Disease as a Mediator of Somatic Mutation - Fitspan Coevolution: Model Analysis and Empirical Tests

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Abstract

Multicellular organisms are confronted not only with germline mutations, but also mutations emerging in somatic cells. Somatic mutations can lead to various conditions, diseases, and cancers in particular. Somatic mutation rate is limited by evolved protection mechanisms, notably those repairing damaged DNA or eliminating mutated cells. However, in a broader context, life history traits such as body mass, age of first reproduction and reproductive lifespan, can also be subject to selection due to the negative fitness impacts of disease. Here, I analyze a simple coevolutionary model of somatic mutation rate (SMR) and fitness lifespan (hereafter called 'fitspan'), the latter measured as the age at which inclusive fitness becomes negligible. Evolution in the model is driven by the fitness costs of disease, because as organisms age: disease is more extensive, disease prevention mechanisms are less effective and more costly, and fitness payoffs of disease prevention are lower. I investigate relations between selective forces and (co)evolutionary responses, notably showing the possibility of either monotone or oscillatory non-equilibrium dynamics and fast or slow returns to equilibrium. I then compare model predictions to recently published data on body mass, lifespan and somatic mutation rate. I show that the model (1) can explain the non-linear empirical relationship between somatic mutation and lifespan, (2) predicts the evolution of longer lifespans through a heretofore ignored feedback loop, and (3) the model is consistent with the idea that the linear relation between somatic mutation accumulation and age is the net result of mutational washing-out. I argue that the findings here generalize to other decreases in condition with age that are submitted to selection, including aging itself.

Keywords: aging, cancer, coevolution, disease, humans, non-linearity, Peto's Paradox, somatic mutation, wall of disease

Introduction

Somatic mutation is observed throughout multicellular forms, including animals, plants and fungi. Mutations can occur from the first cell divisions, through juvenile development and growth, and continuing during adulthood in non-dividing cells or at cell divisions to replace aged, damaged or dead cells. Our current understanding of somatic mutation is based on its cumulative burden in humans [1], its causes and impacts, including genome maintenance [2, 3, 4, 5], aging [5, 6, 7], the immune system [8], and the origin and progression of conditions and pathologies, including somatic mosaicism [3, 9, 10, 11, 12, 13] and cancer [10, 14, 15]. Relatedly, studies of the ecological and evolutionary dynamics of somatic mutation have gained attention with research focusing on aging [15, 16], clonal expansions [3, 7, 8, 17, 18, 19, 20], disease [11, 15], and life history traits [21, 22]. An outstanding question emerging from these and other studies is the extent to which mutation-derived disease is under selection, either directly through genomic and cellular maintenance or downstream disease prevention, or indirectly through life history evolution.

Somatic mutations can manifest in several non-mutually exclusive ways. They may occur in nuclear or mitochondrial DNA [23, 24], emerge in otherwise healthy cell lineages either during organism development [10, 12, 25, 26] or tissue renewal or regeneration [27, 28], be limited to a single cell or small group of cells [29], or they may expand and accumulate following (and possibly contribute to) oncogenesis and tumorigenesis [19, 20, 30, 31, 32]. Although exceptions exist (discussed in [8, 33]), confined single cell and cell lineage mutations that evade protective mechanisms (e.g., DNA repair, apoptosis, the complement system/innate immunity, cell division and cell-cell competition [34, 35], tissue architecture [20]) will be limited in their impacts on tissue structure and organ system function [19, 36]. In contrast to confined mutational effects, intrinsic (e.g., inflammation, aging) or extrinsic (e.g., UV radiation, lifestyles) conditions can lead to mutated cells becoming widespread and increased risks of disease-associated morbidity and mortality [32, 37].

Mutations leading to cell gain of function and clonal expansions [19, 36, 38, 39], and specifically to invasive carcinoma, are manifestations of how mutations can produce pathologies years or decades after the first lesions in humans [40]. Here, genomic and cellular dynamics are influenced by host environments, including the pathology itself [15], the surrounding (aging) microenvironment and tissues [41], and individual lifestyles [42]. Physiological aging (used here as progressive decline in function) too can be an important mediator in the downstream effects of somatic mutation, though the causal effects of mutations on aging parameters is controversial [5, 6, 7, 43, 44]. Evidence suggests that chronological age correlates little or not at all with the accumulation *rate* of mutations [45], but rather that their *occurrence* increases in a clock-like pattern [46]. Aging nevertheless has been hypothesized to exacerbate the chronological manifestations of certain genetic or epigenetic cellular changes. These changes may result in increases in disease risk [44, 47, 48] and associate with increases in the population incidence and individual severity of certain diseases and in cancers in particular [37, 49, 50, 51].

Evolutionary theories suggest that the accumulation of deleterious variant cells, cell lineages (e.g., somatic mosaicism) and cell aggregates (e.g., neoplasms) will be influenced by age-specific selection on their negative fitness effects [52, 53, 54]. The extent to which selection acts on genomic and cellular maintenance and/or attenuating downstream mutation-associated disease is little explored, but arguably mutation rates are subject to forces of natural selection at ages which associated *fitness* effects occur. For example, in humans, estimates of prenatal somatic mutation rates are elevated [55, 56], but subsequently level off and generally remain constant throughout life. This is consistent with theory and data indicating relaxed selection in certain contexts at prenatal or juvenile stages [57, 58, 59, 60]. Other studies have considered how various factors

could lead to age-dependence in disease resistance and tolerance (e.g., [61, 62, 63]). A theoretical expectation is that negative selection on less-fit variants is significant leading up to reproduction, eventually decreasing at some point during reproductive ages [64] and eventually giving way to relaxed selection at older ages. In this perspective, pleiotropies and time lags between somatic mutations and their downstream effects can explain why mutations are tolerated to some extent at young ages, and why associated conditions and diseases are tolerated at sufficiently advanced ages [31, 65].

Theories to explain the evolution of somatic mutation rate (SMR) generally invoke negative fitness effects of mutations [66] and/or costs of DNA repair [67]. Germline evolution to lower SMR is expected to occur when negative effects are manifested at ages where the force of selection is sufficient to offset costs of enhanced protection [68, 69]. This manifests, for example, in age-related cancer incidence associating with the inverse shape of the force of selection [31, 37], which suggests that selection has, to some extent, eliminated fitness-threatening cancers in humans, where this effect is well understood. This is despite the frequent presence of cancer-associated mutations in otherwise normal cells (e.g., [70]) and tumors that have little effect on survival and reproduction. Moreover, given the large number of cell divisions during a lifetime in vertebrates such as mammals, birds, and some reptiles, together with the expectation that many mutations are either of negligible effect or are deleterious and the cell short-lived, a prediction is that (costly) genomic maintenance will be imperfect, and will be supplemented by mechanisms focused on the more direct costs to survival and reproduction due to negative downstream effects (see also [71]).

Evolutionary responses to somatic disruption can extend beyond proximal mechanisms such as DNA repair (including telomere length) and apoptosis [72, 73], to life history traits such as body size [74, 75, 76] and reproduction [21, 77, 78]. Support for associations between mutation and life history variables comes from several sources. As first suggested by Failla [79], there is an inverse relationship between SMR and lifespan across species [22], with metabolic rates as a possible mediator [80]. Similarly, there is evidence for a positive relationship between DNA repair and body size across species [81]. In contrast, comparative analysis of relations between DNA repair and lifespan are supported within species [82], but equivocal between species [81]. Despite these empirical patterns, limited attention has been given to testable theory on the coevolution of mutation rate and life history traits (but see [74, 76]).

Here, I develop theory for how pathologies stemming from somatic mutation – and cancer in particular – can arbitrate not only SMRs but also life history in the form of fitness over the lifespan, or 'fitspan': the typical age at which the force of selection becomes insignificant (for alternative situations, see [83, 84]). I use fitspan rather than lifespan or age of reproductive maturity, because (*i*) fitspan provides an age-accurate metric for the ensemble of the action of natural selection, and (*ii*) fitspan and the above metrics are expected to correlate [85, 86].

My objective is to elucidate the key processes driving three central concepts in organismal biology: mutation rate, life history, and disease. The present study takes an initial step in developing and analyzing a simple mathematical model of SMR - fitspan coevolution. I begin with a formal definition of fitspan. I then focus on equilibrium and non-equilibrium conditions of the coevolutionary model to make predictions of how different selection scenarios could translate into single species dynamics and cross-species phylogenetic patterns. I finally compare model predictions with data from a recent study by Cagan et al (2022), the results of which provide insights into possible links between mutation rate, life history and cancer. I conclude by proposing a novel mechanism of how cancer could be a central driving force in the evolution of lifespan in multicellular organisms. I finally claim that the findings generalize to the coevolution between homeostasis, aging, and life history.

Defining Fitspan

I formalize the concept of fitspan below. The mathematics are not integrated into the toy model in the following sections, but rather intended for future, more realistic developments. Note that the parameter conventions below are not the same as those employed in the main text.

Three continuous-time functions describe the life history of an individual. $l(b)$ is the probability of surviving from birth to age b. $m(b)$ is expected reproductive output (offspring produced per unit time) at age b. $u(b)$ is the reproductive value at age b, i.e. the expected future genetic contribution of an individual of age b, relative to the population growth rate and age structure. These functions combine to define age-specific fitness, $\phi(b)$:

$$\phi(b) = l(b)\, m(b)\, u(b),$$

which is the instantaneous expected contribution to future gene copies made by an individual at age b. Here $u(b)$ weights reproduction at age b by the expected future genetic contribution of offspring produced at that age.

The total *lifetime* contribution to fitness is the integral over all ages:

$$\Phi = \int_0^{\omega} \phi(b)\, db,$$

where ω denotes maximum longevity. Φ is proportional to the net reproductive rate (R_0) under appropriate normalization of $u(b)$.

For a given quantile $h \in (0, 1)$, fitspan F_h is the age by which a fraction h of all expected lifetime fitness contributions has occurred:

$$F_h = \inf \left\{ A \geq 0 \ : \ \int_0^{A} \phi(b)\, db \geq h\, \Phi \right\},$$

where inf denotes the smallest age at which the cumulative fitness reaches the chosen fraction of total fitness. As such, A is the minimum age at which cumulative fitness reaches the chosen proportion $h\,\Phi$. Thus, for example, $F_{0.5}$ is the median fitspan—the age at which half of lifetime fitness has been realized. $F_{0.95}$ is the age by which 95% of fitness has been realized. A small difference between lifespan and, e.g., $F_{0.95}$ implies that most of the lifespan contributes to fitness, whereas a large difference indicates an extended post-fitness phase (e.g., post-reproductive senescence).

Note that in social or cooperative species, fitness contributions may extend beyond direct reproduction. We can generalize the expression for $\phi(b)$ to include kin effects:

$$\phi(b) = l(b) \left[m(b)\, u(b) + \sum_j s_j(b)\, \Delta w_j(b) \right],$$

where $s_j(b)$ is the genetic relatedness between the focal individual (at age b) and recipient class j, and $\Delta w_j(b)$ is the expected per-unit-time change in reproductive success or survival of class j caused by the individual's action at age b. This formulation can, in turn, be introduced into the cumulative fitness measure Φ.

In the evolutionary model presented below, fitspan F is assumed to be the lifespan measurement correlating highest with underlying health and aging traits. Multiple traits and environments influence lifespan [87, 88, 89] and although not modeled below, we hypothesize that fitspan will be subject to identifiable evolutionary drivers. Fitspan and its evolution therefore stand as a theory requiring future development.

Model Assumptions

We develop a simple differential equation model as a first step in analyzing germline evolution of SMR and fitspan. Our core assumption that SMR and fitspan are evolutionarily linked is supported by data indicating age-related (*i*) accumulation of somatic mutations [45, 70, 90, 91], (*ii*) increases in mutation-associated diseases including cancers [8, 92, 93], (*iii*) decreases in DNA repair [94, 95], and (*iv*) decreasing performance (aging) at different biological scales [96]. Additional empirical support for evolutionary links between SMR and fitspan comes from work showing associations between enhanced cancer protection mechanisms and life history traits [2, 16, 97, 98].

The key mediator of model SMR - fitspan coevolution is assumed to be cancer for the following reasons: (*i*) the omnipresence of cancer-associated mutations in certain tissue types, at least for humans [38], (*ii*) the pervasiveness of neoplastic phenomena in multicellular biology [99, 100], (*iii*) evidence that cancers are based on cellular variants, either inherited or acquired [101] (but see [102]), (*iv*) the prevalence of (costly) mechanisms limiting cancer emergence [103], (*v*) the temporal separation between mutation events and disease [40], and (*vi*) evidence that life history traits can evolve with parasitic diseases (and cancer being phenomenologically similar) [77] and correlate with cancer resistance [21, 97, 104].

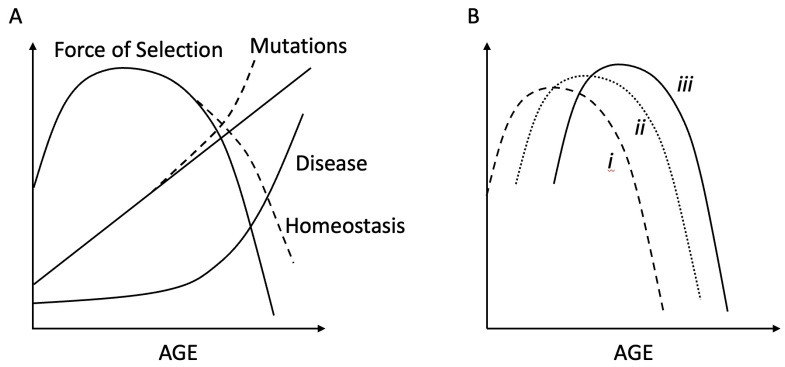

Figure 1: *A*. Illustration of relations between individual age and key features of the theoretical framework. Disease encompasses any age-related condition, the potential prevention of which is submitted to natural selection. Homeostasis includes any mechanism that maintains functional set-points and is only shown as it breaks down at sufficiently old ages. *B*. Hypothetical evolutionary responses to age-dependent disease. *i*. Only sufficiently early mutations are targets of selection due to downstream disease occurring at ages of significant fitness. Selection principally targets traits influencing somatic mutation rate (e.g., DNA repair, apoptosis). *ii*. The frequency and severity of disease both tend to increase with age, meaning that (in addition to some selection against mutation) larger-scale defenses are selected (e.g., cellular senescence, microenvironmental variables, tissue architecture). *iii*. Should the aforementioned defenses (*i* and *ii*) have limited effect against fitness-reducing disease, then an alternative evolutionary strategy is to invest in earlier reproduction, shortening fitspan. Although not considered in the theoretical model, changes in population demography associated with the action of one or more of these three strategies will result in modulation and shifting in one or more of the three hypothetical curves shown.

The impacts of cancers on the evolution of SMR and fitspan is expected to be complex for

the following reasons. Similar to the selective pressures regulating cancers occurring before reproduction maturity [105], post-age-of-reproductive-maturity (but pre-senescent) cancers are expected to exert a negative selective force on both SMR and on fitspan, due to their increased probability of impacting health as a function of age. The balance between evolved defenses that directly target advanced disease versus those focused on preventing neoplastic emergence has received scant attention [72]. DNA repair and cell variant elimination will sometimes expend unnecessary energy (e.g., culling non-threatening cells), whereas mechanisms focused on advanced disease will be both energetically-costly and occur at ages of lower metabolic energy supply, yet have limited impact on disease progression and severity. Moreover, given the expectation that advanced disease tends to occur at advanced ages [51, 77, 88], the most health-threatening situations will tend to be shielded from natural selection. The late action of disease defenses will be costly because (*i*) anti-disease systems age, (*ii*) disease is increasingly more extensive with age, and (*iii*) the fitness payoff of defense decreases at sufficiently old age (Fig. 1A). Depending on the ages at which disease negatively impacts fitness, responses to selection may include some combination of mechanisms influencing SMR (e.g., prevention: DNA mismatch repair, reaction: apoptosis, autophagy) [68, 74], or altered age-specific investment in reproduction [106] and homeostasis [107] influencing fitspan (Fig. 1B).

My approach is to investigate evolutionary equilibrium and non-equilibrium model behavior, because these indicators provide descriptions and testable predictions of how single species evolutionary dynamics could unfold, and permit cross-species comparisons of key variables. Disease – and more specifically cancer – evolution is implicit in the model, insofar as selective disease impacts depend on and modulate both SMR and fitspan. The model assumes continuous evolution and that key variables and selective impacts can be represented by simple population means. Selection is hard-coded into the model so as to focus on evolutionary responses, leaving implicit the following important factors: survival and reproduction (ecology), additive genetic variation and its heritability, distributions in the relative fitnesses of trait variants, epistasis, and trade-offs. Furthermore, we assume that SMR and fitspan – as compound traits – are submitted to several selective forces possibly resulting in a steady state, but also experience (possibly transient) directional selection following (implicit) environmental forcing or ecological change. Importantly, the assumption that species traits could equilibrate does not preclude component selective effects can and will be non-zero at equilibrium. These selective effects are represented in the model as constants, linear or bi-linear variables, and thus are intended to capture to a first approximation some of the countervailing forces driving mutational and fitspan evolution. (Note that when we refer to 'evolution' in somatic mutation rate and fitspan, we are assuming that the evolution is occurring in underlying trait variants). Finally, as mentioned above, the model focuses on *aggregate* sources of selection and does not account for realisms such as the mechanistic roles of specific mutated genes, the precise actions of disease prevention or resistance mechanisms, within-organism mutational or cell dynamics, homeostatic or immune responses, or the age-dependent shape of the force of selection. Despite these oversimplifications, the theoretical predictions constitute an initial benchmark for more realistic models.

Somatic Mutation - Fitspan Coevolution

We present a simple model in which SMR and fitspan coevolve in a single species. These two quantities are encapsulated in a pair of differential equations, $\dot{M}$ for the evolution of SMR, and $\dot{F}$ for the evolution of fitspan. The mean population SMR at time t is M, and the mean fitspan is F. Table 1 presents definitions of model parameters and state variables. Unless otherwise stated, the constants below are all assumed greater than or equal to zero.

Table 1: Model parameters, basic biological interpretation, general entry into model equations, and specific entry at equilibrium. See main text for detailed descriptions.

Parameter	**Selection Source**	**Model Term**	**Term at Equilibrium**
Q	Body mass	Qa	Qa
a	Allocation away from somatic maintenance	Qa	Qa
d	Disease - tolerance	$-dMF$	$-Qa$
v	Allocation to somatic function	Qv	Qv
r	Disease - tolerance	$-rMF$	$-rQa/d$
g	External mortality	$-gF$	$rQa/d - Qv$

The model takes the form:

$$\dot{M} = aQ - d\,MF + p\,MF \tag{1a}$$

$$\dot{F} = vQ - gF - r\,MF + f\,MF \tag{1b}$$

The evolution of SMR (1a) integrates several processes:

aQ is selection for allocation away from costly genome maintenance (resulting in higher SMR) and to organism growth, functioning, protection, and reproduction [108, 109, 110]. This effect is proportional to body mass, Q, based, in part, on study showing that high body mass species have evolved short telomeres [111], possibly as a protection against cancer [72, 73].

$d\,MF$ is selection against SMR due to the fitness costs of advanced disease. Higher mutation rates in high body mass species can be resolved by enhanced DNA repair [112] or tolerated since many mutations are benign [29, 113]. Longer lives mean more time for the negative fitness effects of mutation residence and/or mutation accumulation to manifest via disease consequences of, for example, certain somatic mosaicisms or clonal expansions [22]. Recent work indicates early tumor immune evasion [114], consistent with a tradeoff with (less costly and more effective) mutational control. As such, selection against SMR due to downstream pathologies (d) is assumed to scale with mutation rate itself (M) and with fitspan (F). In contrast, the model is kept simple by assuming the fitness effects of single or small numbers of mutated cells are negligible, and thus a negative selection term proportional to M alone can be ignored.

$p\,MF$ is the lowering of selection against somatic mutation (p) due to selection for protection against downstream disease. That is, evolved protection is assumed to result in the tolerance of what are likely benign somatic mutations. Note that protection from disease cannot conceivably increase mutation rate beyond the decrease due to disease itself, that is, $p \leq d$.

The evolution of fitspan (1b) assumes many of the same forces to those influencing the evolution of SMR:

$vQ - gF$ is the net evolution of fitspan in the absence of somatic mutation. v and g are constants representing the relative weights of selection based on fitspan increases due to investment in somatic functions (proportional to body mass: vQ) [115] and lifespan decrease due to age-dependent increases in extrinsic mortality, due to, for example, predators, parasites and abiotic environmental vagaries (gF) [21, 77, 116, 117].

rMF is selection for shorter fitspan due to the negative selection of disease. Here, an alternative to direct protection against disease-causing mutations (dMF), is to shift investments in reproduction to younger ages (e.g., [77]), correlatively resulting in earlier ages at which senescence begins [54].

Lastly, evolved protection mechanisms against the negative fitness effects of downstream pathologies [118] promotes fitspan extension at rate fMF. Note that (similar to parameter p in equation 1a) selection for longer fitspan via protection cannot exceed fitspan loss due to disease alone, i.e., $f \leq r$. *However*, protection from disease may have indirect effects, such as lowered predation or parasitism from natural enemies. In such situations, f may exceed r. The latter scenario will turn out to be important in what follows.

Given the same bilinear forms occurring in both equations, system (1a,b) can be simplified to

$$\dot{M} = aQ - d\,MF \tag{2a}$$

$$\dot{F} = vQ - gF - r\,MF \tag{2b}$$

where parameter conventions have been redefined as: $d - p \to d$ and $r - f \to r$. Below, we only make reference to p and f when relevant to results.

We investigate how selection terms and their components in equations (2a, b) influence the two-state equilibrium and its non-equilibrium behavior. Evolutionary dynamics matter since they may help uncover the action of underlying selective forces and their biological underpinnings [119].

We focus on (i) how constant parameter values affect equilibrium trait levels and (ii) how a small perturbation to the two-trait equilibrium is followed by a direct, oscillatory or no return to the steady state. The former (i) considers hypothetical variations in parameter values and resulting relations between equilibrium mutation rate and fitspan. Comparing the shapes of these relations with cross-species data constitute a (weak) test of the validity of the underlying model and steady state assumptions. The latter (ii) is intended to represent environmental perturbations that change mean trait levels without changing (evolved) parameter values. There is some empirical evidence for ecological perturbations of genetic variation (trait values) and subsequent recovery [120, 121, 122]. Understanding non-equilibrium dynamics and implications for larger-scale phylogeny is important, since it may help explain puzzling empirical observations, for example, evolutionary trajectories that show a time lag or change in direction through time [76, 123].

Equilibrium

Equations 2a,b have a single, interior equilibrium point M^*, F^*:

$$M^* = \frac{ag}{S} \tag{3a}$$

$$F^* = \frac{QS}{dg} \tag{3b}$$

where $S = vd - ar$ represents selection for longer fitspans and lower SMR, due in part to gains in evolved defenses against disease. S integrates both intrinsic effects (a, v) and interactive effects (d, r).

Equilibrium somatic mutation rate (M^*) and fitspan (F^*) are jointly and inversely determined by the composite parameter $S = vd - ra$ and the extrinsic mortality parameter g. At equilibrium, $M^* = ag/S$ increases with extrinsic mortality (g) and with stronger coupling between mutation and fitness loss (r), whereas selection favoring longer fitspans through increased investment in somatic maintenance (v) typically reduces M^*, all else being equal. In contrast, equilibrium fitspan $F^* = QS/dg$ increases linearly with body mass Q and decreases with extrinsic mortality g. Increasing the mutational input parameter a reduces F^* when $r > 0$, but increases F^* when

$r < 0$. Importantly, although body mass enters the fitspan equilibrium directly, it does not affect equilibrium mutation rate, a prediction consistent with comparative analyses reporting weak or absent correlations between body mass and somatic mutation rate across species [22].

Nevertheless, the equilibrium selection terms listed in Table 1 show the pervasiveness of body mass Q in arbitrating selection changes in both SMR and fitspan. Most of these terms are dominated by either constant selection for somatic growth (a) or somatic function (v). Notably, external mortality at equilibrium ($-gF^*$) exactly balances the two other terms in equation (2b), since at equilibrium

$$-gF^* = -(vQ - rM^*F^*) = -vQ + \frac{raQ}{d},$$

where $M^*F^* = aQ/d$. Thus, although g enters into both equilibrium levels (3a,b), it does not appear explicitly in the component selective terms listed in Table 1.

The conditions for a positive interior equilibrium point are:

$$d,\, g > 0 \tag{4a}$$

and

$$S = vd - ar > 0. \tag{4b}$$

Condition (4a) says that selection against mutation rate due to disease must exceed mutational tolerance resulting from disease protection ($d > p > 0$ from eq. 1a), and there must be some form of intrinsic limitation to fitspan ($g > 0$). Condition (4b) says there must be sufficiently large selection for fitspan and lower SMR. When these conditions are violated, M or F can evolve without bound or to zero (Supplementary Information).

The effects of parameter increases on the interior equilibrium can be found by taking the partial derivative of each, with $M^* = ag/S$ and $F^* = QS/dg$.

We have for the effects on equilibrium mutation rate M^*:

$$\begin{aligned}
\partial M^*/\partial a &= gvd/S^2 > 0,\\
\partial M^*/\partial d &= -agv/S^2 < 0,\\
\partial M^*/\partial Q &= 0,\\
\partial M^*/\partial v &= -agd/S^2 < 0,\\
\partial M^*/\partial g &= a/S > 0,\\
\partial M^*/\partial r &= a^2g/S^2 > 0.
\end{aligned}$$

Not surprisingly, selection terms in (2a) translate into parallel effects on equilibrium levels of M^*, whereas longer fitspans (high v, low r in eq. (2b)) decrease equilibrium mutation rate. Note the pervasiveness of parameters g and S, such that increasing extrinsic mortality g increases the magnitude of effects on M^*, whereas – as is intuitive – increasing S (fitspan growth relative to SMR growth) decreases the magnitude of all parameter effects on M^*. As before, note again that body mass Q has no effect on equilibrium mutation rate M^*.

Depending on mutational parameters, the impact of mutation may be to increase or decrease

equilibrium fitspan:

$$
\begin{aligned}
\partial F^*/\partial Q &= S/dg > 0, \\
\partial F^*/\partial v &= Q/g > 0, \\
\partial F^*/\partial g &= -QS/(dg^2) < 0, \\
\partial F^*/\partial r &= -aQ/(dg) < 0, \\
\partial F^*/\partial a &= -Qr/(dg), \\
\partial F^*/\partial d &= Q\,ra/(d^2 g).
\end{aligned}
$$

Note, interestingly, that the magnitude of all parameter effects is proportional to body mass Q (with the exception of Q itself), and inversely proportional to fitspan reduction, due to age-increasing extrinsic mortality g. Interesting too is that the impacts of *mutational* parameters (a, d) on the fitspan equilibrium are contingent on the sign of r. Mutation decreases fitspan if $r > 0$, whereas it increases it if $r < 0$. The latter condition corresponds to evolved protection against disease indirectly reducing extrinsic mortalities. Moreover, if $r < 0$, then selection for higher mutation rates (high a, low d) *increases* fitspan.

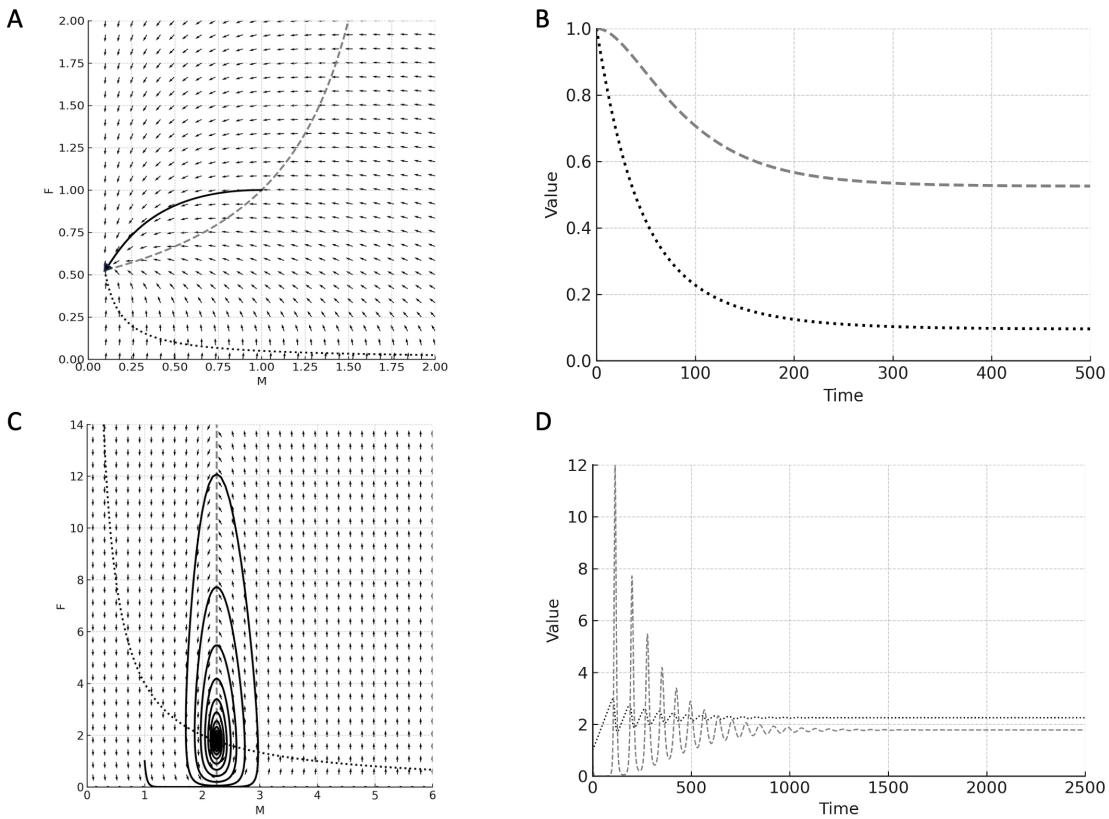

Figure 2: Null clines (left) and time course (right) of somatic mutation rate (M, dotted, black) and fitspan (F, dashed, gray). Solid black line is the time course of M, F starting at initial values of $(1, 1)$. Parameter values (A, B) $Q = 1, a = 0.001, v = 0.01, d = 0.02, r = -0.01, g = 0.02$. (C, D) $Q = 1.0$, $a = 0.02$, $v = 0.0001$, $d = 0.005$, $r = -0.4$, $g = 0.9$.

Local Stability and Non-Equilibrium Dynamics

We take a first step in understanding the impacts of the environment on the steady state M^*, F^* by considering how small perturbations affect the dynamics of M, F (see also Suppl Info). We find that if the interior equilibrium exists, then it is locally stable, but damped oscillatory returns are possible for some $r < 0$ (Figs. 2, 3).

Local stability of the interior equilibrium requires

$$-g \; - \; \frac{arg}{S} \; - \; \frac{QS}{g} < 0,$$

which is always satisfied whenever the interior equilibrium exists. Furthermore, the equilibrium is a locally stable focus (damped oscillatory return) if and only if

$$g \; + \; \frac{arg}{S} \; + \; \frac{QS}{g} < 2\sqrt{QS},$$

a condition that can only be met when $S > 0$ and for some $r < 0$; otherwise, the equilibrium is a locally stable node. Visual inspection indicates that the condition for damped oscillations holds for intermediate parameter values (Suppl Info).

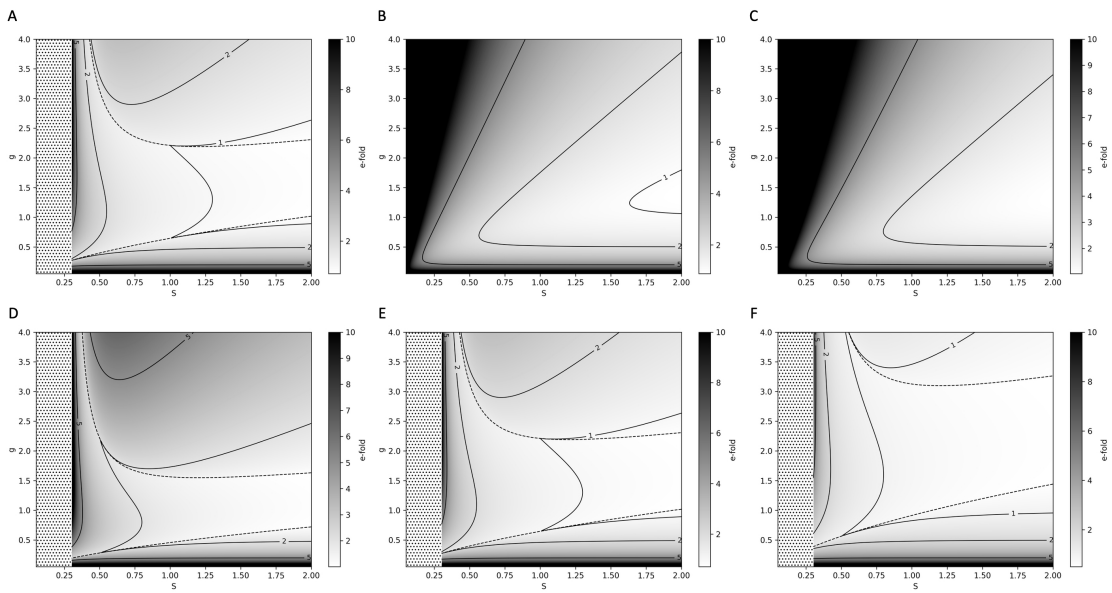

Figure 3: Rate of return to interior equilibrium M^*, F^* following a small perturbation. Returns expressed as e-fold (see main text) and truncated to 10. Darker shading corresponds to slower returns. Black curves are bounds in e-fold return times. Dashed lines in A, D, E, F delimit damped oscillations (inside areas) from monotonic returns after perturbation. Stippled area in A, and $D - F$ corresponds to no interior equilibrium. Parameters set at 1.0, except for v varied over intervals [min,max] to achieve values of S. A: $r = -0.3$, v $[0.0, 1.7]$; B: $r = 0.1$, v $[0.15, 2.1]$; C: $r = 0.3$, v $[0.35, 2.3]$; D: $r = -0.3$, $Q = 0.5$, v $[0.0, 1.7]$; E: $r = -0.3$, $Q = 1.0$, v $[0.0, 1.7]$; F. $r = -0.3$, $Q = 2.0$, v $[0.0, 1.7]$. Note that A and E are the same and only repeated for comparative purposes.

Linearized return times to the interior equilibrium, quantified by an e-fold index [124], provide a standard local measure of non-equilibrium relaxation near a steady state. The parameter effects are complex (Fig. 3, Suppl Info). First, in the stable-focus regime (damped oscillations) of

the M^*, F^* equilibrium, increasing body mass Q strictly accelerates return times. Moreover, within the focus regime, increasing either v or d also accelerates return, because both parameters strengthen the stabilizing feedbacks that govern decay of small perturbations. In contrast, the effects of a, r, and g in the focus regime are contingent on the sign of the expression: $QS^2 - dg^2v$, reflecting the relative levels of coupling strength (bilinear MF terms) and dissipation (g). Second, in the stable-node regime, e-fold return times depend jointly on how parameters shift stabilizing versus destabilizing effects. Changes in a, v, and d can simultaneously strengthen some stabilizing contributions while weakening others, reducing the scope for general monotonic predictions of how e-fold times vary with parameters. Overall, the most robust and readily interpretable accelerations of return are associated with larger Q, and, for $r < 0$, also larger v or d in the stable-focus regime.

Analysis of Cross-Species Patterns

Testing the above theory will require data (i) examining either published accounts or conducting controlled experiments of the evolution of single species state variables under different conditions, or (ii) comparing published accounts (i.e., parameters and state variables in equations 2a,b) to variables across species. We are unaware of data for animals to accomplish (i). In contrast, data from a recent study [22] can be employed to predict expected relations, based on equilibrium assumptions.

Cagan and colleagues collected data from the literature on 15 mammal species, including somatic mutation rates, lifespan and body mass. The data are limited in numerous ways, most importantly in being phylogenetically restricted, based on small sample sizes, and reporting measures at the species level (e.g., not considering different breeds of dogs). As a first step, we employ their mean estimates, equating their somatic mutation rate with our equilibrium SMR, M^*, their lifespan with equilibrium fitspan, F^*, and their body mass with the appearance of Q in the equilibrium of fitspan.

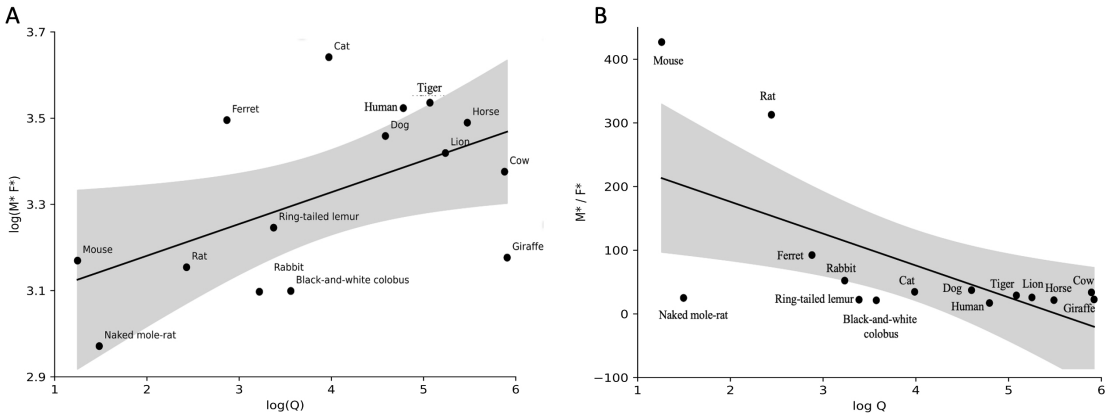

Figure 4: *A*. Regression of log Q vs log M^*F^* for data from 15 species given in Cagan et al 2022. $R^2 = 0.298$ $p = 0.035$. *B*. Regression of log Q vs M^*/F^* for data from 15 species given in Cagan et al 2022. $R^2 = 0.387$ $p = 0.0175$. Shaded area is 95%confidence limits based on Student's t, $df = 13$.

Cagan and colleagues found a convex non-linear relationship between lifespan and mutation rate. Our equilibrium relations (equations 3a,b) can approximate this relationship parsimoniously if $S \to 0$, yielding high mutation rate and short fitspan, and $g \to 0$, yielding low mutation rate and long fitspan. The former condition corresponds to the limit of equilibrium validity, whereas the latter is more interesting, saying that low selection from external mortality alone can drive low

mutation rate and high fitspan. This is because of the action of g in mediating coevolution: longer fitspans, (implicitly) more disease, and selection for disease protection resulting, in turn, in lower SMR and longer fitspans. Also possible is that the empirical shape of the lifespan - mutation rate curve could be explained by variation in multiple model parameters, but this would require additional assumptions about tradeoffs between parameters.

We then examined two measures of mutational burden, one which is the number of mutations occurring over a lifespan (Fig. 4A) and the second being the number of mutations occurring per unit lifespan (Fig. 4B). In both assessments we assume that fitspan in our model is approximated by measures of mean lifespan in Cagan et al. (Note that Cagan et al. measured mutational burden as mutations per size of genome; our model does not incorporate genome size and therefore we cannot make this comparison).

Figure 4A plots how log Q associates with log M^*F^*, the latter being a measure of mutation accumulation over a lifespan, and predicted by our model, at equilibrium, to be proportional to aQ/d, which is the force of mutation independent of lifespan parameters. Based on previous analyses and the tenets of Peto's paradox, we expect little or no relationship between body mass Q and SMR [22, 125]. However, when considering *mutations over a lifespan* (log M^*F^*) the regression is statistically significant with a positive slope, indicating that despite expected increases in evolved protection mechanisms, higher body mass species experience more mutation over their lifespan than do smaller-bodied species. This suggests that mutations are tolerated to some extent in high body mass species.

In contrast, when plotting the data as log Q vs. mutations per unit lifespan, M^*/F^*, we see that the regression slope is negative, such that larger-bodied organisms have fewer mutations *per unit* lifespan (Fig. 4B). Cagan and coworkers found that mutation rate tended to decrease with body mass (their Figure 3e) and that burden (e.g., mutations per genome) tended to decrease with lifespan (their Figure 4). Note that the negative slope in our regression is disproportionately due to short-lived, small body-sized mice and rats, both of which, if removed, result in a flat line (see also [4, 22].

Finally, as noted above, although our model simplifies body mass to a non-evolving constant, our finding that equilibrium mutation rate should not vary with body mass is supported by the empirical results of Cagan and colleagues and the absence of the latter in the model parameters arbitrating the equilibrium of M^*.

Discussion

Understanding mutation in the germline and in the soma is a central challenge in disease biology and more generally in evolutionary biology. Empirical study reveals the daunting complexity of mutational processes and the factors responsible for variations within individuals, between individuals in a population, and between species. Beyond the necessity that comparative and experimental approaches seek to uncover the inner workings of this complexity, mathematical theory has an important role to play in exploring possible interrelations and predicted patterns, which can, in turn, form the basis for empirical tests. The general takeaway of the present study is that somatic disease, and in particular cancer, can act as a driver in the evolutionary dynamics of somatic mutation rate and fitness lifespan, and that some emerging patterns were not predictable from the very simple structure of the mathematical model. Although we view cancer as a pervasive driver of the patterns elucidated here, the model concepts are general to any condition or disease resulting from a breakdown in homeostasis (e.g., somatic mutation), threatening to grow in severity with age, impacting individual fitness, and susceptible to the

evolution of prevention or remediation.

Despite the simplicity of our model, several interesting results emerge. First, we found that approaching the limit conditions for a positive equilibrium is associated either with in a linear decrease in fitspan, and an exponential increase in somatic mutation rate (SMR), or the reverse. This is consistent with recent empirical findings [22]. Our model suggests that the overall shape of the relationship largely depends on the relative gains in mutation rate and fitspan (S) and the direct impact of external mortality (g) on fitspan. Notably, the non-linear effect is driven by low g for low SMR - high fitspan species, and $S \to 0$ for high SMR - low fitspan species. Second, we found that body size (Q) associates with equilibrium fitspan, but not SMR, again, consistent with empirical findings [22]. Although not considered in our model, over sufficiently long timescales we would expect body size (Q) to evolve [21]. Should selection over long timescales reduce body size, then our model would predict no change in SMR at equilibrium, and given expected correlations between SMR and neoplasms [126], this would be consistent with recent theoretical findings suggesting that evolutionary decreases in body size do not necessarily result in increases in cancer prevalence [75, 123]. Finally, we showed, that beyond how evolved cancer protection compensates for otherwise lost fitspan, sufficient protection against growing neoplasms can further increase fitspan due to collaterally-reduced external mortality to natural enemies and environmental vagaries. This effect could obtain, for example, if otherwise unchecked neoplasms reduce organism condition, resulting in increased predation or parasitism [37]. Species with long lifespans have evolved defense mechanisms against mutation accumulation and cancer [4, 16, 97, 127], but it is not known the extent to which longer life is due to indirect reductions in external mortality due, in turn, to evolved cancer protection.

All else being equal, mutations occurring early in life are more likely to lead to life-threatening cancers and more extensive mosaicisms [128] and therefore be more subject to negative selection and the evolution of protective mechanisms. Consistent with this and in accord with model predictions, data on human prenatal SMRs suggest relaxed selection (tolerance) relative to those post-birth [55, 56]. The models presented here however do not explicitly consider age specifics and, as such, cannot be used to make detailed predictions. Investigating this is important since clonal expansions often require years or decades to produce life-threatening cancers (e.g., [129]), many of the latter escaping natural selection [19]. This comforts our prediction that costs to the evolution of cellular integrity (e.g., low mutation) and the downstream effects of disease on fitness both play key roles in life history, and specifically fitspan evolution.

We moreover predict that should pathologies be prevented, attenuated, or delayed due to selection [21, 105, 130], then many diverse maladies will parallel the inverse of the force of selection (i.e., accelerate and coincide in their incidences). Should this be the case, then our theory could provide a mechanism (i.e., mutation-fitspan-protection coevolution) by which tolerated mutations and, more generally, somatic anomalies, accumulate and contribute to aging phenotypes [7], and possibly shift disease incidence to and beyond fitspan-limit ages. Data are consistent with these predictions (e.g., [8, 44]) suggesting a 'wall of disease' at ages where selection becomes negligible, but nevertheless still operative (for cancer see [31, 54, 105]) (Fig. 5A). (Contrast this with the 'wall of death', which predicts 100% mortality at the age at which selection on accumulating mutations is zero [131]). Overlapping disease incidences could be a consequence of selection as posited here, but might also result from aging alone [19] or, more simply, similar rates of disease development, independent of aging. To the extent that certain diseases and conditions are a product of single mutations (somatic mosaicism), breakdown in homeostasis (aging), or clonally expanding cells (cancer), specific predictions of appropriately modified models should be possible concerning age-incidence profiles.

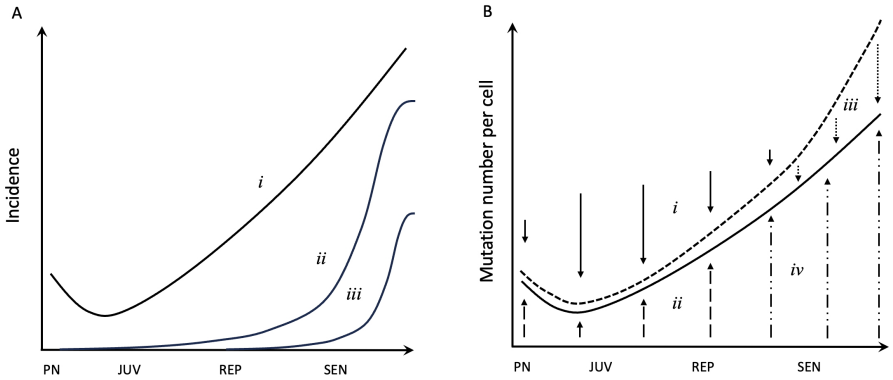

Figure 5: Hypothetical trends in key measures and events. *A*. *i:* Shape of observed mutation accumulation through the lifespan, *ii:* Wall of disease, *iii:* Wall of death. See main text for detailed descriptions. *B*. Hypothesis for the possible non-detection of exponential increases in mutations with age. Lower curve: observed. Upper curve: actual. *i:* Selection for protection against disease, *ii:* Tolerance of early mutations, *iii:* Mutation loads never seen due to earlier death of the most mutated cells; *iv:* Tolerance of late mutations. See main text for detailed descriptions. Abbreviations: PN=Prenatal; JUV=Juvenile; REP=Reproductive; SEN=Senescence.

Consistent with theory on the force of selection, DNA repair declines with age in selected mammals [94], suggesting that somatic aberrations should accumulate with age. Considerable data validates this as a statistically linear increase in mutation load (e.g., [22, 46, 90, 91, 132, 133]), although a small number of studies indicate exponential increases [89, 134, 135, 136]. This discrepancy may be real, or it may be some combination of artifact and unaccounted-for biological processes. For the former, actual mutations and cellular anomalies such as protein misfolding are not easily observed [137] and thus can be underestimated [7, 138]. However, it is not straightforward to see why such affects disproportionally manifest at older ages. In contrast, evolved mutational tolerance is a possible mechanistic explanation for why exponential increases may not be observed (see also [19]), and the subsequent 'washing out' of highly mutated cells due to cellular senescence or cell death [139, 140, 141] (Fig. 5B). Although our model makes no specific predictions regarding age profiles of mutation accumulation, it does provide the parameter relations that modulate SMR *per* unit of fitspan (as a proxy for mutational pressure during fitspan): adg^2/QS^2. Higher mutational accumulation should occur with some combination of low body mass (Q), high external mortality (g), and a balance in selection pressure between the competing demands of somatic protection and somatic growth (low S). This prediction that small, short-lived species are more likely to exhibit non-linear increases in somatic mutation load with age is supported by previous findings [22, 118].

Although the theory developed here focuses on cancer, we claim it applies more generally to age-dependent diseases and conditions. This includes clonal expansions other than cancer [36, 142] and somatic mosaicism [25], but possibly also diseases associated with aging [143] and aging as a condition itself [96, 144, 145]. For our model to apply to aging, associated fitness deficits must be subject to a selective response (i.e., heritable genetic variation for prevention or remediation). More generally, specific diseases or conditions may have characteristic age-dependent dynamics (tending to increase in frequency and severity with age), meaning that selective responses can target early intracellular disruption (e.g., DNA repair, proteostasis), subsequent cellular or tissue functioning defects (e.g., apoptosis, autophagy, immune responses, senescence), or larger-scale life history (e.g., development, reproductive effort, body size). Untangling the roles of somatic mutation and costs associated with evolved protection in the aging process will be highly challenging

[5, 6, 13, 146, 147].

Future research should consider the following limitations of the current study: (*1*) Greater theoretical integration of ecological and evolutionary dynamics, particularly to understand how short-term demographic processes interact with long-term selection on somatic maintenance and life-history traits. (*2*) More realistic evolutionary models based on quantitative traits, allowing continuous trait variation and explicit genetic architectures. (*3*) Age-specific schedules of both external mortality and trait expression, as selective pressures and phenotypic effects are unlikely to be constant across the lifespan. (*4*) Tissue-specific differences in the coevolution of somatic mutation rates and life-history traits. (*5*) Mutation rate - fitspan coevolution within a broader multivariate framework that includes other key traits, such as body size and reproductive effort. (*6*) Models tailored to specific age-dependent diseases and pathological conditions, enabling closer connections between evolutionary predictions and biomedical data. (*7*) Coevolutionary models to include germline mutation processes. (*8*) Comparative phylogenetic analyses focusing on variation in evolutionary rates, with particular emphasis on identifying and explaining lineages that deviate from general scaling relationships. (*9*) How interspecific variation in regressions linking cancer incidence and life-history parameters may reflect the evolution of enhanced cancer protection mechanisms, increased tolerance of somatic mutation, or both.

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Conflict of interest disclosure

The author declares that he complies with the PCI rule of having no financial conflicts of interest in relation to the content of the article.

Supplementary Python code to reproduce figures is available at https://zenodo.org/records/18208523. Supplementary Information is available at https://zenodo.org/records/18220977.

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