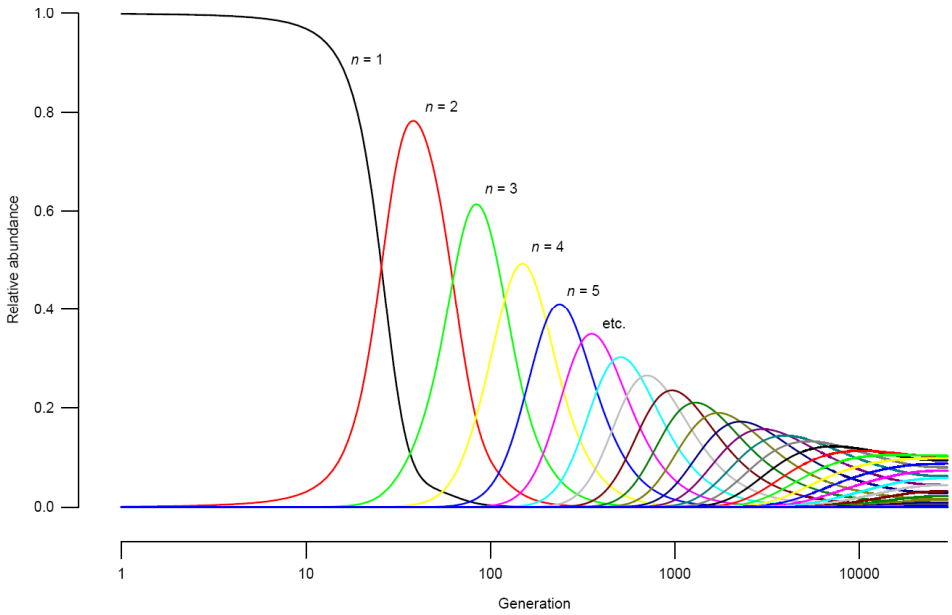
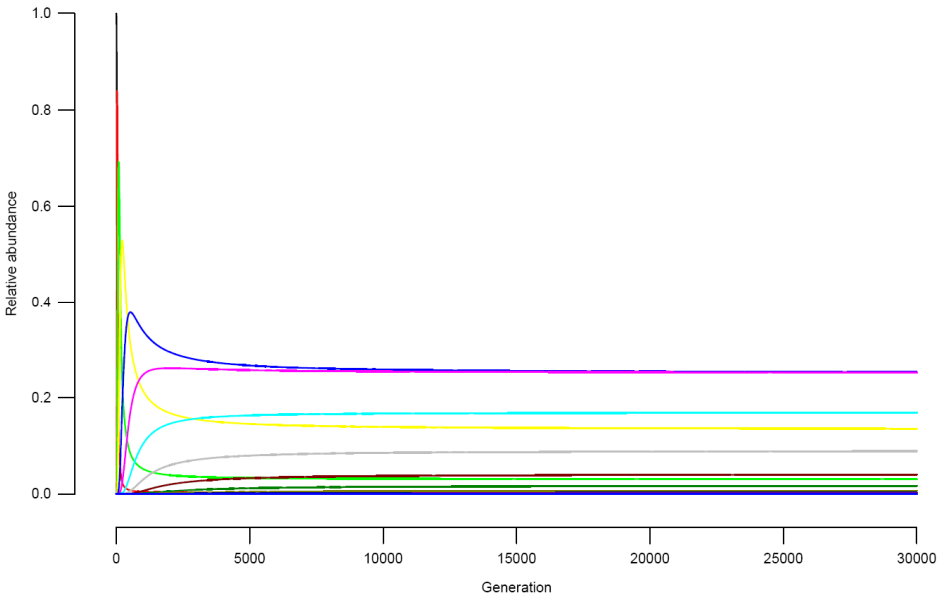


Fig. B.2. (a) Example of discrete-generation quasispecies evolution for the discrete-time version of the Parallel model. The figure shows the evolutionary trajectories of the relative abundances of 50 genotypes (colours, corresponding to individuals with $n = 1$ to 50 parallel elements) over 30,000 generations. The damage rate was $d = 0.01$, the birth rate was $b = 1$, the extrinsic mortality rate was $q^{ext} = 0.02$, and the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively. At the start, every individual had $n = 1$ element. Over the 30,000 generations, a gradual and slowing replacement of the genotypes took place, so that eventually there was a stable equilibrium distribution of genotypes (shown for these parameter values in the bottom panel of Fig. 5b in the main text. (b) The same data as shown in panel (a), only with a log-transformed x-axis; this was done to better see the early evolutionary dynamics of the relative abundances of the different genotypes, the first five of which are noted. Although in panel (b) it may appear that a stable distribution of genotypes has not been approached, this is merely an optical illusion caused by the compression of the x-axis. In fact, the relative abundances of all genotypes changed by less than 1% in the last 1000 generations; panel (a) confirms that the relative abundances of the genotypes became almost constant well before the end of the quasispecies analysis.

(a)



(b)

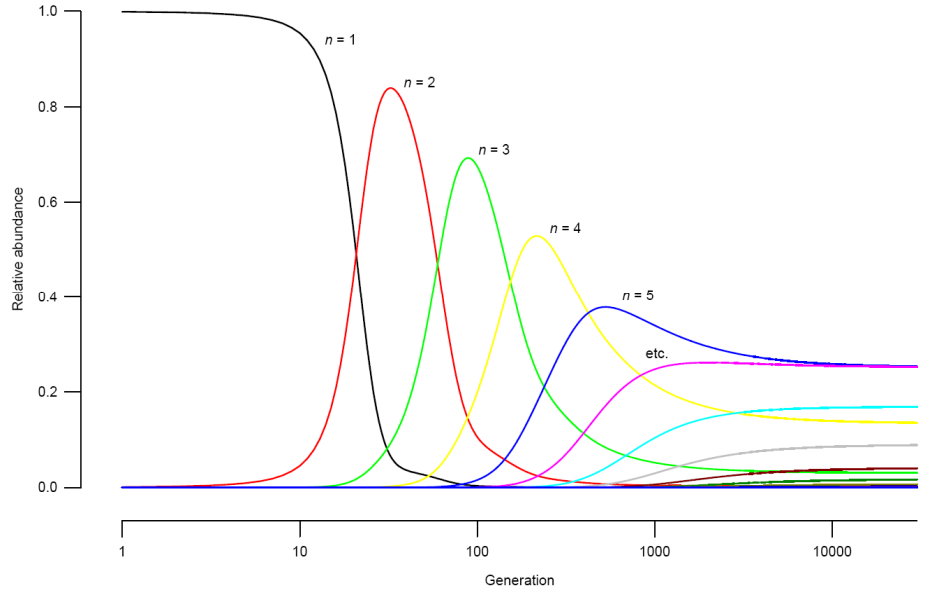


Fig. B.3. (a) Example of discrete-generation quasispecies evolution for the discrete-time version of the Cascade model. The figure shows the evolutionary trajectories of the relative abundances of 50 genotypes (colours, corresponding to individuals with $n = 1$ to 50 elements that repair one another in a cascading fashion) over 30,000 generations. The damage rate was $d = 0.01$, the birth rate was $b = 1$, the extrinsic mortality rate was $q^{ext} = 0.02$, and the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively. At the start, every individual had $n = 1$ element. Over the 30,000 generations, a gradual and slowing replacement of the genotypes took place, so that eventually there was a stable equilibrium distribution of genotypes (shown for these parameter values in the bottom panel of Fig. 5c in the main text. (b) The same data as shown in panel (a), only with a log-transformed x-axis; this was done to better see the early evolutionary dynamics of the relative abundances of the different genotypes, the first five of which are noted.

Appendix C. Comparison of evolved *n* and mean longevity derived from eigenvector analysis and 30,000 recursions of the discrete quasispecies equation

The evolution of senescence in multi-component systems

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Mean evolved redundancy (Fig. C.1) and mean longevity in captivity (Fig. C.2) are the same whether calculated by 30,000 recursions of the discrete quasispecies equation [Eq. (18)] or eigenvector analysis.

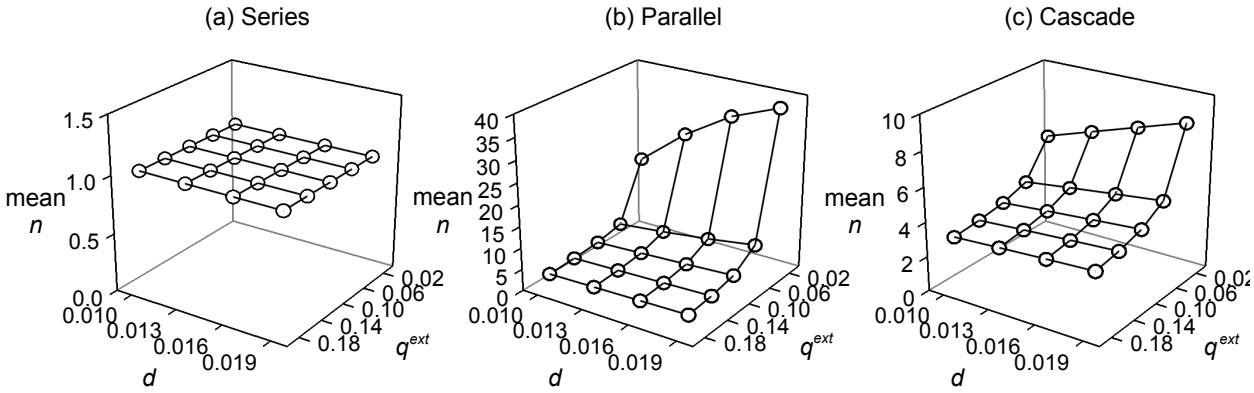

Fig. C.1. The equilibrium mean number of elements (mean *n*) as calculated by 30,000 discrete generations of quasispecies evolution (symbols) and eigenvector analysis (mesh) for twenty combinations of damage rate (*d*: 0.01, 0.013, 0.016, and 0.019) and extrinsic mortality (q^{ext}: 0.02, 0.06, 0.1, 0.14, and 0.18) for the discrete-time version of the (a) Series, (b) Parallel, and (c) Cascade models. In all cases, the birth rate was $b = 1$, the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively, and at the start, every individual had $n = 1$ element.

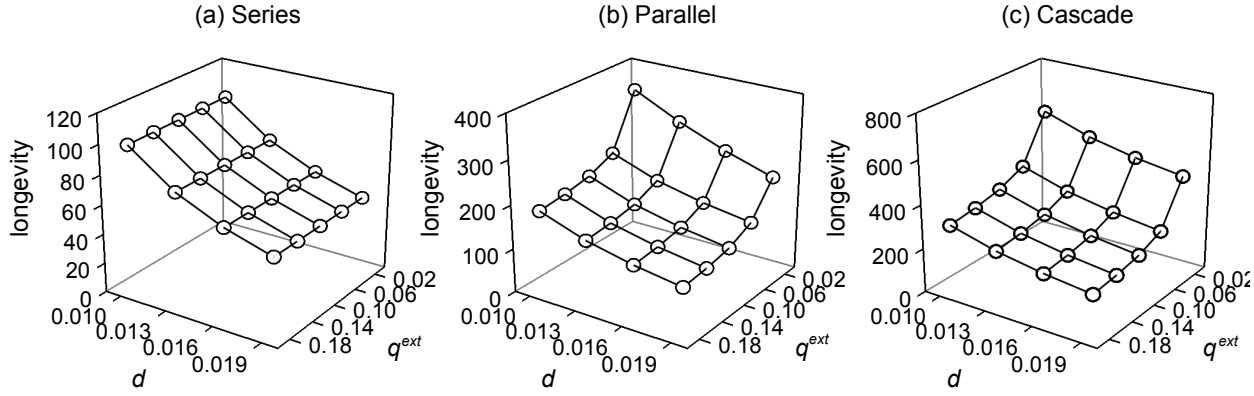

Fig. C.2. The mean longevity in captivity (i.e., $q^{ext} = 0$) for mixed-*n* populations that originally evolved for 30,000 discrete generations of quasispecies evolution (symbols) or as determined by eigenvector analysis (mesh) for twenty combinations of damage rate (*d*: 0.01, 0.013, 0.016, and 0.019) and extrinsic mortality (q^{ext}: 0.02, 0.06, 0.1, 0.14, and 0.18) for the discrete-time version of the (a) Series, (b) Parallel, and (c) Cascade models. In all cases, the birth rate was $b = 1$, the up- and down-mutation rates were $\alpha = 0.001$ and $\beta = 0.01$, respectively, and at the start, every individual had $n = 1$ element.