Somatic maintenance alters selection acting on mutation rate

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Abstract

The evolution of multi-cellular animals has produced a conspicuous trend toward increased body size. This trend has introduced at least two novel problems: an elevated risk of somatic disorders, such as cancer, and declining evolvability due to reduced population size, lower reproduction rate and extended generation time. Low population size is widely recognized to explain the high mutation rates in animals by limiting the presumed universally

negative selection acting on mutation rates. Here, we present evidence from stochastic modeling that the direction and strength of selection acting on mutation rates is highly dependent on the evolution of somatic maintenance, and thus longevity, which modulates the cost of somatic mutations We argue that this mechanism may have been critical in facilitating animal evolution.

Keywords: somatic maintenance, longevity, body size, mutation rate, selection

30 **Introduction**

31 Increasing body size has been one of the major trends in animal evolution across many
32 taxa, as formulated in Cope's rule (*1, 2*). The evolution of larger bodies introduces some
33 fundamentally new evolutionary challenges. The carrying capacity of ecosystems limits
34 biomass per group/species, so larger body size leads to reduced population size. Furthermore,
35 large animals generally demonstrate lower reproduction rates and longer generation times. In
36 aggregate, such changes weaken selection that can act on a population and thus negatively
37 affect evolvability. This general reduction in evolvability should, however, be at least partially
38 alleviated by diversity facilitated by sexual reproduction.

39 The mutation rate (MR) is another critical evolvability parameter. It is believed that
40 selection generally acts to lower MR (*3-5*), and the significantly higher MRs observed in
41 animals compared to unicellular organisms have been argued to result from the reduced power
42 of selection imposed by small population sizes (*6-8*). Germline (gMR) and somatic (sMR)
43 mutation rates are linked, as they employ the same basic DNA replication and repair
44 machinery (*9-11*). While elevated gMR improves evolvability, the ensuing higher sMR should
45 elevate the risk of somatic disorders, such as cancer (*12*). For cancer, increasing body size is
46 expected to increase the frequency of oncogenic mutations by increasing the number of target
47 cells (*13*). Somatic mutations also contribute to aging and a variety of aging-related diseases
48 (*14*). The increased cost of sMR should thus exert negative selective pressure on gMR in
49 larger animals.

50 Recent evidence demonstrates that the sMR in some animal tissues can be significantly
51 higher than the rate inferred from observed mutations, because somatic purifying selection is
52 very effective at eliminating damaged somatic cells (*15*). Many mechanisms, such as various
53 tumor suppressor gene functions (including DNA damage induced apoptosis) (*16*), autophagy
54 (*17*), purifying somatic selection (*15, 18*), and immune surveillance (*19*), should buffer the
55 costs of somatic mutation and in aggregate promote lifespan extension by maintaining tissue

integrity. We will collectively call these mechanisms – the *somatic maintenance program* (SMP).

We present theoretical evidence from Monte Carlo modeling indicating that somatic maintenance not only improves individuals' survival for large animals by reducing sMR costs, but should have played a crucial role in animal evolution by substantially modifying selection acting on gMR. We show that positive selection for increased body size promotes positive selection for extended longevity by improving SMP. Our results also indicate that positive selection acting on traits that do not impact somatic risks also promotes selection for an improved SMP. In both cases, positive selection acting to increase gMR was observed because of the reduced sMR cost, which dramatically improved evolvability of the simulated population.

Results

Theoretical introduction to the modeling. We built a stochastic model of evolution in animal populations, incorporating reproduction and survival (**Fig. 1**), whereby each individual's trait is inherited with variance proportional to gMR (for code, see **Supplements: Section 1a**). Traits are assumed to be polygenic and exhibit phenotypic variation in the population. In particular, MR is assumed to be a highly polygenic trait, given the many genes responsible for DNA repair, DNA replication, damage avoidance (e.g. anti-oxidant defenses), and mutagen detoxification, which in aggregate can determine MR. The evolution of body size, somatic maintenance and germline mutation rate was then tracked under various regimens of selection (see also **Methods: Model algorithm**).

The model should reasonably approximate a sexually reproducing population. The model operates with single-parent reproduction model so that each individual descends from one parent. In this regard, technically it is tempting to view it as a model of an asexual population. However, at a higher level of abstraction the fundamental difference between sexual and

83 asexual populations (aside from the issue of purging deleterious mutations) is the amount of
84 variation produced per the same size population per generation. Variance of inheritance in our
85 model is too high to be assumed as being generated by mutations accumulating along a clonal
86 lineage and equals 10% of a trait's value per generation within 95 percentile. As the modeled
87 traits are assumed to be *multigenic* and have a continuous phenotypic range in the population,
88 we did not need to simulate the processes of allelic segregation by recombination in order to
89 reconstruct a sexual population. Moreover, to model allelic segregation would require
90 assumptions regarding the number of genes and alleles underlying a trait, the dominance of
91 these alleles, and their relative contributions to the phenotype. As such, the model only
92 operates with the net ultimate change of a trait over generations. The assumed multigenic
93 nature of the simulated traits also means that both segregation of alleles by recombination and
94 aggregation of alleles by co-selection are impeded. The efficiency of allele segregation for
95 multigenic traits is inversely proportional to the number of genes encoding a trait. We therefore
96 assume that the net co-evolution of a pair of multigenic traits will ultimately depend on
97 selection acting on these traits that can overcome allele segregation effects.

98 The model incorporates three major factors of mortality, including aging. Human life tables
99 indicate that aging proceeds exponentially, whereby mortality and diseases accelerate at
100 advanced ages (e.g. https://www.ssa.gov, https://seer.cancer.gov). The combined action of
101 SMP mechanisms provides for an extended early period of high body fitness with little to no
102 decline. We generalized this complex program in a curve that describes modeled animal
103 mortality of physiological causes schematically shown in **Fig. 2A** and based on the following
104 equation:

$$D_A = M \times e^{A^{Som}} \qquad (1)$$

105 where D_A is the probability of dying of physiological causes at age A, M is mutation rate,
106 and Som is a composite parameter that determines SMP efficiency. The cumulative
107 distribution function of D_A, or the probability of dying of physiological causes by age A,
108 resembles human mortality (**Fig. 2B**). The equation should thus provide a robust model for
109 aging-related mortality, reflecting the extended period of high fitness and the late-life

accelerating mortality. **Fig. 2A** also demonstrates the relative effects of MR, which is a linear contributor, and the *Som* parameter, which stands for the total damage buffering capacity of the SMP (for details and theory see **Methods: The somatic maintenance program paradigm**). It is important to keep in mind that the *M* parameter (mutation rate) in **Eq. 1** is responsible for the somatic costs of MR (higher MR in **Fig. 2A** accelerates aging-related mortality). Improved SMP, just as body size or other trait, may come at a cost on a short evolutionary time scale, which is later diminished by further adaptation. We did not include this cost in the modeling, since if a trait responds to directional selection this means that the benefit outweighs the cost. Since the amount of change of a trait as a result of positive selection in our model is arbitrary (not exactly copying any particular natural species), we can conclude that this amount of change could already incorporate the net benefit minus cost. In other words, if the benefit of an evolutionary change exceeds its cost, then modeling benefit and cost on an arbitrary scale is mathematically equivalent to modeling only benefit.

The evolution of SMP promotes selection for increased body size through better tolerance of MR. In our simulations, positive selection for increased body size (**Fig. 2C, green**) led to a concurrent selection for elevated gMR (**Fig. 2D, green**) and improved SMP (**Fig. 2E, green**). Artificially blocking SMP evolution by fixing SMP at the initial value (**Fig. 2E, blue**) significantly slowed the evolution of body size (**Fig. 2C, blue; $p << 0.001$**) and triggered selection for lower gMR (**Fig. 2D, blue**). We implemented the ecosystem carrying capacity by setting a maximum biomass for the population; therefore, increasing body size led to a corresponding decline in population numbers, amplifying the power of drift (**Fig. 2F,G**). When SMP was allowed to evolve, however, the population entered a “drift zone” when its size decreased to ~4,000 individuals, which shortly thereafter was overcome by selection for even larger body size, visible also by a continuing decline in population numbers (**Fig. 2F**). When we artificially blocked SMP, however, the drift zone was more profound. It occurred earlier at the population size of ~6,000-7,000 individuals, and the population was not able to escape from it (for ~1,000 generations) and restore its initial rates of evolution (**Fig. 2G**), indicating an important role of SMP evolution in maintaining evolvability. We further generated a population with two

simulated genotypes – Genotype A that could evolve SMP (10% of the population) and Genotype B with SMP fixed at the initial value (90%). We set a maximum population size and removed the maximum biomass limit to rule out body mass effects on population size and selection, and tracked Genotype A and Genotype B frequencies under positive selection for increased body size (for code see **Supplements: Section 1b**). Despite the initial abundance, Genotype B (with fixed SMP) lost the competition in less than 200 generations, reflecting a direct competitive advantage of the capacity to evolve enhanced SMP (**Fig. 2H**). Hereafter, we will call the setting with positive selection for increased body size and freely evolving SMP and gMR the *standard condition* (usually shown in green, unless otherwise indicated) used in comparisons with other selection regimens.

Abrogating selection for increased body size reduces selection for gMR and SMP. In the absence of positive selection for increased body mass (**Fig. 3A, blue**), both gMR (**Fig. 3B, blue**) and SMP (**Fig. 3C, blue**) demonstrate early positive selection, which appeared to have been caused by rapid evolution of reproductive parameters (see **Supplement: Section 2**). Overall, gMR demonstrates a significant general decrease (non-overlapping confidence intervals (CIs) at the beginning relative to the end of the simulation), and SMP undergoes a significantly smaller improvement compared to the standard condition (green; $p \ll 0.001$). Blocking the evolution of body mass (**Fig. 3D, blue**) and SMP (**Fig. 3F, blue**) expectedly led to strong selection for lower gMR (**Fig. 3E, blue**) compared to the standard condition ($p \ll 0.001$), which we interpret as being driven by the sMR costs in the absence of benefits of high gMR. In other words, mutation rate is selected against because of its somatic costs and the absence of benefits of higher gMR in static conditions. In natural populations that are under stabilizing selection, gMR will have costs due to greater phenotypic variance from a well-adapted state that are independent of sMR, but we do not model stabilizing selection in this study.

Decoulpling sMR cost from gMR enhances the evolution of larger bodies. To investigate the role of the putative gMR benefit versus sMR cost balance in evolution, we further decoupled gMR and sMR by allowing gMR to evolve but making sMR cost fixed and independent of gMR (see **Methods: Model variations**). Decoupling sMR cost from gMR

166 significantly accelerated the evolution of body size (**Fig. 3G, blue**) relative to the standard
167 condition (green; $p = 0.0052$), revealing that sMR costs can limit the evolution of larger body
168 size. During the early fast evolution of body mass, gMR (**Fig. 3H, blue**) and SMP (**Fig. 3I, blue**)
169 demonstrate a corresponding positive response. Later, further body mass evolution becomes
170 impeded (likely because of the severe depletion in population numbers), coinciding with
171 selection for lower gMR. SMP plateaus during this second phase at a significantly lower level
172 compared to the standard condition ($p << 0.001$), indicating that the somatic costs of mutation
173 rate stimulate the evolution of more robust SMP.

174 *Selection acting on a somatic cost-unrelated trait still promotes selection for increased*
175 *gMR and SMP.* As we have seen under blocked selection for increased body size (**Fig. 3B,C,**
176 **blue**), SMP demonstrates an early phase of positive selection (**Fig. 3C, blue**) that is apparently
177 reflected in a corresponding positive selection for higher gMR (**Fig. 3B, blue**). This observation
178 suggests that both SMP and gMR may also respond to selection acting on some other traits,
179 e.g. reproductive parameters (**Supplements: Section 2**). This raises the question whether SMP
180 and gMR evolution would be sensitive to strong selection for a trait that does not affect somatic
181 risks (greater body size increases the target size for somatic mutations). We simulated a
182 condition that was similar to the standard condition, except positive selection was applied to a
183 trait that did not affect sMR related somatic costs (see **Methods: Model variations**); e.g. if SMP
184 improvement is solely a response to the increased sMR cost imposed by larger body, selection
185 acting on an sMR cost unrelated trait should not drive improvements in SMP. As shown in **Fig.**
186 **3J (blue)**, unimpeded by increased sMR costs and declining population size, the evolution of
187 an sMR cost unrelated trait is significantly faster compared to the evolution of increased body
188 size ($p << 0.001$). Interestingly, gMR (**Fig. 3K, blue**) also demonstrated an early phase of
189 positive selection during early rapid evolution of the selected trait and remains above the initial
190 gMR throughout the entire simulation. As anticipated, SMP is positively selected; however, in
191 the absence of an increasing sMR cost associated with larger bodies, SMP's improvement is
192 significantly smaller (**Fig. 3L, blue,** $p << 0.001$). Notably, even with much less enhanced SMP,
193 gMR is still under positive selection in response to positive selection for the sMR cost

194 unrelated trait (**Fig. 3K, blue**), consistent with the sMR/gMR cost/benefit ratio being an
195 important factor regulating selection acting on gMR. Regardless, the results demonstrate that
196 both gMR and SMP are responsive to selection for somatic risk unrelated traits, which
197 indicates that high mutation rate is beneficial in positively selective conditions.

198 *SMP enables maintenance of gMR when directional selection is weak.* As we have seen in
199 **Fig. 3D-F**, in the absence of strong positive selection for increased body size and SMP
200 efficiency, selection acts to lower gMR. **Fig. 4** shows, however, that this selection is
201 significantly modified by the efficiency of SMP. Stronger SMPs (lower *Som* value) relax
202 selection for lower gMR when directional selection is weak (non-overlapping CIs between the
203 standard (red) and either of the improved SMPs). As will be explained further below, this
204 observation may have significant implication on long-term species survival in relatively static
205 environments.

206 *Modeling competition between a wildtype and mutator phenotypes.* Under strong positive
207 selection, whether for increased body mass (**Fig. 2A-C, blue**) or a sMR cost unrelated trait (**Fig.**
208 **3H,I, blue**, and **Fig. 3K,L, blue**), we observed consistent signs of positive selection for higher
209 gMR. However, because gMR and sMR are linked, higher gMR is a trait that should negatively
210 impact individual fitness and therefore be under negative selection. To investigate this
211 question, we mixed two simulated genotypes, one "wild-type" (50%) and one "mutator" (50%)
212 in a population of stable size and under positive selection for a sMR cost unrelated trait. We
213 then observed the genotypes' frequencies in the population using varying strength of mutators.
214 **Fig. 5A** demonstrates that while the mutator's fitness initially is lower compared to wild-type,
215 eventually the mutator outcompetes its wild-type counterpart. Interestingly, with increased
216 mutation rate, the magnitude of the mutator's initial decline increases, but so does the speed at
217 which it subsequently overtakes the population. This result provides a clue for how higher
218 mutation rate, being a trait with negative impact on fitness, can be selected for. Because net
219 organismal fitness is a composite trait impacted by the fitness value of many individual traits,
220 the initial fitness of the "mutator" is lower because, all other traits equal, higher MR incurs
221 increased sMR cost. However, in response to selection, mutator is capable of more rapidly

222 developing other (adaptive) traits (**Fig. 5B**) and thus its overall fitness soon becomes higher
223 compared to wild-type.

224

225 **Discussion**

226 Our study demonstrates that positive selection for increased body size triggers a
227 concurrent selection for improved somatic maintenance to mitigate the increased somatic risks
228 of larger bodies. Improved somatic maintenance, in turn, promotes selection for higher
229 germline mutation rates by reducing the cost of somatic mutations and thus altering the
230 sMR/gMR cost/benefit ratio. Conditions of strong positive selection for somatic cost
231 independent traits, as our model shows, can also alter this balance by elevating the benefits of
232 higher gMR. Under stable conditions, alternatively, the sMR/gMR cost/benefit balance is
233 altered by the existing cost of somatic mutations and by the increased cost and
234 absent/reduced benefits of gMR itself, which ultimately favors lower mutations rates. Under
235 stasis, gMR exerts a cost independent of somatic risks by increasing deviation of progeny
236 phenotypes from population mean/median and thus reducing their fitness. Our study thus
237 demonstrates that the evolution of mutation rate is not under a universal population size-
238 dependent selection acting to lower it, but is highly tunable and governed by selection acting
239 on other traits. Importantly, our modeling indicates that under certain conditions elevated
240 mutation rate, unlike perhaps any other trait, can be positively selected despite its negative
241 effects on individual fitness (as explained in **Fig. 5**).

242 Mutation rate in eukaryotes is a highly polygenic trait encoded by multiple genes involved
243 in DNA replication, repair, damage avoidance, and cell division machineries (*9, 11*). Animals
244 mostly reproduce sexually, which should generate an extensive population allelic diversity for
245 these genes. This diversity should provide for a relatively continuous distribution of mutation
246 rate in populations, rather than being a uniform trait marked with sporadic monogenic mutants,
247 as may occur in asexual populations (*20-22*). Such intra-population variation (*23, 24*), as well
248 as the ability of mutation rate to rapidly evolve (*25*), has been shown for humans . However,

249 sexual reproduction would be supposed to effectively segregate alleles contributing to mutation
250 rate from alleles for other (e.g. adaptive) traits. It has been argued based on other evidence
251 that the efficiency of such segregation in sexual populations is limited (*26*). In particular, as
252 argued in **Theoretical introduction to the modeling**, the multi-genic nature of the gMR trait
253 should substantially slow segregation of gMR from other traits.

254 It also appears from our results that animal evolution, with the macroscopic trend toward
255 larger bodies, should have driven a concurrent evolution of extended longevity, the latter being
256 determined by the efficiency of species-specific somatic maintenance programs. Even though
257 extended longevity tentatively appears to be a benefit on its own, e.g. due to extended
258 reproduction period, our model demonstrates that somatic maintenance (and thus longevity) is
259 under a much weaker positive selection in the absence of other positively selected traits. This
260 observation can explain why extended longevity demonstrates significant deviations across
261 animal taxa from the general rule larger body → longer lifespan. Our results indicate that the
262 evolution of longevity (as a function of somatic maintenance efficiency) should be greatly
263 impacted by the rate of evolution of other traits, and not necessarily body size.

264 Interestingly, our study predicts an important evolutionary role for the mechanisms of
265 somatic maintenance in addition to their evolution as a means of improving individual survival
266 of large animals (*13, 18*). Our results demonstrate that selection for enhanced somatic
267 maintenance goes well beyond the evolution of body size and is promoted by strong directional
268 selection acting on any trait. This result indicates that SMPs may have had an important role in
269 the evolution of large animals. Selection for higher gMR following improved SMP may be an
270 important mechanism "rescuing" the reduced evolvability imposed by reduced population size,
271 extended generation times and lower reproduction rates. Therefore, SMPs and longevity may
272 have an important contribution to species' long-term survival. For example, a prolonged
273 evolutionary stasis (*27-30*) should trigger selection for lower mutation rates. By relaxing
274 selection for lower mutation rate and thus maintaining evolvability (as shown in **Fig. 4**),
275 enhanced SMPs can ensure better survival of animal groups facing rapid evolutionary
276 transitions or drastically changed environments after such relatively static periods. All other

277 traits equal, species with extended longevity may survive such transitions with higher
278 probabilities.

279 Lynch and colleagues have provided extensive arguments supporting the idea that the
280 higher MRs in animals compared to unicellular organisms are likely to be caused by reduced
281 population sizes that limit the ability of selection to lower mutation rate (*6-8*). In conjunction
282 with population size, in large animals the strength of selection will be further attenuated by
283 lower reproduction rates and extended generation times. Based on our results, Lynch's theory
284 can be extended by recognizing that somatic maintenance programs (and longevity) should
285 have substantial influence on the general relationship between population size and mutation
286 rates, and on the strength and directionality of selection acting on mutation rates. For example,
287 in our simulation, populations of the same initial size but with different SMP efficiencies
288 demonstrate profound differences in the effects of population size driven weakening of
289 selection (**Fig. 2F,G**, as well as discrepant selection for mutation rates (**Fig. 2D**).

290 Selection for higher mutation rates has been shown experimentally in bacteria (*20-22, 31*),
291 whereby engineered or spontaneous mutants with higher mutation rates have been shown to
292 have advantages over wild-type under positively selective conditions. The "mutator hitchhiker
293 hypothesis" explains such selection by the higher probability that adaptive mutations will
294 appear in a mutator cell (*22*). Once such a mutation occurs, the mutator genotype spreads to
295 fixation by being genetically linked to the adaptive phenotype. Modeling studies demonstrate
296 that evolution of evolvability, including varying selection on mutation rates, should be possible
297 in sexually reproducing organisms (*26, 32, 33*). Yet robust experimental corroboration of such
298 a possibility appears to be lacking.

299 In conclusion, our results raise the question of whether the evolution of large body size in
300 animals would be possible without such a complex pattern of selection acting on mutation rate,
301 and whether such a complex relationship is necessary to explain the evolution of large
302 animals. The evolution of large bodies has entailed the cost of losing the ability to evolve via all
303 major parameters that define this ability, such as population size, reproduction rate and

generation time, except mutation rate (which increased). Therefore, one scenario could have been that this cost has been so prohibitive for many species that positive selection for mutation rate was necessary to allow evolution of large animals. Alternatively, mutation rate could have been high enough to maintain evolvability at the selection/drift barrier point where selection was no longer able to reduce it further (*6*). Understanding which of these scenarios prevails in the evolution of large animals requires more research.

Methods

Software. The model was created and all simulations were run in the Matlab environment (MathWorks Inc, MA) version R2014a.

Model algorithm. The model is a stochastic Monte Carlo type model (the exact algorithm can be found in **Supplements: Section 1a**) that runs a total of 1,005,000 updates ("time" in arbitrary units, AU) unless otherwise stated, which represents ~1000 generations of the simulated animal population (see **Fig. 1** for the flow chart). The simulation starts with building an initial population of 10,000 individuals. Each individual has a number of simulated traits: 1) ID, which is 1 (monogenotypic population) or 1 and 2 (in experiments with competition between two genotypes in a mixed population to indicate genotypes); 2) current age, which increments by 1 at each simulation update; 3) inherited body mass, which is inherited with variation by an individual and will be reached by adulthood (at age ~1000) and equals 5000 AU in the initial population; 4) current body mass, which changes during individual growth, following a growth curve, and plateaus at the inherited body mass in adults; 5) inherited birth mass, which in individuals of the initial population is 300 AU; 6) inherited mutation rate of 10^{-9} AU (explained below); 7) inherited reproduction rate, which is the period with variation between successive reproductions in adult individuals and equals ~600 in the initial population; 8) inherited litter size (initially 1), which is the number of progeny produced per individual per reproduction; 9) inherited parameter of somatic maintenance, which determines the strength of the somatic maintenance program as further explained below; 10) age of first reproduction, which dictates that an individual begins reproducing when its current body mass reaches 0.9693 of its inherited adult body mass (the number is derived so that in the initial population maturity is reached at age ~1000 based on the growth curve).

Each inherited trait varies in progeny relative to parental. This variation was produced by multiplying the inherited mutation rate by the parameter of inherited variance (*inhvar* = 250,000,000) and the product was used as the standard deviation (STD) of the normally distributed variation in inheritance. This transformation was not necessary, as the *inhvar* parameter is constant throughout simulation and it simply determines the magnitude of the mutation rate's effects in the germline, which is imaginary and in the initial population simply

341 produces 0.000000001 x 25,000,000 = 0.025 that serves as the STD parameter for the normal
342 distribution from which inheritance variation is drawn. However, we kept this two-parametric
343 model for inheritance because mutation rate is also separately used in the equation of the
344 somatic maintenance program (as will be explained later).

345 Each newborn individual grows, reaches maturity, then reproduces over the rest of its lifetime
346 and eventually dies. The model is asynchronous, so that at every time-point of the simulation
347 the population contains individuals of various ages whose lifecycles develop independently.

348 And finally, three factors of mortality were modelled in the simulations. First, at every timepoint
349 of the simulation, an individual could die of somatic causes with a certain probability. This
350 probability is small at the beginning of life (but still can be caused by some imaginary inherited
351 genetic defects) and increases exponentially with age based on the paradigm of the aging
352 curve, which is primarily determined by an individual's inherited somatic maintenance program
353 (SMP). In humans, the aging curve also depends on lifestyle, however we assume in this
354 model that in a wild animal population lifestyle distribution is sufficiently uniform to be
355 neglected. More detailed description of the somatic maintenance paradigm that we applied will
356 be explained further below. Secondly, the simulated animals had a chance of dying of external
357 hazards, such as predators. We applied the Lotka-Volterra model of predator-prey interactions
358 (*34, 35*) to implement the dynamics of predator pressure (effectively the chance of dying of an
359 external hazard cause per timeunit). Here we should mention that smaller individuals and
360 juveniles had higher chances of dying of external hazards, which effectively created positive
361 selection for increased body size and also reflected the typical high mortality rates among
362 juveniles observed in natural populations. And lastly, individuals could die of intra-specific
363 competition. We implemented such competition by setting the upper limit of population's total
364 biomass, which in nature is imposed by the ecosystem's carrying capacity. Therefore, in the
365 simulated population biomass produced over the biomass limit caused additional mortality, so
366 that stochastically, population total biomass never exceeded the limit. Larger individuals also
367 had lower probability of dying of intra-specific competition, based on the assumption that
368 competition for resources and mates (the failure to reproduce is effectively an evolutionary
369 death) will typically favor larger individuals and this should have been one of the forces that
370 has been driving the macroscopic animal evolutionary trend towards increasing body size. The

371 advantage of size in this mortality model also created additional positive selective pressure for
372 body size. The total age-dependent mortality of all causes in our model did approximate a
373 typical wild animal mortality curve (**Supplements: Section 3**).

374 **The somatic maintenance program paradigm.** In order to replicate natural mortality caused by
375 physiological aging, such as cancer, decreased immune defense and lower ability to avoid
376 predators or to succeed in intra-specific competition, we made use of the aging curve, or
377 somatic maintenance, concept. Modern humans (in developed nations) and captive animal
378 mortality curves (**Fig. 2B** for human) differ from wild animal mortality curves in very high early
379 life survival with most mortality significantly delayed into advanced ages (*36, 37*). This
380 difference is caused by many reasons, such as much lower mortality caused by external
381 hazards and better nutrition and general healthcare. It therefore can be assumed that the
382 human and captive animal mortality curves are close representations of the physiological aging
383 curve. As longevity depends on multiple mechanisms of maintaining the soma, we can also
384 call this curve *the somatic maintenance curve*. In order to reconstruct this curve, we assumed
385 that somatic maintenance depends on the interaction of two opposing forces: 1) the
386 accumulation of genetic and structural damage in the soma that promotes aging and 2) the
387 somatic maintenance program consisting of a number of mechanisms that prevent or buffer
388 the effects of genetic and structural damage. The exact mathematical relationship between
389 these two forces and age is not known, however an example of cancer development can be
390 used as a proxy to explain the equation we derived for it.

391 Oncogenic mutations (including oncogenic epigenetic changes) are the ultimate necessary
392 condition for cancer to develop. The frequency of oncogenic mutations linearly depends on
393 mutation rate on a per cell division basis. Therefore, we assume that linear changes in
394 mutation rate will have linear effects on the odds of the occurrence of oncogenic mutations. An
395 oncogenic mutation provides the initiated cells with a linear change in their fitness relative to
396 normal cells. However, over time an advantageous clone with a constant linear fitness
397 advantage will proliferate exponentially. Therefore, we can already assume that mutation rate
398 should have a linear effect on the cancer curve, while time/age adds an exponential
399 component revealed in an exponential growth of a tumor. We can reasonably assume further
400 that a strong SMP will efficiently suppress such a clone, slowing or even preventing its growth

401 (*38*). A weaker SMP will allow the clone to proliferate faster. Therefore, SMP strength can
402 modulate the effects of mutations and time on cancer risk. The exact relationship between
403 SMP strength and physiological risk factors is not known. However, we know that their
404 interaction leads to a net exponent in physiological decline and disease risk.

405 We therefore reconstructed the human aging curve by maintaining the general principal
406 relationship between these factors as shown in **Eq. 1**. As seen from the equation, mutation rate
407 is a linear contributor to aging. Age itself contributes exponentially, and the somatic
408 maintenance composite parameter *Som* is, in turn, in power relationship to age. The
409 cumulative distribution function of D_A (**Eq. 1**) produces *D(A)* – the probability of dying of
410 somatic/physiological causes by age *A* and yields a shape close to the human mortality curve
411 (**Fig. 2A,B**). We cannot claim that these three factors are in the exact relationship predicted by
412 **Eq. 1**, as it is unknown. As seen in **Fig. 2A**, changes in the *Som* parameter have substantially
413 greater effects on the resulting mortality curve than mutation rate, with mutation rate still
414 having a sizeable effect as well. Yet claims are still made (e.g. (*39*)) that mutation rate is a
415 larger factor in aging than we assume in this model. Validation of our assumption in general
416 comes from the body of solid evidence that up to 50% of mutations in humans accumulate
417 during body growth by the age 18-20 (*40-42*). If mutation accumulation had a significant effect
418 on aging on its own, we should age rapidly until age 18-20 (half-way) and then the rate of
419 aging should decelerate. However, in reality the opposite happens, indicating that the
420 combined strength of the SMP has an overpowering effect in modulating the effects of genetic
421 damage on aging. As a result, we reason that **Eq. 1** might reasonably approximate the natural
422 relationships of these three factors. Therefore, based on an individual's aging curve we
423 calculated the D_A parameter at each simulation time-point (using the individual's mutation rate,
424 age and *Som* parameter) and applied it in a binomial trial as the probability of that individual's
425 dying of somatic/physiological causes in an age-dependent manner. As further explained in
426 **Supplements: Section 4**, the exact relationship between the *Som* parameters and each of the
427 other two (mutation rate and age) has no effect on the model, as the model represents SMP
428 and its variation by using area under the mortality curve. Therefore the sole purpose of **Eq. 1** in
429 the model is to generate an age-dependent curve of physiological mortality whose cumulative

430 function (probability of dying by a certain age) resembles in shape the human mortality/aging
431 curve (see **Supplements: Section 4** for detailed explanation and illustration).

432 **Model variations.** A number of model variations used in simulation experiments are
433 employed. *Fixed trait values* involved simply fixing the initial trait value without inherited
434 variation throughout the entire simulation. *Dislinking of somatic and germline mutation rate* was
435 done by making the value *M* in **Eq. 1** independent of an individual's mutation rate, which
436 resulted in somatic costs independent of transgenerational variation of mutation rate
437 (effectively from germline mutation rate). *Selection for a trait that did not affect somatic risks*
438 was achieved by transforming the "body mass" trait's effects by removing the trait from
439 calculations of the risk of death by somatic causes (unlike body size, it did not influence the
440 risk), then removing the population biomass limit and setting maximum population size (unlike
441 body mass, other traits do not directly affect population numbers) and fixing the growth rate
442 curve so that it reached the initial body mass of 5,000 AU (the current body mass parameter in
443 the model; the inherited body mass variation did not exist and the inherited body mass
444 parameter was replaced with the somatic risk unrelated trait). These manipulations made the
445 selected trait a proxy for a trait unrelated to somatic risks (e.g. hair color). *Competitive assays*
446 included individuals with different ID parameters, such as 1 and 2 to indicate different
447 "genotypes"; traits of the "genotypes" then were tracked and stored separately.

448 **Data processing.** Processing of primary data included removal of outliers (see
449 **Supplements: Section 5**). Occasionally the simulations generated "NaN" (not a number) values
450 in individual parameters, which were rare but quickly propagated if left in the population. We
451 immediately deleted individuals from the population if "NaN" values appeared in any of their
452 parameters. Based on the rarity of such events, we can assume that they had the effect of rare
453 early lethal mutations and affected the population at random. Thus, we assume these did not
454 affect the principal results.

455 **Statistics and data presentation.** Most simulation experiments were made with 25 repeats.
456 Due to heavy skews in sample distributions (inferred by D'Agostino-Pearson test for normality
457 of a distribution), all figure panels represent medians (thick lines) and 95 percentiles on each

tail (color-shaded areas). Statistical differences between experimental conditions were calculated as follows. We first calculated the sum of all values in each run throughout the entire evolution of a trait (typically 1,005,000 time points). In this way, given the small increment over a long time the sum essentially approximated the area under the curve of a trait's evolution. These sums (usually 25 repeats in one experiment/sample) were then compared by applying the Matlab implementation of the Wilcoxon rank sum test, which is considered equivalent to the Mann-Whitney U-test. P-values <= 0.05 were considered as indicating significant difference.

Supplementary Materials

Section 1. Model code.

a. General model for positive selection for body size

```
for iteration = 1 : 25
    disp(iteration);

    newrun = true;

    if(newrun)
        clearvars -except newrun iteration
        fname = 1;
        timeun = 1;
        iter = 1;

        % OUTPUT STORAGE MATRICES
        sommortality = []; % counts of mortality for somatic reasons
        extmortality = []; % counts of mortality caused by external hazard
        capmortality = []; % counts of mortality imposed by ecosystem's
                            %  carrying capacity (intra-specific competition)
        biomassdyn = [];   % population biomas dynamics over time
        popsizedyn = [];   % population size dynamics over time
        births = [];       % counts of new births over time

        bodymassevol = []; % population's average bodymass over time
        birthmassevol = []; % population's average birthmass over time
        littersizeevol = []; % population's average litter size over time
        mutrateevol = []; % population's average mutation rate over time
        rrateevol = []; % population's average reproduction rate over time
        lifespanevol = []; % population's average somatic maintenance
                           %  coefficient over time

    else
        timeun = timeunit + 1;
        if(fname == size(filenames, 2))
            fname = 1;
        else
            fname = fname + 1;
        end
    end
    filenames = ['a' 'b' 'c' 'd' 'e' 'f' 'g' 'h' 'i' 'j' 'k' 'l' 'm' 'n'...
        'o' 'p' 'q' 'r' 's' 't' 'u' 'v' 'w' 'x' 'y' 'z'];




    % GENERAL MODEL PARAMETERS:
    totaltime = 1005000; % total # of simulation updates ("time")
```

```
    popsize = 10000; % initial population size
    mutrate = 0.000000001;
    inhvar = 25000000; % a multiplier of mutation rate determining
                       %  variance in trait inheritance (var=inhvar*mutrate)
                       %  so that inhertance variance is proportional to
                       %  mutation rate
    bodymass = 5000; % initial adult bosymass
    birthmass = 300; % initial body mass at birth

    repbodymass = 0.9693; % multiplier determining at what body mass
                          %  as a fraction of the individual's inherited
                          %  adult body mass the individual begins to
                          %  reproduce
    rrate = 600; % initial time (in # simulation updates)
                 %  between successive reproductions
    littersize = 1; % initial # progeny per reproduction per individual
    littervar = (0.1*littersize)/littersize; % variance of littersize
    rratevar = (0.1*rrate)/rrate; % variance of reproduction rate
    growthrate = 57; % coefficient of body growth rate

    somdeath = 0.34; % an exponential coefficient of the somatic maintenance
equation
    somEnergy = 2231.81365913237; % initial energy invested in somatic
     %  maintenance when somdeath=0.34
                                  %  see SUPPLEMENTS

    aging = mutrate*exp([1:1000000].^somdeath); % the aging function -
                    % probability of dying for somatic reasons over time

    risk = cumsum(aging); % cumulative sum function of the aging curve
    [c riskage] = min(abs(risk-1)); % riskage - age at which risk = 1;
                                    %  explained in METHODS




    %INITIAL BODY GROWTH FUNCTION
    growthcurve = [birthmass]; % curve for body size distribution in the initial
population
                               % initial population is generated with ages
                               % ranging from 1 to riskage, they are
                               % aasigned their current body mass according
                               % to growthfunction
    for i = 2 : riskage
        growthcurve(i) = growthcurve(i-1) + 0.3*growthrate*(1 - (growthcurve(i-
1)/bodymass));
    end

    [c reprodage] = min(abs(growthcurve-(bodymass*repbodymass))); % age
                    % of beginning to reproduce when body weight reaches
                    %   bodymass*repbodymass (slightly smaller than adult)




    repenergy = birthmass*littersize/bodymass; % a koefficient of investment
                       % into reproduction
```

```
                        % used for balancing how much energy an
                        % individual can invest into
                        % different reproductive
                        % parameteres


    exthaz = 0.0001; % koefficient affecting the chance of dying of external
                        % hazards
    a = 1;
    b = 1; % exthaz, a and b are used in the Lotka-Volterra equation that
            % regulates external hazard pressure

    % INITIAL POPULATION
    initpop(1, 1:popsize) = 1:popsize; %1.
    initpop(2, 1:popsize) = randi([1, riskage], 1, popsize); %2.
    initpop(3, 1:popsize) = ones(1, popsize).*bodymass; %3.
    initpop(4, 1:popsize) = growthcurve(1, initpop(2, :)); %4.
    initpop(5, 1:popsize) = birthmass; %5.
    initpop(6, 1:popsize) = mutrate; %6.
    initpop(7, 1:popsize) = rrate; %7.
    initpop(8, 1:popsize) = littersize; %8.
    initpop(9, 1:popsize) = somdeath; %9.
    initpop(10, 1:popsize) = reprodage; %10.
    initpop(11, 1:popsize) = somEnergy; %11.

    %1. individual ID (used in mixed genotype experiments to identify genotype)
    %2. current age
    %3. inherited body mass
    %4. current body mass
    %5. inherited birth mass
    %6. inherited mutation rate
    %7. inherited reproduction rate
    %8. inherited litter size
    %9. parameter of somatic death probability function (somdeath) in the aging
         % function
    %10. age when beginning to reproduce
    %11. energy invested in somatic maintenance (explained in METHODS)

    if(newrun) % initial population is created at the beginning of simulation
        population = initpop;
    end

    %THE CORE SIMULATION RUN
    for timeunit = timeun : totaltime

        disp(timeunit);

        % STORAGE MATRICES KEEP TRACK OF POPULATION PARAMETERS THROUGHOUT
SIMULATION
        biomassdyn(timeunit) = sum(population(4, :))/sum(initpop(4, :));
        popsizedyn(timeunit) = size(population, 2)/size(initpop,2);
        bodymassevol(timeunit) = mean(population(3, :));
        birthmassevol(timeunit) = mean(population(5, :));
        littersizeevol(timeunit) = mean(population(8, :));
        mutrateevol(timeunit) = mean(population(6, :));
        rrateevol(timeunit) = mean(population(7, :));
```

```
        lifespanevol(timeunit) = 1/mean(population(9, :));




        %========================= REPRODUCTION ==========================

        % potreprodpop (potentially reproducing population) collects mature
% subpopulation
        potreprodpop = population(:, population(2, :)-population(10, :)>0);

        % variance is introduced in time between reproductions
        reprodvars = round(normrnd(rrate, rratevar));

        % reprodpop (reproducing population) collects individuals that are
        % past their period between reproduction and are due reproducing
% (+ some additional variance)
        reprodpop = potreprodpop(:, rem(potreprodpop(2, :)-potreprodpop(10, :),
reprodvars) == 0);


        % copies of their parent individual are created as their progeny -
        % newgen
        newgen = zeros(size(reprodpop, 1), 1);
        for i = 1 : size(reprodpop, 2)
            if(~isempty(reprodpop))
                progeny = repmat(reprodpop(1:size(reprodpop, 1), i), 1,
round(normrnd(littersize, littervar)));
                newgen = [newgen, progeny];
            end
        end
        newgen = newgen(:, 2:end);

        % number of new offspring is collected into a storage matrix
        births(timeunit) = size(newgen, 2);

        % inherited variance (proportional to parent's mutation rate)
        % modifies parental parameters producing varying offspring
        newgen(2, :) = 1;
        newgen(3, :) = real(newgen(3, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(3, :)));
        newgen(4, :) = real(newgen(5, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(5, :)));
        newgen(5, :) = real(newgen(5, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(5, :)));
        newgen(5, newgen(5, :) > 0.5.*newgen(3, :)) = 0.5.*newgen(3, newgen(5, :) >
0.5.*newgen(3, :));
        newgen(6, :) = real(newgen(6, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(6, :)));
        newgen(8, :) = real(newgen(8, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(8, :)));
        newgen(7, :) = real(newgen(5, :).*newgen(8, :)./newgen(3,
:)./repenergy.*rrate);
        newgen(10, :) = 0;
```

```
        newgen(11, :) = real(newgen(11, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(11, :)));

        % the somatic maintenance (somdeath) parameter of the aging
        % function is calculated based on the somatic maintenance energy
        % investment with inherited variance (see METHODS)
        newgen(9, :) = real((0.00000072523237903965.*(log(newgen(11, :)).^6))...
            -(0.0000458064654458169.*(log(newgen(11, :)).^5))...
            +(0.00123267215690707.*(log(newgen(11, :)).^4))...
            -(0.0183381238349637.*(log(newgen(11, :)).^3))...
            +(0.162769338153511.*(log(newgen(11, :)).^2))...
            -(0.863957066277595.*(log(newgen(11, :)).^1))...
            + 2.46992883606531000000);

        % new offpsring is added to the population
        population = [population, newgen];



        %========================= MORTALITY ==========================

        %MORTALITY CAUSED BY SOMATIC/PHYSIOLOGICAL FACTORS

        % individual probabilities of dying of somatic causes during this update
        probsdeath = [];

        % version 1 (standard) = death rates are affected by body mass
         % (increased somatic risk)
         % and the performance of the somtic maintenance program in
         % mitigating somatic risk
        probsdeath = population(6, :).*(population(4, :)/bodymass)...
            .*exp(population(2, :).^population(9, :));


        % version 2 = somatic cost unrelated
    % (used when the "body mass" parameter is converted into
         % a trait that is selected for but does not affect somatic risks)
%       probsdeath = population(6, :)...
%           .*exp(population(2, :).^population(9, :));

        probsdeath(probsdeath > 1) = 0;
        probsdeath(probsdeath < 0) = 0;

        % individuals actually dying of somatic causes during this update
        % based on binomial trials using probsdeath
        death = [];
        death = binornd(1, probsdeath(1, :));


        % data on mortality of somatic causes is stored in a storage matrix
        sommortality = [sommortality, population(2, death(1, :) == 1)];
        %------------------------

        % dead individuals are eliminated from the population
```

```
        population(:, death(1, :) == 1) = 0;
        population = population(:, population(1, :) > 0);



        % MORTALITY CAUSED BY EXTERNAL HAZARDS (predation, disease, etc)
        % (the Lotka-Voterra model of predator-prey dynamics was used as a basis)

        % population size-dependent external hazard pressure (exthazard)
        exthazard = exthaz...
            +((a*popsizedyn(timeunit)*exthaz) - (b*exthaz));

        % probabilities of dying of external hazards (development of bodymass
         % or other selected trait reduces chances of dying
         % of external hazards)
        extprobs = [];
        extprobs = exthazard.*(bodymass./population(4, :));
        extprobs(1, extprobs > 1) = 1;
        extprobs(1, extprobs < 0) = 0;

        % individuals actually dying of causes related to external hazards
         % based on binomial trials using extprobs
        extdeath = [];
        extdeath = binornd(1, extprobs(1, :));

        % data on mortality caused by external hazards is stored in a storage
matrix
        extmortality = [extmortality, population(2, extdeath(1, :) == 1)];
        %------------------------

        % dead individuals are eliminated from the population
        population(:, extdeath(1, :) == 1) = 0;
        population = population(:, population(1, :) > 0);



        % MORTALITY IMPOSED BY ECOSYSTEM'S CARRYING CAPACITY
         % (essentially reflects mortality caused by intra-specific competition)

        % Version 1 = used when maximum biomass is kept stable
         % (in experiments when body mass evolves)
         % (development of body mass reduces the chances of dying
         % in intra-specific competition)
        overkill = sum(population(4, :))/ sum(initpop(4, :));
        invs = 1./population(4, :);
        capprobs = invs/sum(invs);
        capprobs = capprobs-(mean(capprobs));
        capprobs = capprobs+(1-(1/overkill));

        % Version 2 = used when population size is kept stable
         % (in experiments when "body mass" is trasformed
         % into another selected trait)
         % (development of body mass or other selected trait
         % reduces the chances of dying in intra-specific competition)
%         overkill = size(population, 2) / size(initpop, 2);
```

```
%          invs = 1./population(4, :);
%          capprobs = invs/sum(invs);
%          capprobs = capprobs-(mean(capprobs));
%          capprobs = capprobs+(1-(1/overkill));

         capprobs(capprobs < 0) = 0;
         capprobs(capprobs > 1) = 1;

         % individuals actually dying in intra-specific competitioN
          % based on binomial trials using extprobs
         capdeath = [];
         capdeath = binornd(1, capprobs(1, :));



         % data on mortality caused by intra-specific competition
          % is stored in a storage matrix
         capmortality = [capmortality, population(2, capdeath(1, :) == 1)];

         % dead individuals are eliminated from the population
         population(:, capdeath(1, :) == 1) = 0;
         population = population(:, population(1, :) > 0);




         % ============UPDATING AGE AND BODY MASS DUE TO GROWTH==============
         population(2, :) = population(2, :) + 1;
         population(4, :) = population(4, :) + 0.3*growthrate*(1 - (population(4,
:)./population(3, :)));



         % =============ASSIGNING MATURITY AGES FOR THE NEW OFFSPRING========
         newborns = find(population(10, :) == 0);
         grownnewborns = find(population(4, :)./population(3, :) >= repbodymass);
         mature = intersect(newborns, grownnewborns);
         population(10, mature) = population(2, mature);



         % ================SAVING VARIABLES INTO FILES=======================
         if(fname > size(filenames, 2))
             fname = 1;
             iter = iter+1;
         end
         if(rem(timeunit, 15000) == 0)
             its(1:iter) = 'z';
             save(['D:\' its filenames(fname) '.mat']);
         end
         if(rem(timeunit, 30000) == 0)
             fname = fname + 1;
         end

```

```
        % =========REMOVAL OF OCCASIONAL NaNs==============================
        population(:, isnan(sum(population(:, :)))) = 0;
        population = population(:, population(1, :) > 0);

    end


    % =========ENTIRE SIMULATION RUN IS SAVED IN A FILE====================
    these(1:iteration) = '0';
    save(['D:\' these 'zzh.mat']);
end

% ======TOTAL SIMULATION TIME MEASURES=====================================
time = toc;
hours = floor(time / 3600);
time = time - hours * 3600;
mins = floor(time / 60);
secs = time - mins * 60;
secs = round(secs);

fprintf('Execution time (HH:MM:SS) - %d:%d:%d        \n\n', hours, mins, secs);
```

b. ***Competitive model for competition between two genotypes.***

```
for iteration = 1 : 25
    disp(iteration);

    newrun = true;

    if(newrun)
        clearvars -except newrun iteration
        fname = 1;
        timeun = 1;
        iter = 1;

        % OUTPUT STORAGE
        sommortality = []; % counts of mortality for somatic reasons
        extmortality = []; % counts of mortality caused by external hazard
        capmortality = []; % counts of mortality imposed by ecosystem's
                            %  carrying capacity (intra-specific competition)
        biomassdyn = [];   % population biomas dynamics over time
        popsizedyn = [];   % population size dynamics over time
        births = [];       % counts of new births over time

        fracspec1 = []; % fraction of genotype 1

        % individual parameters for genotype 1
        bodymassevol1 = []; % population's average bodymass over time
        birthmassevol1 = []; % population's average birthmass over time
        littersizeevol1 = []; % population's average litter size over time
        mutrateevol1 = []; % population's average mutation rate over time
        rrateevol1 = []; % population's average reproduction rate over time
        lifespanevol1 = []; % population's average somatic maintenance
```

```
                            %  coefficient over time

        % individual parameters for genotype 2
        bodymassevol2 = []; % population's average bodymass over time
        birthmassevol2 = []; % population's average birthmass over time
        littersizeevol2 = []; % population's average litter size over time
        mutrateevol2 = []; % population's average mutation rate over time
        rrateevol2 = []; % population's average reproduction rate over time
        lifespanevol2 = []; % population's average somatic maintenance
                            %  coefficient over time
    else
        timeun = timeunit + 1;
        if(fname == size(filenames, 2))
            fname = 1;
        else
            fname = fname + 1;
        end
    end
    filenames = ['a' 'b' 'c' 'd' 'e' 'f' 'g' 'h' 'i' 'j' 'k' 'l' 'm' 'n'...
        'o' 'p' 'q' 'r' 's' 't' 'u' 'v' 'w' 'x' 'y' 'z'];

   % GENERAL MODEL PARAMETERS:
    totaltime = 1005000; % total # of simulation updates ("time")
    popsize = 10000; % initial population size
    mutrate = 0.000000001;
    inhvar = 25000000; % a multiplier of mutation rate determining
                       %  variance in trait inheritance (var=inhvar*mutrate)
                       %  so that inhertance variance is proportional to
                       %  mutation rate
    bodymass = 5000; % initial adult bosymass
    birthmass = 300; % initial body mass at birth

    repbodymass = 0.9693; % multiplier determining at what body mass
                          %  as a fraction of the individual's inherited
                          %  adult body mass the individual begins to
                          %  reproduce
    rrate = 600; % initial time (in # simulation updates)
                 %  between successive reproductions
    littersize = 1; % initial # progeny per reproduction per individual
    littervar = (0.1*littersize)/littersize; % variance of littersize
    rratevar = (0.1*rrate)/rrate; % variance of reproduction rate
    growthrate = 57; % coefficient of body growth rate

    somdeath = 0.34; % an exponential coefficient of the somatic maintenance
equation
    somEnergy = 2231.81365913237; % initial energy invested in somatic
     %  maintenance when somdeath=0.34
                                  %  see SUPPLEMENTS

    aging = mutrate*exp([1:1000000].^somdeath); % the aging function -
                    % probability of dying for somatic reasons over time

    risk = cumsum(aging); % cumulative sum function of the aging curve
    [c riskage] = min(abs(risk-1)); % riskage - age at which risk = 1;
                                    %  explained in METHODS

```

```
    %INITIAL BODY GROWTH FUNCTION
    growthcurve = [birthmass]; % curve for body size distribution in the initial
population
                               % initial population is generated with ages
                               % ranging from 1 to riskage, they are
                               % aasigned their current body mass according
                               % to growthfunction
    for i = 2 : riskage
        growthcurve(i) = growthcurve(i-1) + 0.3*growthrate*(1 - (growthcurve(i-
1)/bodymass));
    end

    [c reprodage] = min(abs(growthcurve-(bodymass*repbodymass))); % age
                    % of beginning to reproduce when body weight reaches
                    %   bodymass*repbodymass (slightly smaller than adult)



    repenergy = birthmass*littersize/bodymass; % a koefficient of investment
                        % into reproduction
                        % used for balancing how much energy an
                        % individual can invest into
                        % different reproductive
                        % parameteres


    exthaz = 0.0001; % koefficient affecting the chance of dying of external
                        % hazards
    a = 1;
    b = 1; % exthaz, a and b are used in the Lotka-Volterra equation that
            % regulates external hazard pressure

    %initial population
    initpop(1, 1:ceil(popsize/2)) = 1; %1 genotype 1
    initpop(1, ceil(popsize/2)+1:popsize) = 2; %1 genotype 2
    initpop(2, 1:popsize) = randi([1, maxage], 1, popsize); %2
    initpop(3, 1:popsize) = ones(1, popsize).*bodymass; %3
    initpop(4, 1:popsize) = growthcurve(1, initpop(2, :)); %4
    initpop(5, 1:popsize) = birthmass; %5
    initpop(6, 1:ceil(popsize/2)) = mutrate/10; %6 genotype 1
    initpop(6, ceil(popsize/2)+1:popsize) = mutrate; %6 genotype 2
    initpop(7, 1:popsize) = rrate; %7
    initpop(8, 1:popsize) = littersize; %8
    initpop(9, 1:popsize) = somdeath; %9
    initpop(10, 1:popsize) = reprodage; %10
    initpop(11, 1:popsize) = somEnergy; %11

    %1. individual ID (used in mixed genotype experiments to identify genotype)
    %2. current age
    %3. inherited body mass
    %4. current body mass
    %5. inherited birth mass
    %6. inherited mutation rate
    %7. inherited reproduction rate
    %8. inherited litter size
    %9. parameter of somatic death probability function (somdeath) in the aging
```

```
         % function
    %10. age when beginning to reproduce
    %11. energy invested in somatic maintenance (explained in METHODS)



    if(newrun) % initial population is created at the beginning of simulation
        population = initpop;
    end


    %THE CORE SIMULATION RUN
    for timeunit = timeun : totaltime
        disp(timeunit);

         % STORAGE MATRICES KEEP TRACK OF POPULATION PARAMETERS THROUGHOUT
SIMULATION
        biomassdyn(timeunit) = sum(population(4, :))/sum(initpop(4, :));
        popsizedyn(timeunit) = size(population, 2)/size(initpop,2);

        bodymassevol1(timeunit) = mean(population(3, population(1,:)==1));
        birthmassevol1(timeunit) = mean(population(5, population(1,:)==1));
        littersizeevol1(timeunit) = mean(population(8, population(1,:)==1));
        mutrateevol1(timeunit) = mean(population(6, population(1,:)==1));
        rrateevol1(timeunit) = mean(population(7, population(1,:)==1));
        lifespanevol1(timeunit) = 1/mean(population(9, population(1,:)==1));

        bodymassevol2(timeunit) = mean(population(3, population(1,:)==2));
        birthmassevol2(timeunit) = mean(population(5, population(1,:)==2));
        littersizeevol2(timeunit) = mean(population(8, population(1,:)==2));
        mutrateevol2(timeunit) = mean(population(6, population(1,:)==2));
        rrateevol2(timeunit) = mean(population(7, population(1,:)==2));
        lifespanevol2(timeunit) = 1/mean(population(9, population(1,:)==2));

        fracspec1(timeunit) = numel(population(1, population(1,:) ==
1))/size(population, 2)*100;

         %========================= REPRODUCTION ==========================

        % potreprodpop (potentially reproducing population) collects mature
        % subpopulation
        potreprodpop = population(:, population(2, :)-population(10, :)>0);

        % variance is introduced in time between reproductions
        reprodvars = round(normrnd(rrate, rratevar));

        % reprodpop (reproducing population) collects individuals that are
        % past their period between reproduction and are due reproducing
        % (+ some additional variance)
        reprodpop = potreprodpop(:, rem(potreprodpop(2, :)-potreprodpop(10, :),
reprodvars) == 0);


        % copies of their parent individual are created as their progeny -
```

```
        % newgen
        newgen = zeros(size(reprodpop, 1), 1);
        for i = 1 : size(reprodpop, 2)
            if(~isempty(reprodpop))
                progeny = repmat(reprodpop(1:size(reprodpop, 1), i), 1,
round(normrnd(littersize, littervar)));
                newgen = [newgen, progeny];
            end
        end
        newgen = newgen(:, 2:end);

        % number of new offspring is collected into a storage matrix
        births(timeunit) = size(newgen, 2);

        % inherited variance (proportional to parent's mutation rate)
        % modifies parental parameters producing varying offspring
        newgen(2, :) = 1;
        newgen(3, :) = real(newgen(3, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(3, :)));
        newgen(4, :) = real(newgen(5, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(5, :)));
        newgen(5, :) = real(newgen(5, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(5, :)));
        newgen(5, newgen(5, :) > 0.5.*newgen(3, :)) = 0.5.*newgen(3, newgen(5, :) >
0.5.*newgen(3, :));
        % mutation rates are fixed and differ between two genotypes
        % newgen(6, newgen(1, :) == 1) = real(newgen(6, newgen(1, :) == 1) +
(normrnd(0, newgen(6, newgen(1, :) == 1)*inhvar).* newgen(6, newgen(1, :) == 1)));
        newgen(8, :) = real(newgen(8, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(8, :)));
        newgen(7, :) = real(newgen(5, :).*newgen(8, :)./newgen(3,
:)./repenergy.*rrate);
        newgen(10, :) = 0;
        newgen(11, :) = real(newgen(11, :) + (normrnd(0, newgen(6, :)*inhvar).*
newgen(11, :)));

       % the somatic maintenance (somdeath) parameter of the aging
        % function is calculated based on the somatic maintenance energy
        % investment with inherited variance (see METHODS)
        newgen(9, :) = real((0.00000072523237903965.*(log(newgen(11, :)).^6))...
            -(0.0000458064654458169.*(log(newgen(11, :)).^5))...
            +(0.00123267215690707.*(log(newgen(11, :)).^4))...
            -(0.0183381238349637.*(log(newgen(11, :)).^3))...
            +(0.162769338153511.*(log(newgen(11, :)).^2))...
            -(0.863957066277595.*(log(newgen(11, :)).^1))...
            + 2.46992883606531000000);

        % new offpsring is added to the population
        population = [population, newgen];



        %========================= MORTALITY ==========================

        %MORTALITY CAUSED BY SOMATIC/PHYSIOLOGICAL FACTORS
```

```
        % individual probabilities of dying of somatic causes during this update
        probsdeath = [];

        % version 1 (standard) = death rates are affected by body mass
         % (increased somatic risk)
         % and the performance of the somtic maintenance program in
         % mitigating somatic risk
        probsdeath = population(6, :).*(population(4, :)/bodymass)...
            .*exp(population(2, :).^population(9, :));


        % version 2 = somatic cost unrelated
    % (used when the "body mass" parameter is converted into
         % a trait that is selected for but does not affect somatic risks)
%       probsdeath = population(6, :)...
%           .*exp(population(2, :).^population(9, :));

        probsdeath(probsdeath > 1) = 0;
        probsdeath(probsdeath < 0) = 0;

        % individuals actually dying of somatic causes during this update
        % based on binomial trials using probsdeath
        death = [];
        death = binornd(1, probsdeath(1, :));


        % data on mortality of somatic causes is stored in a storage matrix
        sommortality = [sommortality, population(2, death(1, :) == 1)];
        %------------------------

        % dead individuals are eliminated from the population
        population(:, death(1, :) == 1) = 0;
        population = population(:, population(1, :) > 0);



        % MORTALITY CAUSED BY EXTERNAL HAZARDS (predation, disease, etc)
        % (the Lotka-Voterra model of predator-prey dynamics was used as a basis)

        % population size-dependent external hazard pressure (exthazard)
        exthazard = exthaz...
            +((a*popsizedyn(timeunit)*exthaz) - (b*exthaz));

        % probabilities of dying of external hazards (development of bodymass
         % or other selected trait reduces chances of dying
         % of external hazards)
        extprobs = [];
        extprobs = exthazard.*(bodymass./population(4, :));
        extprobs(1, extprobs > 1) = 1;
        extprobs(1, extprobs < 0) = 0;

        % individuals actually dying of causes related to external hazards
         % based on binomial trials using extprobs
```

```
        extdeath = [];
        extdeath = binornd(1, extprobs(1, :));

        % data on mortality caused by external hazards is stored in a storage
matrix
        extmortality = [extmortality, population(2, extdeath(1, :) == 1)];
        %------------------------

        % dead individuals are eliminated from the population
        population(:, extdeath(1, :) == 1) = 0;
        population = population(:, population(1, :) > 0);



        % MORTALITY IMPOSED BY ECOSYSTEM'S CARRYING CAPACITY
         % (essentially reflects mortality caused by intra-specific competition)

        % Version 1 = used when maximum biomass is kept stable
         % (in experiments when body mass evolves)
         % (development of body mass reduces the chances of dying
         % in intra-specific competition)
        overkill = sum(population(4, :))/ sum(initpop(4, :));
        invs = 1./population(4, :);
        capprobs = invs/sum(invs);
        capprobs = capprobs-(mean(capprobs));
        capprobs = capprobs+(1-(1/overkill));

        % Version 2 = used when population size is kept stable
         % (in experiments when "body mass" is trasformed
         % into another selected trait)
         % (development of body mass or other selected trait
         % reduces the chances of dying in intra-specific competition)
%         overkill = size(population, 2) / size(initpop, 2);
%         invs = 1./population(4, :);
%         capprobs = invs/sum(invs);
%         capprobs = capprobs-(mean(capprobs));
%         capprobs = capprobs+(1-(1/overkill));

        capprobs(capprobs < 0) = 0;
        capprobs(capprobs > 1) = 1;

        % individuals actually dying in intra-specific competitioN
         % based on binomial trials using extprobs
        capdeath = [];
        capdeath = binornd(1, capprobs(1, :));



        % data on mortality caused by intra-specific competition
         % is stored in a storage matrix
        capmortality = [capmortality, population(2, capdeath(1, :) == 1)];

        % dead individuals are eliminated from the population
        population(:, capdeath(1, :) == 1) = 0;
        population = population(:, population(1, :) > 0);
```

```
        % ============UPDATING AGE AND BODY MASS DUE TO GROWTH==============
        population(2, :) = population(2, :) + 1;
        population(4, :) = population(4, :) + 0.3*growthrate*(1 - (population(4, :)./population(3, :)));



        % =============ASSIGNING MATURITY AGES FOR THE NEW OFFSPRING========
        newborns = find(population(10, :) == 0);
        grownnewborns = find(population(4, :)./population(3, :) >= repbodymass);
        mature = intersect(newborns, grownnewborns);
        population(10, mature) = population(2, mature);



        % ================SAVING VARIABLES INTO FILES=======================
        if(fname > size(filenames, 2))
            fname = 1;
            iter = iter+1;
        end
        if(rem(timeunit, 15000) == 0)
            its(1:iter) = 'z';
            save(['D:\' its filenames(fname) '.mat']);
        end
        if(rem(timeunit, 30000) == 0)
            fname = fname + 1;
        end


        % =========REMOVAL OF OCCASIONAL NaNs==============================
        population(:, isnan(sum(population(:, :)))) = 0;
        population = population(:, population(1, :) > 0);

    end


    % =========ENTIRE SIMULATION RUN IS SAVED IN A FILE====================
    these(1:iteration) = '0';
    save(['D:\' these 'zzh.mat']);
end

% ======TOTAL SIMULATION TIME MEASURES=====================================
time = toc;
hours = floor(time / 3600);
time = time - hours * 3600;
mins = floor(time / 60);
secs = time - mins * 60;
secs = round(secs);

fprintf('Execution time (HH:MM:SS) - %d:%d:%d        \n\n', hours, mins, secs);
```

Section 2. Evolution of reproductive traits under fixed adult body mass. As shown in Fig. S1, the early simulation period is linked with rapid evolution of reproduction rate and body mass at birth, which is likely to have caused positive selection for gMR shown in Fig. 2B. Litter size, however, in our simulations did not show any consistent evolution under this condition.

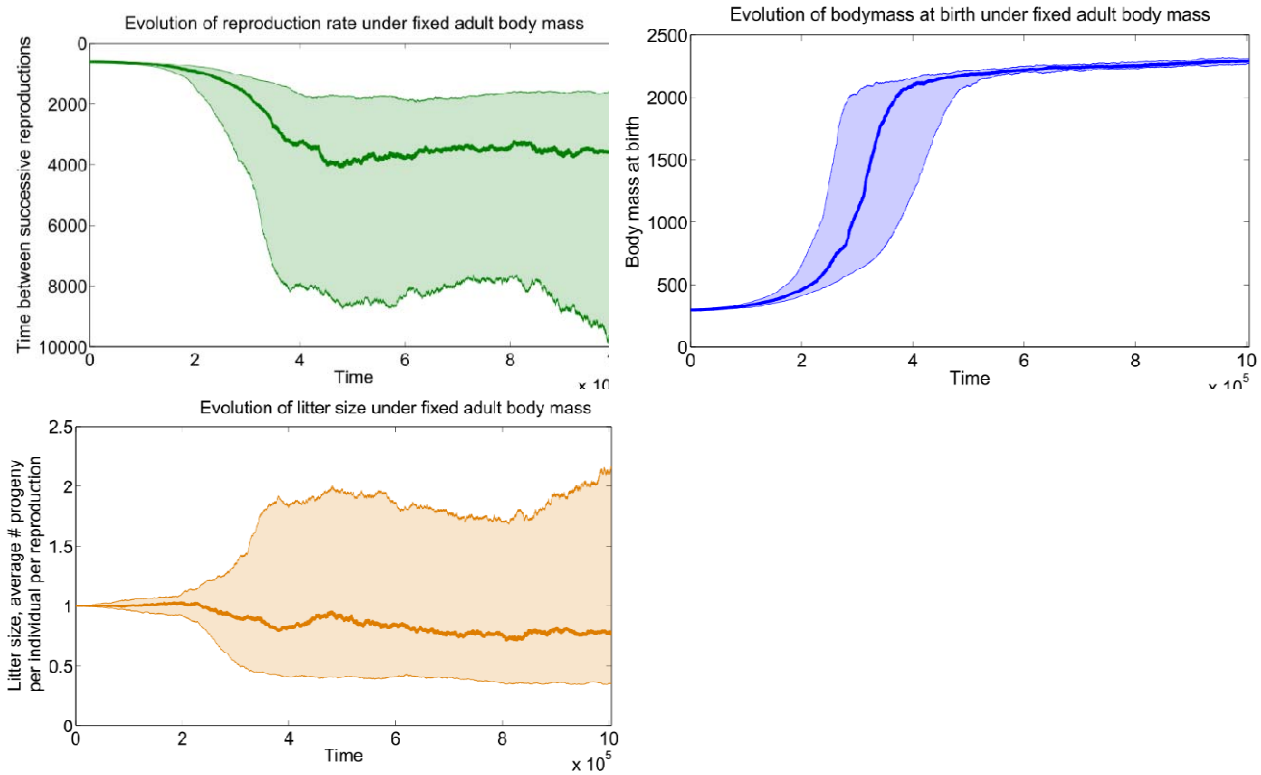


Fig. S1. Evolution of reproductive parameters in simulations with fixed adult body mass.

Section 3. All-cause age-dependent mortality in the model. The model recapitulates a typical age-dependent mortality chart for wild animals (Fig. S2). Early life is accompanied with the very high mortality rates which drop until maturity. Fig. S3 demonstrates natural log data.

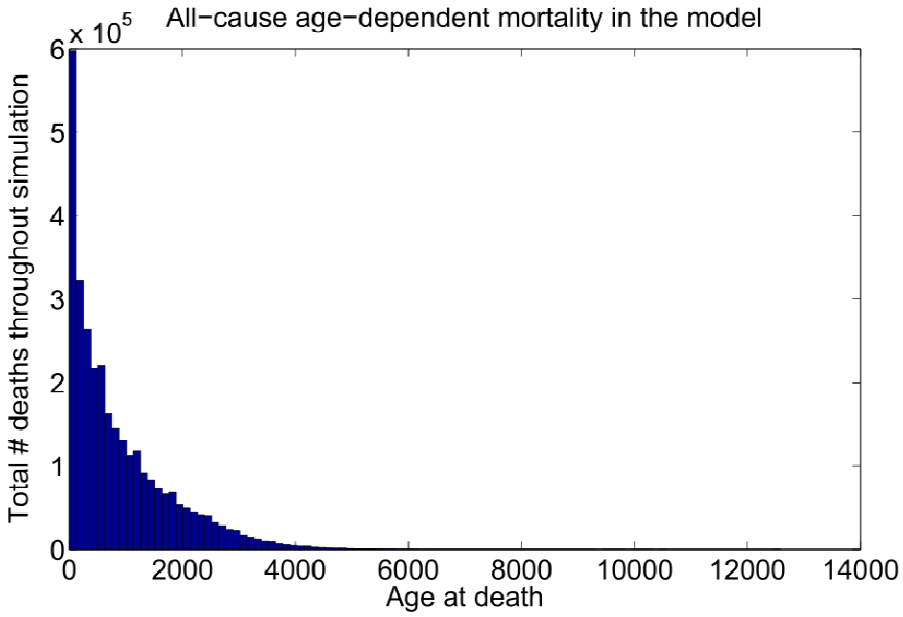


Fig. S2. Total mortality by age in absolute numbers.

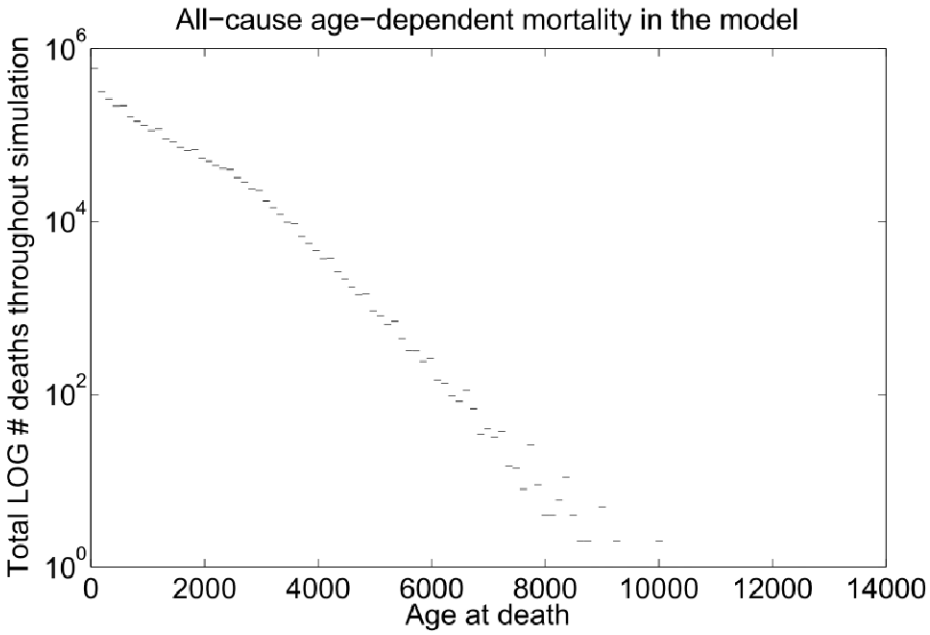


Fig. S3. Total mortality by age in log-absolute numbers.

Section 4. The aging curve calculations. In order to model inherited variation of SMP strength, we needed a method of linearly varying SMP (e.g. +1%, -5% etc). Since the *Som* parameter in Eq. 1 is in a complex non-linear relationship with the resulting aging curve, this parameter is not suitable for such manipulation. We therefore reasoned that the best representation of the efficiency of SMP is using the area under the physiological mortality curve as a measure of the general efficiency of SMP over lifetime. Eq. 1 generates the probability D_A of dying of physiological causes at age A. Its cumulative probability function generates probability *D(A)* of dying by age A. *D(A)* thus is directly related with longevity (like the human mortality curve). However, the *D(A)* function decelerates as the cumulative probability of dying approaches 1 (it can be seen in the human mortality curve in Fig. 1B and is a general property of cumulative probability functions). In order to avoid these effects, we did not use the area under the *D(A)* function as a measure of SMP strength, but instead we applied the area under the cumulative sum function of the D_A probability, as shown in the figure below, starting from the simulated age 1 and until the age at which this function reaches 1. In Fig. S4, the green curve represents extended longevity compared to the blue curve, since the sum of its probabilities of dying accumulates more slowly (slower aging). As a result, the area under the green curve is larger, corresponding to a stronger SMP program. In order to model inherited variation in SMP, we used this area as a representation of the SMP strength. The area was stochastically varied from generation to generation as explained in Methods, and its new value in progeny was used to calculate the *Som* parameter for Eq. 1 (determines the probability of dying at age A). The calculation was based on the observation that the area shown in Fig. S4 demonstrates a strong non-linear log-log relationship with the *Som* parameter (polynomial regression of the 6th order; R^2>0.99999) as shown in Fig. S5.

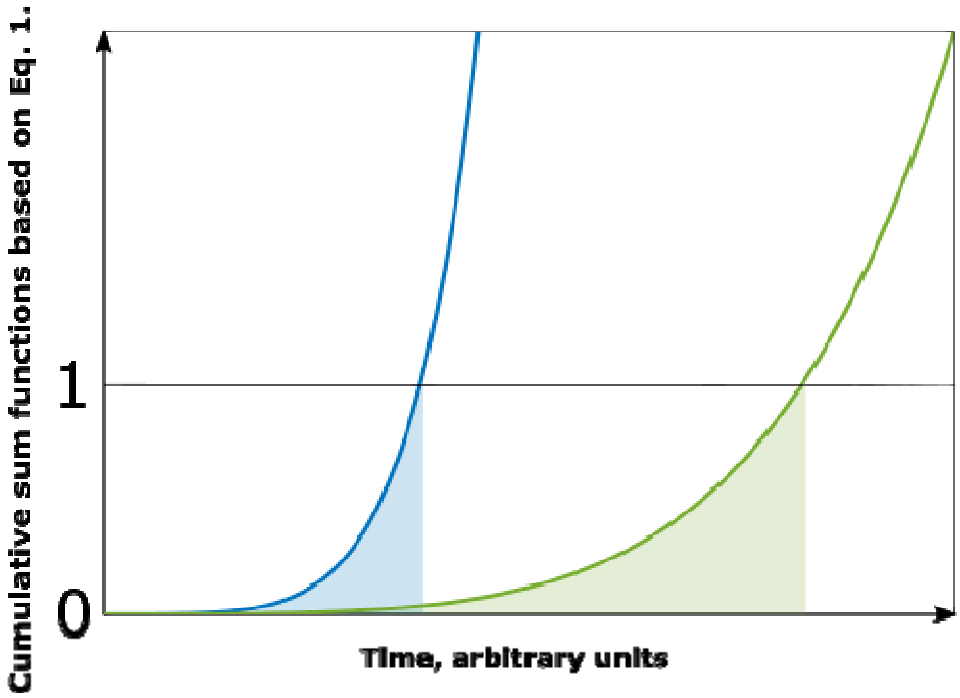


Fig. S4. Area under cumulative sum function of Eq. 1 as a measure of the relative efficiency of SMP.

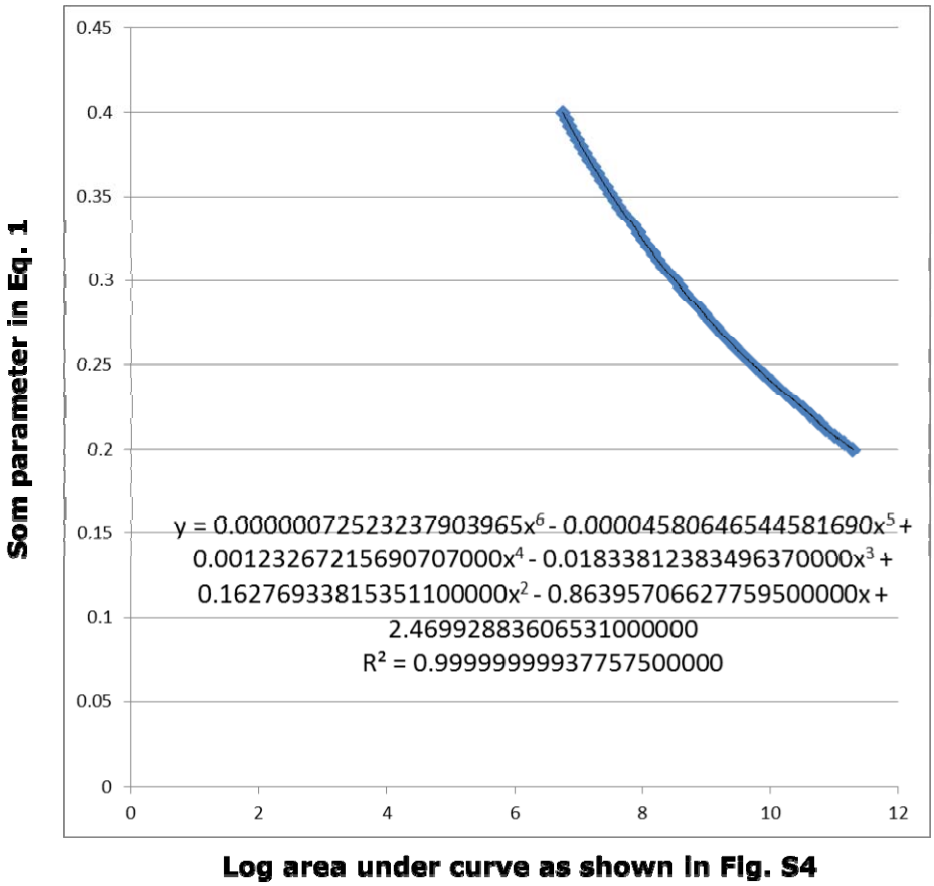


Fig. S5. Relationship between log-area in Fig. S4 (log-efficiency of SMP) and the *Som* parameter in Eq. 1 (probability of dying at age A).

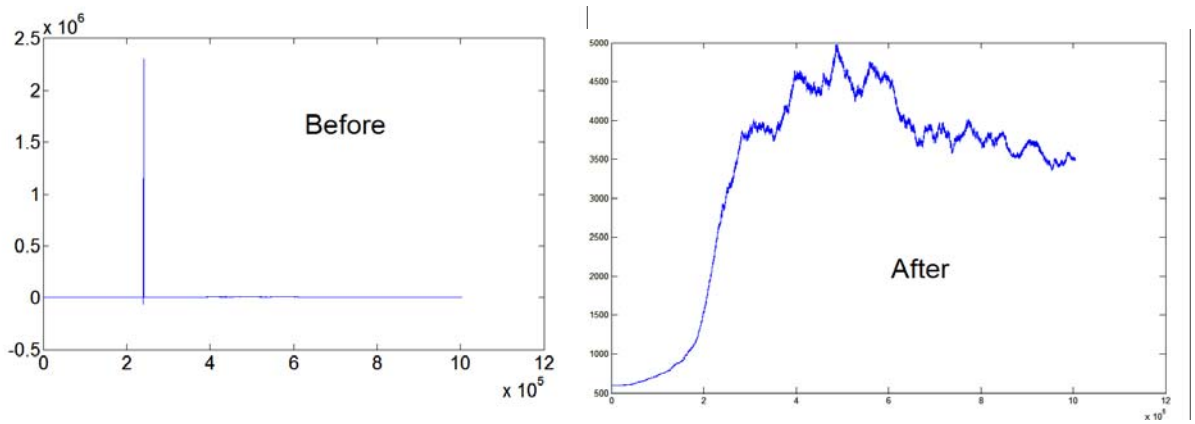
Section 5. Removal of outliers. Occasionally the model demonstrated unnatural “spikes” in the evolution of some traits under some conditions. We had to apply the following code to remove them:

```
input = aaccbmbllsev_lit(22,:); % a certain problematic model run

threshold = 0.15; % arbitrary value

for row = 1 : size(input, 1)
    for col = 2 : size(input, 2)
        if input(row, col-1)/input(row, col) > 1+threshold ||...
                input(row, col-1)/input(row, col) < 1-threshold
            input(row, col) = input(row, col-1);
        end
    end
end
```

The illustration below demonstrates an example (from a standard condition run) of the result:



The parameter “threshhold” required manual alteration until the spike was cleaned by the code above. Such spikes were visibly outstanding from the normal trend, so that the trend in the evolving trait continued after the spike with values similar to those immediately preceding the spike, indicating that the spikes were some artifacts that neither related to nor influenced the modeled trait evolution. We were not able to determine the source of such spikes

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1447

1448 ## Acknowledgments

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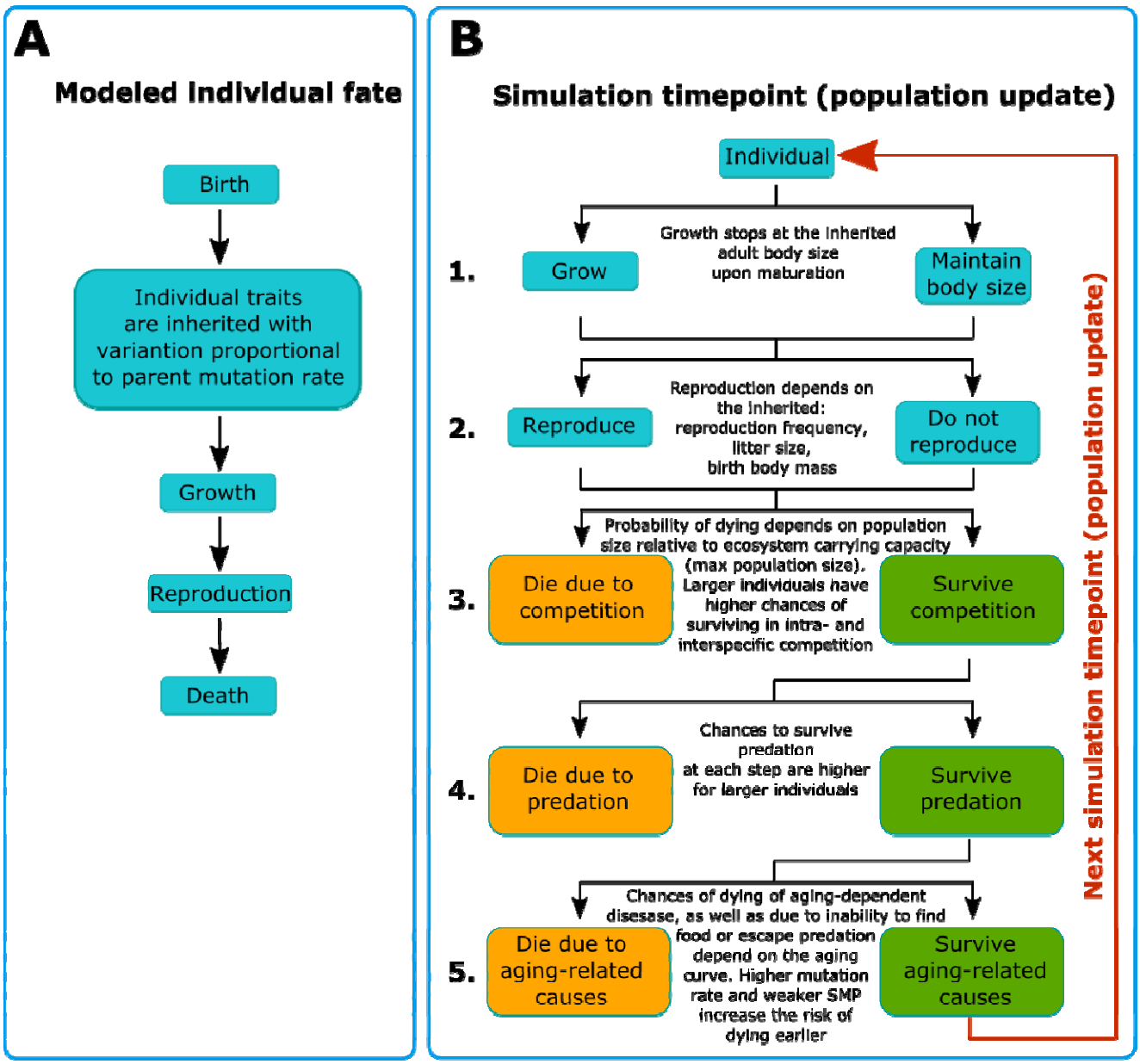
1456 ## Figures and Legends



1457

1458 **Fig. 1. A scheme of the model simulations.** (**A**) Stages of an individual simulated lifespan. (**B**) At each
1459 timepoint during the simulation the modeled population undergoes 5 main updates: 1. Individuals that have not
1460 reached maturity increase their body mass following their growth curve, starting from the initial birth mass and up
1461 until they reach their inherited body mass (parent body mass with variation proportional to parent mutation rate);
1462 mature individuals remain at the same body mass. 2. Each individual past maturation reproduces with a certain
1463 inherited frequency of reproduction, producing on average an inherited number of progeny per litter, each
1464 progeny's birth body mass is inherited from parent with variation proportional to parent's mutation rate. Each

individual is tried in a binomial trial with a small probability (at each timepoint) of dying of three main causes: 3. Death following limitations imposed by ecosystem carrying capacity which allows for a certain maximum population size and promotes intra-specific and inter-specific competition for resources if population numbers exceed this capacity. 4. Death caused by predation is modelled based on the Lotka-Volterra model of predator-prey interaction (*34, 35*). 5. Death caused by physiological aging, such as due to cancer, frailty or other age-related causes; the probability is negilgible early in life but increases exponentially with age; the speed of increase of the probability of death caused by aging depends on an individual's aging profile which is determined by the aging curve as explained in **Fig. 2A**, "Theoretical introduction to the modeling" subsection of **Results** and "The somatic maintenance program paradigm" subsection of **Methods**.

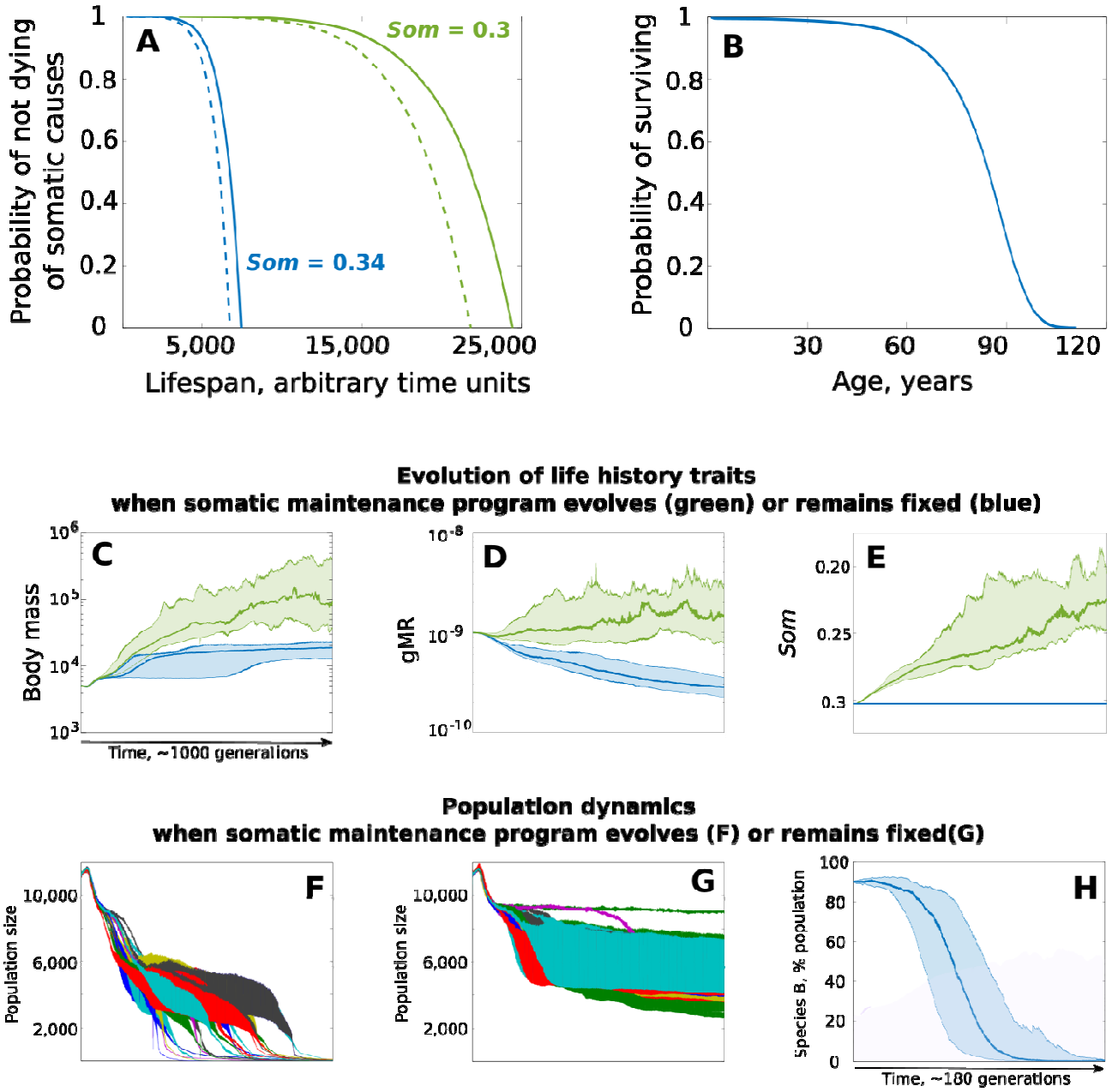
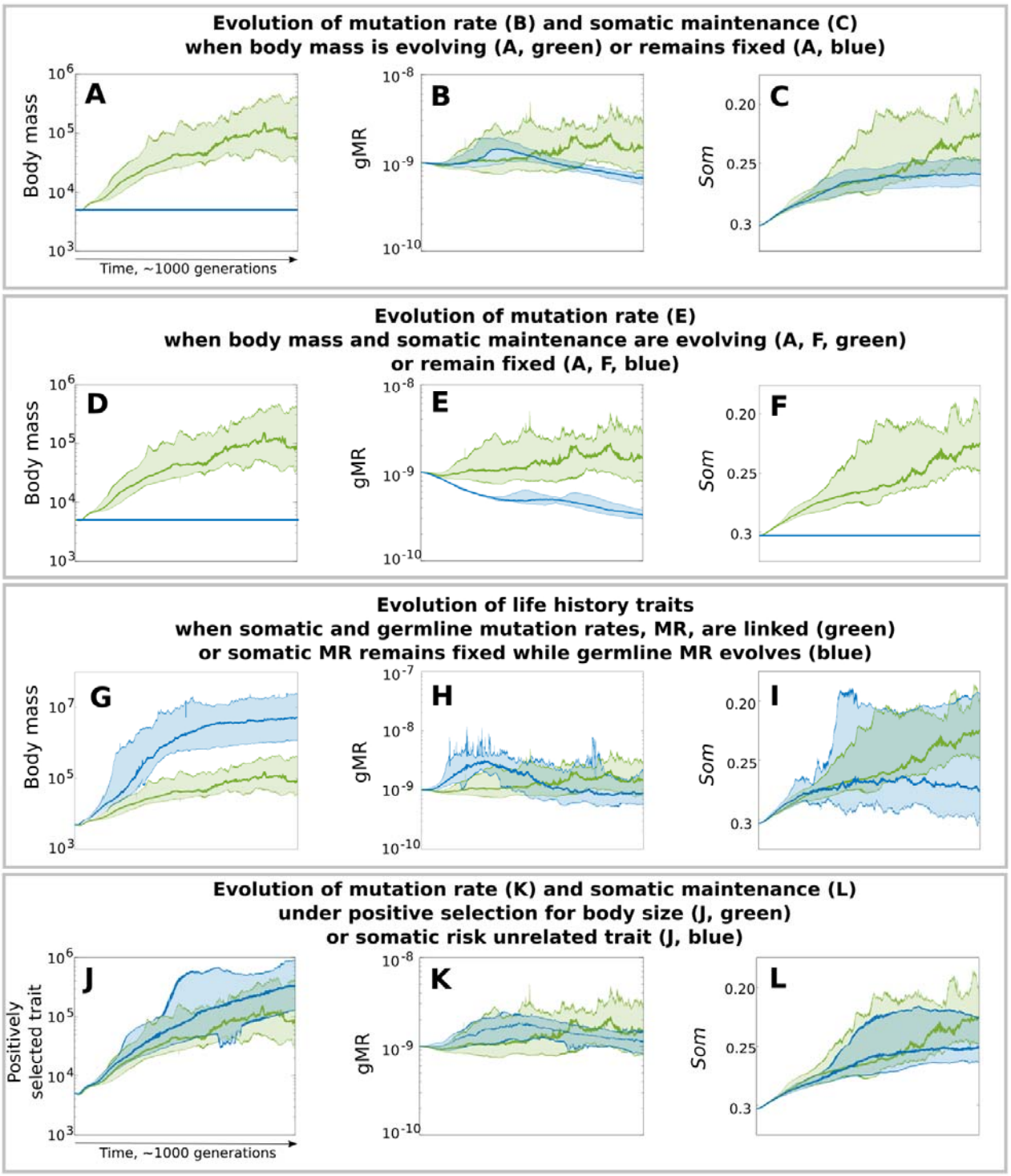


Fig. 2. The effect of SMP evolution on the evolution of body mass and mutation rate. (**A**) physiological/aging related mortality curves generated based on the cumulative distribution function of D_A (Eq. 1). Colors represent the effect of the *Som* (SMP) parameter (Eq. 1). Dotted lines were generated by elevating mutation rate 2-fold. (**B**) modern human mortality in the U.S.A (https://www.ssa.gov). (**C-E**) evolution of life history traits under positive selection for body size. (**F,G**) population size dynamics when SMP can evolve (corresponds to green in *C-E*) or SMP evolution is blocked (blue in *C-E*); colors indicate individual populations. (**H**) relative frequency of Species B (SMP evolution blocked, blue in *C-E*) in a mixed population with Species A (SMP can evolve, green in *C-E*). For

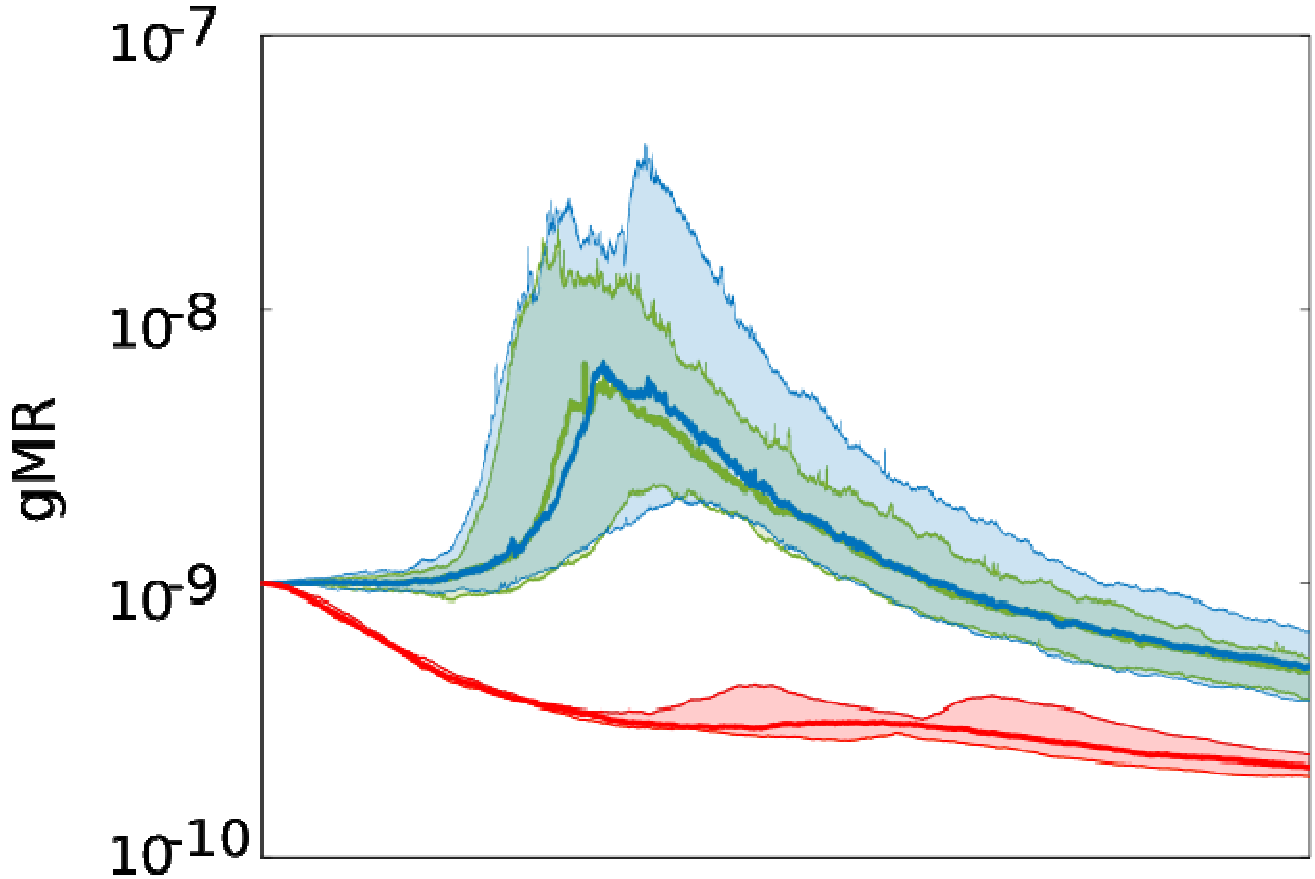
1484 (*C*), (*D*), (*E*) and (*H*) (and similar graphs in other figures), 25 simulations are combined, with the dark line
1485 reflecting the mean and shaded area denoting the 95% confidence intervals.



1486

1487 **Fig. 3. Evolution of body mass, gMR and SMP under various regimens of selection.** Separate experiments
1488 are stacked as indicated in their subtitles. The layout: left – body size, middle – gMR, right – SMP (the *Som*

1489 parameter in Eq. 1) is maintained as in Fig. 2C-E. Green – the standard condition (as green in Fig. 2C-E); blue –
1490 alternative conditions with fixed values of a trait (blue horizontal line in *A,D,F*), when gMR and sMR are dislinked
1491 so that the somatic cost is fixed while gMR can evolve (blue in G-I), and under selection for a somatic risk
1492 unrelated trait (blue in *J-L*).

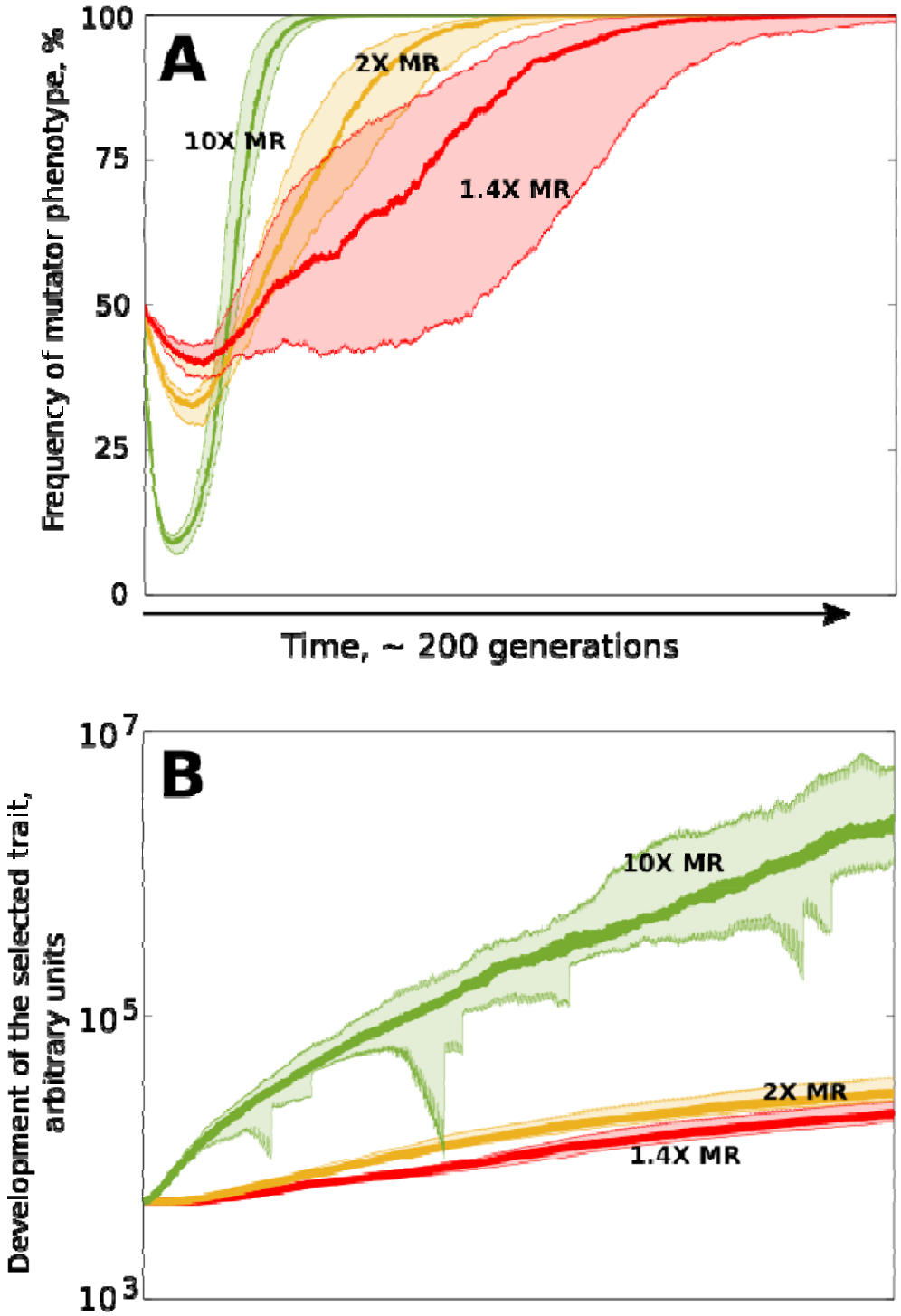


1493

1494 **Fig. 4. The evolution of gMR in in the absence of positive selection for body mass and SMP.** The SMP's
1495 *Som* parameter was fixed at 0.34 (red), 0.24 (green; enhanced 10X) and 0.2 (blue; enhanced 40X); a linear
1496 decrease in the *Som* value results in a substantially improved SMP, so that the green SMP is ~10X more efficient
1497 compared to red, and the blue is a ~4X more efficient SMP than the green. The standard (red) SMP leads to a
1498 significantly stronger selection for lower gMR (non-overlapping 95% CIs); however, the absence of difference
1499 between the 10X (green) and 40X (blue) improved SMPs indicates that overly improved SMPs might not provide
1500 any further difference for how selection acts on gMR.

1501

1502



1503

1504 **Fig. 5. Positive selection for mutators.** (**A**) frequency of a mutator phenotype in a mixed competitive
1505 population with "wild-type" species. Red (1.4X), orange (2X) and green (10X) are mutators of different fold
1506 increase in MR relative to the competitor as indicated by the respective numbers. (**B**) positive selection for a
1507 somatic cost neutral trait demonstrates faster evolution (and so adaptation) of mutators. Colors and MR fold
1508 increase as in (*A*).

1509