

1 **Protection from epidemics is a driving force for evolution of lifespan setpoints**

2

3

4 Peter V. Lidsky and Raul Andino<sup>1</sup>

5 Department of Microbiology and Immunology, University of California, 600 16<sup>th</sup> Street, GH-  
6 S572, UCSF Box 2280, San Francisco, California 94143-2280, USA.

7

8 **Most living organisms age, as determined by species-specific limits to lifespan<sup>1-6</sup>. The**  
9 **biological driving force for a genetically-defined limit on the lifespan of a given species**  
10 **(herein called “lifespan setpoint”) remains poorly understood. Here we present**  
11 **mathematical models suggesting that an upper limit of individual lifespans protects their**  
12 **cohort population from infection-associated penalties. A shorter lifespan setpoint helps**  
13 **control pathogen spread within a population, prevents the establishment and progression**  
14 **of infections, and accelerates pathogen clearance from the population when compared to**  
15 **populations with long-lived individuals. Strikingly, shorter-living variants efficiently**  
16 **displace longer-living individuals in populations that are exposed to pathogens and exist in**  
17 **spatially structured niches. The beneficial effects of shorter lifespan setpoints are even**  
18 **more evident in the context of zoonotic transmissions, where pathogens undergo adaptation**  
19 **to a new host. We submit that the selective pressure of infectious disease provides an**  
20 **evolutionary driving force to limit individual lifespan setpoints after reproductive maturity**  
21 **to secure its kin’s fitness. Our findings have important public health implications for**  
22 **efforts to extend human’s lifespan.**

23

24

25 As early as 1889<sup>1</sup>, theories attempted to explain the evolution of the paradoxical phenomenon of  
26 aging<sup>2-5</sup>. The majority of theories can be organized in two classes. Non-optimality<sup>2</sup> theories  
27 argue that aging is an inevitable property of life due to somatic<sup>6</sup> or genetic<sup>7</sup> damage. Whereas  
28 optimality theories propose that aging results from the trade-off between maintenance and  
29 reproduction (disposable soma theory)<sup>8</sup>, or that aging is neutral because extrinsic causes of death  
30 precede the lifespan setpoints (selection shadow)<sup>7</sup>. Further, aging has also been proposed to  
31 result from detrimental side effects of genes that are beneficial in early stages of development  
32 (antagonistic pleiotropy)<sup>9</sup>. Additional theories proposing that aging itself is adaptive have not  
33 been well supported by either theoretical or experimental evidence<sup>5</sup>.

34 Taking together these theories are consistent with many lifespan phenomena, however each of  
35 them, if taken individually, only explain a subset of observations. For example, the existence of  
36 single gene mutations that individually can extend lifespan<sup>10</sup> is not consistent with non-  
37 optimality theories given that both somatic or genetic inevitable damages are unlikely to be  
38 controlled by a single “master” gene. On the other hand the current optimality theories cannot  
39 explain why the ecological cases that favor the biological immortality are so infrequent, that it is  
40 almost never observed. If aging itself is adaptive, and therefore genetically programmed,  
41 immortal individuals should be detected due to mutations in genes responsible for aging  
42 mechanisms. Another general problem with adaptive aging theories – benefits from individual’s  
43 death allocated to its kin should exceed the price of its own life. Some examples of abnormally  
44 long-living species (e.g. tuatara, bowhead whale, proteus) can be explained by most existing  
45 theories, while some (birds, bats, naked mole rats) – only by few of them (see Extended Data  
46 Table 1 for detailed discussion). Attempts to integrate different aging concepts did not yet  
47 resulted in a comprehensive unifying theory<sup>4</sup>. Here we propose a kin-selection evolutionary  
48 theory, whereby limiting the lifespan-setpoints of a population provides a selective advantage  
49 that helps control the impact of infectious diseases and reduces the likelihood of zoonotic  
50 transmission where pathogen adaptation to a new host is required to establish epidemics. The  
51 theory proposed here is general in the sense that explains the majority of the lifespan-related  
52 phenomena (Extended Data Table 1), provides a rationale for the absence of immortal organisms,  
53 as well as how specific lifespan setpoints are selected to benefit individual kin.

54 To examine whether lifespan setpoints are linked to protection from infection, we developed a  
55 agent-based *in silico* model that incorporates lifespan into a previously developed host-pathogen  
56 theoretical framework<sup>11</sup>. In the initial simulation experiments, we considered populations of  
57 individuals with a range of defined lifespans. Time units we use are arbitrary and might reflect  
58 days, months or years depending on a given organism. All of our conclusions are nicely scalable  
59 along the time axis since pathogens tune the length of their life cycles according to the host's  
60 longevity. These were exposed to ten pathogen species that are able to infect susceptible  
61 individuals independently of each other (Fig. 1, Extended Data Fig. 1). For simplicity, efficiency  
62 of transmission and the fitness penalty produced by each of these ten pathogens were assumed to  
63 be identical. The fitness of each infected individual declined gradually up to a 20% maximum  
64 penalty for a single pathogen infection. Therefore, an individual's fitness was reduced to zero if  
65 infected with five pathogens ( $20 \times 5 = 100$ ), leading to its death. The model assumes that there are  
66 no other reasons for death except disease caused by infection or reaching the maximum age span,  
67 there is no recovery from diseases, neither vertical pathogen transmission. In addition, an  
68 individual's reproduction efficiency is set to correlate linearly with its fitness, i.e. uninfected  
69 individuals have more progeny (Fig. 1a). We also assumed a maximum population number for a  
70 single ecological niche of ten thousand individuals. Infection efficiency depends directly of  
71 density of individuals in a population, which is deemed to be uniform and ideally mixed using  
72 previously described conditions<sup>11</sup>. The model examines the effect of different pathogen  
73 transmission rates and assumes that pathogens are never fully eliminated from the system: when  
74 the last infected host dies, pathogens are reintroduced from another host species or from the  
75 environment. In this manner, our model not only considers the progression of existing infections,  
76 but also acquisition of new epidemics. Using this model and starting from an uninfected  
77 population, we observe that both the population size and the number of pathogens fluctuate in  
78 cycles, until an equilibrium is reached overtime (Fig. 1b, c), consistent with previous models and  
79 simulations<sup>11</sup>. The oscillation can be rationalized in terms of infected individuals dying reducing  
80 the availability of uninfected hosts. We monitored the number of individuals in the population  
81 and the pathogen load, as well as the total population fitness calculated as the sum of the fitness  
82 of all its members.

83 We initially analyzed whether different lifespan setpoints impact the total fitness of populations  
84 upon infection. We examined pathogens with different transmission efficiencies ( $\beta$ ) and  
85 individuals with different arbitrary lifespans ( $A$ ). Total population fitness captured after reaching  
86 equilibrium was plotted as a function of lifespan and pathogen transmission efficiency (Fig. 1d,  
87 1e). All lifespan ranges (excluding the biologically immortal control) were indistinguishable with  
88 respect to fitness when the pathogen transmission efficiency was very low (Fig. 1e,  $\beta = 0.005$  to  
89  $0.01$ ). Interestingly, at slightly higher, but still low, pathogen transmission rates ( $\beta = 0.015$  to  
90  $0.045$ ), fitness of the population was negatively correlated with longer lifespans (Fig. 1d, e).  
91 Individuals with the longest lifespans render the population more susceptible to poorly  
92 transmitted pathogens, compared with a population of individuals with shorter lifespans (Fig. 1d,  
93 asterisk). Thus, as individual lifespan shortens, population fitness increases (Fig. 1d, red zone)  
94 when faced with low transmission infections. This analysis suggests that longevity decreases  
95 population fitness due to the increased susceptibility to epidemics outbreaks (Extended Data Fig.  
96 2c).

97 An analytic solution to the model also supports these conclusions. The basic requirement for  
98 pathogens to spread in the population is that the number of susceptible individuals infected by  
99 pathogens shed by a single infected host (herein  $R_0$ ) – should exceed 1.  $R_0$  can be expressed as  
100 transmission efficiency ( $\beta$ ) multiplied by duration of the infection, which we initially assumed to  
101 average half of the host lifespan ( $\frac{A}{2}$ ). For simplicity, the population density-related component  
102 is considered to be 1 and it is omitted from the calculations. The interdependence  $\frac{\beta \cdot A}{2} > 1$  or  
103  $\beta > \frac{2}{A}$  demonstrates that the establishment of infection at low transmission efficiencies is  
104 determined by lifespan (Fig. 1f). If the lifespan is shorter than the time required for transmission,  
105 pathogens are unable to establish an epidemic. Thus, populations composed of shorter-lived  
106 individuals are expected to be more protected from invasion of pathogens, particularly if  
107 pathogens have lower transmission rates ( $\beta = 0.005$  to  $0.045$ ). These results suggest that the  
108 benefit of a limited lifespan is to protect populations from low or moderately transmissible  
109 diseases that establish persistent infections; for humans many such persistent infections are  
110 common, including AIDS, hepatitis B and C, leprosy, herpes, tuberculosis, and helminths.

111 Even if an epidemic is established, i.e. when pathogen transmission efficiency becomes high ( $\beta =$   
112 0.1 to 0.24), populations with shorter-lived individuals also experience a fitness benefit arising  
113 from the *metastability* of host and pathogen populations (Fig. 1d, e, light blue zones highlighted  
114 as “metastable populations”). The benefit results from the significant reduction in host  
115 population density caused by rapid spread of the infection, which, when combined with shorter  
116 lifespans, leads to a dramatic decline in pathogen numbers thereby allowing the population to  
117 recover from infection (Extended Data Fig. 3e-f).

118 Populations often migrate to colonize new environments. To further study the role of lifespan  
119 setpoints in controlling infection, we next examined the relationship between lifespan and  
120 pathogen load in the case of host populations dispersing to a new environment. In our modified  
121 simulation and analytical models, dispersal involves extreme population size reduction,  
122 “bottlenecking”<sup>12</sup>, whereby a small group (10) of random individuals from infected population  
123 colonize the new environment (Fig. 2a, b). Under these conditions, since the population density  
124 is low, pathogens will not spread efficiently soon after migration. The model predicts that in  
125 populations with shorter lifespans, the infected founders will die before the population density  
126 has reached a level that allows for efficient transmission. Consequently, populations composed  
127 by shorter lifespan individuals more efficiently clear pathogen than populations composed of  
128 longer-lived individuals (Fig. 2b-f). Of note, clearance efficiency also depends on the basal  
129 fecundity rate (*B*-number of progeny produced by 100% fit individual per time unit). Populations  
130 with highly fecund individuals will reach high densities faster and, thus, the probability of  
131 pathogen spread in a population by infected founders will increase accordingly (Fig. 2g,  
132 Extended Data Fig. 3h, i).

133 We also observed a minor positive effect of lifespan limitation on the fitness of highly infected  
134 populations as shown previously<sup>13,14</sup>. Since older animals possess more chronic pathogens than  
135 younger ones, their removal could increase the total population fitness (Fig. 1d, diamonds, 1e,  
136 “epidemics reduced”; Extended Data Fig. 3a-d). Importantly, our model suggests that this is a  
137 minor effect, compared to the more significant consequences resulting from epidemics  
138 prevention and pathogen clearance following host population bottleneck dispersal (Fig. 1d-f, and  
139 Fig. 2).

140 Individuals that live longer should reproduce for longer times and be more effective in passing  
141 on their genes. Thus, the evolution of traits that limit lifespan, common to most organisms, is  
142 counter-intuitive. We thus examined the whether long-living variants can displace a population  
143 of short-living individuals. To this end, we modified our simulation to allow for variants with a  
144 very long lifespan ( $A=\infty$ ) to emerge in a population of individuals with a defined lifespan (e.g.  
145  $A=60$ ). Under conditions where all individuals in a population intermix evenly, and thus long  
146 and short lifespan individuals have equal probabilities to interact with each other, the longer-  
147 living variants efficiently outcompete shorter-living individuals (Fig. 3b), even if this leads to  
148 establishment of epidemics (Extended Data Fig. 4a). However, under conditions of severe  
149 epidemics, premature death caused by pathogens equilibrated the number of short and long-  
150 lifespan individuals, thus limiting the advantage of long-lived variants (Fig. 3c, blue zone,  
151 Extended Data Fig. 4b, c). Populations located in the region of parametric space with short  
152 lifespan-associated benefits, i.e. the region where epidemics can't get established and metastable  
153 populations (Fig. 1e), were susceptible to displacement by longer-living individuals (Fig. 3c,  
154 Extended Data Fig. 4b, c, area below the dashed line). Thus, in ideally mixed populations long-  
155 living variants will displace short-living individuals.

156 The conclusions are different when populations are composed of sub-populations or clusters that  
157 are spatially separated, for instance by living in different niches. These spatially separated sub-  
158 populations may interact by exchanging individual members that move from one sub-population  
159 to another. We studied competition between longer-lived and shorter-lived organisms in this  
160 context of clustered populations, by modifying our model and introducing barriers between  
161 subpopulations (Fig. 3, Extended Data Fig 5). We based our analysis on a previously proposed  
162 computational model used to explain the seemingly altruistic effect of programmed cell death in  
163 unicellular organisms<sup>15</sup>. We observe that in the context of infection of clustered populations, the  
164 shorter-lived individuals outcompete long-lived variants. As a result of infection, the density of  
165 individuals in uninfected clusters is higher than in infected clusters. Accordingly, uninfected  
166 individuals from overcrowded clusters are more likely to migrate to infected clusters where the  
167 density is lower. This “asymmetric dispersal” model proposes that the direction of dispersal  
168 indirectly depends on the fitness of the individuals in a given cluster, which is linked to infection  
169 (Fig. 3a).

170 Using this model, we initially performed a source-sink density-dependent dispersal  
171 simulation<sup>16,17</sup> consisting of a 10 x10 grid of niches with capacities for three hundreds  
172 individuals each (Extended Data Fig. 5b). We introduced additional fitness penalties on  
173 reproduction to simulate the overpopulation effects and density pressures more adequately  
174 (Extended Data Fig. 5a for details). As mentioned, asymmetry in population densities between  
175 clusters forces migration of individuals from high density niches to a less populated cluster. At  
176 the start of the experiment all clusters were populated with individuals of a given limited  
177 longevity. Then a small group of long-lived ( $A=\infty$ ) mutants was introduced into one of the  
178 central clusters (Fig. 3d, e, Extended Data Fig. 5b) and the competition between genotypes was  
179 simulated. Our analysis revealed that when pathogen activity is low ( $\beta=0.005$ ) (Fig. 3d) long-  
180 lived mutants displace the short-lived individuals with efficiencies comparable to those in  
181 uniform populations (Fig. 3b). If we examine this process considering density-independent  
182 dispersal, with individuals migrating at a high frequency (e.g. birds or bats, Fig. 3f, mobility  $10^7$   
183 <sup>1</sup>), we find that clusters behave as a well mixed environment (similar to Fig. 3b-d). Thus, longer  
184 lifespan will also be selected in populations of highly mobile individuals (Fig. 3f, Extended Data  
185 Mov. 1). In contrast, when we consider a density-dependent dispersal under higher pathogen  
186 transmissibility conditions ( $\beta=0.03$ ), shorter lifespan individuals displace long-lived variants  
187 (Fig. 3e, Extended Data Mov. 1). Our analysis further revealed an area where the short lifespan is  
188 beneficial and long-living strains are not able to prevail (Fig. 3g, \*). Our model also suggest that  
189 upon infection, the emergence of longer-lived mutants also leads to extinction of the shorter-  
190 lived individuals in that cluster (Fig. 3e, dashed with yellow); as a result, the generation of longer  
191 lived mutants is detrimental to all individuals within the cluster.

192 We next examined the role of fertility. Asymmetry in population numbers between healthy short-  
193 lived and infected long-lived population strongly depends on their fecundity (Fig. 3h-j). Thus,  
194 using deterministic equations (Fig 3h), we modeled growth of short-lived and longer-lived  
195 populations with arbitrarily distinct birth rates ( $B$ ). We propose that short-lived individuals  
196 outcompete long-lived ones in a birth rate-dependent manner, because high fertility allows  
197 asymmetry in density between clusters to develop more rapidly (Fig. 3i). We further propose the  
198 existence of an equilibrium when the population growth of healthy short-lived individuals  
199 approach that of infected long-lived individuals (Fig 3j, black circle). Our model predicts a

200 simple interdependence between fecundity, lifespan and pathogen effects on fitness ( $P$ ) (Fig. 3j,  
201 equation). This dependency, together with fecundity effects during bottleneck dispersal (Fig. 2g,  
202 Extended Data Fig. 3h, i) explains the negative correlation between longevity and fecundity, as  
203 previously proposed in the context of the disposable soma theory<sup>8</sup>.

204 An important source of new pathogens in natural populations is the horizontal transmission  
205 between species, also called zoonotic transmission. The species-to-species barrier often requires  
206 that pathogens undergo several cycles of replication in the new hosts before adapting and gaining  
207 optimal transmissibility (Fig. 4a). We next considered how longevity impacts the ability of  
208 zoonotic infections to become established in a population, by modeling how populations with  
209 short-lived or long lived individuals influence pathogen adaptation to the host. We used a model  
210 similar to that used in Fig. 1e, with the exception that the pathogens are initially attenuated with  
211 a 10-fold transmissibility reduction; adaptation requires the pathogen to be passed between ten  
212 host individuals to reach higher transmission efficiency. Under these “zoonotic infection”  
213 conditions, we observed that the range of efficiency of pathogen transmission in which  
214 epidemics cannot get established is increased dramatically for populations with shorter lifespan  
215 individuals (Fig 4b zone below the dashed line), while the invasion of populations with long-  
216 living mutants ( $A=\infty$ ) remains unaffected (Fig. 4c). This suggests that the advantage of short  
217 lifespan is particularly important in the context of zoonotic epidemics. Thus, our model suggests  
218 that asymmetric dispersal and pathogen adaptation to a new host are two critical factors  
219 enhancing the benefits and evolutionary stability of shorter lifespan.

220 Taken together, our analyses indicate that host–pathogen coexistence and coevolution played a  
221 key role in determining the lifespan setpoints of a species. A population of longer-lived  
222 individuals is more susceptible to introduction of pathogens from other species, less effective to  
223 clear the infection following bottlenecking, and is less fit than a population of shorter-lived  
224 individuals when epidemics progress. Extension of the lifespan setpoint is beneficial only in the  
225 absence of pathogens, which for most species is not a realistic scenario in an evolutionary  
226 context. However, tolerance to pathogens (e.g. in bats) might alleviate selection pressure  
227 resulting in expansion of lifespan. The asymmetric dispersal from uninfected highly populated  
228 niches to infected less populated ones disfavors the emergence of longer lived individuals (Fig.



229 3). A series of asymmetric dispersal events should then lead to fixation of lifespan-setpoints  
230 optimized for the elimination of pathogens from a given population. Importantly, during  
231 epidemic outbreaks following asymmetric dispersal, we find that longer-lived individuals place  
232 even shorter-living individuals in the same cluster under the risk of extinction (Fig. 3e). Thus,  
233 infection is likely to be a major evolutionary force dictating the puzzling near-absence of  
234 immortal or extremely long-living individuals in nature. Indeed, subpopulations able to produce  
235 such long-lived variants are exposed to the catastrophic risk of being decimated during  
236 outbreaks. We thus conclude that lifespan of a species is a result of a trade-off between the  
237 pressure produced by pathogens and the pressure towards life extension and fecundity.

238 It is now generally accepted that host-pathogen interactions constitute major driving force during  
239 evolution<sup>18</sup>. The limitation of lifespan, leading to aging, may be one of the earliest and more  
240 robust population-level defense mechanisms against the spread of new pathogens and clearance  
241 of those that have been already established. A crucial role in the evolution of lifespan may be  
242 played by chronic low-transmissible diseases that persist for a significant part of a host's life and  
243 cannot be cleared by immune system. A major selective pressure towards shorter lifespans may  
244 also arise from prospective pathogens that are present in the environment but did not yet adapted  
245 to a given hosts or established epidemics.

246 Our work does not negate but complement and extend previous evolutionary theories of aging.  
247 For example, our model is consistent with selection shadow and antagonistic pleiotropy theories  
248 (Fig 4d, Extended Data Table 1). However, we identify host-pathogen interactions as a major  
249 selective pressure driving evolution of lifespan setpoints. It should be also emphasized that our  
250 study does not invoke group selection<sup>19</sup>, but rather proposes the selection of shorter lifespan  
251 depends on the inclusive fitness of the individuals in the context of the population. Hence we  
252 consider evolution of lifespan a kin selection strategy that favors the reproductive success of an  
253 organism's relatives, even at a cost to the organism's own survival. Finally, considering lifespan  
254 termination as an adaptive trait, our theory does not provide mechanistic insights of aging. The  
255 lifespan setpoints likely exploit similar mechanisms across different species, such as the  
256 modulation of DNA and protein damage responses, stress responses and senescence pathways<sup>6,20-</sup>  
257 <sup>22</sup>.

258 Research on aging, searching for lifespan determinants may lead to an effective increase in  
259 human and animal lifespans. Our ability to describe and model aging as an evolutionary process  
260 linked to infection, provides a new paradigm to identify lifespan mechanistic programs which  
261 can be prevented or even reverted. On the other hand, our theory also alerts to potential  
262 epidemiological risks associated with extended lifespan (Extended Data Fig. 6h). Conversely  
263 development of efficient mechanisms to limit or tolerate infections weakens the evolutionary  
264 pressure towards lifespan shortening. We propose this as an explanation for abnormal longevity  
265 in bats, mole rats (Extended Data Tables 1) and humans.

266

267 **Figure legends:**

268 **Fig 1. Length of lifespan controls epidemics establishment and progression.** **a.** Schematic  
269 representation of an epidemic model that considers the effect of lifespan on pathogen  
270 transmission. Pathogen transmission is assumed to occur from one individual to another or from  
271 the the environment if no infected individuals are left alive. Infected individuals are less efficient  
272 in reproduction but give birth to healthy progeny. **b.** Mathematical simulation of pathogen co-  
273 circulating in a host population where the lifespan setpoint is 100 time units and transmission  
274 efficiency – 0.12. Number of different pathogens is shown. **c.** Results of same simulation as in b.  
275 Number of host, average fitness, overall population fitness are represented over time. **d.** Analysis  
276 of steady state total population fitness of individuals with different lifespans ( $A$ ) exposed to  
277 pathogens with different transmission efficiencies ( $\beta$ ).  $A$  is the lifespan setpoint of an individual.  
278  $\beta$  - probability of pathogen transmission from an infected to uninfected hosts within a population  
279 of susceptible uninfected hosts. The lifespan-dependent ability to establish epidemics is marked  
280 with asterisk (\*). Region where populations are metastable is seen by extended standard  
281 deviation bars. The effects of epidemics reduction due to removal of highly infested elderly  
282 individuals is labeled with diamonds (◆◆◆). **e.** Analytic solution of steady state values with  
283 different lifespan ( $A$ ) and transmission efficiencies ( $\beta$ ). Total fitness of populations is shown by  
284 color; other parameters are displayed in Extended Data Fig. 2. **f.** Analytical prediction of the  
285 region inaccessible for epidemics establishment.  $R_0$  – number of individuals in fully packed  
286 susceptible population infected by one contaminated host per total time of infection.

287  
288 **Fig 2. Lifespan limitation facilitate pathogens clearance during bottleneck host dispersal.** **a.**  
289 Pathogen clearance model following host migration to a new environment. Infected individuals  
290 of short lifespan die before population reached the density sufficient for epidemics expansion. As  
291 a consequence, pathogens suffer severe bottlenecking and therefore are clear from the population  
292 in the new niche. **b.** An example of a single simulation. Random 10 individuals from highly  
293 infested population were released into a sterile compartment. Age of programmed death is 150  
294 time arbitrary units (AU), transmission efficiency – 0.13. **c.** Systematic analysis of number of  
295 epidemics that survive bottleneck dispersal. Solid line corresponds to one in Fig. 1e, dotted line  
296 is a prediction of border age able to clear pathogens, produced from deterministic model shown  
297 in panel d. **d.** Analytic solution using a deterministic model.  $H_s$  and  $H_i$  are numbers of

298 susceptible and infected hosts correspondingly,  $B$ -birth rate,  $P$ -pathogen effect on birth rate,  $N$  –  
299 maximum population density, other variables as in Fig. 1d. **e.** Simulation results of equations  
300 shown in *d*. If  $\log(H_i)$  is below zero, we considered pathogen is cleared from the population. (*i*)  
301 Initial input parameters were:  $A=50$ ,  $B=0.05$ ,  $H_{s(0)}=0$ ,  $H_{i(0)}=10$ ,  $P=0.5$ ,  $N=10^5$ ,  $\beta=0.05$ . **f.** An  
302 increase in age of programmed death results in inability to clear pathogens via bottleneck  
303 dispersal. Same experiment as in panel *e* was performed with different values of  $A$ . **g.** Effect of  
304 fecundity on pathogen clearing. Simulation results with different values of  $B$  reveals negative  
305 correlation between fecundity and clearing efficiency (see also Extended Data Fig. 3h, i for more  
306 detailed analysis).

307  
308 **Fig 3. Asymmetric dispersal.** **a.** Schematic representation of the host asymmetric dispersal or  
309 migration. **b** and **c.** Long-living (LL) individuals displace short-living (SL) individuals in  
310 uniform population. **b.** A small group (10) of long-lived ( $A=\infty$ ) individuals is introduced at time  
311 0 into a population of short-lived ( $A=60$ ) individuals. **c.** Systematic analysis reveals that region  
312 where shorter lifespan gives benefits (below the dashed line, taken from Fig. 1e) is susceptible to  
313 invasion of long-living mutants in uniform populations. Percent of long-living individuals is  
314 shown. **d** to **g.** Analysis of clustered metapopulations. **d.** Long-living strain invade efficiently if  
315 pathogens transmission rate is low ( $\beta=0.005$ ). **e.** In presence of higher pathogens transmission  
316 rate ( $\beta=0.03$ ) shorter-living strain displace the longer-living individuals. Parental cluster (yellow  
317 hatched area) and new clusters (red hatched area). Note individuals from the parental cluster are  
318 eliminated and mutants arise (yellow hatched area). **f** and **g.** Systematic analysis of competitions  
319 in clustered metapopulations reveals a region (\* in **g**) where the long-living mutant can not  
320 invade and short lifespan is beneficial. The existence of this region strongly depends on low  
321 levels of density-independent dispersal. Percent of individual simulations where long-lifespan  
322 mutant took over is plotted. **h-j.** Individual's birth rate strongly affects asymmetry between  
323 short-living and long-living infected populations densities. **h.** Deterministic equations describing  
324 population growth of short-living, long-living and long-living infected individuals. Variables are  
325 used exactly as in Fig. 2d. Simulation of population growth.  $A=100$ ,  $H_0=100$ ,  $B=0.05$ ,  $P=0.5$ . **i.**  
326 Higher birth rates are resulting in increased spread between short-living and long-living infected  
327 population growth. Three pairs of curves are shown. **j.** Lifespan prediction. Simulations  
328 essentially as in **j** were run with different values of  $B$ . Results at  $time=40$  are shown. At small

329 values of  $B$  populations of infected long-living individuals are replicating faster than populations  
330 of healthy aging individuals, therefore favoring fixation of longer lifespan. At larger values of  $B$   
331 healthy short-lived individuals can overgrow infected long-living ones, thus favoring the former  
332 strain. Equilibrium point, where two lines were crossing (black circle), was found analytically at  
333  $H_{LL(t)} = H_{SL(t)}$  from the equations shown in  $h$ . Therefore in this simplified condition the  
 $_{disease}$   
334 equilibrium lifespan  $A'$  can be estimated from known  $B$  and  $P$  (equation).

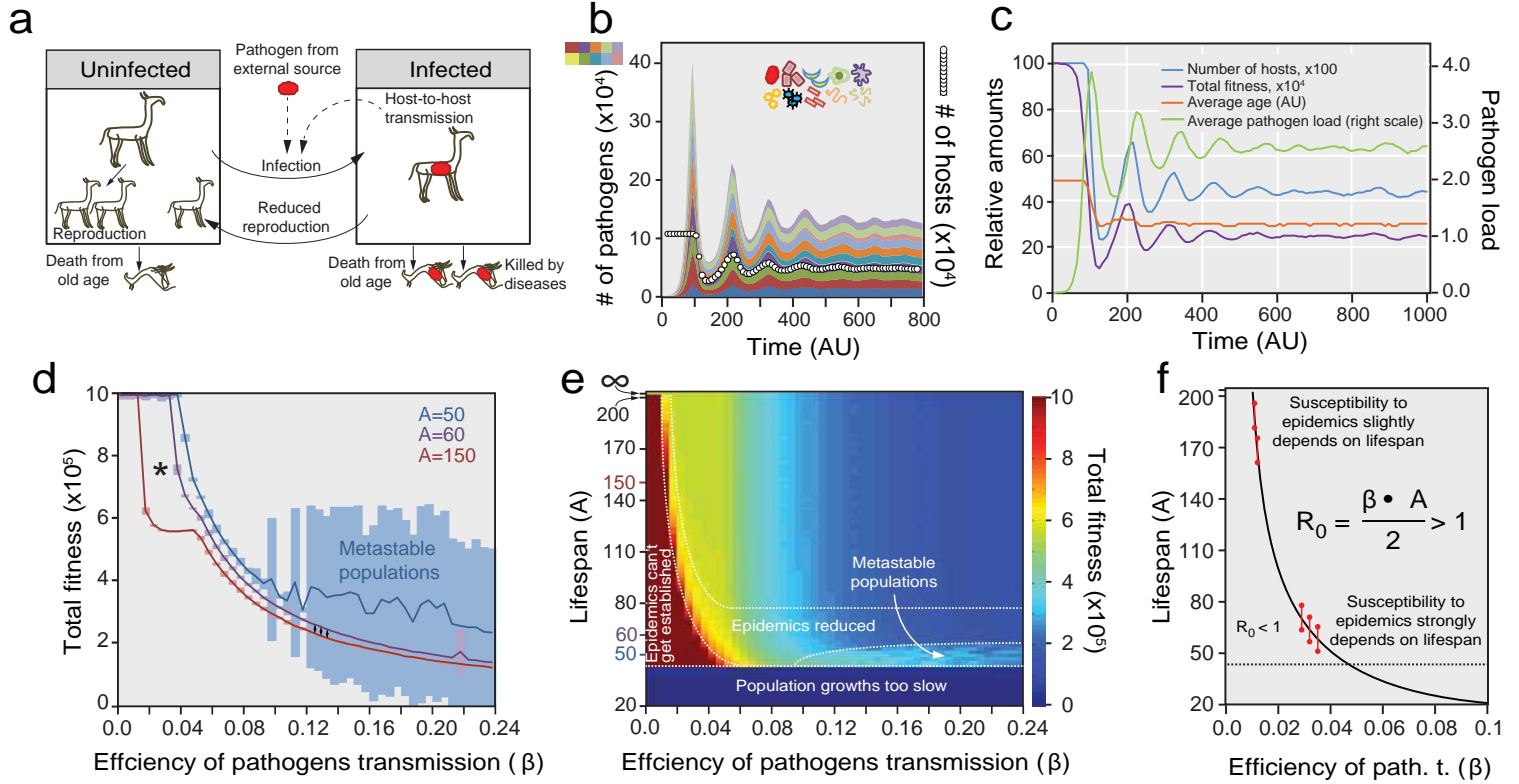
335 **Fig 4. The role of pathogen adaptation in lifespan selection.** **a.** Schematic representation of  
336 pathogen adaptation in the context of zoonotic transmission. **b.** Pathogens misadaptation results  
337 in significant increase of the area on parametric space where shorter lifespan is beneficial.  
338 Experiment was performed as in Fig. 1d, but initial pathogen transmission was decreased 10-fold  
339 relatively to values shown on the axis. Pathogens required 10 passages to reach its adapted state  
340 and increase transmission. Dashed line is from Fig. 1f. **c.** Pathogen misadaptation does not affect  
341 invasiveness of long-living mutant. Asterisk labels the continuous area where non-aging mutant  
342 cannot invade (blue) and aging gives selective advantages (below the dashed lines) at the same  
343 time. **d.** Evolution of shorter lifespan or origins of aging. Fixation of shorter lifespan demands an  
344 ongoing epidemics as a prerequisite. Under this conditions replication success of short-living  
345 individuals is equal to those of their long-living counterparts. However short-living animals have  
346 a selective advantage for cleaning pathogens via the bottleneck dispersal. Healthy short-living  
347 individuals might displace long-living strain from the parental cluster due to asymmetric  
348 dispersal process.  
349

350

351

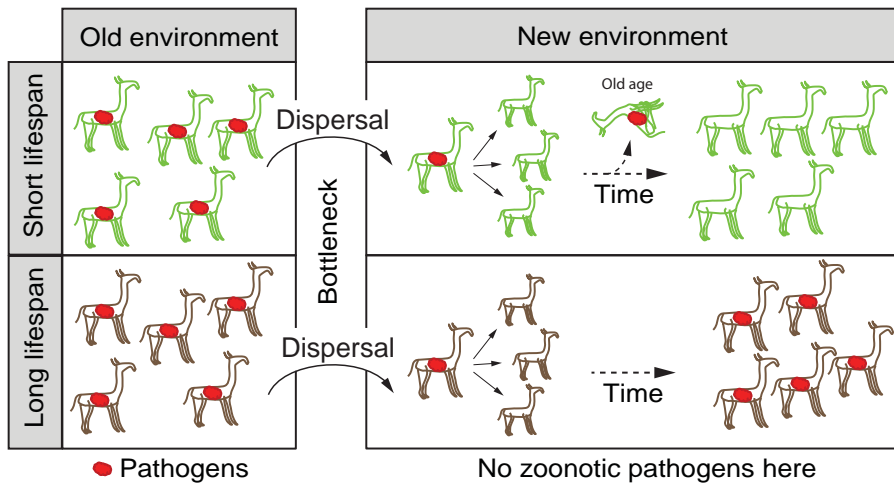
- 352 1 Weismann, A. *Essays Upon Heredity and Kindred Biological Problems*. . Oxford: Clarendon Press  
353 **Vol.I.** (1891).
- 354 2 Partridge, L. & Barton, N. H. Optimally, mutation and the evolution of ageing. *Nature* **362**, 305-  
355 311 (1993).
- 356 3 Kirkwood, T. B. L. & Austad, S. N. Why do we age? *Nature* **408**, 233-238 (2000).
- 357 4 Trindade, L. S. *et al.* A novel classification system for evolutionary aging theories. *Frontiers in*  
358 *genetics* **4**, 25, doi:10.3389/fgene.2013.00025 (2013).
- 359 5 Kowald, A. & Kirkwood, T. B. L. Can aging be programmed? A critical literature review. *Aging cell*  
360 **15**, 986-998, doi:10.1111/acer.12510 (2016).
- 361 6 Gladyshev, V. N. Aging: progressive decline in fitness due to the rising deleteriome adjusted by  
362 genetic, environmental, and stochastic processes. *Aging cell* **15**, 594-602,  
363 doi:10.1111/acer.12480 (2016).
- 364 7 Medawar, P. B. *An Unsolved Problem of Biology*. London:H.K. Lewis&Co. (1952).
- 365 8 Kirkwood, T. B. & Holliday, R. The evolution of ageing and longevity. *Proceedings of the Royal*  
366 *Society of London. Series B, Biological sciences* **205**, 531-546 (1979).
- 367 9 Williams, G. C. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution;*  
368 *international journal of organic evolution* **11**, 398-411 (1957).
- 369 10 Kenyon, C. J. The genetics of ageing. *Nature* **464**, 504-512, doi:10.1038/nature08980 (2010).
- 370 11 May, R. M. & Anderson, R. M. Epidemiology and genetics in the coevolution of parasites and  
371 hosts. *Proceedings of the Royal Society of London. Series B, Biological sciences* **219**, 281-313  
372 (1983).
- 373 12 Mayr, E. *Systematics and the origin of species, from the viewpoint of a zoologist*. (Harvard  
374 University Press, 1942).
- 375 13 Kirchner, J. W. & Roy, B. A. The Evolutionary Advantages of Dying Young: Epidemiological  
376 Implications of Longevity in Metapopulations. *The American Naturalist* **154**, 140-159,  
377 doi:doi:10.1086/303232 (1999).
- 378 14 Mitteldorf, J. & Pepper, J. Senescence as an adaptation to limit the spread of disease. *Journal of*  
379 *Theoretical Biology* **260**, 186-195, doi:<http://doi.org/10.1016/j.jtbi.2009.05.013> (2009).
- 380 15 Iranzo, J., Lobkovsky, A. E., Wolf, Y. I. & Koonin, E. V. Immunity, suicide or both? Ecological  
381 determinants for the combined evolution of anti-pathogen defense systems. *BMC Evolutionary*  
382 *Biology* **15**, 43, doi:10.1186/s12862-015-0324-2 (2015).
- 383 16 Amarasekare, P. The role of density-dependent dispersal in source–sink dynamics. *Journal of*  
384 *Theoretical Biology* **226**, 159-168, doi:<https://doi.org/10.1016/j.jtbi.2003.08.007> (2004).
- 385 17 Sæther, B.-E., Engen, S. & Lande, R. Finite metapopulation models with density–dependent  
386 migration and stochastic local dynamics. *Proceedings of the Royal Society of London. Series B:*  
387 *Biological Sciences* **266**, 113-118, doi:10.1098/rspb.1999.0610 (1999).
- 388 18 Enard, D., Cai, L., Gwennap, C. & Petrov, D. A. Viruses are a dominant driver of protein  
389 adaptation in mammals. *eLife* **5**, e12469, doi:10.7554/eLife.12469 (2016).
- 390 19 Nowak, M. A. Five rules for the evolution of cooperation. *Science (New York, N.y.)* **314**, 1560-  
391 1563, doi:10.1126/science.1133755 (2006).
- 392 20 Labbadia, J. & Morimoto, R. I. The Biology of Proteostasis in Aging and Disease. *Annual review of*  
393 *biochemistry* **84**, 435-464, doi:10.1146/annurev-biochem-060614-033955 (2015).
- 394 21 Sontag, E. M., Samant, R. S. & Frydman, J. Mechanisms and Functions of Spatial Protein Quality  
395 Control. *Annual review of biochemistry* **86**, 97-122, doi:10.1146/annurev-biochem-060815-  
396 014616 (2017).

397 22 Gottschling, D. E. & Nyström, T. The Upsides and Downsides of Organelle Interconnectivity. *Cell*  
398 **169**, 24-34, doi:10.1016/j.cell.2017.02.030.  
399  
400

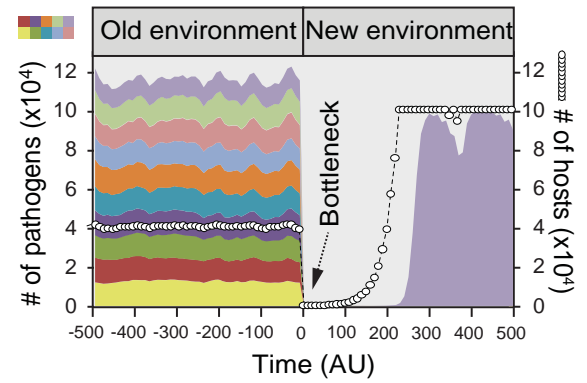




**a**

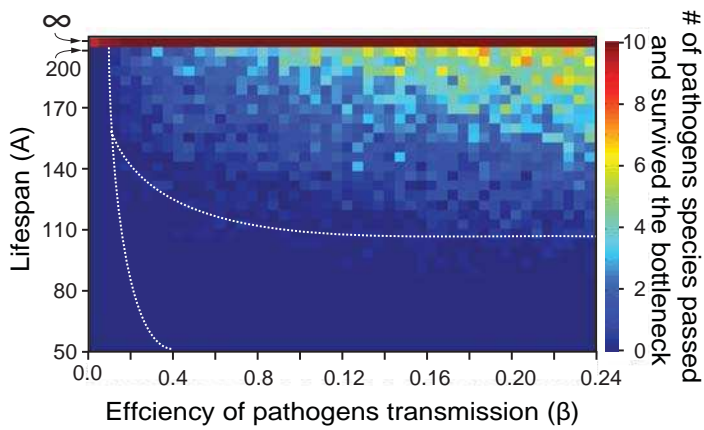


**b**

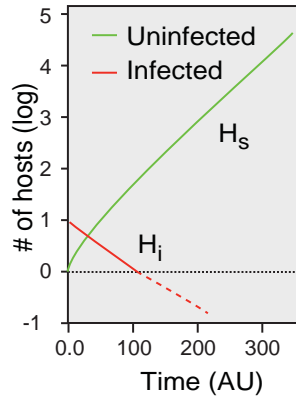


$$d \begin{cases} H_{s(t+1)} = H_{s(t)} \cdot \left(1 - \frac{1}{A}\right) \cdot (1+B) + H_{i(t)} \cdot B \cdot P - \frac{H_{i(t)} \cdot H_{s(t)} \cdot \beta}{N} \\ H_{i(t+1)} = H_{i(t)} \cdot \left(1 - \frac{1}{A}\right) + \frac{H_{i(t)} \cdot H_{s(t)} \cdot \beta}{N} \end{cases}$$

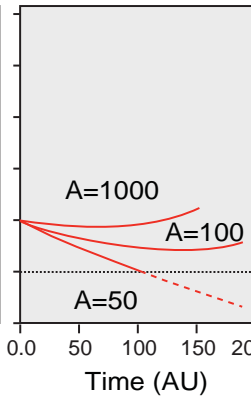
**c**



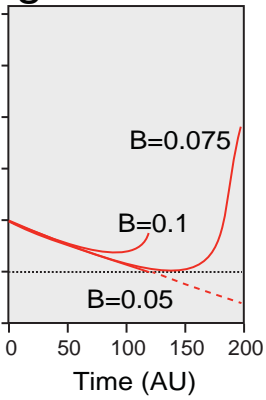
**e**

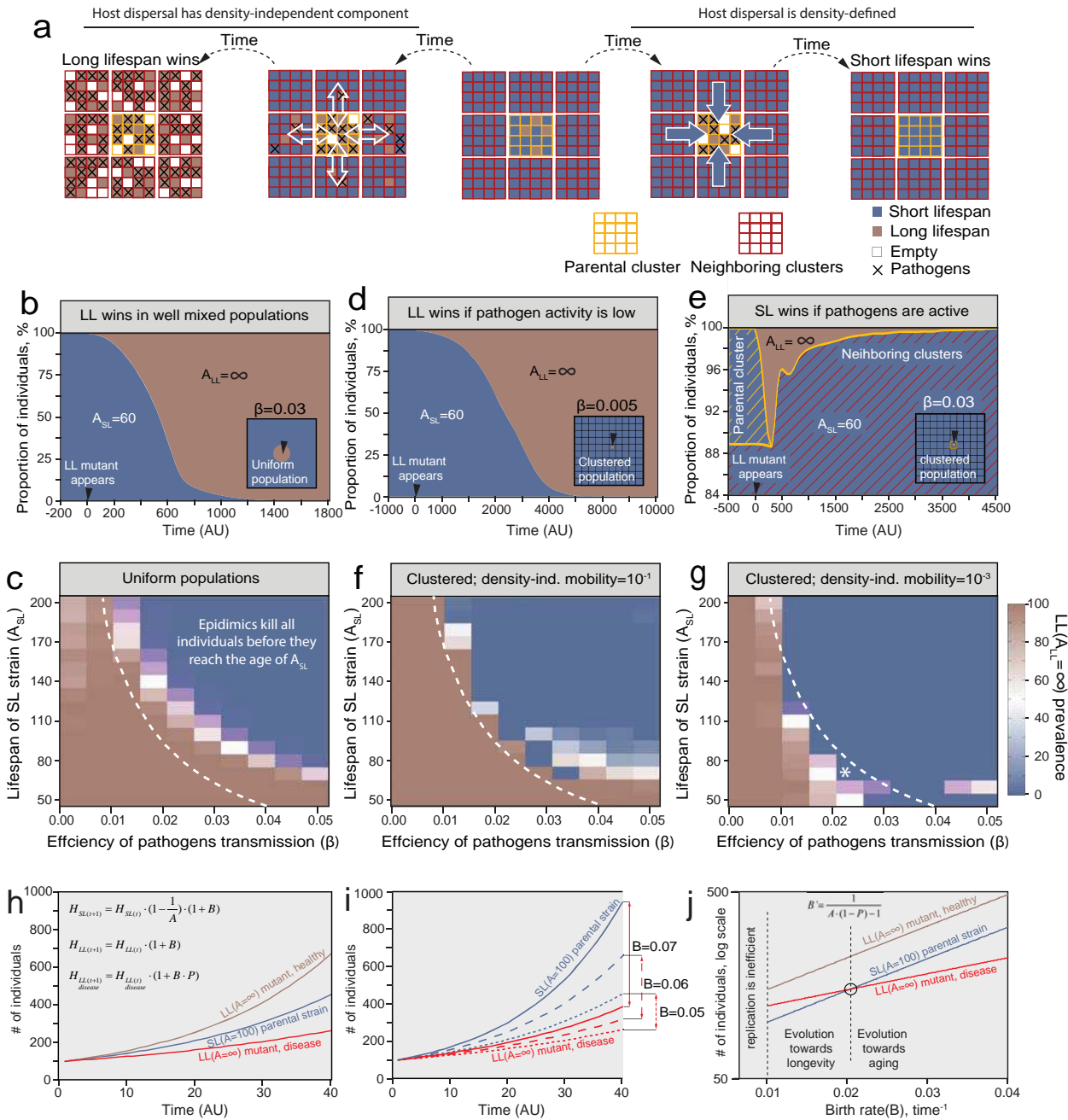


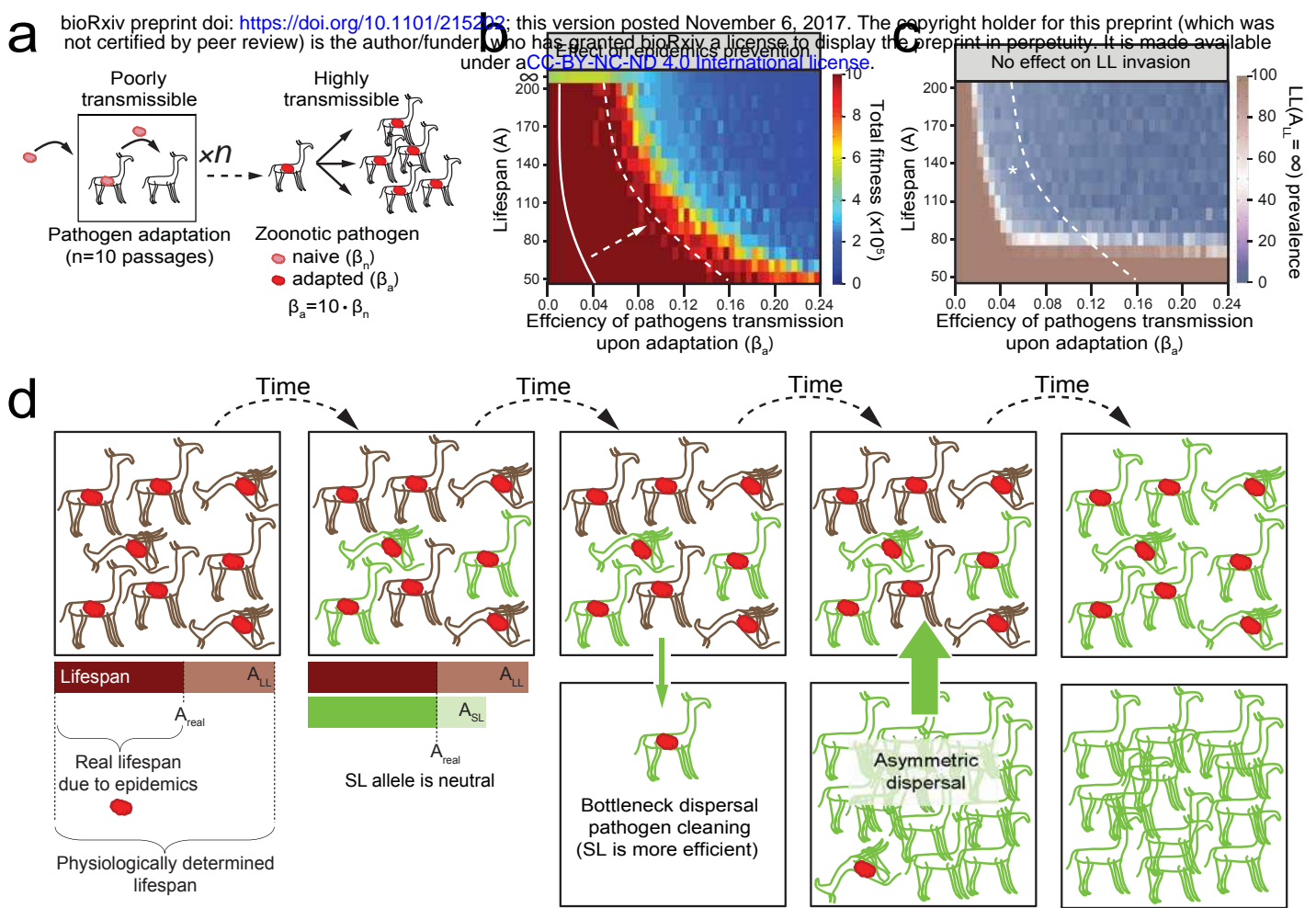
**f**



**g**







## Methods.

### Data collection and presentation

All simulation scripts were coded and compiled with Python 2.7 (Python Software Foundation). Data was plotted with Excel (Microsoft) and MatLab (Mathworks).

### Models.

While our infectious catastrophe theory is well supported by previously published empirical evidence (see Extended Data Table 1a), this manuscript does not include any original experimental data supporting its predictions. Therefore it is crucial to demonstrate that our models are adequate and the values of parameters we use are realistic.

Our models are based on classical host-pathogen interaction models<sup>1</sup>, adapted to agent-based simulations to better account for the individual life-history effects on how epidemics proceed. The basic algorithm is presented in Extended Data Fig. 1. The values and main processes are listed in Extended Data Table 2a, b.

The host's population sizes we used (10 thousand individuals in uniform simulations and  $300 \times 100 = 30000$  in clustered metapopulations) were big enough to exclude any effect of stochastic factors on our final results.

In the beginning of simulations the niches were filled with maximum number of individuals with randomly generated ages ( $a$ ) and replication values ( $r$ ). Generation of uniformly distributed random numbers in all cases was performed with *random.py* Python library (Python Software Foundation) which uses standard Mersenne Twister algorithm.

Host's reproduction was simulated the following way. Each round a value has been added to the replication value in each host:

$$r = r + B \cdot f$$

where  $B$  is birth rate (0.05 in all simulations, 0.075 and 0.1 in Extended Data Fig. 3h, i) and  $f$ -individual's fitness ( $f_{\max} = 100$  for an uninfected animal). When  $r$  was reaching value of  $r_{\max} = 100$ , the individual gave birth to another genetically identical individual.  $r$  of both parent and daughter individuals were set to zero. One generation of healthy individuals in typical simulation could therefore be calculated as:

---

$$\frac{r_{\max}}{B \cdot f_{\max}} = \frac{100}{0.05 \cdot 100} = 20 \text{ arbitrary time units.}$$

New born animal was always considered to be

uninfected. If population has reached its maximum ( $N_{\max}$ ) in simulations of uniform populations, the newborns were considered to be aborted or expelled, while the  $r$  of the parental animal was still set to zero. For metapopulation experiments we used a fitness-dependent algorithm of population limits. To increase the pathogen effect on birth rate and to simulate overcrowding effects more adequately, the

progeny was delivered to an individual only if  $\frac{f}{f_{\max}} > \left(\frac{N}{N_{\max}}\right)^2$ . We assume that under conditions of

resource shortage only the fittest individuals could leave progeny. However results similar to ours could be obtained with increase of pathogen's adverse effect on birth rate without changing its effects on lifespan (unpublished).

Dying due to reaching the lifespan setpoint was simulated by incrementing the age of individuals ( $a$ ) each round and comparing it to the preset age of death ( $A$ ). For simplicity we assumed no visible fitness declines were preceding the individual's death: very first "symptoms" of aging were considered to be lethal.

As mentioned in the main text, time units we use are arbitrary and might reflect days, months or years depending on a given organism. All of our conclusions are nicely scalable along the time axis since pathogens tune the length of their life cycles according to the host's longevity.

In this study we considered only chronic pathogens that cannot be cleared by the immune system. Such diseases are numerous and well known. We suggest long-lasting diseases, but not ones with rapid recovery, are contributing to the selection pressure towards lifespan shortening. Simulations in Extended Data Fig. 7d shows that introduction of recovery degrades the benefit produced by lifespan setpoint.

Infections were simulated in the following way: in the first step the infection load of the population ( $L_{pi}$ ) has been estimated for each pathogen as a number of individuals infected with this pathogen. If this value was declining below 1, we assumed the presence of zoonotic pathogen reservoir and set as  $L_{pi}=1$ . Next the infection efficiency was estimated as  $\beta \cdot L_{pi}$ , where  $\beta$  is transmission efficiency analyzed in a broad range of values of 0.005-0.24. To calculate number of pathogen attacks  $\beta \cdot L_{pi}$  has been transformed into integer using stochastic rounding algorithm (e.g. 4.89 was giving 5 in 89% of cases and 4 in 11% of cases). Then these attacks were then randomly firing in the population. If the attack was hitting the susceptible individual it was infected, however if it hit an empty slot or an individual already infected with this pathogen, the attack was considered to have no consequences. Therefore numerically number of newly infected individuals in each round was equal to classical models:  $\beta \cdot L_{pi} \cdot H_{pi=0}$ , where  $H_{pi=0}$  is a number of

susceptible animals in population. The non-canonical algorithm of infection was used to simulate multiple independent infections and pathogen's evolution (Fig. 4) more easily.

We have used multiple (10) pathogen species in all our simulations. In each experiment all of them had the same parameters. We assumed no interactions between pathogens; so they were able to infect hosts in any combinations. It was important to show that selective pressure towards shorter lifespan could be produced by the cumulative effect of several different pathogens with relatively mild pathogenesis. Multiplicity of pathogens also allowed us to minimize a number of disease parameters and still simulate fertility decline, long chronic infections as well as disease-inflicted death with a true stochastic component. It was also technically convenient, since it reduced noise in our simulations. Usage of a single pathogen with very strong adverse effects (e.g. developing its fitness penalties non-linearly over time, similarly to HIV, hepatitis or syphilis) would immediately raise questions about the universality of the simulation results. Using the parameters of humans diseases listed above would also require introducing vertical transmission as well as many additional conditions and parameters that would further complicate the model. Nevertheless all our conclusions are also clearly valid for such a single “terminator superpathogen” (unpublished). It should be also noted that vertical pathogen transmission (infection of the progeny by the parent immediately upon birth) will strongly increase key effects observed in Figs. 1 and 3 (unpublished).

A penalty that limits a host's fertility due to disease ( $P$ ) is an accepted fact: resources to be invested in reproduction are hijacked by pathogens and/or reallocated into deployment of immune responses. For analytical experiments (Fig. 2e to g, 3 h to j) we have used a 50% penalty, while in simulations a 20% (elsewhere stated) decrease in fitness per pathogen was used. The latter, more moderate number was selected so as to allow for several pathogens in the system. We did not introduced lifespan shortening by the single pathogen as it would complicate the interpretation in regions with low  $\beta$ . The gradual development of disease severity within 15 time points should be considered as a minor factor, introduced to eliminate some unaesthetic oscillations. In Fig. 1f we assume population density-dependent component to be equal to 1, and therefore  $R_0 = \frac{\beta \cdot A}{2}$ . We consider this as an adequate simplification in the region of parametric space, where  $R_0 \approx 1$ . Adverse effects of epidemics are minimal in this region and proportion of susceptible animals in the population is  $\approx 1$ . If the ages in population are distributed evenly, average age of infecting, as well as its duration is  $\frac{A}{2}$ . It should be noted that tiny fading outbreaks are happening in stochastic models even if  $R_0 < 1$  (not shown).

---

In Fig. 2 we demonstrate how infection can be cleaned following the bottlenecking of the host populations. To simulate highly infected starting populations, we have run the long-living individuals ( $A=\infty$ ) until they have reached the steady state adapting all 10 pathogen species. Then 10 random individuals were selected from this population and their lifespan setpoints were changed to the indicated value. Therefore the initial sampling was not affecting the pathogen composition immediately after the bottleneck. It was made from analogous moieties and usually retained all 10 diseases. For simplicity in the main text we discuss the dispersal of small population of founders to a new niche (Fig. 2), free from external pathogens. However taking in account the concept of pathogen adaptation (Fig. 4) it is clear that efficient cleaning from pathogens might follow the population decreases caused by diseases or predator-prey interactions occurring on the same territories: individuals might clean up the well-adapted pathogens, while the exposure to external non-adapted ones will not result in immediate restart of epidemics.

Simulation of competition between long-lived and short-lived individuals was performed in two ways that gave similar results (Extended Data Fig. 4). First, *in situ* generation of long-living mutant was simulated. Populations of short-living animals were run until reaching the steady state. Next, 25 random animals were transformed into long-living mutants ( $A=\infty$ ) and simulations have been running until the new steady state was reached and data was collected. Second, extrinsic invasion of long-living mutants was studied. Two isolated populations of short-living and long-living ( $A=\infty$ ) mutants were run in parallel under identical conditions. Upon reaching the steady-state, 25 slots were randomly swapped between two compartments with period of 100 rounds.

Source-sink density-dependent dispersal simulation (asymmetric dispersal) is one of the key results of the paper (Fig. 3, Extended Data Movie 1). Both empirical and theoretical studies show that dispersal as well as the underlying movement behavior are condition-dependent and informed processes. Local population density is considered to be a major factor affecting dispersal<sup>2-5</sup>. It should be emphasized that activation of a specific program for dispersal upon overcrowding was reported even in bacteria (swarming and quorum sensing)<sup>6,7</sup> leaving no doubt that our assumption for universality of density-dependent dispersal is valid. Intraspecific competition and resource shortages push excess individuals into neighboring, less populated regions. We also note that purging the long-living mutants occurs rapidly in the course of epidemics progression. We suggest this to be much faster than most of evolutionary processes, since it does not require rare events (mutations) to happen. Taking this into account, we consider that the minimal stringency of physical barriers that separate different parts of population is less than in most other evolutionary models. Therefore our simulations (Fig 3d to g, Extended Data Movie 1) are based on adequate presuppositions. Simulations for clustered metapopulations (Extended Data Fig. 5) were performed first for each cluster as it would be a uniform population, and after density-dependent and

density-independent dispersal were simulated. To exclude potential artifacts coming from the same order of cluster analysis, the sequence of cluster calculations was randomized at each round.

Equation if Fig. 3j was obtained from:  $\frac{H_{LL}^{disease}}{\Delta t} = \frac{H_{SL}}{\Delta t}$ . Under these conditions (and if density-

independent dispersal is insignificant) the evolution of lifespan does not go neither towards lifespan elongation, nor shortening since the equilibrium between populations is reached. Thus from equations

shown in Fig. 3h we obtain:  $(1 - \frac{1}{A}) \cdot (1 + B) = 1 + B \cdot P$ , and the birth rate in the equilibrium point:

$B' = \frac{1}{A \cdot (1 - P) - 1}$ . Decrease in birth rate will result in evolution towards longer lifespan and will move

$B'$  to the left, while an increase in birth rate will lead to lifespan shortening and increase  $B'$ .

The concept of pathogen adaptation to new species is widely accepted. We can illustrate this with an example of HIV-2. Closely related viruses are persisting in sooty mangabeys (*Cercocebus atys atys*). While most serotypes of HIV-2 are known from single human hosts only, some can also be transmitted from human to human<sup>8</sup>. Thus it seems while most HIV-2 variants that infect humans result in a dead-end, a few are taking an opportunity to adapt enough to establish epidemics. Since HIV pathogenesis occurs in prolonged periods of time comparable to human's lifespan, we suggest that longevity could assist pathogen adaptation in the end resulting in epidemic outbreaks. To simulate pathogen adaptation (Fig. 4b, c), each pathogen in each host obtained an additional parameter – passage number (x). For pathogens coming from the environment x was set as zero. At the stage of infecting the program assembled an array of passage values from a pathogen's populations. Representation of each passage in the array was calculated as the number of individuals infected with the pathogen at the given passaging age multiplied by the relative transmission efficiency of this pathogen ( $\beta_n$  or  $\beta_a$ ). Next for every successful pathogen attack, the algorithm randomly selected a passage number from this array and incremented it with 1 to assign to a newly infected host. Therefore the composition of a pathogen's metapopulation was carefully simulated.

Simulation data was collected upon the epidemics was reaching steady-state. In experiments with uniform populations  $3 \times 10^3$  of rounds were sufficient. For simulations of lifespan variants competition in uniform populations we used  $9 \times 10^3$  rounds after mutant introduction. In clustered metapopulations the run was stopped after one of the variants was winning.

---



Number of replicate simulations is at least 10 per data point in all heatmaps presented. In panels 3f and g number of simulations is 40 per data point.

---

## Extended Data.

### Extended Data Fig. 1. Simulation algorithm.

**Extended Data Fig. 2. Detailed demographics data of simulated populations from Fig. 1e.** **a.** Average number of individuals. **b.** Average fitness. **c.** Average number of pathogens per individual. **d.** Standard relative deviation of total fitness reveals the area of population metastability. See Extended Data Fig 3e-g for more details. **e.** Average age. All data were collected after epidemics had reached a steady state.

**Extended Data Fig. 3. Lifespan setpoints effect on epidemic progression, population metastability and pathogen clearance during host population bottleneck.** **a.** A conceptual scheme of lifespan setpoints effects on epidemics control: older individuals have statistically more parasites than their younger counterparts since the probability of getting infected increases with the time. **b-d.** Analysis of individuals stratified by their ages. Simulation was performed with individuals with an age of programmed death of 90 time units, exposed to pathogens with a transmission efficiency of 0.095. Confidence intervals are standard deviations. It should be noted that similar effects were previously reported and discussed as an independent reason for aging evolution<sup>9</sup>. However conservation of lifespan setpoints according to this concept would require severe epidemics to go on constantly in all the species, which is a questionable assumption. **b.** Demographic pyramid of infected populations. **c.** An individual's average fitness decreases with age. **d.** Average number of pathogens per individual increases with age. Therefore elimination of older individuals increase population fitness. **e-g.** Detailed data on metastable populations. **e.** Total population fitness of individuals with different lifespan setpoints. Standard deviations were high in simulations with short hosts lifespans. **f.** Number of individuals in populations with two different values of lifespan setpoints. **g.** Two peaks from panel f are overlaid with pathogen composition. When the population reaches a certain threshold, epidemics rise, kill a majority of individuals and then vanish. Results are shown for pathogen transmission efficiency of 0.2. **h-i.** Efficiency of pathogen clearance during bottleneck dispersal strongly depends on birth rate. Simulations were carried out as in Fig 2c using an birth rate of 0.075 (**h**) and 0.1 (**i**). Solid lines are from Fig 1e, while dotted lines are predicted borders of pathogen clearance for a given birth rate produced from the deterministic model shown in Fig 2d.

**Extended Data Fig. 4. Long-living mutants are efficiently displacing short-living ones in uniformly mixed populations.** **a, b.** Populations of individuals with an age of programmed death of 60 were exposed to pathogens with a transmission efficiency of 0.04. At the time point designated by 0, 25 random individuals were transformed into long-living mutants. Dynamics of paternal strain elimination (solid lines) and epidemic explosion (dashed lines) are shown for three different simulations with the longevity of long-living mutants set at 80, 100 or  $\infty$ . **c,d.** Systematic analysis of short-living individuals' displacement by long-living ( $A=\infty$ ) mutants. Percent of non-aging mutants at the last time interval is shown. Dashed lines are from Fig 1e. **c.** *In situ* generation of a long-living mutant. Simulation was performed as in panel *a* with different longevities of short-living mutants and pathogen transmission parameters. **d.** External invasion of a long-living strain. Short-living and long-living populations were run in parallel. After epidemics have reached the steady state, random groups of 25 slots were swapped between two compartments every 100 time points.

**Extended Data Fig. 5. Metapopulation simulations algorithm.**

**Extended Data Fig. 6. Effects of extrinsic death on epidemics progression.** **a-c.** Demographic pyramids of populations exposed to different levels of aging and disease-unrelated death risks. No pathogens were present in these simulations. **d-f.** Populations exposed to high extrinsic death risks are less efficient in establishing epidemics. Simulations were run as in Fig 1e with different values of extrinsic death. Dotted lines are from Fig. 1f. **g and h.** Adverse effects of non-aging mutant production and radical lifespan management. **g.** Production of long-living ( $A=\infty$ ) mutants result in pathogen load increase after 10-15 average lifespans have passed. Displacement of the short-living ( $A=50$ ) line requires a long period of time. **h.** Transformation of all the short-living individuals into long-living ones (e.g. by removal of extrinsic death or by pharmacological treatment) results in rapid emergence of epidemics, within 2-3 average lifespan lengths. Pathogen transmission was 0.04 in both panels.

**Extended Data Fig. 7. Effects of hypersensitivity and recovery from diseases on aging evolution n.** **a-c.** Increase in pathogen-associated fitness penalties prevents epidemics and makes immortality feasible. Simulations of long-living ( $A=\infty$ ) individuals population dynamics were performed with fitness penalties of -20% as elsewhere or with increased (-100%) ones. Average pathogen load (**a**) and death rate (**b**) were clearly minimal in increased fitness penalty situations. **c.** Average individual age was stabilized by disease-inflicted mortality when pathogen-associated fitness penalty was low, but grew throughout the simulation if the penalty was high. Therefore individuals were virtually immortal in the last case. Pathogen transmission efficiency ( $\beta$ ) was 0.04 in these simulations. **d.** Aging-related benefits are produced by diseases with slow or no recovery. Simulation experiment as in Fig 1e was performed with

diseases having different recovery times. The profile of the region inaccessible for epidemics was convex if the disease was long lasting (recovery = 500 time units, longer than host's lifespan), and becomes almost vertical (and thus aging-independent) if recovery was fast (10 time units).

**Extended Data Movie. 1. Outcome of competition between short-living and long-living strains in clustered populations depends on the ratio between density-dependent and density-independent dispersal.** Simulations were made with the age of programmed death at 70 time units, pathogen transmission efficiency was 0.03, the probability of stochastic dispersal is shown in the bottom-left corner of each sample. The proportion of long-living ( $A=\infty$ ) individuals in each cluster is shown by color, dark blue corresponds to 0, dark red - to 1.

**Extended Data Table 1. a. Aging-related observations explained by different evolution theories.**

Traits which fit the corresponding theory are marked green, traits which contradict the theory are marked red, while traits that are not clearly explained by the theory yet do not appear to clearly contradict it are marked yellow. The prediction itself is marked blue. It should be stated that contradicting facts here are not proving any theory wrong, but rather imply a stronger selection factor that acts against the direction predicted by a given theory.

<sup>a</sup> Universality of aging defined our historical views on senescence as an unavoidable entropic process alike friction or rust. Theories of **damage accumulation**<sup>10,11</sup> extend this traditional concept. However, other theories published up to now are not able to explain why virtually all species age. The concept of a **selection shadow**<sup>12</sup> explains well why aging might be neutral in animals exposed to high external risks of death (e.g. small rodents, insects). However many animals that developed efficient protective mechanisms (e.g. porcupines, skunks etc), large animals (e.g. elephants, rhinos) or predators (e.g. orcas, lions, bears etc) do not have obvious high risks of extrinsic death, but still display senescence. The theory of antagonistic pleiotropy<sup>13</sup>, which usually goes hand-in-hand with selection shadow, proposes multiple senescence-related traits to be genetically linked to early-life beneficial functions, thus resulting in aging conservation. However, such genetic or functional linkages are evolvable properties by themselves, and it remains unclear why evolution cannot overcome this barrier or compensate for the impaired functions by mutations in other regions of the genome. Obvious facts of lifespan evolution, evident from analysis of related species (e.g. mouse deer/baleen whales ~14 / ~100 years respectively; hyraxes/elephants ~12 / ~80 years etc)<sup>14</sup>, make this concept even shakier.

**The disposable soma**<sup>15</sup> theory proposes that (i) individuals are limited in resources and (ii) faster reproduction rates are favored by natural selection, forcing individuals to accelerate replication and

underinvest in maintenance. While being convincing in explaining aging of small exponentially growing organisms, this theory does not exclude full biological immortality. Sufficient amounts of resources might allow maintaining the parent's body indefinitely if reproductive expenses are low as is true for slow reproducers (e.g. large animals, tuataras etc). We believe it cannot explain aging in high animals which usually have high external death risks in youth, low external death risks in adulthood and stable population numbers. **Acceleration of evolution** theories<sup>16</sup> cannot explain why slow evolving groups of animals (e.g. sharks or tadpole shrimps) still retain senescence levels comparable to rapidly evolving ones. In our opinion faster evolution is not an adequate benefit for universal aging and mortality taking in account slowness of beneficial mutation accumulation. Furthermore strong selection factors would remove all unfit individuals by itself without the involvement of aging. Strengthening of minor selection factors by costly means of aging will not result in guaranteed long-term success of the species, since these minor factors might turn out to be not very important. In summary, we think that acceleration of evolution is impossible to substantiate outside the framework of altruistic behavior and/or group selection.

**Infectious catastrophe** theory proposes infectious disease as a major factor for the evolution of lifespan setpoints and senescence. Ubiquity of parasites in the biosphere makes aging an almost general property of living matter.

<sup>b</sup> Lifespan varies dramatically between different species and its evolution is clearly evident across the tree of life<sup>14,17</sup>. On the contrary, intra-species variations are usually moderate. Extremely long-living mutants (~6 fold increase) were described in *C.elegans*<sup>18</sup>, however this phenomenon might be attributed to a non-conventional activation of the natural mechanisms underlying roundworm lifespan extension – the so-called dauer stage. Long-living mice mutants display no more than two-fold lifespan extension<sup>18,19</sup>. Being in good agreement with **damage accumulation**, this observation cannot be explained well neither by **selection shadow**, nor by **disposable soma** theories, which consider aging to be a secondary trait, and therefore should be variable across broad ranges. **Acceleration of evolution** is inadequate here as well. Since longer lifespan produces clear benefits at least within a short evolutionary scale, we should have observed at least some senescence escapers. **Infectious catastrophe** theory is able to explain this by elimination of individuals in the region where long-living mutants emerged. If the fitness penalty associated with immortality or exceptionally long lifespan spreads locally (therefore majorly across the mutant's parental breed), selection should disfavor even the ability to produce such mutants (Fig 3e).

<sup>c</sup> Existence of single gene mutants with extended lifespans significantly changed our views on senescence<sup>20-22</sup>. These observations led to scrutiny of the **damage accumulation** group of theories, which assume aging as an inevitable entropic process. **Selection shadow** theory in cooperation with antagonistic

pleiotropy could explain these mutant phenotypes since senescence appeared to be linked to stress response and, sometimes, fertility<sup>22,23</sup>. However uncoupling longevity and fecundity directly contradict the **disposable soma** theory. On the other hand, **evolution acceleration** and **infectious catastrophe** theories assume aging to be an adaptive mechanism that obviously can be affected by single gene mutation at least slightly.

<sup>d</sup> Many environmental conditions can increase lifespan. This includes exposure to heat, oxidative stress, reduction in respiration and translation<sup>22</sup>. The most striking example of hormesis in aging is the effect of caloric restriction on lifespan<sup>24</sup>. Rodents, worms and flies limited in nutrients live significantly longer, demonstrating lower body mass, delayed maturity and sometimes reduced fertility<sup>22</sup>. **Damage accumulation** theories in general do not predict the existence of a pathway for delayed aging. One might speculate, that some specifically harmful metabolic processes slow down under caloric restriction conditions, however this idea does not completely fit the experimental data: dietary restriction in *Drosophila* might prolong life even if applied in late ages<sup>25</sup>. **Selection shadow** theory cannot explain why the existing mechanism of life elongation is not utilized under optimal conditions. Predictions made by the **disposable soma** theory are opposite to experimental observations. Resource deficiency should affect longevity and fecundity unidirectionally in individual life history, e.g. caloric restriction should lead to decrease in lifespan or fertility (or both). Opposite changes are difficult to explain in the frame of this theory. Robin Holliday made an attempt to remove this contradiction by saying that caloric restriction prolongs lifespan by activation of the program for “famine survival”<sup>26</sup>. However it remains unclear why similar programs for aging prevention cannot be activated in *ad libitum* situations when available resources are sufficient for both maintenance and reproduction. To the contrary, **evolution acceleration** and **infectious catastrophe** are in good agreement with tunable aging. If an organism’s death is adaptive, its optimal timing can vary between different environments and change in response to external stimuli. Short-living species reproduction is specifically vulnerable to adverse environmental conditions, e.g. a single poor season might strongly affect the whole species population in case its duration is comparable to the length of the animal’s lifecycle. To survive periods of low productivity, these species could evolve mechanisms to slow down the aging clock in response to hunger, abnormal temperatures or oxidation. In agreement with this idea, signals from the reproductive system also influence aging in some short-living species<sup>22</sup> – there is probably no ecological benefit to keep animals alive for longer than required for replication. It is important to note that model organisms used as laboratory models for aging research are usually short-living, therefore one should be specifically careful when extrapolating hormesis results on long-living species whose reproduction is less dependent on environmental fluctuations.

<sup>e</sup> Field studies suggest senescence is detectable in wild animal populations<sup>27</sup>. The effects of aging on mortality could be also extrapolated from the analyses of an animal's survivorship curves. If the input of aging is minimal, and the majority of individuals die due to extrinsic reasons (e.g. predation, hunger and diseases), the logarithmic curve is linear (Type II, mortality is age-independent) or concave (Type III, mortality is higher in younger ages). If the old age-related reasons play an important role, the curve is convex (Type I, mortality increases with age). Type I survivorship curves are found in many large animal species thus directly supporting that aging plays a role in the wild populations<sup>17</sup>. This goes into a critical contradiction with the **selection shadow** theory, which assumes aging to occur only beyond the period of real survival. All the other discussed theories agree with this observation nicely.

<sup>f</sup> Several simple metazoans including planarian flatworms (e.g. *Schmidtea mediterranea*)<sup>28</sup>, cnidarian *Hydra vulgaris*<sup>29</sup> and *Turritopsis dohrnii*<sup>30</sup> are considered to be biologically immortal, contradicting all theories of non-adaptive aging. These facts cannot be explained by **damage accumulation** theories, since they show that senescence can be ultimately avoided. A possible argument on existence of exquisite repair mechanisms in these primitive animals immediately raises a question, why have similar adaptations not evolved in more advanced taxa? These species are not protected from external death risks and do not display abnormally low fecundity, therefore challenging both **selection shadow** and **disposable soma** theories. **Evolution acceleration** and **infectious catastrophe** consider that these primordial animals could have lost adaptive aging, perhaps because they did not evolve genetic linkages, preventing this in higher animals. It also might be that aging is mechanistically unavailable for them e.g. due to a functional linkage between regeneration and reproduction.

It is also interesting to speculate about connections between sexual reproduction and aging. Senescence-positive sexual lineages of planarian worms (*Schmidtea mediterranea*) are less efficient in telomere length maintenance than "immortal" asexual ones<sup>28</sup>. We propose that since sexual reproduction requires two animals to contact each other, this opportunity might be used by pathogens for transmission. Therefore asexual species should withstand lower selective pressure towards lifespan shortening.

<sup>g</sup> Negative correlation between longevity and metabolic rate is widely accepted<sup>31-33</sup>. It is obvious that animals with slow metabolism require a longer time to reproduce. But why do metabolically active animals age faster? This can be easily explained from the positions of **damage accumulation** and **disposable soma** theories, assuming maintenance costs are growing with increase of metabolism rates due to faster accumulation of toxic metabolites, damaged molecules or aberrant mutations. On the contrary, **selective shadow** theory cannot explain this interdependence. **Evolution acceleration** and **infectious catastrophe** theories propose natural selection moves toward adaptive lifespan shortening.

Furthermore, infectious catastrophe theory provides an additional level of explanation: since the speed of chronic pathogen reproduction correlates with a host's metabolic rates, the efficiency of transmission should scale accordingly, relaxing the evolutionary pressure on longevity.

<sup>h</sup> Correlation between body size and longevity is probably the most obvious life history-related trait<sup>34,35</sup>.

Growth and gestation of large animals require prolonged periods of time, but it still remains unclear why smaller animals acquire faster senescence. The positive correlation between size and longevity comes into a contradiction with **damage accumulation** theories, not only because larger bodies should accumulate more errors (e.g.: more cell divisions are required during development, toxic metabolites excretion is more difficult from a bigger volume etc), but also because large animals set the theoretical limits of longevity to a remarkably high level. There is no explanation why damage control systems in small species cannot be as efficient as in bigger ones. A counter argument may address the negative correlation between body size and metabolism levels<sup>36</sup>, however this correlation does not seem to be strong enough to explain huge differences in longevity in different species. For example birds have high metabolic rates and their lifespans are significantly longer than mammals of their sizes (see row <sup>m</sup>). **Selection shadow** argues that body size better protects from predation, while **disposable soma** theory might suggest a faint argument that body size often negatively correlates with fecundity. In our opinion size/longevity correlation is a strong argument pointing towards shorter lifespan setpoint adaptability: since (i) gigantic species have evolved independently in virtually all the taxa, longer lifespan can emerge without major mechanistic problems, (ii) evolution goes not only towards increases in size, but also vice versa, therefore smaller species that originated from bigger ones should have lost their longevity very efficiently, thus justifying the existence of selective pressure towards lifespan shortening. Thus **evolution acceleration** and **infectious catastrophe** theories are postulating adaptability of aging and therefore explain why animals might limit their lifespan if they physically can replicate within shorter timeframes. In further support of infectious catastrophe theory it should be noted that since increases in body size usually results in decreases of population density<sup>37</sup>, risks of novel pathogen adaptation might go down as well.

<sup>i</sup> Negative correlation between longevity and fecundity is well established<sup>38</sup>. This observation is the basis for the **disposable soma** theory. However, while longevity/fecundity trade-off seems to be obvious when comparing different species<sup>39</sup>, analysis of individual life histories in some studies did not show great correlation between childbirth and lifespan in mammalian, bird and insect systems<sup>40-43</sup>, suggesting that fecundity is an ecological rather than a physiological factor of aging evolution at least in some cases. **Damage accumulation** theories can explain this with adverse side effects of high energies, individuals invest in reproduction. **Selection shadow** concept might produce an indirect reasoning that high fecundity is compensating for high population losses from external deaths. **Evolution acceleration** and **infectious catastrophe** might explain the longevity/fecundity trade-off on an individual level with a reverse

argument of disposable soma theory: unavoidable rapid (adaptive) senescence can be an evolutionary cause for higher fecundity. Indeed the preexistence of lifespan setpoint might force individuals to exhaustively invest in replication as described<sup>44</sup>. As for as the fitness price of decreasing residual lifespan, its loss can be balanced by one successful act of reproduction. The second argument, specific for short-living species, is signaling from the reproductive system that can manage lifespan (discussed in detail in row<sup>d</sup>). In addition to this, **infectious catastrophe** theory provides two strong reasons for longevity/fecundity trade-off on ecological level: we claim that high fecundity can (i) degrade short lifespan-related benefits in pathogen clearance (Fig 2g, Extended Data Fig. 3h, i) and (ii) favors shorter lifespan fixation during asymmetric dispersal (Fig 3h to j). Thus we posit a connection between longevity and fecundity as a complex ecological and physiological entity, involving many different factors.

<sup>j</sup>High external death risk is believed to have a negative correlation with longevity<sup>45</sup>. In this paper we propose revisiting some examples frequently cited as supporting this idea (see e.g. rows<sup>m, l, o</sup>), but we do not question this rule itself. This correlation is a key element of **selection shadow** theory. **Damage accumulation** and **disposable soma** theories can produce indirect arguments, by linking external death to requirement for high fecundity and therefore high metabolic rates. **Evolution acceleration** theory comes into a direct contradiction with this fact, since the reasons to maintain senescence in the presence of strong selective forces seem to be questionable. **Infectious catastrophe** theory claims that the exact mechanism of an individual's death does not play a role in pathogen control, and even massive death by predation or hunger might help to cease the epidemics (Extended Data Fig. 6a to f). Animals exposed to high extrinsic death risks adapt their immunity and fecundity to relatively low pathogenic loads as if they had naturally short lifespan. In this situation transitional relaxation of death risks pressure (decrease in carnivore's numbers or abundant crops) might result in even more severe adverse epidemiological effects than long-living mutant production (Extended Data Fig. 6h). Hence the species exposed to high extrinsic death risks should keep senescence as a reserve security mechanism to kill elderly animals at ages comparable to their death from extrinsic reasons.

<sup>k</sup>Accelerated aging and suicidal behavior observed in many semelparous species<sup>46,47</sup> clearly indicate an organism's death itself (and not just its removal from the next replication round) is favored by selection. All theories except **infectious catastrophe** cannot address this. We consider semelparity is an adaptation of short-living species that guarantee them a successful round of replication and a prompt removal from the population. If their senescence would depend on time only, some individuals would not be able to reproduce due to random variations in the environment. We explain striking examples of accelerated aging in semelparous fish of the *Salmonidae* family<sup>48</sup> by the necessity to control the spread of parasites in the overcrowded rivers they spawn in. See also row<sup>d</sup> for discussion on semelparity.



<sup>l</sup> Queens of social insects live much longer than workers or soldiers<sup>49</sup>. This fact contradicts the **damage accumulation** and **disposable soma** theories: highly fertile and metabolically active animals are living far longer than sterile individuals from the very same species. The argument of efficient allocation of resources and underinvestment into workers' maintenance will not work here, since it assumes that building up a new individual from a fertilized egg is cheaper than maintaining an existing one. On the contrary, **selection shadow** explains this by efficient protection of queens and exposure of workers to high external death risks. **Evolution acceleration** theory would expect the replicating animals to have the shortest rather than longest lifespan, coming into a direct contradiction with the observed fact. According to **infectious catastrophe** theory a worker's senescence is crucial for control of epidemics, while a single long-living queen does not have a major effect due to the low probability of being exposed to a zoonotic pathogen.

<sup>m</sup> Birds are known to live significantly longer than most mammals of comparable size<sup>34,35</sup>. This comes into a direct contradiction with the **damage accumulation** theories since birds have very active metabolisms. **Selection shadow** theory claims birds are well protected from predation due to their ability to fly and this is one of the most frequent examples mentioned in support of this theory. Large flightless birds have remarkably shorter lifespan<sup>35</sup>, emphasizing the connection between volation and longevity. However, the existence of specialized avivore predators among other birds, reptiles and mammals is well established. Indeed even in classical works describing animals' life-histories<sup>50</sup> many species of volation-competent and relatively long-living birds are ascribed to possess Type II survivorship curves, pointing that extrinsic reasons of death play a key role in their mortality. While possessing average lifespan compared to those of small mammals when in the wild, these birds are able to survive for decades in captivity<sup>35</sup>. It is also difficult to consider the songbird's longevity as atavistic: short-living flightless species are believed to evolve independently from flying ancestors<sup>51</sup>, thus demonstrating an efficient convergent evolution towards lifespan shortening. We consider these arguments to point a contradiction in the selection shadow concept. **Disposable soma** and **evolution acceleration** theories are not capable of producing a strong explanation for birds' longevity. **Infectious catastrophe** theory predicts that the longevity of birds is associated with their high mobility due to volation. During asymmetric dispersal phases highly mobile animals more readily achieve longer lifespan (Fig. 3a, f, g). Large flightless birds have lost their mobility and therefore experience a stronger pressure towards lifespan shortening. See also Extended Data Table 1b, row<sup>f</sup>.

<sup>n</sup> Some species of bats live extraordinary long lives for mammals of their sizes<sup>35,52</sup>, even when compared to birds. To the arguments listed in row<sup>m</sup> we should add that bats have a unique immune system that makes them tolerant to a wide class of pathogens<sup>53</sup>. This fact nicely fits the **infectious catastrophe** theory: tolerance to infections relaxes the pathogen-related pressure towards shorter lifespan.

<sup>o</sup> Naked mole rats (*Heterocephalus glaber*) are eusocial subterranean rodents of extraordinary long lifespan, which are considered to have negligible senescence or even be biologically immortal<sup>54</sup>. Moreover mole rat queens remain fertile until the end of their lives. This puzzling observation fits neither damage accumulation, nor disposable soma, nor evolution acceleration theories. The concept of **Selection shadow** might explain it by good protection produced for queens, which reside in the middle of the colony. Workers' longevity therefore is atavistic. Trying to understand naked mole rats from the **infectious catastrophe** perspective we questioned whether there may be a specific case where biological immortality is evolutionally stable under non-sterile conditions. We found that an increase in fitness penalties caused by pathogens in our simulations results in their inability to establish epidemics. If the very first individual infected by zoonotic pathogen always dies, the populations are sterile from disease and can evolve towards immortality (Extended Data Fig. 7a-c). Such high penalties cannot be evolutionary stable if the fitness losses are programmed by pathogens, since then infectious agents will evolve towards milder pathogenesis<sup>1</sup>. Fitness loss resulting from a suicidal program of the host in response to infection - hypersensitivity - is clearly an altruistic trait and cannot be fixed by selection. However, hypersensitivity combined with eusociality might be both beneficial and evolutionary stable. Little is known about naked mole rat's immunity, however one case report claims these animals are much more sensitive to herpes simplex virus than mice<sup>55</sup>. Our model predicts that this is a pathogen-triggered suicidal phenomenon that should be also true for other infections. We predict that in mole rats the function of pathogen control was shifted from aging to a mechanism of systemic apoptosis (phenoptosis<sup>56</sup>), and thus removing the selection pressure towards shorter lifespan.

<sup>p</sup> Recent works showed that two huge arctic animals, bowhead whale (*Balaena mysticetus*)<sup>57</sup> and Greenland shark (*Somniosus microcephalus*)<sup>58</sup> have extraordinarily long lifespan of ~200 and ~400 years respectively. These animals are huge and have relatively slow metabolism, therefore their longevity can be explained by all evolutionary theories listed here. From the side of **infectious catastrophe** theory we want to add a probable factor of low pathogenic pressure they experience by living in poorly populated polar seas.

<sup>q</sup> Proteus (*Proteus anguinus*)<sup>59</sup> is a long-living (~70 years) troglodyte amphibian inhabiting caves in southern Europe. Its slow reproduction, absence of natural enemies and life in poor biocoenosis as discussed in row <sup>p</sup> makes it easy to explain by all theories.

<sup>r</sup> Tautaras (*Sphenodon sp.*)<sup>60</sup> are relic New Zealand medium-sized reptiles with an estimated lifespan of more than 100 years. Their longevity can be attributed to their low fecundity, slow metabolism and absence of natural enemies. It is also tempting to speculate that their biochemical differences from other reptiles, creates additional barrier for pathogens to get established in their populations.

## **b. Predictions made by infectious catastrophe theory.**

<sup>a</sup> As it is shown in Fig. 3, highly mobile animals are less prone to fix short lifespans when undergoing asymmetric dispersal processes. Thus if all other ecological parameters are the same between two species, less mobile animals should possess shorter lifespans. This prediction is nicely corroborated for an extreme case of mobility – volation. Indeed birds and bats have surprisingly longer lifespans than terrestrial animals of comparable sizes (see Extended Data Table 1a, rows <sup>m</sup> and <sup>n</sup> for discussion). Further field and laboratory studies are necessary to test this correlation in a broader range of species.

<sup>b</sup> Range size is also an important parameter in asymmetric dispersal process. Indeed, the same animals inhabiting a small range (e.g. island) will more easily fix longer lifespans since there are not enough refugia, whereas short-lived variants can shelter during initial expansion of a long-living strain. If the long-living mutant conquered the whole range, it will be fixed regardless of the epidemiological consequences. Curiously a comparative study on lifespans of insular and mainland Virginia opossums (*Didelphis virginiana*) directly shows that islanders live significantly longer lives (23% of increase)<sup>61</sup>. However this result cannot be considered as a pure corroboration of the correlation between longevity and range size: the involvement of other factors, such as low pressure from predators (as concluded in<sup>61</sup>, see also Extended Data Table 1a, row <sup>j</sup>) and parasites (this Table, row <sup>d</sup>) is not excluded. This prediction has to be accurately tested with multiple different species with control for all of the factors listed above.

<sup>c</sup> Efficiency of pathogens transmission depends on the frequency of contacts between individuals. Thus if the animals are living as a sparse population with rare contacts between individuals, the model would predict lower probabilities for establishment of new epidemics and therefore longer lifespans. On the other hand, high levels of intermixing would result in shorter lifespans. Solitary, asexual animals are the best candidates to be centenarians. Interestingly, the planarian flatworm considered to be “immortal” is indeed asexual (see Extended Data Table 1a, row <sup>f</sup>).

<sup>d</sup> The ability of zoonotic pathogens to adapt to a given species is a key factor of lifespan evolution according to our theory. Therefore frequencies of interspecies contacts are crucial. Thus predation should be an important factor pushing the lifespan towards shortening; however population densities of carnivores are usually smaller than those of herbivores, thereby complicating the analysis. Animals living in abiotic environments such as troglobionts (e.g. proteus, see Extended Data Table 1a, row <sup>f</sup>) are expected to live longer. One more important factor is biochemical compatibility: highly diverged animals are expected to fix zoonotic pathogens with lesser efficiency. Therefore “living fossils” that do not have many related species in their surroundings should live longer (e.g. tautara, see Extended Data Table 1a,

row <sup>q</sup>). Accurate modeling approaches together with high quality ecological data should support these predictions.

<sup>e</sup> We predict that naked mole rats are hypersensitive to infections, and this feature is responsible for zoonotic pathogen control making aging redundant (see Extended Data Table 1a, row <sup>o</sup>). Experimental research should test this hypothesis accurately, although one case report has already shown a similar effect<sup>55</sup>.

<sup>f</sup> Flightless ratite birds have relatively short lives compared to their flight-competent counterparts. This observation is counterintuitive since these birds are larger in size and have low metabolism even among flightless birds<sup>62</sup>. The classical explanation, based on the selection shadow theory argues that flightless birds are not protected from predators and increased extrinsic mortality leads to the evolution of shorter lifespans, thus implying the survivorship curve in ratites should be of Type II. Our theory explains the ratite's short lifespans by the loss of mobility associated with volation. Therefore based on our prediction large flightless ratites should have Type I survivorship curves in the wild, as it would be generally expected for animals of their sizes (see also Extended Data Table 1a, row <sup>m</sup>). Unfortunately high quality field data are not available for these birds. We think that investigations of survivorship curves in wild populations of large flightless ratites, such as common ostriches (*Struthio camelus*), emus (*Dromaius novaehollandiae*), rheas (*Rhea sp.*) and cassowaries (*Casuarius sp.*) are needed to corroborate this prediction.

**Extended Data Table 2. List of parameters and processes involved in simulations. a.** Parameter's list.

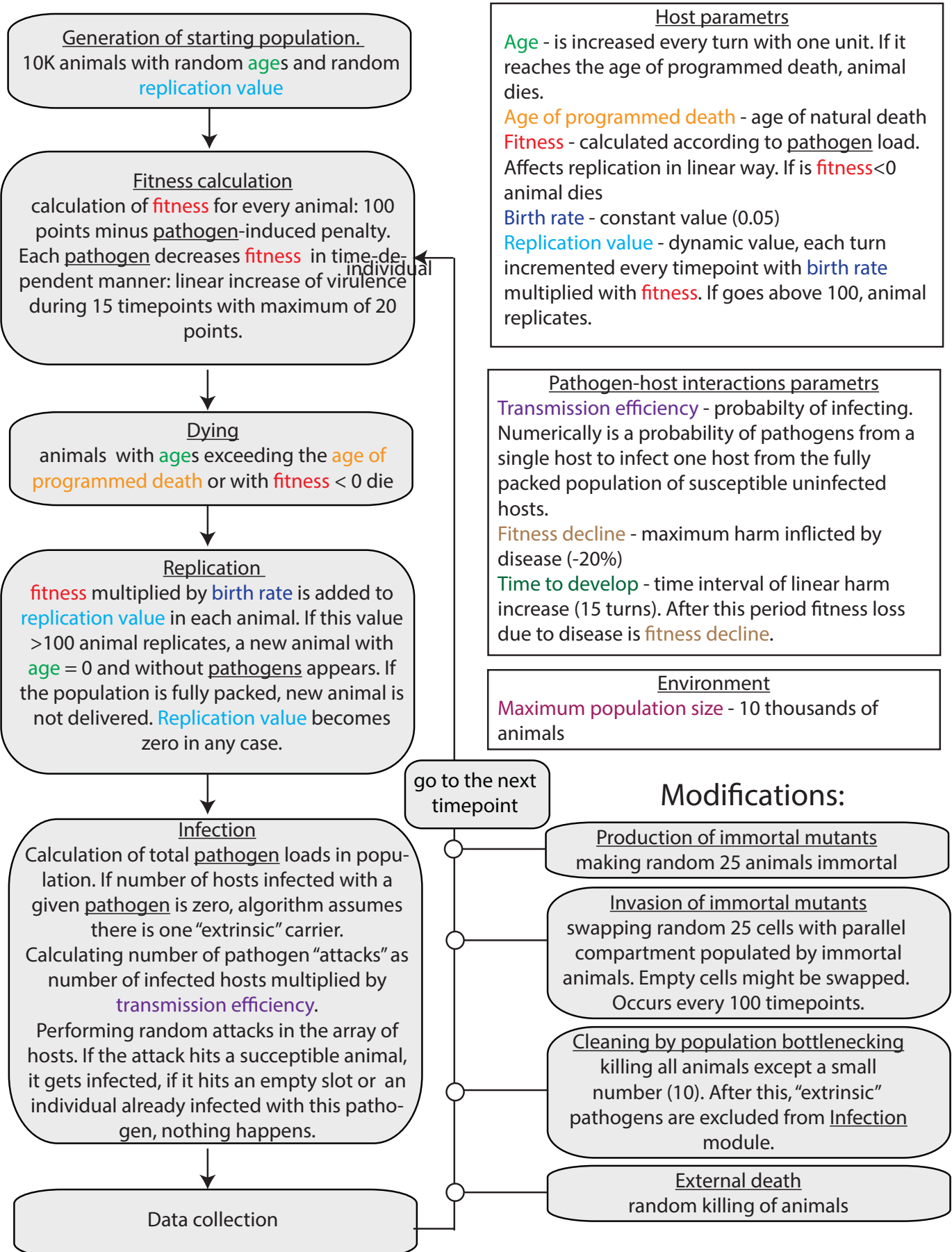
**b.** List of processes. *H* stays for host individual. It's parameters are shown as superscript, while presence of pathogens in this host, as well as their passage number – as a subscript. E.g.  $25 \times H_{(\cdot, \pi=1 \cdot)}$  means 25 individuals infected with pathogen *i*.  $H_{(\cdot, \pi=0 \cdot)}$  stays for one host not infected with pathogen *i*.

- 1 May, R. M. & Anderson, R. M. Epidemiology and genetics in the coevolution of parasites and hosts. *Proceedings of the Royal Society of London. Series B, Biological sciences* **219**, 281-313 (1983).
- 2 Amarasekare, P. The role of density-dependent dispersal in source–sink dynamics. *Journal of Theoretical Biology* **226**, 159-168, doi:<https://doi.org/10.1016/j.jtbi.2003.08.007> (2004).
- 3 Clobert, J., Le Galliard, J. F., Cote, J., Meylan, S. & Massot, M. Informed dispersal, heterogeneity in animal dispersal syndromes and the dynamics of spatially structured populations. *Ecology letters* **12**, 197-209, doi:[10.1111/j.1461-0248.2008.01267.x](https://doi.org/10.1111/j.1461-0248.2008.01267.x) (2009).
- 4 Fronhofer, E. A., Kropf, T. & Altermatt, F. Density-dependent movement and the consequences of the Allee effect in the model organism *Tetrahymena*. *The Journal of animal ecology* **84**, 712-722, doi:[10.1111/1365-2656.12315](https://doi.org/10.1111/1365-2656.12315) (2015).
- 5 Nathan, R. *et al.* A movement ecology paradigm for unifying organismal movement research. *Proceedings of the National Academy of Sciences of the United States of America* **105**, 19052-19059, doi:[10.1073/pnas.0800375105](https://doi.org/10.1073/pnas.0800375105) (2008).

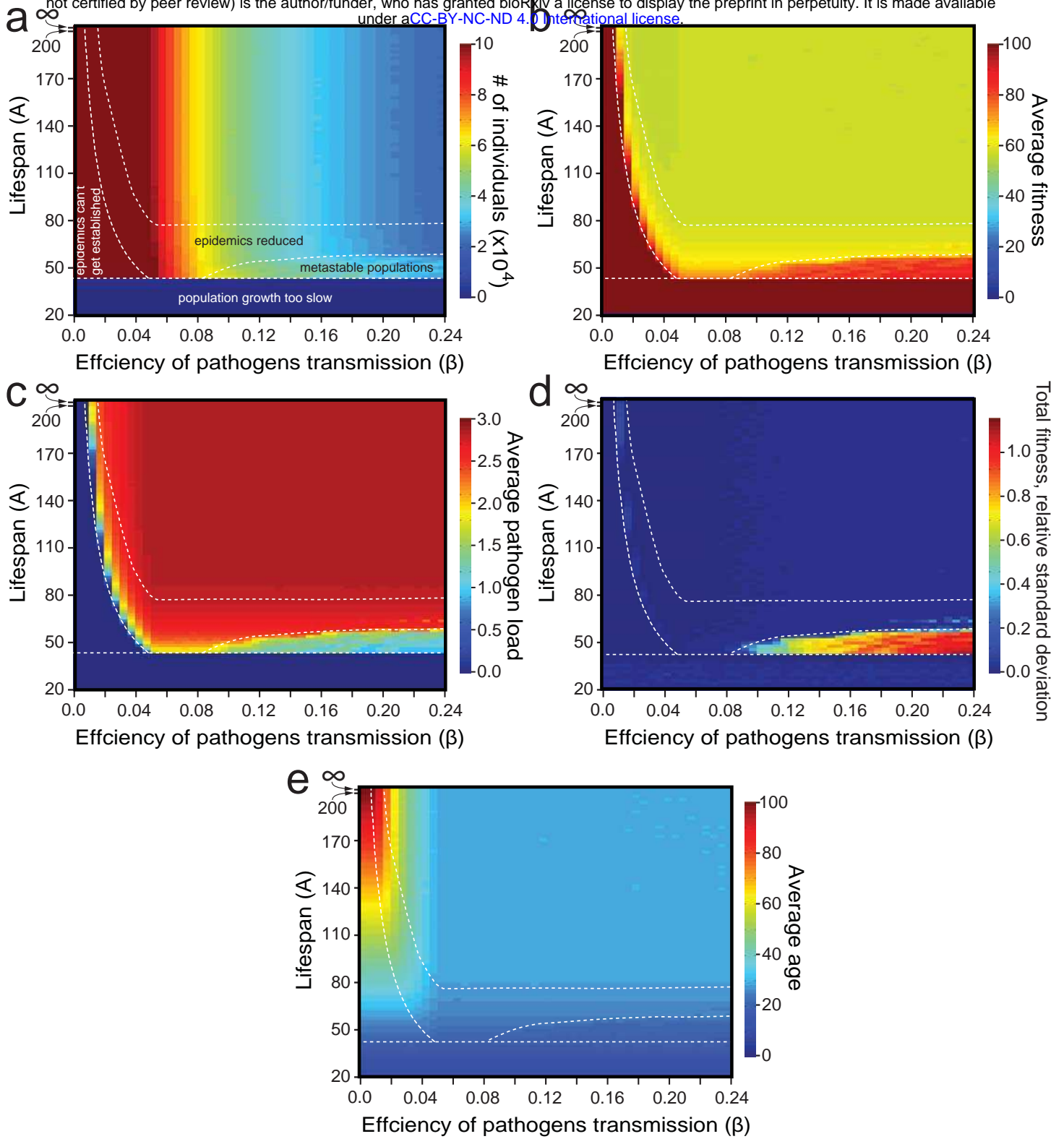
- 6 Pérez-Velázquez, J., Gölgeli, M. & García-Contreras, R. Mathematical Modelling of Bacterial Quorum Sensing: A Review. *Bulletin of Mathematical Biology* **78**, 1585-1639, doi:10.1007/s11538-016-0160-6 (2016).
- 7 Even-Tov, E. *et al.* Social Evolution Selects for Redundancy in Bacterial Quorum Sensing. *PLOS Biology* **14**, e1002386, doi:10.1371/journal.pbio.1002386 (2016).
- 8 Santiago, M. L. *et al.* Simian Immunodeficiency Virus Infection in Free-Ranging Sooty Mangabeys (*Cercocebus atys atys*) from the Taï Forest, Côte d'Ivoire: Implications for the Origin of Epidemic Human Immunodeficiency Virus Type 2. *Journal of Virology* **79**, 12515-12527, doi:10.1128/JVI.79.19.12515-12527.2005 (2005).
- 9 Kirchner, J. W. & Roy, B. A. The Evolutionary Advantages of Dying Young: Epidemiological Implications of Longevity in Metapopulations. *The American Naturalist* **154**, 140-159, doi:doi:10.1086/303232 (1999).
- 10 Kauppila, T. E. S., Kauppila, J. H. K. & Larsson, N.-G. Mammalian Mitochondria and Aging: An Update. *Cell Metabolism* **25**, 57-71, doi:<http://doi.org/10.1016/j.cmet.2016.09.017> (2017).
- 11 Behrens, A., van Deursen, J. M., Rudolph, K. L. & Schumacher, B. Impact of genomic damage and ageing on stem cell function. *Nat Cell Biol* **16**, 201-207, doi:10.1038/ncb2928 (2014).
- 12 Medawar, P. B. An Unsolved Problem of Biology. *London:H.K. Lewis&Co.* (1952).
- 13 Williams, G. C. Pleiotropy, Natural Selection, and the Evolution of Senescence. *Evolution; international journal of organic evolution* **11**, 398-411 (1957).
- 14 Tacutu, R. *et al.* Human Ageing Genomic Resources: Integrated databases and tools for the biology and genetics of ageing. *Nucleic Acids Research* **41**, D1027-D1033, doi:10.1093/nar/gks1155 (2013).
- 15 Kirkwood, T. B. & Holliday, R. The evolution of ageing and longevity. *Proceedings of the Royal Society of London. Series B, Biological sciences* **205**, 531-546 (1979).
- 16 Lenart, P. & Bienertová-Vašků, J. Keeping up with the Red Queen: the pace of aging as an adaptation. *Biogerontology* **18**, 693-709, doi:10.1007/s10522-016-9674-4 (2017).
- 17 Jones, O. R. *et al.* Diversity of ageing across the tree of life. *Nature* **505**, 169-173, doi:10.1038/nature12789 (2014).
- 18 Kenyon, C. The plasticity of aging: insights from long-lived mutants. *Cell* **120**, 449-460, doi:10.1016/j.cell.2005.02.002 (2005).
- 19 Bartke, A. *et al.* Longevity: Extending the lifespan of long-lived mice. *Nature* **414**, 412-412 (2001).
- 20 Kenyon, C., Chang, J., Gensch, E., Rudner, A. & Tabtiang, R. A *C. elegans* mutant that lives twice as long as wild type. *Nature* **366**, 461-464 (1993).
- 21 Clancy, D. J. *et al.* Extension of Life-Span by Loss of CHICO, a *Drosophila* Insulin Receptor Substrate Protein. *Science* **292**, 104-106, doi:10.1126/science.1057991 (2001).
- 22 Kenyon, C. J. The genetics of ageing. *Nature* **464**, 504-512, doi:10.1038/nature08980 (2010).
- 23 Kenyon, C. A Conserved Regulatory System for Aging. *Cell* **105**, 165-168, doi:[http://doi.org/10.1016/S0092-8674\(01\)00306-3](http://doi.org/10.1016/S0092-8674(01)00306-3) (2001).
- 24 Masoro, E. J. Overview of caloric restriction and ageing. *Mechanisms of ageing and development* **126**, 913-922, doi:<http://doi.org/10.1016/j.mad.2005.03.012> (2005).
- 25 Mair, W., Goymer, P., Pletcher, S. D. & Partridge, L. Demography of dietary restriction and death in *Drosophila*. *Science* **301**, 1731-1733, doi:10.1126/science.1086016 (2003).
- 26 Holliday, R. Food, reproduction and Longevity: Is the extended lifespan of calorie-restricted animals an evolutionary adaptation? *BioEssays : news and reviews in molecular, cellular and developmental biology* **10**, 125-127, doi:10.1002/bies.950100408 (1989).
- 27 Lemaître, J.-F. *et al.* Early-late life trade-offs and the evolution of ageing in the wild. *Proceedings of the Royal Society B: Biological Sciences* **282**, doi:10.1098/rspb.2015.0209 (2015).

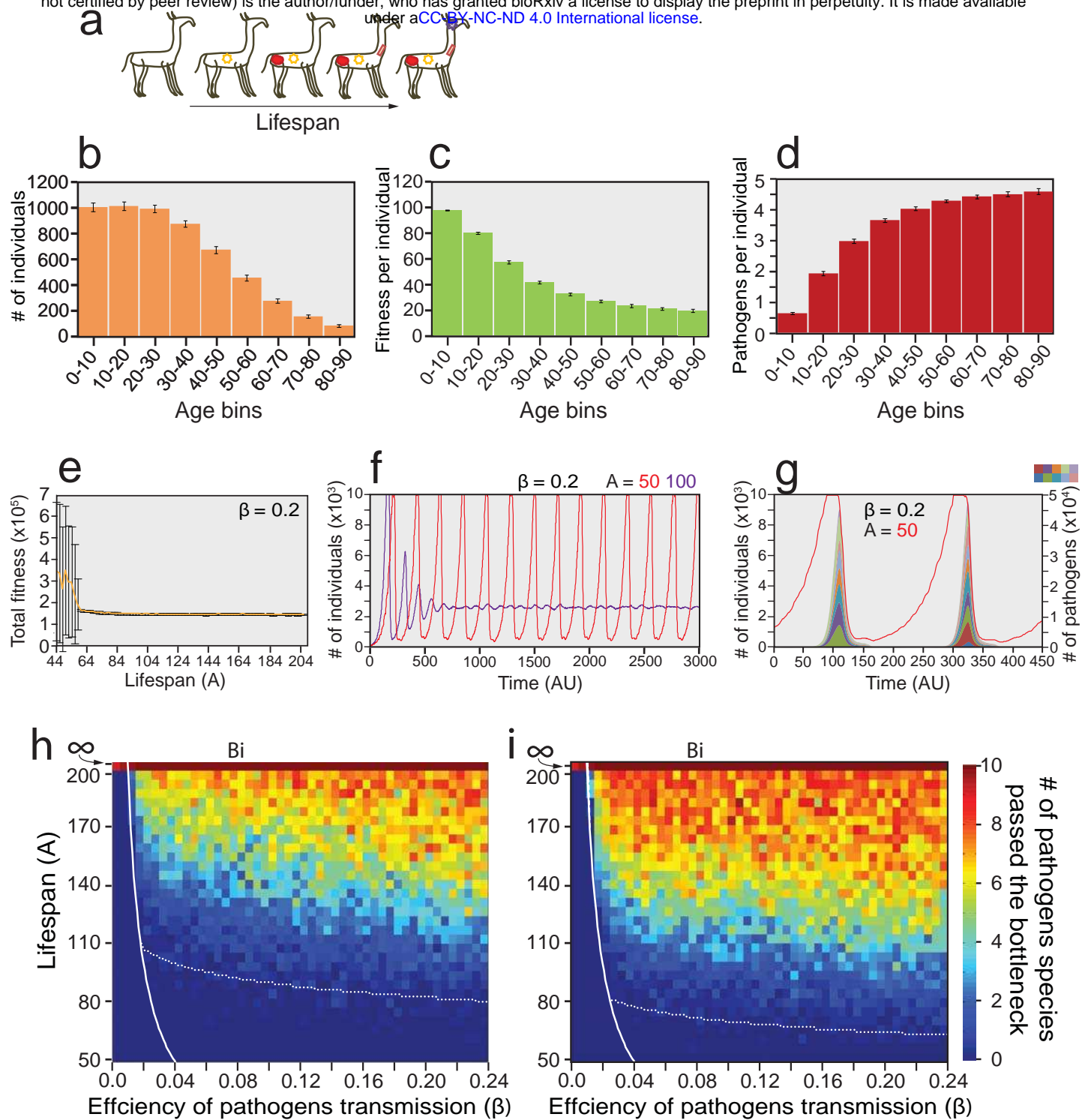
- 28 Tan, T. C. J. *et al.* Telomere maintenance and telomerase activity are differentially regulated in asexual and sexual worms. *Proceedings of the National Academy of Sciences* **109**, 4209-4214, doi:10.1073/pnas.1118885109 (2012).
- 29 Martínez, D. E. Mortality Patterns Suggest Lack of Senescence in Hydra. *Experimental Gerontology* **33**, 217-225, doi:[http://doi.org/10.1016/S0531-5565\(97\)00113-7](http://doi.org/10.1016/S0531-5565(97)00113-7) (1998).
- 30 Piraino, S., Boero, F., Aeschbach, B. & Schmid, V. Reversing the life cycle: medusae transforming into polyps and cell transdifferentiation in *Turritopsis nutricula* (Cnidaria, Hydrozoa). *The Biological Bulletin* **190**, 302-312 (1996).
- 31 Rubner, M. Das Problem der Lebensdauer und seiner Beziehungen zum Wachstum und Ernährung. . *Munich, Germany: Oldenberg* (1908).
- 32 Boddington, M. J. An absolute metabolic scope for activity. *Journal of Theoretical Biology* **75**, 443-449, doi:[http://dx.doi.org/10.1016/0022-5193\(78\)90355-7](http://dx.doi.org/10.1016/0022-5193(78)90355-7) (1978).
- 33 Hofman, M. A. Energy Metabolism, Brain Size and Longevity in Mammals. *The Quarterly Review of Biology* **58**, 495-512, doi:10.1086/413544 (1983).
- 34 Lindstedt, S. L. & W. A. Calder, I. Body Size, Physiological Time, and Longevity of Homeothermic Animals. *The Quarterly Review of Biology* **56**, 1-16, doi:doi:10.1086/412080 (1981).
- 35 Healy, K. *et al.* Ecology and mode-of-life explain lifespan variation in birds and mammals. *Proceedings. Biological sciences* **281**, 20140298, doi:10.1098/rspb.2014.0298 (2014).
- 36 Gillooly, J. F., Brown, J. H., West, G. B., Savage, V. M. & Charnov, E. L. Effects of size and temperature on metabolic rate. *Science* **293**, 2248-2251, doi:10.1126/science.1061967 (2001).
- 37 Damuth, J. Population density and body size in mammals. *Nature* **290**, 699-700 (1981).
- 38 Ricklefs, R. E. Life-history connections to rates of aging in terrestrial vertebrates. *Proceedings of the National Academy of Sciences of the United States of America* **107**, 10314-10319, doi:10.1073/pnas.1005862107 (2010).
- 39 Holliday, R. Understanding Ageing. . *Cambridge: Cambridge University Press.* (1995).
- 40 Le Bourg, E., Thon, B., Légaré, J., Desjardins, B. & Charbonneau, H. Reproductive life of french-canadians in the 17–18th centuries: A search for a trade-off between early fecundity and longevity. *Experimental Gerontology* **28**, 217-232, doi:[http://doi.org/10.1016/0531-5565\(93\)90030-H](http://doi.org/10.1016/0531-5565(93)90030-H) (1993).
- 41 Gurven, M. *et al.* Health costs of reproduction are minimal despite high fertility, mortality and subsistence lifestyle. *Scientific reports* **6**, 30056, doi:10.1038/srep30056
- <https://www.nature.com/articles/srep30056#supplementary-information> (2016).
- 42 Leroi, A. M., Chen, W. R. & Rose, M. R. Long-Term Laboratory Evolution of a Genetic Life-History Trade-Off in *Drosophila melanogaster*. 2. Stability of Genetic Correlations. *Evolution; international journal of organic evolution* **48**, 1258-1268, doi:10.2307/2410383 (1994).
- 43 Ricklefs, R. E. & Cadena, C. D. Lifespan is unrelated to investment in reproduction in populations of mammals and birds in captivity. *Ecology letters* **10**, 867-872, doi:10.1111/j.1461-0248.2007.01085.x (2007).
- 44 Boonekamp, J. J., Salomons, M., Bouwhuis, S., Dijkstra, C. & Verhulst, S. Reproductive effort accelerates actuarial senescence in wild birds: an experimental study. *Ecology letters* **17**, 599-605 (2014).
- 45 Reznick, D. N., Bryant, M. J., Roff, D., Ghalambor, C. K. & Ghalambor, D. E. Effect of extrinsic mortality on the evolution of senescence in guppies. *Nature* **431**, 1095-1099, doi:[http://www.nature.com/nature/journal/v431/n7012/supinfo/nature02936\\_S1.html](http://www.nature.com/nature/journal/v431/n7012/supinfo/nature02936_S1.html) (2004).

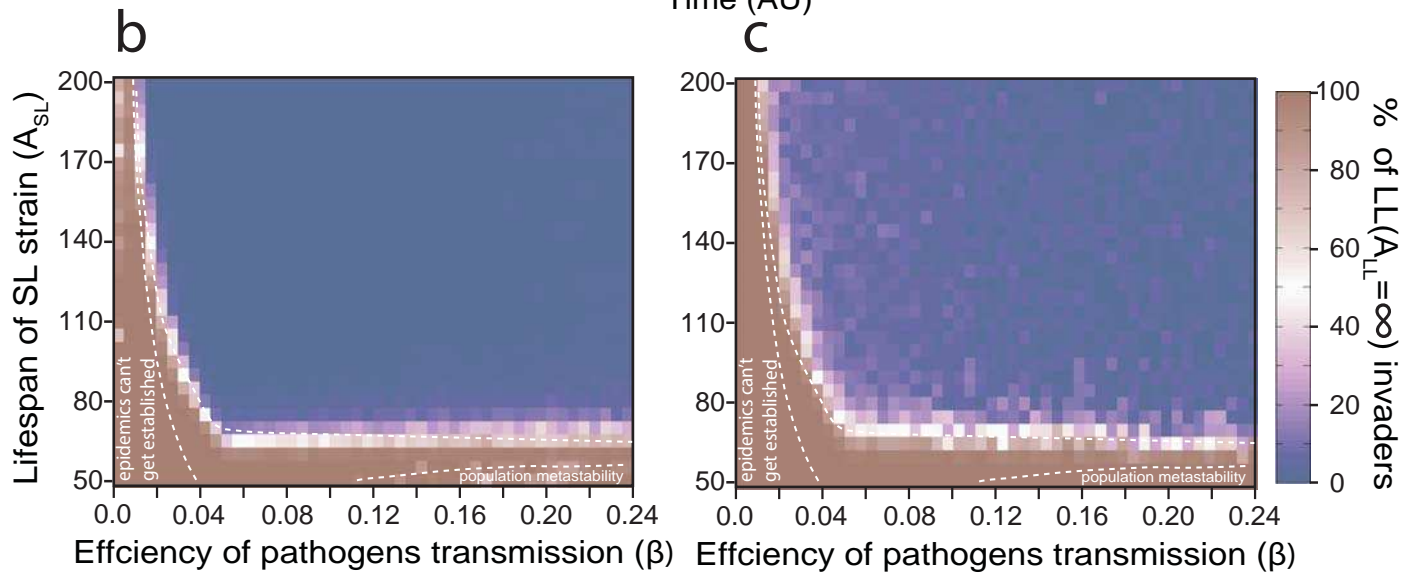
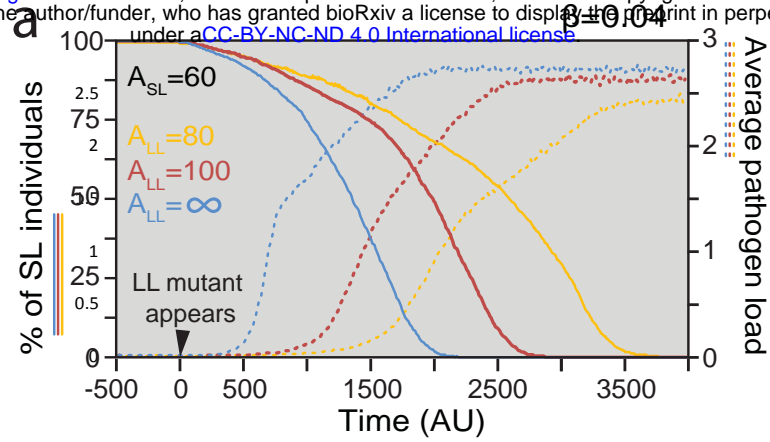
- 46 Leiner, N. O., Setz, E. Z. & Silva, W. R. Semelparity and factors affecting the reproductive activity of the Brazilian slender opossum (*Marmosops paulensis*) in southeastern Brazil. *Journal of Mammalogy* **89**, 153-158 (2008).
- 47 WODINSKY, J. Hormonal Inhibition of Feeding and Death in *Octopus*: Control by Optic Gland Secretion. *Science* **198**, 948-951, doi:10.1126/science.198.4320.948 (1977).
- 48 Morbey, Yolanda E., Brassil, Chad E. & Hendry, Andrew P. Rapid Senescence in Pacific Salmon. *The American Naturalist* **166**, 556-568, doi:10.1086/491720 (2005).
- 49 Keller, L. & Genoud, M. Extraordinary lifespans in ants: a test of evolutionary theories of ageing. *Nature* **389**, 958-960 (1997).
- 50 Deevey, E. S. Life Tables for Natural Populations of Animals. *The Quarterly Review of Biology* **22**, 283-314 (1947).
- 51 Mitchell, K. J. *et al.* Ancient DNA reveals elephant birds and kiwi are sister taxa and clarifies ratite bird evolution. *Science* **344**, 898 (2014).
- 52 Seim, I. *et al.* Genome analysis reveals insights into physiology and longevity of the Brandt's bat *Myotis brandtii*. *Nature Communications* **4**, 2212, doi:10.1038/ncomms3212
- <https://www.nature.com/articles/ncomms3212#supplementary-information> (2013).
- 53 Brook, C. E. & Dobson, A. P. Bats as 'special' reservoirs for emerging zoonotic pathogens. *Trends in Microbiology* **23**, 172-180, doi:<http://doi.org/10.1016/j.tim.2014.12.004> (2015).
- 54 Buffenstein, R. Negligible senescence in the longest living rodent, the naked mole-rat: insights from a successfully aging species. *Journal of comparative physiology. B, Biochemical, systemic, and environmental physiology* **178**, 439-445, doi:10.1007/s00360-007-0237-5 (2008).
- 55 Artwohl, J. *et al.* Extreme susceptibility of African naked mole rats (*Heterocephalus glaber*) to experimental infection with herpes simplex virus type 1. *Comparative medicine* **59**, 83-90 (2009).
- 56 Skulachev, V. P. Phenoptosis: programmed death of an organism. *Biochemistry. Biokhimiia* **64**, 1418-1426 (1999).
- 57 Keane, M. *et al.* Insights into the Evolution of Longevity from the Bowhead Whale Genome. *Cell Reports* **10**, 112-122, doi:10.1016/j.celrep.2014.12.008 (2015).
- 58 Nielsen, J. *et al.* Eye lens radiocarbon reveals centuries of longevity in the Greenland shark (*Somniosus microcephalus*). *Science* **353**, 702-704, doi:10.1126/science.aaf1703 (2016).
- 59 Voituron, Y., De Fraipont, M., Issartel, J., Guillaume, O. & Clobert, J. Extreme lifespan of the human fish (*Proteus anguinus*): a challenge for ageing mechanisms. *Biology Letters*, rsbl20100539 (2010).
- 60 Thompson, M. B. *et al.* Status and longevity of the tuatara, *Sphenodon guntheri*, and Duvaucel's gecko, *Hoplodactylus duvaucelii*, on North Brother Island, New Zealand. *Journal of the Royal Society of New Zealand* **22**, 123-130 (1992).
- 61 Austad, S. N. Retarded senescence in an insular population of Virginia opossums (*Didelphis virginiana*). *Journal of Zoology* **229**, 695-708, doi:10.1111/j.1469-7998.1993.tb02665.x (1993).
- 62 McNab, B. K. Energy conservation and the evolution of flightlessness in birds. *The American Naturalist* **144**, 628-642 (1994).



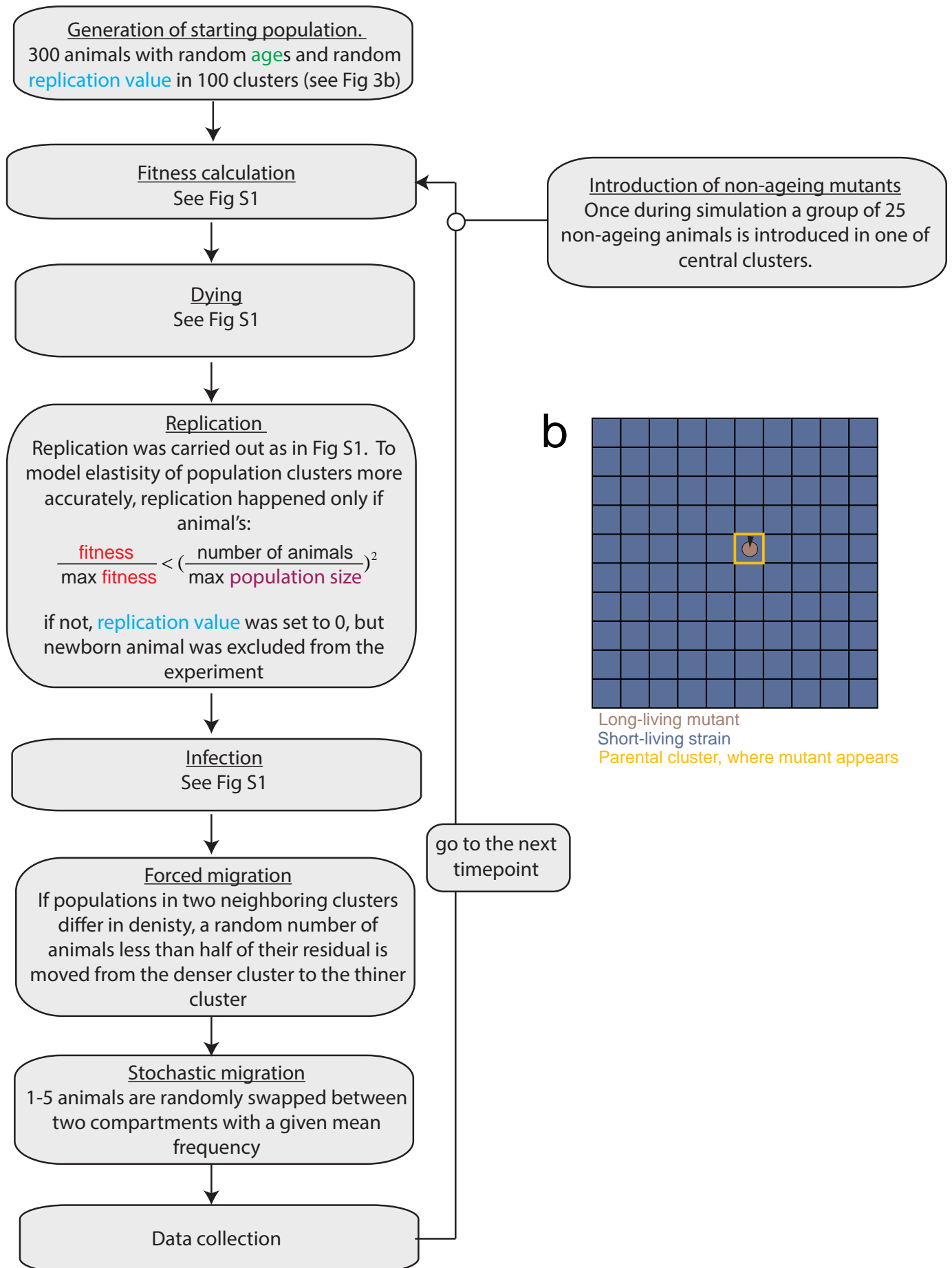


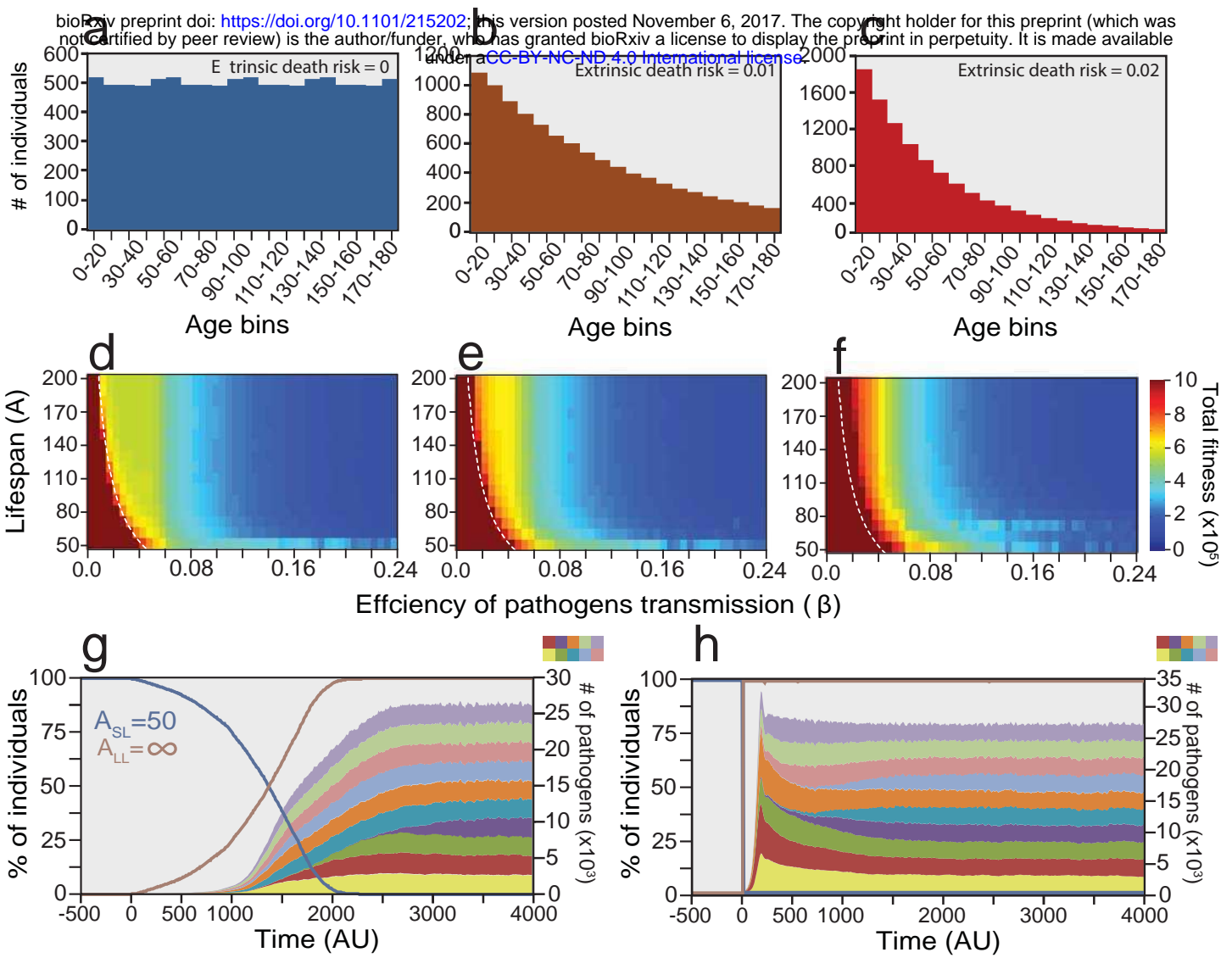


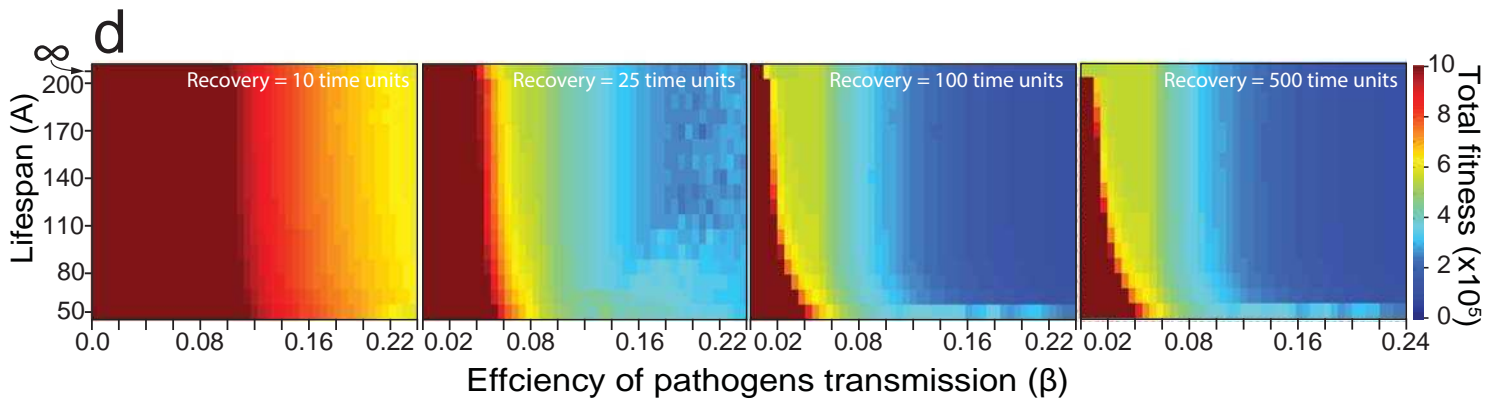
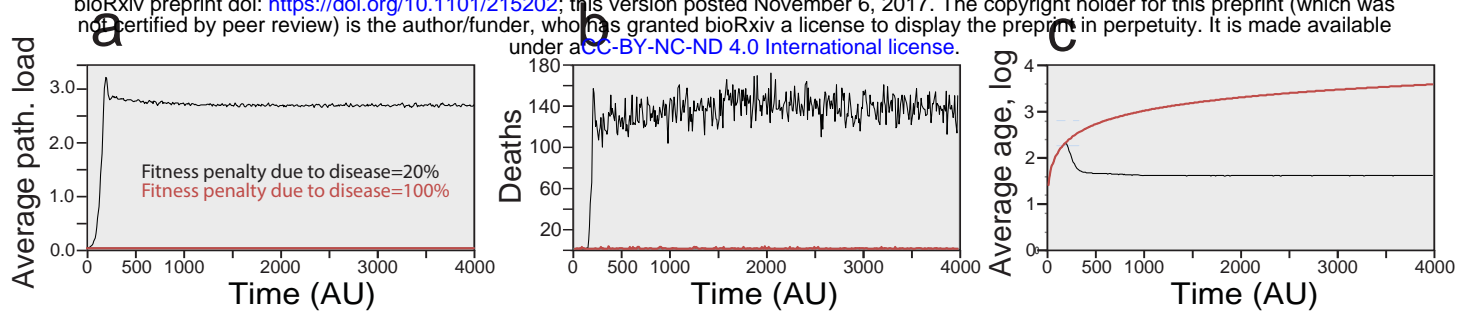




a







a

	Damage accumulation	Selection shadow	Disposable soma	Acceleration of evolution	Infectious catastrophe
Mortality is ubiquitous in advanced animals <sup>a</sup>	Assumes aging as inevitable entropic process	Immortality is absent in species with low external death risks	Immortality is absent from species with slow reproduction rates	Slow evolving species still retain short lifespan	Parasites and infections are ubiquitous factor, affecting all groups of life
No immortal or extraordinary long-living animal mutants are observed <sup>b</sup>	Assumes aging as inevitable entropic process	Extreme longevity is impossible even if external death risks are low	Extreme longevity is impossible even if reproduction expenses are low	No strong explanation	Ability to produce an immortal mutant results in elimination of parental strain
Extension of lifespan is observed in single-gene mutants <sup>c</sup>	Direct contradiction	Antagonistic pleiotropy-coupling of senescence with beneficial traits	Direct contradiction when fertility is not affected by mutation	aging is adaptive and programmed	aging is adaptive and programmed
Hormesis <sup>d</sup>	No strong explanation, no major contradiction	Direct contradiction	Direct contradiction	In a good agreement	In a good agreement
aging is observed in wild population <sup>e</sup>	In a good agreement	Critical contradiction	In a good agreement	In a good agreement	In a good agreement
aging and mortality are absent in some primitive animals <sup>f</sup>	Direct contradiction	Some of these animals are having high external death risks	Immortal species do not show decreased fertility	Adaptive aging did not evolved or lost	Adaptive aging did not evolved or lost
Metabolism speed and longevity correlate negatively <sup>g</sup>	High metabolic rates result in faster damage accumulation	No strong explanation	Growth of maintenance expenses	Animals with fast metabolism can afford to die faster	Slower metabolism results in a slowdown of low-transmissible pathogens
Body size and longevity correlate positively <sup>h</sup>	Larger bodies accumulate more damage, but larger animals are having lower metabolic rates	Big body size protects from predation therefore decreasing external death risks	Big body size is usually associated with low fecundity	Smaller animals can afford shorter lifespan, which is adaptive	Smaller animals can afford shorter lifespan, which is adaptive. Decrease in population density
Fecundity and longevity correlate negatively <sup>i</sup>	High fecundity is associated with higher metabolic rate	Compensation for high population losses	Resources, invested in reproduction are the main reason of aging due to underinvestment into maintenance	Adaptive aging accelerates fecundity	Adverse effects in asymmetric dispersal and pathogen cleaning
External death risks and longevity correlate negatively <sup>j</sup>	No strong explanation, no major contradiction	High external mortality relaxes natural selection in later ages	No strong explanation, no major contradiction	Direct contradiction	Animals, adapted to lifespan, shortened due to external reasons, evolved faster aging to keep it short if external pressure relaxes
Accelerated aging/suicide behavior in semelparous species <sup>k</sup>	No strong explanation	No strong explanation	No strong explanation	Can explain selection for sterility, but not for death	Realization of adaptive aging program
Workers/queens longevity differences in social insects <sup>l</sup>	Direct contradiction	Queens are well protected, while workers are not	No strong explanation	Replicating animals live longer and slow down evolution	A few long-living animals are not a problem for infection control
Birds longevity <sup>m</sup>	Birds have high metabolic rates	Volation protects from predation	No strong explanation, no major contradiction	No strong explanation, no major contradiction	Volation affects asymmetric dispersal
Bats longevity <sup>n</sup>	Bats have high metabolic rates	Volation protects from predation	Low fertility in many bat species	No strong explanation, no major contradiction	Volation, tolerance to infections

Naked mole rats longevity <sup>o</sup>	No strong explanation	Queens are protected, workers longevity is atavistic	No strong explanation	No strong explanation	Prediction: hypersensitivity
Bowhead whales and greenland sharks longevity <sup>p</sup>	Slow metabolism	Low external death risks	Combination of slow metabolism and high body mass	Combination of slow metabolism and high body mass	Combination of slow metabolism, high body mass and probably low pathogen load
Proteus Longevity <sup>q</sup>	Low fecundity	Low external death risks	Low fecundity	Low fecundity	Combination of low fecundity and probably low pathogen load
Tuatara longevity <sup>r</sup>	Combination of slow metabolism and low fecundity	Low external death risks	Combination of slow metabolism and low fecundity	Slow metabolism	Combination of slow metabolism, low fecundity and probably low pathogen load



**b**

Predictions

Positive correlation between longevity and mobility<sup>a</sup>

Negative correlation between longevity and areal size<sup>b</sup>

Negative correlation between longevity and the frequency of contacts between individuals<sup>c</sup>

Negative correlation between longevity and exposure to zoonotic pathogens<sup>d</sup>

Hypersensitivity to infections in naked mole rats<sup>e</sup>

Type I survivorship curves in large flightless ratites<sup>f</sup>

**a**

Variable	Name	Values
<b>host-specific parameters</b>		
A	age of programmed death	range [20-200] and $\infty$
B	birth rate	0.05 if elsewhere stated
<b>individual host's parameters</b>		
$f$	fitness	range [0-100]
$a$	age	age of an individual
$p_1, p_2 \dots p_{10}$	pathogen's composition in a given host	0 or 1 for each value
$r$	replication value	range [0-100]
<b>host-pathogen interaction parameters</b>		
$\beta$	transmission efficiency	range [0.005-0.24]
$\beta_a$	$\beta$ of adapted pathogen (Fig. 4)	same as $\beta$
$\beta_n$	$\beta$ of unadapted pathogen (Fig. 4)	$\beta_n = \beta_a / 10$
$P$	fitness decline due to infection	20%, 50% (in Fig. 2k-j) or 100% (in Extended Data Fig. 11)
$n$	number of passages to adapt	10 (in Fig. 4a-c)
<b>individual pathogen's parameters</b>		
$x$	passage number	range [0->10]
<b>general population parameter's</b>		
$N_{\max}$	maximum number of individuals	300 in Fig. 3fg and $10^5$ elsewhere
$N$	number of individuals	range [0- $N_{\max}$ ]
$L_{p1}, L_{p2} \dots L_{p10}$	total pathogens load in population	range [1- $N_{\max}$ ], pathogen load cannot be less than 1

**b**

Event	Input	Outcome	Comment
<b>individual host parameters calculation</b>			
age increment	$a$	$a = a + 1$	
fitness recalculation	$ff = P$	$\Sigma p_1, p_2 \dots 10$	P is linearly developing to its full value within 15 time units
increment of $r$	$r$	$r = r + Bf$	
<b>individual host events</b>			
dying due to aging	$H^{(a=A)}$	-	when $a = A$
dying due to infections	$H^{(f \leq 0)}$	-	when $f \leq 0$
replication	$H^{(r \geq 100)}, N < N_{\max}$	$2 \times H^{(r=0)}$	when $r \geq 100$ , the newborn does not have pathogens
<b>pathogens calculations (for each pathogen individually)</b>			
pathogen load calculation	$L_{pi}$	$L_{pi} = \Sigma H_{pi=1}$ , if $L_{pi} = 0$ then $L_{pi} = 1$	sum of hosts infected with pathogen $i$
infection	$[n \times H_{(..pi=0..)}, m \times H_{(..pi=1..)}]$	$[(n - n\beta L_{pi}) \times H_{(..pi=0..)},$ $(m + n\beta L_{pi}) \times H_{(..pi=1..)}]$	uninfected hosts are becoming infected with probability of $\beta L_{pi}$
<b>modifications of the models</b>			
long-living mutants	$[n \times H^{(A)}]$	$[(n - 25) \times H^{(A)}, 25 \times H^{(A=\infty)}]$	long-living mutants generation (Figs. 3bc, 4c, Extended Data Fig. 6)
populations intermix	$[n \times H^I], [m \times H^II]$	$[(n - \rho) \times H^I, \rho \times H^II],$ $[(m - \rho) \times H^II, \rho \times H^I]$	$\rho = 25$ , every 100 turns
bottlenecking	$[n \times H]$	$[10 \times H]$	leaving alive 10 random hosts
extrinsic death simulation	$[n \times H]$	$[n(1 - \delta) \times H]$	$\delta$ - extrinsic death rate (Extended Data Fig. 10)
<b>dispersal in clustered population</b>			
density-dependent dispersal	$[n \times H^I], [m \times H^II]$ $n > m, \Delta = (n - m) \times \rho$	$[(n - \Delta) \times H^I],$ $[m \times H^II, \Delta \times H^I]$	$\rho$ is a random value from 0 to 0.5
density-independent dispersal	$[n \times H^I], [m \times H^II]$	$[(n - \rho) \times H^I, \rho \times H^II],$ $[(m - \rho) \times H^II, \rho \times H^I]$	$\rho$ is a random value from 1 to 5
birth rate limits due to overcrowding	$H^{(r \geq 100, f/f_{\max} > \lambda)}$ , $\lambda = (N/N_{\max})^2, N < N_{\max}$	$2 \times H^{(r=0)}$	$f_{\max} = 100$
<b>pathogen adaptation (individually for each pathogen with each passage number)</b>			
infection by non-adapted pathogen	$[n \times H_{(..pi=0..)},$ $m \times H_{(..pi(x)=1..)}]$	$[(n - n\beta_n L_{pi(x)}) \times H_{(..pi=0..)},$ $m \times H_{(..pi(x)=1..)},$ $(n\beta_n L_{pi(x)}) \times H_{(..pi(x+1)=1..)}]$	$x$ is a passage number, if $x \geq 10$ then $\beta = \beta_a$ else $\beta = \beta_n$