Disease as a mediator of somatic mutation – life history coevolution

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Abstract

Multicellular organisms are confronted not only with mutation in germline, but also mutations emerging in somatic cells. Somatic mutations can lead cancers and possibly contribute to aging phenotypes. Prevailing wisdom suggests somatic mutations are limited by evolved defences, either targeting DNA or post-mutational cellular states. Here, I analyse simple models for metazoans and humans in particular, incorporating the possibility that mutation rate trades-off of organism longevity, defined as the age at which natural selection becomes negligible. The models assume selection acts to reduce mutation rate and prevent disease, both of which contribute to selecting for longer lifespan. We detail equilibrium conditions and find coevolutionary oscillations under certain parameter combinations. Notably, disease prevention can lead to mutational tolerance and this can contribute to explaining empirical cross-species patterns in longevity vs. mutation rate. We conclude that mutational disease and cancer in particular have required characteristics to be mediators of mutation rate – lifespan coevolution. The mutational tolerance that results from this coevolution can contribute to explaining the incidences of other diseases and conditions, including aging.

Keywords: aging, cancer, coevolution, disease, humans, lifespan, somatic mutation

Introduction

Somatic mutation is observed throughout multicellular forms, including metazoans and plants. Mutations can occur from the first cell divisions, through juvenile development and growth, and continuing during adulthood in nondividing cells or at cell divisions to replace aging, damaged or dead cells. Our current understanding of somatic mutation is largely based on its cumulative burden in humans (1), its causes and impacts, including genome maintenance (2–5), ageing (4,6–8), the immune system (9), and the origin and progression of conditions and pathologies, including somatic mosaicism (2,10–14) and cancer (12,15–17). Relatedly, studies of the ecological and evolutionary dynamics of somatic mutation have gained recent attention with research focusing on ageing (15,18), clonal expansions (2,6,7,9,19–21), disease (13,15), and life-history traits (22,23). An outstanding question emerging from these and other studies is the extent to which traits leading to disease are under selection, either directly through genomic maintenance or 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 (24,25), be limited to the mutated cell or small group of cells (26), emerge in otherwise healthy cell lineages either during organism development (10,12,27,28), or tissue renewal or regeneration (29,30), or following extrinsic or intrinsic factors they may expand following (and possibly contribute to) oncogenesis and tumorigenesis (7,21,31–33). Although exceptions exist (discussed in (9,34)), 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 (35,36), tissue architecture (21)) will be limited in their impacts on tissue and organ system function (7,37). In contrast, 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 (32,38). Somatic mutations leading to cell gain of function and clonal expansions (21,37,39,40), and specifically to invasive carcinoma, are manifestations of how mutations can produce pathologies years or decades after the first lesions in humans (41), the genomic and cellular dynamics being influenced by host environments, including the pathology itself (15), the surrounding aging microenvironment and tissues (7,42), and lifestyles (43). Physiological aging can be an important mediator of the downstream effects of somatic mutation, but evidence suggests that chronological age correlates little or not at all with the accumulation *rate* of mutations in tissues (44) and causal effects of mutations on aging parameters is equivocal (4,6,8,45–47). Aging has been hypothesized to exacerbate the chronological age-related manifestations of certain genetic or epigenetic changes, resulting in increases both in disease risk (48–50) and in the population incidence and individual severity of certain diseases and in cancers in particular (38,51–53).

Theories to explain the evolution of somatic mutation rate generally invoke negative fitness effects of mutations (54) and/or costs of DNA repair (55–57). Germline evolution to lower somatic mutation rate is expected to occur when negative effects are manifested at ages where the force of selection is sufficient to offset costs of enhanced protection (58). Thus, age-related cancer incidence is consistent with the inverse shape of the force of selection (31,38), suggesting that selection has largely eliminated fitness-threatening cancers in humans (38,59,60) despite the frequent presence of cancer-associated somatic mutations in otherwise normal cells (e.g., (61)) and tumours that have little effect on survival and reproduction (38,62). Moreover, given the large number of cell divisions during a lifetime in metazoans together with the observation that many mutations are either of negligible effect or are deleterious and the cell short-lived (63), an

expectation is that costly genomic maintenance will be imperfect and have additional robust layers focused on the more direct fitness costs of negative downstream effects (see also (64)). The extent to which selection acts on genomic maintenance and/or genome-derived disease is little explored, but arguably will be subject to the force of selection at ages which mutations and subsequent effects occur. For example, in humans, estimates of prenatal somatic mutation rates are high (65,66), but subsequently level off and generally remain constant throughout life. This is consistent with predicted age-dependent forces of selection on genome maintenance. As first argued by Failla (71), data suggest an inverse relationship between somatic mutation and lifespan across species (23) (with metabolic rates as a possible mediator (17)) and between DNA repair and body size across species (55), whereas comparative analysis of relations between DNA repair and lifespan are supported within species (46), but equivocal between species (55). With a few possible exceptions (e.g., hydra, planarian flat worms), evolutionary trade-offs, constraints and time lags between mutations and their downstream effects ensure that somatic mutation and associated conditions and diseases are tolerated to some extent (9,31,72,73).

Neoplastic diseases such as cancers are fundamental arbitrators of multicellular biology (74,75) and based on the above discussion, an expectation is that multicellular organisms will have robust mechanisms to reduce the negative fitness effects of neoplasms. However, populations may respond in diverse ways to phenotypic trait selection and given the temporal dynamics of somatic mutations and of their phenotypic manifestations, elucidating precise selective responses remains challenging. Compounding this, research has shown that responses to parasitism, cancer and somatic maintenance more generally can go beyond proximal mechanisms, and may include life history trait evolution such as body size (76), reproductive lifespan (22,77) and clutch size (78). To the best of my knowledge, no previous study has developed theory on the co-evolution of the three levels at which responses to somatic mutations may occur: somatic mutation rate (e.g., DNA repair), cellular regulation (apoptosis, immune systems, microenvironments…), and life history evolution (body mass, reproductive maturity, fitness lifespan).

Evolutionary theories of costly defence and of aging and senescence suggest that the accumulation of neutral or mildly deleterious variant cells, cell lineages and cell aggregates will be influenced by selection on the timing of the negative fitness effects they produce. I employ this idea in the development of theory for how mutational disease – and cancer in particular – can arbitrate various facets of multicellular biology, including somatic mutation rates, lifespan, the incidence of age-related somatic diseases, and aging itself. I apply this theory to phenomena in metazoans, focussing on humans as the most studied species. The theoretical arguments result from a simple mathematical model of the co-evolution of somatic mutation rate and lifespan (defined as the age beyond which natural selection is inoperative). The model assumes that the negative fitness effects of disease can be reduced either through selection against somatic mutations or selection for shorter lifespans (79), resulting in a shift in disease towards post-reproductive ages. The model is then extended to the multi-evolution of mutation rate, lifespan and protection against mutational disease. I evaluate various processes in isolation and interaction, leading to predictions of how disease, and more specifically cancer, impacts life-history evolution, disease biology and conditions such as aging. I discuss implications for observations of somatic mutation rates and cancer incidence across the tree of life and conclude with several outstanding questions for future research.

Model development and Results

We develop a simple differential equation model as a first step in analysing how traits influencing somatic mutation rate coevolve with traits influencing reproductive lifespan. We expect that this coevolution is arbitrated by manifestations of mutational disease and cancer in particular. Placing cancer at the centre of this theory is based on (*i*) omnipresence of cancer-associated mutations in certain tissue types, at least in humans (40), (*ii*) the pervasiveness of neoplastic phenomena in multicellular biology (75), (*iii*) evidence that cancers are based on cellular variants, either inherited or acquired (80), (*iv*) the prevalence of costly mechanisms limiting cancer emergence (81,82), (*v*) the temporal separation between mutation events (intra-cellular, cellular) and disease (cellular, tissue, organ system) (41,83), and (*vi*) evidence that life history traits can evolve with parasitic diseases (77,84) and correlate with cancer resistance (22,85,86).

Somatic mutation rate is the probability per unit time that an arbitrary base pair in the nucleus is mutated. (Although not strictly equivalent, we include epigenetic changes in DNA in this definition (87)). Somatic mutation rate is challenging to estimate, since it is based on a (possibly small and biased) cell sample (see also Discussion). Actual mutations and anomalies such as protein misfolding, and at larger scales, cellular transformation, are not necessarily observed since they may be either corrected or eliminated by mechanisms such as DNA repair, apoptosis or cellular senescence (88). These and other intracellular, cellular (including immune) and microenvironmental (89) phenomena mean that actual rates will often be underestimated. Given the complexity of within-cell states and cell fates, identifying and modelling key heritable traits impinging on somatic mutation rates present an enormous challenge. This problem is further exacerbated by unknowns regarding the dynamics of such traits (e.g., changes with age), trait interactions and epistasis with other fitness-influencing traits (23,90). A fundamental difference however between regulation at microscopic (DNA, cells…) and macroscopic (homeostasis, metabolic rates, immune systems…) levels is the greater number of layers in the latter compared to the former (91). However, it is not known how these different scales translate into different evolutionary potentials. Finally, akin to mutation rates, multiple traits and environments influence lifespan (92–94). We do not explicitly model the above complexity, but rather assume that the composite effects can be described by simple linear functions.

Excepting the possible maintenance of certain cancers as late-life antagonistic pleiotropic effects of early-life positively selected genes (95), cancers are expected to exert a negative selective force on both somatic mutation rates and on lifespan. Importantly, mutational and cell variant prevention will sometimes unnecessarily expend energy and cull non-threatening cells, whereas mechanisms focused on advanced disease will be both energetically-costly and occur at ages of lower energy supply, yet have little effect on disease progression and severity. These costly phenomena can result in some degree of mutational and disease tolerance possibly in conjunction with random drift (54). Moreover, given the expectation that advanced disease tends to occur at advanced ages (52,77,94), late disease will be partly or completely shielded from natural selection and therefore resistance to early and mid-life asymptomatic variants will be limited or absent in the population. In contrast, shorter lifespan, although potentially costly to reproductive output, may reduce the fitness impact of the most threatening neoplasms.

The differential equation models below consider how key selective effects contribute to macroscopic traits in a species, meaning importantly that at any non-trivial evolutionary equilibrium, each component selective effect will be non-zero. These are represented in the model as linear variables and thus capture to a first approximation some of the countervailing forces

driving mutational and life history evolution. The model assumes continuous evolution and that key variables can be represented by population means. Individual survival and reproduction are thus ignored, as are explicit representations of distributions in the relative fitnesses of trait variants. Finally, the model does not account for realisms such as genetic or trait variation, the mechanistic roles of specific mutated genes or actions of 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 its over-simplicity, the theoretical predictions constitute a benchmark for future, more realistic models.

Model 1: Mutation – Lifespan Coevolution

We begin with a simple model in which somatic mutation rate and lifespan can coevolve (**figure 1a**). These two quantities are encapsulated in a pair of differential equations, $d\mu/dt$ for the population evolution of somatic mutation rate μ_t, and de/dt for the evolution of reproductive lifespan, with e_t assumed to be the age at which the force of selection becomes negligible. Somatic mutation rate is assumed to correlate with the likelihood and intensity of disease and therefore its correlative selective impact on mutation prevention (d) and shorter lifespans (P), the latter which reduces the downstream negative consequences of mutation by preventing their pathologies at fitness-sensitive ages. **Figure 1a** shows a schematic of how rates impact mutation and lifespan.

The model takes the form:

$$d\mu/dt = \Lambda\, Q - d\, \mu_t\, e_t \tag{1a}$$

$$de/dt = V\, Q - g\, e_t - P\mu_t\, e_t + R\mu_t\, e_t \tag{1b}$$

Λ is the net constant energy conserved in tolerating (96,97) somatic mutations. This intrinsic tolerance assumes mutation prevention is costly both as a constitutive mechanism (e.g., DNA repair), and one that eliminates harmless neutrals, positives, and harmful mutations not sufficient to elicit a selective response. Q is body mass, reflecting the sum of the unit Λ over the whole organism, assuming that fitness benefits of conserving energy scale with cell number. Selection against mutation rate and their downstream effects occurs via, for example, increased fidelity in DNA mismatch repair, with d as the constant coefficient. Selection against mutation rate is assumed to scale with mutation rate itself (μ_t) and with lifespan (e_t); longer lives mean more time for the negative fitness effects of mutation residence or accumulated to manifest via the disease consequences of, for example, somatic mosaicism or clonal expansions (i.e., cancer). Thus, a negative association between mutation rate and lifespan is built into the model.

The evolution of reproductive lifespan is assumed to be promoted at constant rate V in proportion to body mass Q (22,98). This could be a consequence of reduced extrinsic mortality in larger-bodied species (22). Clearly, species do not evolve ever-longer reproductive periods and we account for this through the rate parameter g, extrinsic factors limiting reproductive lifespan (99). The time-dependent accumulation of mutational effects can result in disease and possibly contribute to aging. Direct selection against age-specific pathologies themselves is a possibility, but an alternative is to mature at younger ages and reproduce prior to some fraction of the negative fitness effects (P) (e.g., (77)). Similarly, direct evolved defences against mutational disease may relax selection against longer lifespans or even promote longer lifespans, with rate constant R. Thus, all mutation- and disease-related selection terms in our model involve both mutation rate and lifespan. Finally, we note that although it is assumed that body mass Q scales with intrinsic (non-

interactive) gains Λ and V, it is possible (but unknown whether) that Q impacts other processes in the model. We leave this question for future research.

Note from eqn. (1b) that in the limit of no mutation (μ=0), lifespan equilibrates to a locally stable equilibrium at $e^* = VQ/g$. As $\mu \to \infty$, lifespan grows without bound if $R>P$, whereas e shrinks to zero if $P>R$. In contrast, as $e \to 0$, mutation rate grows without bound, whereas as $e \to \infty$, mutation rate goes to zero.

Model 1 has a single, positive equilibrium point

$$\mu^* = \frac{\Lambda g}{\Lambda(R-P)+dV} \quad (2a), \quad e^* = \frac{\Lambda\,(R-P)+dV}{dg} \quad (2b)$$

Mutation rate is inversely related to reproductive lifespan via the terms $\Lambda\,(R - P) + dV$ and g, since longer fitness life increases vulnerability to mutational disease and, in turn, selects against mutation rate. Interestingly, we see that body mass, Q, drops out of the equilibrium, which is consistent with cross-species empirical results showing a lack of significant correlative effects between body mass and mutation rate (23). Therefore, without loss of generality, below we normalize the models with Q=1.

A condition for a positive equilibrium is

$$R + dV/\Lambda > P \tag{3}$$

In other words, protection (R) against the downstream negative effects of mutation (P) on the evolution of lifespan needs to be sufficiently positive, but R need not exceed P. If $P>R$, then satisfaction of condition (3) is fostered by low selection for mutation Λ/d and high selection for lifespan V. Interestingly, selection against mutation rate (d) is scaled by V/Λ relative to protection yielding longer lifespan (R) contributing to equilibrium feasibility. If condition (3) is violated, e_t evolves to zero and μ_t increases without bound. Although biologically unrealistic, a qualitative interpretation is of a species that has a short reproductive span terminating before the effects of any mutations have negative fitness consequences.

Higher equilibrium mutation μ^* is fostered by selection for shorter lifespan (high g, P, low V) whereas e^* increases with higher mutation (Λ/d), but only if protection exceeds damage, or $R>P$; otherwise, mutation has the opposite effect on lifespan. Specifically, by taking $\partial e^*/\partial\,(\Lambda/d)$ we have $(R - P)/g$. Thus, the magnitude of the positive effect on lifespan of increasing mutation rate increases with increases in selection parameters for lifespan in equation (1b). We note that it is interesting that the system can persist when evolved protection is less than evolved cost of disease ($R<P$). In such cases persistence requires sufficient selection for lifespan (V/g) relative to selection for mutation rates (Λ/d).

Examination of the eigenvalues of the positive equilibrium point reveals local stability, either a direct or an oscillatory approach from a local perturbation. Thus if

$$d^2 g^4 V^2 + (\Lambda\,(R-P) + dV)^4 - 2g^2\,(\Lambda\,(R-P) + dV)^2\,(2\Lambda\,(R-P) + dV) > 0 \tag{4a}$$

then the approach is direct, whereas when (4a) is reversed the approach is oscillatory (**figures 2a,b**).

A necessary but not sufficient condition for (4a) to be violated is

$$2\Lambda\,(R-P) + dV > 0 \tag{4b}$$

and under the constraint of equilibrium feasibility (condition (3)), this simplifies to $R>P$; that is, a oscillatory approach can only occur if there is sufficient protection.

Some limiting assumptions reveal interesting properties of condition (4a).

In the limit of $V\rightarrow 0$ we have

$$\Lambda\ (R\ -\ P)^2 - 4g^2\ (R\ -\ P) > 0 \tag{4c}$$

for a direct approach to the equilibrium point. If $R > P$, then the condition simplifies to $\Lambda\,(R\ -\ P) - 4g^2 > 0$. This is promoted by sufficient selection for mutation (Λ) and selection for long lifespans (low g). If, on the other hand, $R < P$, then condition (4c) always holds.

Furthermore, assuming $R=P$, condition (4a) can be approximated as

$$(g^2 - dV)^2 > 0 \tag{4d}$$

which always holds as long as the term in parentheses is $\neq 0$. Thus, as protection matches reduction ($R=P$), the approach is always direct.

Moreover, in the positive equilibrium limit $\Lambda\,(R - P) + d\,V = 0$, which requires insufficient protection to offset disease selection against lifespan ($P > R$), condition (4a) becomes

$$V^2 d^2 g^2 > \Lambda\,(R - P) \tag{4e}$$

which is always true, since the right-hand side is defined as equal to $-d\,V$.

In sum, according to these limiting cases, *indirect* approaches to equilibrium are promoted by intermediate, but sufficient protection favouring lower mutation rate, d, and/or increased lifespan, R. Importantly, mutation and lifespan coevolve, which although assumed by the model structure (the three bilinear $\mu_t\, e_t$ terms), yields novel predictions based on the relative levels of selective reactions to disease, d, P and R.

Non-linearities

Equations (1a,b) assume linear effects of variables μ_t and e_t on selection. This assumption could hold if the negative effects of disease on mutation rates (d), lifespan (P), and the positive effects of prevention (R) on lifespan were not subject to, for example, clonal expansions or nonlinear age-related increases in disease severity (e.g. (100)). As a first exploration of the many possible modifications to equations (1a,b) representing somatic mutational diseases that increase in intensity through a life, we consider only those associated with one of the following: selection against mutation rate (d), selection against lifespan (P), and selection for lifespan (R).

I argue that tumour expansions and correlated exponential increases in cancer incidence and mortality will translate into sub-linear increases for protection ($R\mu e^x, d\mu e^x$) and super-linear increases for mortality ($P\mu e^x$). We expect sublinear (x<1.0) changes due to increasing per unit investment costs and super-linear (x>1.0) changes due to increasing per unit mortality. Evidently, these are oversimplifications of varying non-linearities with lifespan and study is needed to determine these potentially important effects on selection. **Table 1** presents the impact of increasing or decreasing exponents x in the term e_t^x on the equilibrium levels and dynamics for an oscillatory parameter set (see legend **figure 2**).

Model 2: Mutation – Lifespan - Disease Multievolution

Model 1 is an oversimplification of the evolution of somatic mutation rate and reproductive lifespan. As such, some of the results were expected, with the notable exception of the sensitivity of non-equilibrium dynamics to disease protection resulting in longer lifespans (R). Specifically, protection against mutational disease leading to the evolution of longer lifespans is key to both the existence of an equilibrium point and to the coevolutionary dynamics. The narrow satisfaction of condition (3) or its violation are possible outcomes, and the inverse entry of $\Lambda\,(R - P) + dV$ in the equilibrium levels (2a,b) predicts a negative correlation between mutation rate and lifespan across species. The pivotal role of protection against mutational disease (R) on condition (3) and on both equilibrium levels and non-equilibrium dynamics argue for a more realistic description of disease prevention and its direct impact on mutation and lifespan. We explore the more general situation where disease prevention (r_t) evolves together with mutation rate and reproductive lifespan (**figure 1b**), whence

$$d\mu/dt = \Lambda + \alpha\, r_t - d\, e_t\, \mu_t \tag{5a}$$

$$de/dt = V + \beta\, r_t - P\, \mu_t\, e_t - g\, e_t \tag{5b}$$

$$dr/dt = R\, \mu_t\, e_t - h\, r_t \tag{5c}$$

where α and β are constants gauging the direct impacts of disease protection on mutation and lifespan evolution, respectively, and h is the constant cost of prevention (below we assume a unit cost h=1). α can be interpreted as reductions in the costs of mutations (i.e., mutational tolerance), given that their downstream disease impacts are reduced by protection r_t. Note that when prevention dynamics are faster than mutational or lifespan dynamics (i.e., $dr/dt \approx 0$), substituting r_t from (5c) into (5b), we recover system equation (1b).

Model 2 has a single positive equilibrium point

$$\mu^* = \frac{g\Lambda}{dV - RV\alpha - P\Lambda + R\beta\Lambda} \quad (6a), \quad e^* = \frac{dV - RV\alpha - P\Lambda + R\beta\Lambda}{g\,(d - R\alpha)} \quad (6b), \quad r^* = \frac{R\Lambda}{d - R\alpha} \quad (6c)$$

Given the similar form of r_t (5c) to $R\mu_t\, e_t$ in (1b) it is not surprising that equilibrium mutation rate and reproductive lifespan are unchanged with respect to Model 1 in the limits of $\alpha = 0$ and $\beta = 1$. Also, as expected, the equilibrium prevention rate is proportional to constant R and otherwise only affected by selection for mutation rate, Λ/d. Thus, although lifespan e_t enters into equation (5c), r^* is *not* affected by the lifespan parameters found in equation (5b). The impact of prevention (R) on equilibrium lifespan e^* can be found by taking $\partial e^*/\partial R$, giving the condition for marginal increases in R resulting in higher e^*

$$\beta/P > \alpha/d \tag{7}$$

Not surprisingly, the positive effects of disease prevention on lifespan, relative to the negative effects of disease itself on lifespan, need to exceed the positive effects of disease prevention on mutation, relative to the negative effects of disease on mutation.

The conditions for a positive equilibrium (6a-c) are

$$d > R\alpha \tag{8a}$$

and

$$V\,(d - R\alpha) + \Lambda\,(R\beta - P) > 0 \tag{8b}$$

that is, sufficient regulation of the mutation rate ($d - R\alpha$) and if this holds, then necessarily sufficient lifespan extension rates ($V, R\beta$); and, if $R\beta < P$, then sufficiently small intrinsic mutational tolerance (Λ).

The eigenvalues for system (5) are too complex for straightforward local stability analysis (e.g., using the Routh-Hurwitz conditions; see p. 196 in (101)). Numerical experiments did not reveal qualitative differences with the non-equilibrium behaviour of Model 1, which is expected given what amounts to the displacement of $R\mu_t e_t$ from eqn. (1b) into eqn. (5c). Thus, condition (8a) is equivalent to the necessary $d>0$ in Model 1, and condition (8b) is analogous to condition (3) in Model 1.

Nevertheless, in examining oscillatory dynamics in this multi-scale evolutionary system, we found that lifespan and disease protection were persistently and strongly positively correlated (**figure 3a**), whereas mutation rate - lifespan (**figure 3b**) and mutation rate - disease protection (**figure 3c**) went through periods of no, positive, and negative correlation. Notably, oscillatory dynamics are associated with evolutionary lags, particularly those involving mutation rates (**figures 3b,c**). To gain an analytical understanding of the evolutionary system dynamics, we consider some limiting cases in the **Supplementary Material**. A central finding of these studies is that mutation rate evolution is necessary, but not sufficient, to observe oscillatory evolutionary dynamics in reproductive lifespan. Thus, in contrast to mutation rate, lifespan can be non-evolving and still yield an oscillatory approach.

Predictive Indices

Finally, the above results provide meaningful indicators of evolutionary outcomes. Below we present several indices based on Model 2.

(*i*) The selective force, or mass, of mutation over an average reproductive lifetime at equilibrium can be represented as

$$\mu^* e^* = \frac{\Lambda}{d - R\alpha} \tag{9}$$

Interestingly, equilibrium lifetime mutational production is based on mutational effects and not lifespan parameters. The condition $d - R\alpha > 0$ suggests that as long as mutational tolerance is greater than zero ($\alpha > 0$), then increased protection (R) increases overall mutational burden.

(*ii*) In contrast to (*i*), a measure of mutation rate *per unit* lifespan is

$$\mu^* / e^* = \frac{g^2 \Lambda (d - R\alpha)}{(\Lambda (R\beta - P) + V (d - R\alpha))^2} \tag{10a}$$

In the limit $\alpha \to 0$, increasing protection R decreases the index, whereas the limit of $\beta \to 0$, the opposite effect is observed. Thus, the marginal impact of increasing R depends to some extent on how protection impacts mutation (α) relative to lifespan (β). Taking $X = d - R\alpha$ as a measure of mutation limitation and $Y = R\beta - P$ as a measure of lifespan extension, this index of how protection increases two components of fitness (decrease in μ and increase in e) can be more simply expressed as

$$\mu^* / e^* = \frac{g^2 \Lambda X}{(VX + \Lambda Y)^2} \tag{10b}$$

with the constraints for Model 2 equilibrium point positivity (6a-c), $X > 0$ and $VX + \Lambda Y > 0$. Not surprisingly, increasing lifespan selection (higher Y and V, and lower g) lowers mutations per unit lifespan. In contrast, the marginal effect of changing mutation can either increase or decrease this index. The marginal effect of *decreasing* mutation, $\partial\ (\mu^*/e^*)/\partial(X)$, results in the following condition for marginal *increases* in the index (note $\partial\ (\mu^*/e^*)/\partial(-\Lambda)$ produces the same result)

$$Y^2/V^2 > X^2/\Lambda^2 \tag{10c}$$

With suitable parameter values, marginally increasing X, that is (all else being equal), *selecting against* mutation rate can actually *increase* mutations per unit lifespan at equilibrium. This is promoted by high standing mutation parameters (low X^2/Λ^2) and/or low intrinsic selection for lifespan (V), and/or high selection for lifespan based on protection (Y). Thus, sufficient protection (R) is necessary but not sufficient to give this counter-intuitive result, noting that tolerance (α) favors the result, but is neither necessary or sufficient.

(*iii*) An dimensionless index of disease or residual mutation risk over a lifetime is

$$\mu^* e^*/\ r^* = 1/R \tag{11}$$

suggesting that selection for protective mechanisms alone explains lifetime residual disease (and aging, should it correlate). (Note that this index can be normalized to be less than or equal to the numerator by letting the denominator equal $(r^* + 1)$).

(*iv*) A similar index, here in units of μe is

$$\mu^* e^* -\ r^* = \Lambda\ (1 - R)/\ (d - R\alpha) \tag{12}$$

In the limit of no protection, R =0, the index is simply Λ/d. If there is protection R and tolerance α, then by taking the partial derivative with respect to R ($\partial\ (\mu^* e^* - r^*)/\partial R$), we see that marginal increases in protection R increase this index if $\alpha > d$. Otherwise, if reversed, then marginal increases in protection decrease the index. Thus, marginal increases in protection will increase mutational load (and residual disease) if protection results in sufficient mutational tolerance compared with selection against mutation, otherwise it will decrease mutational load.

(*v*) An index of tolerance bias, that is how tolerance contributes to mutation rate per lifespan unit is

$$\alpha r^*/e^* = \frac{R\alpha g\Lambda}{dV - R\alpha V - P\Lambda + R\beta\Lambda} \tag{13}$$

The effect of a marginal increase in protection on this index can be found by taking $\partial\ (\alpha r^*/e^*)/\partial R$. Assuming positivity of the equilibrium point (6a-c), increasing investment in protection R results in increased tolerance bias if $V/P - \Lambda/d > 0$. Thus, counterintuitively, lifespan must have the potential to grow faster than mutation rate (both independent of protection, R). Note that the marginal effect of increasing protection R on lifespan alone at equilibrium $\partial e^*/\partial R$ is positive if $\beta/P - \alpha/d > 0$. Thus, under certain conditions, increasing R can increase both $\alpha r^*$and e^*, but given the previous result, increase the former faster than the latter. We would therefore expect that selection for protection, in conjunction with low mutation and long lifespan should be associated with bias towards mutational tolerance. That is, if these conditions hold, then longer-lived species should *tolerate* more mutations per unit lifespan than shorter-lived species. If the inequality is reversed, then the opposite effect is expected.

DISCUSSION

The key processes driving the species evolution of somatic mutation rate are little understood. Theory suggests direct selection for both genome and cell integrity (54,97), and data support predicted associations between life history traits and mutation rates (23). Study is however yet to consider the extent to which selective responses are manifested in somatic mutation rate, and/or mutational disease incidence and severity, and/or life history variables such as longevity and body mass. Moreover, the possibility that somatic mutation rate could be evolutionarily labile is generally associated with macroevolutionary interspecific differences and not intraspecies adaptive evolution *per se*. We take a first step by analysing simple coevolutionary models in metazoans and humans in particular to make testable predictions about how selection on mutation rate, cellular fates and lifespan can be intertwined by disease. We make several novel findings, including non-equilibrium oscillations, unexpected associations between mutation rate, disease protection and longevity, and the scope for consistency with previous empirical findings. Based on its omnipresence throughout the tree of life (75) and consistent with previous discussion (23,60), we hypothesize that progressive mutational disease – and more specifically cancer – is this key mediator. Our hypothesis differs notably from previous work in predicting that disease defence can have either negative or positive impacts on somatic mutation rates.

The models analysed here substantially abstract realism in ecological and evolutionary processes and are thus intended to establish preliminary predictions of how mutation rate and lifespan can coevolve under simple scenarios. Nevertheless, our core assumption that somatic mutations and lifespan are linked is supported by data indicating age-related (*i*) accumulation of somatic mutations (44,61,67,68), (*ii*) increases in mutation-associated diseases including cancers (9,102,103), (*iii*) decreases in DNA repair (104,105) and (*iv*) decreasing performance (aging) at different biological scales (91). Consistent with recent empirical findings (23), we found that approaching the limit condition (3) in Model 1, or (8a) in Model 2, for a positive equilibrium is associated with in a linear decrease in lifespan e^* and an exponential increase in μ^*. According to our models, the exponential increase in short-lived species shown by Cagan and coworkers (23) could be due to some combination of lower defences (d) or/and higher tolerance (α). Support for our results also comes from associations between enhanced cancer protection mechanisms and life-history traits (3,5,18,86). These findings, although encouraging, are only first steps in the validation of our model framework. Specifically, given diverse mechanisms associated with aging (93) and the possible role of somatic mutation or epigenetic changes in aging processes (4,8,14,106), it is premature to conclude that cancer, independent of aging, is the main (or even a significant) driver in the evolution of somatic mutation rates and life history traits.

Finally, despite the fact that causal links between somatic mutation and aging are controversial, and that the mechanisms associated with each may differ both within and between species, both mutation and aging markers ultimately 'accumulate' with chronical age in the majority of animal species. Given that aging has its own diverse set of heritable regulatory mechanisms, we speculate that our main results (coevolution and its dynamics) would hold for associations between aging rate and reproductive lifespan. Below we discuss some implications of our findings and present questions for further research (table 2).

Predictions I: Cancer as a driver

Cancer can correlate with, and possibly mediate, the evolution of life history traits (22,23,78). The results presented here confirm and extend this insight by showing, counterintuitively, how cancer, although itself selecting for shorter lifespans, can select indirectly for longer lifespans by selecting for resistance to neoplasms (see also (22)). This mechanism can explain observations that species with long lifespans have evolved commensurate levels of specific defence mechanisms against cancer (18,38,86,107). Assuming that the ancestral state is small body size and short lifespan, factors in addition to mutational disease resistance, such as reduced extrinsic mortality (increases in our model parameters V and Q), could contribute to driving the system towards longer lifespans (22). Should selection over long timescales reduce body size (Q) with commensurate increases in defences against extrinsic mortality (V), then our model would predict longevity and cancer resistance could be maintained, as has been previously shown (108).

Our findings are based on the assumed equivalence of the age-specific force of selection and lifespan, the latter which arbitrates the accumulation of mutations and progression of disease, both of which, in turn, influence lifespan evolution. One interesting prediction is as cancer defences are increasingly easy to acquire (e.g., metabolically cheap), low cancer prevalence in the population becomes sufficient to bring defence mutants to fixation. Should low cancer risk be responsible for widespread resistance, then we would expect little or no selective effect to increase lifespan with respect to lifespan prior to resistance. A similar argument could be made for disease severity (impact on individual fitness), that is, a high risk of low pathogenicity could select for cheap resistance, but not influence life history evolution. These predictions merit future research.

Although our hypothesis focuses on cancer, we claim it applies more generally to mutationally-generated disease. This includes clonal expansions other than cancer (37,109) and somatic mosaicism (110), but possibly also diseases associated with aging (111). Different diseases may have characteristic dynamics meaning that selection may be against mutations (e.g., DNA mismatch repair preventing somatic mosaicism and cancers) or/and against cellular defects (e.g., apoptosis, autophagy, immune responses to counter tumorigenesis). We expect that given the randomness of mutation, general defences will tend to enhance DNA repair and cull neutral mutations as well as protect against downstream pathologies, whereas more specialized disease defences will directly target particular classes of post-mutational (cellular) pathologies. Although not explicitly studied here, we predict should pathologies be prevented, attenuated, or delayed due to selection (22,59,112), then many diverse maladies could parallel the inverse of the force of selection and coincide in their incidences. Data are consistent with this prediction (9) suggesting a 'wall of disease' at ages where selection becomes negligible but nevertheless still operative (for cancer see (31,59,113)) (**figure 4a**). (Contrast this with the 'wall of death', which predicts 100% mortality at the age at which selection on accumulating mutations is zero (114)). Overlapping disease incidences could be a consequence of selection as posited here, but might also result from aging alone (115) or, more simply, similar rates of disease development (independent of aging). To the extent that certain diseases are a product of single mutations (somatic mosaicism), the accumulation of changes (e.g., aging), or clonally expanding cells (cancer), specific predictions should be possible concerning age-incidence profiles. An interesting avenue for future research is determining whether the interactions highlighted in our study explain variation in physiological and actuarial aging across species (116).

Predictions II: Mutational Tolerance

We assumed that resistance to mutational disease can lead to mutational tolerance. Many of these mutations will be or become neutral, but some will form pathologies that are 'tolerated' either because selection is ineffective at countering them, or because they emerge at ages in the selection shadow. Insofar as mutations can generate disease at different ages and there are characteristic delays between mutations and disease impacts, an expectation based on decreasing forces of selection with age is that age-specific disease and the mutations responsible are increasingly tolerated as an organism ages (117). Should this be the case then our theory could provide a mechanism (mutation-lifespan-protection coevolution) by which tolerated mutations and more generally deleterious changes (73), accumulate and contribute to aging phenotypes. Moreover, our models predict that increased mutational tolerance (parameters Λ, α) should associate with cross-species negative correlations between mutation rate and lifespan. We assumed that increased resistance to disease with increasing lifespan can 'release' costly DNA protection, resulting in higher-than-expected mutation rates in long-lived species. However, the fact that correlations between mutation rate and lifespan are negative (23) indicates this route to mutational tolerance is, at most, limited, possibly because the evolution of protection disproportionately favors lifespan extension (exposing more mutations to selection, but not per unit time).

An expectation of aging theory is that somatic mutations should accumulate, possibly exponentially (118,119). Considerable data indicate, however, a statistically linear increase in mutation load with age (23,67–70) (but see, e.g., (120)). Should exponential increases be real as would be predicted by studies showing increased genomic instability with age (93), the theory presented here could explain this discrepancy as a consequence of the tolerance of early and late mutations (12), giving away to differential cellular senescence, 'washing out', or ceiling of cell death of accumulated mutations (121) at ages during and beyond which the force is significant (**figure 4b**). Consider cancers. Defence against the negative fitness impacts of cancers can occur in one or more of driving mutations, cellular phenotypes, tissue (microenvironment) variables (21,89), and finally incipient tumours (122). The general rule suggested by the present study is selection against cancer will increase with the severity of the disease and lead to both less disease at older (but fitness-sensitive) ages, and to tolerance of previous causal events. Thus, for example, depending on relative costs, selection against transformed cells will reduce selection against earlier mutations, selection against tumour microenvironmental variables will tolerate both earlier mutations and transformed cells, etc. In terms of *observed* mutations per somatic cell in humans, the net expectation is higher than expected mutation numbers prenatally and at very early ages, reducing initially and then increasing – possibly linearly – with age. This effect will be exacerbated by the costly nature of direct mutational prevention, given the likelihood that most somatic mutations have insignificant selective effects (123).

All else being equal, lifelong processes initiated during development are more critical to organism fitness than those starting after reproductive maturity. By this reasoning, early mutations are more likely to lead to early cancers and more extensive mosaicisms (124) and therefore be more prone to negative selection and evolved protective mechanisms. The costs and benefits of protection are, however, little understood (108). Although data are sparse, some estimates of human prenatal somatic mutation rates suggest relaxed or positive selection relative to post-birth (65,66) (but see (125)). The models presented here do not explicitly consider age specifics and as such cannot be used to make detailed predictions. It is currently unknown how the procession of mutations and disease over age-specific forces of selection will lead to profiles in mutational and disease defence

and tolerance. This is important, for example, in most cancers where not only do clonal expansions leading to overt disease require years or decades (126), but causal driving mutations themselves may be temporally spaced and never generate significant pathology (62) and therefore escape natural selection (115). This comforts our prediction that selection for longer lifespans can be consistent with either mutation rate reductions or increases, the latter presupposing that the costs of mutational suppression are sufficiently large. Thus, our model or modifications of it provide a testing ground for how mutational disease drives the evolution of mutational and disease defences, and life history evolution.

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Table 1 – Effect of non-linear relations between lifespan e^x and selection μe^x for each of mutation rates (d), disease leading to lifespan reduction (P), and prevention leading to lifespan increase (R). Symbols: — (no or negligible effect); ↓ (reduction); ↑ (increase). Parameters: $\Lambda = 0.02, d = 0.005, V = 0.0001, R = 0.5, P = 0.1, g = 0.9$. The exponent x is decreased (increased) from simulation to simulation from 1.0 to 0.05 (1.0 to 2.0) in steps of 0.05 for $d\mu e^x$ and $R\mu e^x$ ($P\mu e^x$). Note, although argued in the main text as unrealistic, increasing x beyond 1.0 (decreasing x below 1.0) for $R\mu e^x$ ($P\mu e^x$) destabilizes the system, and for a range of x and certain parameter values, persistent cycles obtain. Dynamic Effect: a= increase in oscillations/time; b= decreasing oscillation amplitude in lifespan; c= deceasing oscillations/time.

	$\mu *$	$e *$	**Dynamic Effect**
$d\mu e^x$	—	↓	↓[a,b]
$R\mu e^x$	↓	↑	↓[a]
$P\mu e^x$	↑	↓	↑[c]

Table 2 – Questions for future research

Which is more evolutionarily malleable, defence against somatic mutations, protection against mutation-related disease, or variation in lifespan?
Do aging rate parameters show the same temporal patterns as diseases?
To what extent are selection for lifespan and body size coupled or decoupled?
What patterns emerge from mutation – lifespan coevolution in plants?
What is the expected somatic mutation rate given body size and lifespan?
Do larger, longer lived species have a larger fraction of silent vs. disease-causing mutations?
What is the frequency distribution of specific mutated genes in terms of their influence on different diseases?
What is the relative role of antagonistic pleiotropy in explaining tolerated mutations and post-reproductive disease?
Would we expect linkage disequilibrium of genes affecting mutation rate and lifespan?

Figure 1. Schematic diagrams of (*a*) Model 1 and (*b*) Model 2. See main text for descriptions.

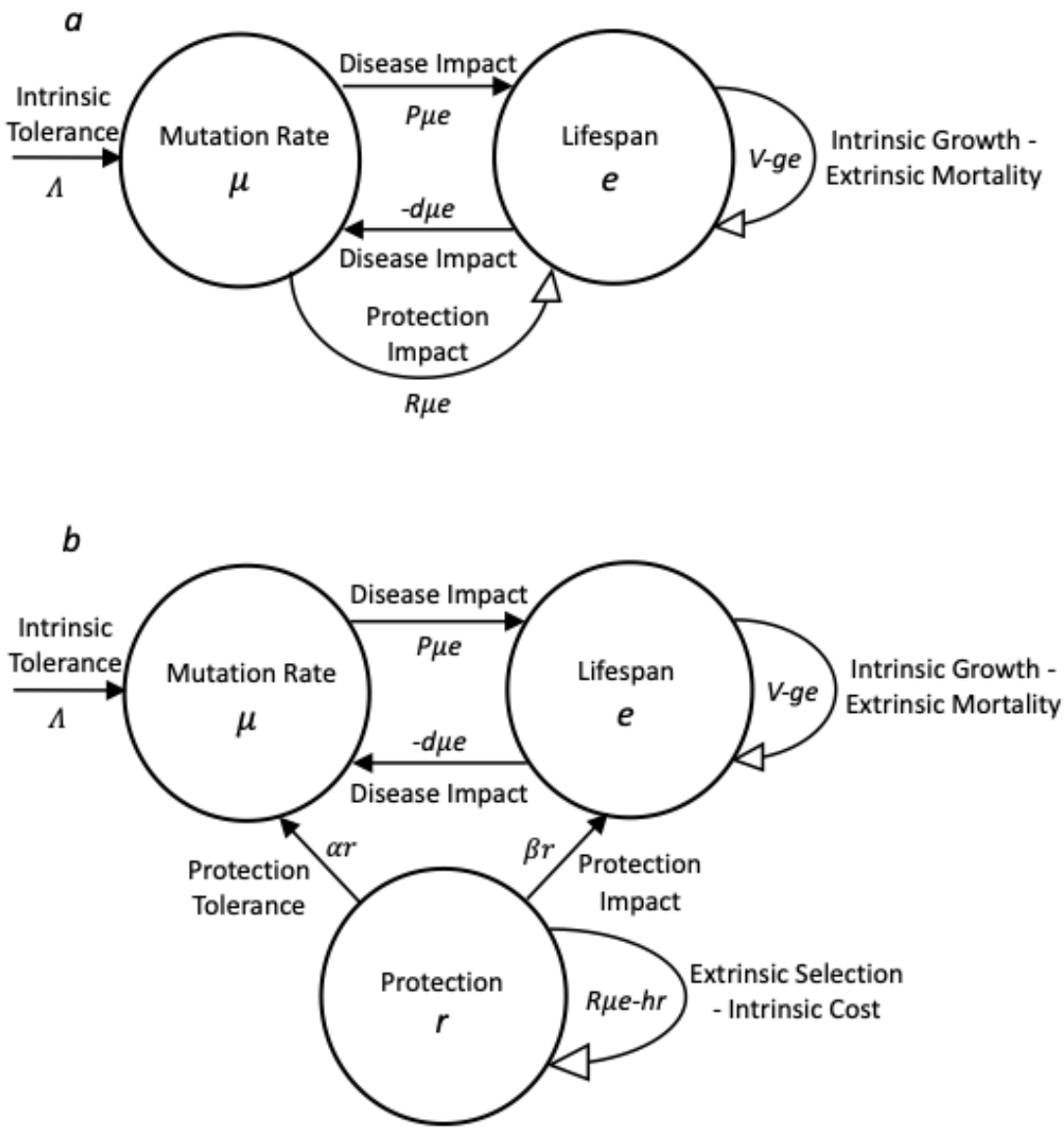


Figure 2. Illustrative example of coevolutionary dynamics of Model 1, between mutation rate μ_t and reproductive lifespan e_t. (*a*) Dynamics as a function of time showing damped oscillations. (*b*) Dynamics of μ_t vs e_t showing temporally changing correlations and cyclic evolutionary lags. Parameter values: Λ =0.02, d=0.005, V=0.0001, R=0.5, P=0.1, g=0.9.

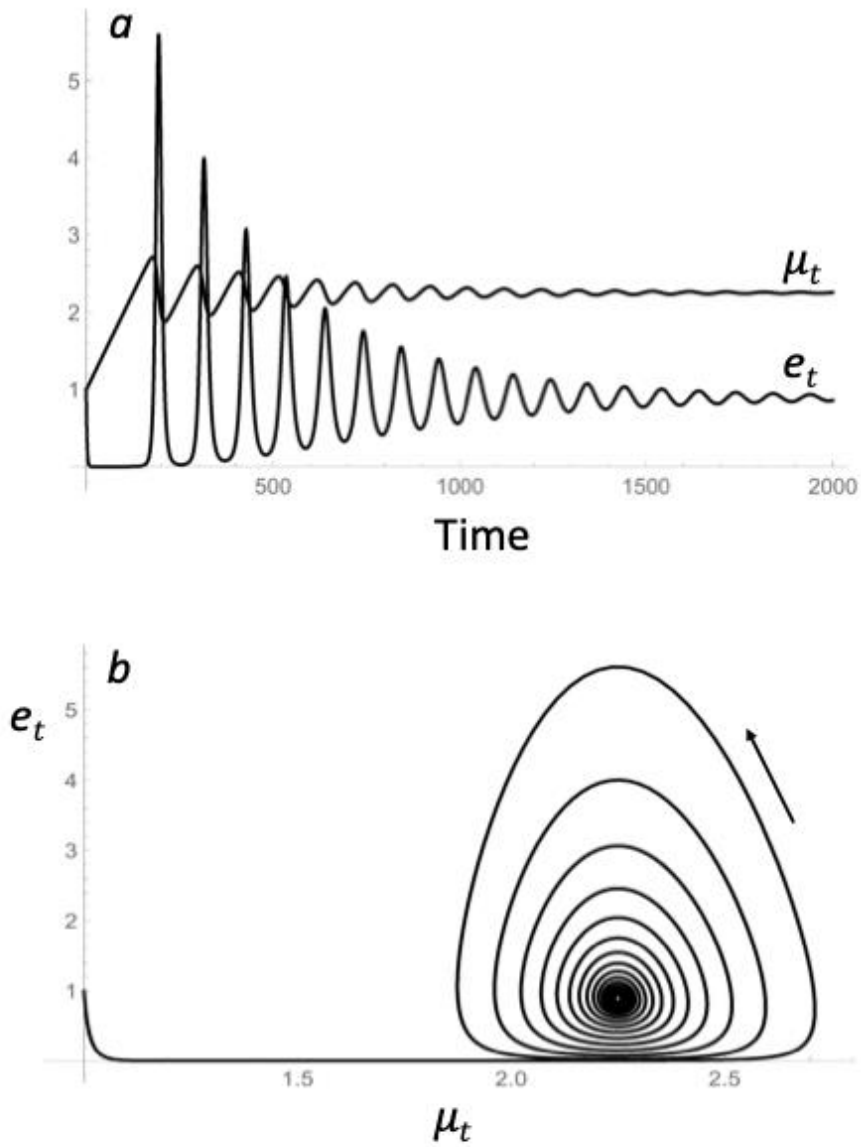


Figure 3. Illustrative example of coevolutionary dynamics of Model 2, between mutation rate μ_t and reproductive lifespan e_t. (*a*) Dynamics as a function of time showing damped oscillations. (*b*) Dynamics of μ_t vs e_t showing temporally changing correlations and cyclic evolutionary lags. Parameter values: Λ =0.02, d=0.005, V=0.0001, R=0.5, P=0.1, g=0.9, α =0.002, β=0.7.

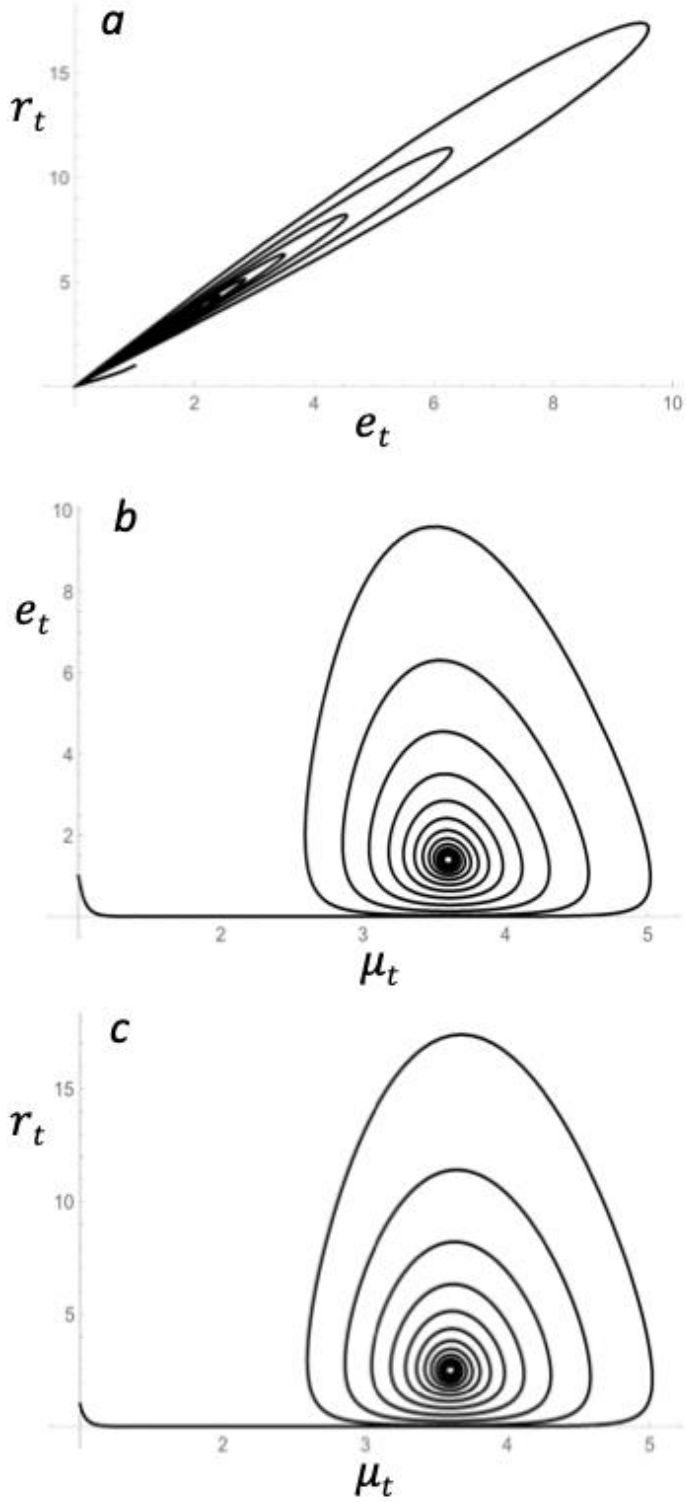
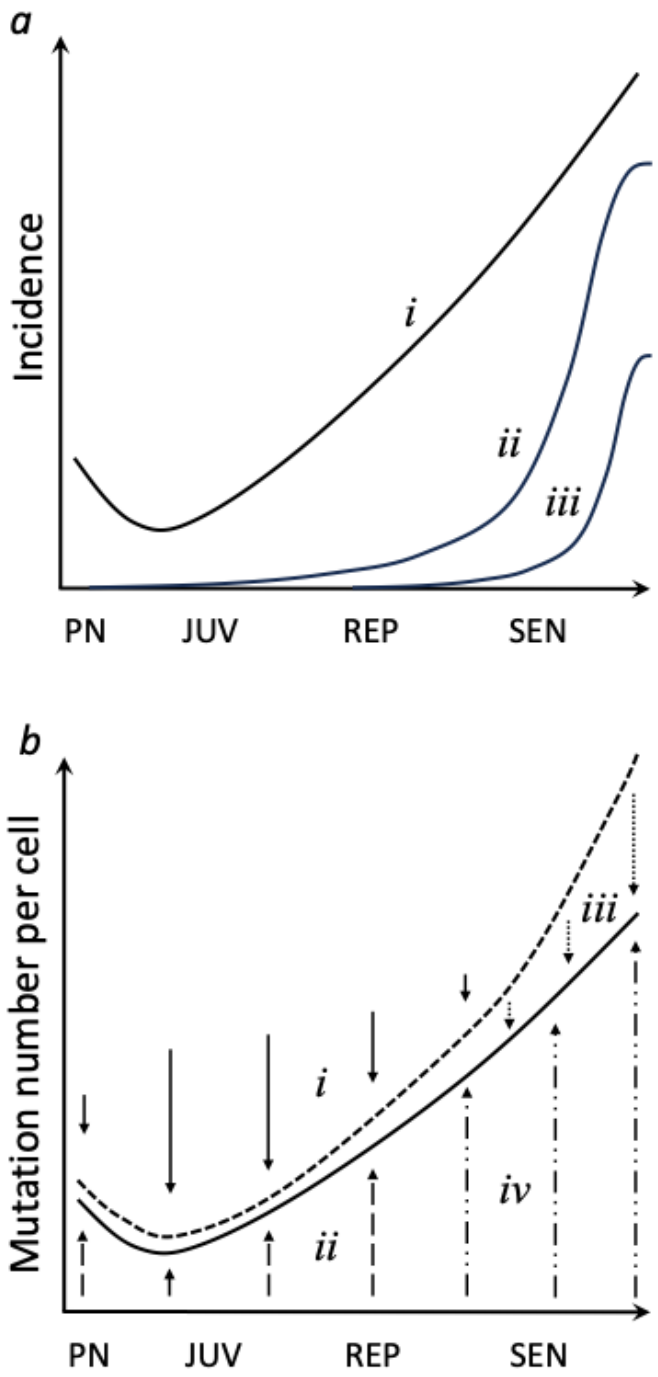


Figure 4. Hypothetical trends in key measures and events in humans. (*a*) *i:* Shape of observed mutation accumulation through the lifespan, *ii:* Wall of disease, *iii:* Wall of death. (*b*) Hypothesis for the possible non-detection of exponential increases in mutations with age. Lower curve: observed. 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 descriptions. Abbreviations: PN=Prenatal; JUV=Juvenile; REP=Reproductive; SEN=Senescence.



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