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Research paper

The effect of the demographic history on the evolution of senescence: a potential new test of the mutation accumulation theory

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Running title: Senescence of island endemics

Abstract : The different evolutionary theories of senescence predict different directions for the correlation between the population size and the intensity of senescence. Using simulations, I highlighted how the effect of the population size on the intensity of senescence could be reinforced by the time since populations have been large or small. I devised a mutation-selection model in which the effect of the mutations was age-specific. Several small populations diverged from a same large population at different points in time. At the end of the simulation, the correlation between the time since the populations had been small and the rate of senescence was positive under the mutation accumulation theory and negative under the antagonistic pleiotropy theory. The phenomenon was strong enough to reverse the usually negative relationship between the intensity of senescence and the generation time. These mutually-exclusive predictions could help broaden the taxonomic support for the mutation accumulation theory of senescence, currently mostly supported in humans and lab invertebrates. I briefly mention a few potential applications in real-life systems.

Key-words: ageing, demographic history, island syndrome, disposable soma, mutation-selection model

1 Introduction

2 In evolutionary theory, the deterioration of biological functions and fitness components when
3 individuals grow older, i.e., senescence, stems in the decline in the strength of selection with age
4 (Charlesworth, 2001; Hamilton, 1966; Rose, 1994). Under that general rule, two main types of
5 senescence-inducing mutations have been considered by theorists. Senescence-inducing mutations
6 can have a deleterious effect that increases with age (Medawar, 1952); or they can have a pleiotropic
7 effect, characterized by a beneficial effect during early life followed by a deleterious effect later on
8 (Kirkwood and Holliday, 1979; Williams, 1957). The first type of mutation corresponds to the
9 mutation accumulation theory of senescence (MA), according to which deleterious alleles with
10 effects restricted to late stages of life equilibrate at higher frequencies at mutation-selection balance
11 than alleles that act earlier (Charlesworth, 2001; Medawar, 1952). The second type of mutation
12 corresponds to the antagonistic pleiotropy theory (AP), according to which alleles with positive
13 effects on performance early in life, but with negative effects due to trade-offs later on, are more
14 likely to be established by selection than alleles with the opposite pattern (Charlesworth, 2001;
15 Williams, 1957).

16 Even if AP invokes the notion of life-history strategy and trade-offs (Lemaître et al., 2015; Maklakov
17 and Chapman, 2019) whereas under MA, senescence may be interpreted as a genetic disease
18 (Johnson et al., 2017; Rubinsztein and Carmichael, 2003; Yuan et al., 2024), the two theories yield
19 strikingly similar predictions regarding the variation in the intensity of senescence along the slow/fast
20 continuum of life histories (Jones et al., 2008; Péron et al., 2010), and have overall proven hard to
21 separate empirically. Indeed, even with detailed data on age-specific genotype-phenotype
22 associations, excluding AP can be challenging. For example, Hudson et al. (2023) reported an increase
23 in the rate of actuarial senescence with the rate of inbreeding among European badgers *Meles meles*.
24 This result verified a major prediction of MA (Charlesworth and Hughes, 1996; Escobar et al., 2008;
25 Hughes et al., 2002) and was *a priori* unexpected under AP. However, if inbreeding also had a
26 positive effect on survival during the immature stages, or on fecundity, which the aforementioned
27 authors did not test, then the same dataset would support AP instead of MA (Hudson et al., 2023). In
28 addition, the age-specificity in inbreeding depression was only revealed upon infection with bovine
29 tuberculosis, and thereby the support for MA depended on the occurrence of that pathogen (Hudson
30 et al., 2023).

31 As a result of this sort of issue, unambiguous empirical support for MA is currently restricted, to my
32 knowledge, to a handful of species including humans and lab invertebrates. More precisely, a few
33 population genetics studies supported MA, but they often supported AP at the same time (Escobar et

34 al., 2008; Hughes et al., 2002; Lohr et al., 2014; Mallet et al., 2011; Promislow et al., 1996); and a few
35 genetic associations studies supported MA by identifying genes or alleles that verified the MA
36 assumptions (Johnson et al., 2017; Rubinsztein and Carmichael, 2003; Yuan et al., 2024), but without
37 ruling out AP for the rest of the genome.

38 In this context, I looked into an alternative way to empirically support MA and potentially exclude AP
39 in more species and *in natura*: the correlation between the population size and the intensity of
40 senescence.

41 **The predicted direction of the correlation between the population size and the rate of senescence** 42 **changes depending on the theoretical framework**

43 MA involves “nearly neutral” selection (Leroy et al., 2021) on mutations whose effect is expressed
44 after most individuals have already died from other causes (Medawar, 1952). The evolution of
45 senescence under MA is thus similar to genetic drift (Charlesworth, 2001; Escobar et al., 2008;
46 Hughes et al., 2002; Lohr et al., 2014). Genetic drift is faster in small than large populations (Jordan
47 and Snell, 2008; Leroy et al., 2021; Lynch et al., 1995). Therefore, under MA, senescence should be
48 more intense in small than large populations (Lohr et al., 2014).

49 By contrast, under AP, senescence-inducing mutations are under active positive selection because
50 they confer early-life benefits (Williams, 1957). Active positive selection is less effective in small than
51 large populations (Lanfear et al., 2014), due in part to the relatively larger effect of demographic
52 stochasticity on the transmission of genes (Lande and Barrowclough, 1987). Therefore, under AP,
53 senescence should be less, not more, intense in small than large populations.

54 In summary, the correlation between the population size and the intensity of senescence should go
55 into different directions depending on whether MA or AP is contributing the most to the evolution of
56 senescence.

57 **Empirical tests can be confounded**

58 To test the aforementioned predictions about the effect of the population size on the evolution of
59 senescence, the intuitive approach would be to correlate the population size and the intensity of
60 senescence across natural populations of different sizes (Lohr et al., 2014). However, such
61 comparisons can be confounded by factors that covary with the population size. In Lohr et al. (2014),
62 the latitude, the distance to the coast, and the geological substrate covaried with the effective size of
63 *Daphnia* populations, and were acknowledged as potentially confounding factors in the correlation
64 between the rate of senescence and the effective population size. In island/mainland comparisons,
65 many factors covary with the size of populations being compared, such as the lack of predators in
66 small islands (Terborgh, 2023). These confounding environmental factors can weaken the inference

67 derived from correlations between the population size and the rate of senescence across populations
68 from different locations.

69 **Replacing small/large comparisons with old/young comparisons**

70 Instead of comparing populations from different places, I propose to compare populations from the
71 same place, thus exposed to the same environmental factors, but with a different history in that
72 place (Péron and Vollot, 2024). More precisely, I focused on small islands and the time since their
73 inhabitants have colonized them. Following Fjeldså and Lovett (1997), I used the phrase “species
74 age” or “population age” to refer to the time since a population colonized a given island system, and
75 thereby the time since the population had been small.

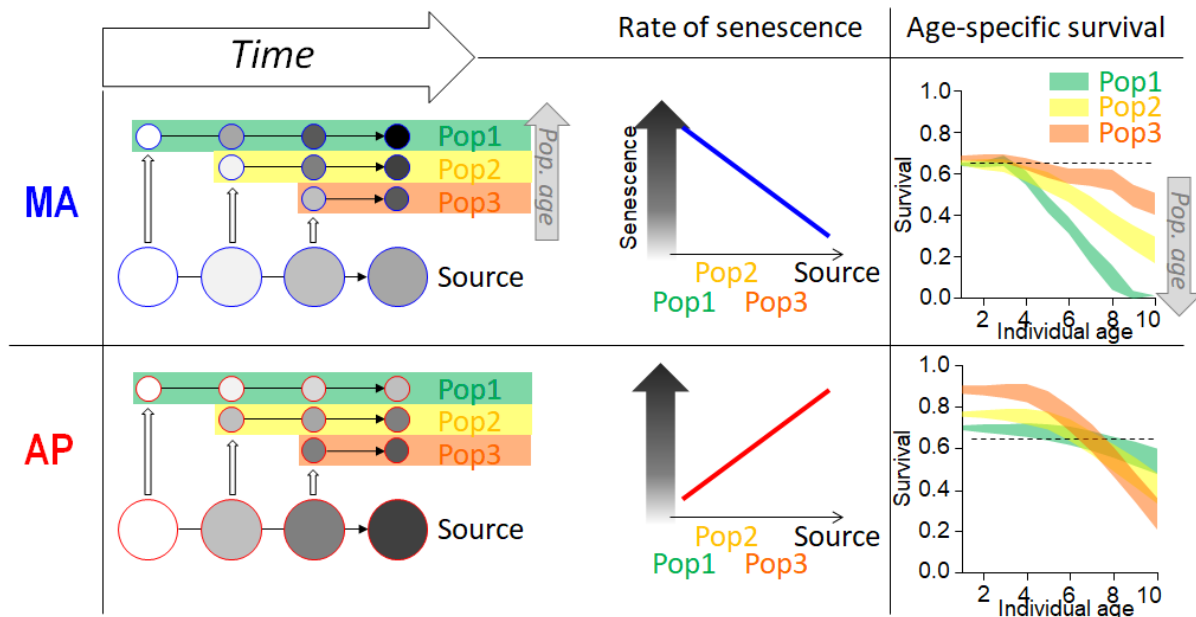
76 To illustrate this idea, I simulated the parallel evolution of senescence in four populations according
77 to the scenario in Fig. 1. The scenario featured one large source population, and three small island
78 populations that diverged from the source at different points in time. The four populations evolved
79 throughout the simulation, at a pace that I expected to depend on the population size. At the end of
80 the simulation, I expected that the rate of senescence would eventually depend on the time since the
81 divergence from the source, i.e., the “population age” as per the above definition. Furthermore, I
82 expected that the direction of the correlation between the population age and the rate of
83 senescence would depend on whether MA or AP was operating.

84 In other words, contrary to previous studies into the relationship between the population size and
85 the evolution of senescence (Charlesworth, 2001; Escobar et al., 2008; Lohr et al., 2014), I did not
86 focus on the mutation-selection balance. Instead I focused on the non-stationary dynamics before
87 the balance is reached, when the effect of the demographic history is still visible. In practice, I used a
88 fully numerical approach. In an *in silico* experiment, I empirically monitored the evolution of allele
89 frequencies and I compared the eventual rates of senescence rates across populations at the end of
90 the simulation (Fig. 1).

91

92 Fig. 1: Schematic representation of the simulated system with a large source population and three
 93 small island populations of different ages (different amounts of time since they have colonized their
 94 home island). The expected differences in the rate of senescence under MA (mutation accumulation
 95 theory) and AP (antagonistic pleiotropy theory) are represented to the left. In the age-specific
 96 survival plots, the dashed horizontal line represents the baseline rates of survival at the start of the
 97 simulation before the evolution of senescence. The population age at the end of the simulation
 98 (uniform grey arrow) increases from population 3 to population 1.

99



100

101

102 Material and Methods

103 Mutation-selection model focusing on non-stationary dynamics

104 The vital rate values were chosen to mimic those of small passerines like the *Zosterops* genus (Knapé
 105 et al., 2011), which are iteroparous and in which the generations overlap (details of the parameter
 106 values in Table 1). In the model, the population size influenced the rate of apparition of new
 107 mutations and the transmission of alleles through demographic stochasticity and density-
 108 dependence. Precisely, I implemented a binomial survival process in which the annual survival
 109 probability $S(a_i, \mathbf{G}_i, N_t)$ depended on the age a_i , the genotype \mathbf{G}_i and the population size N_t of
 110 individual i and year t . Upon surviving and if not already in the breeding state, individuals could
 111 switch from non-breeding to breeding if one of K territories was left vacant by the death of a
 112 territory holder, at which point one of the non-breeders was drawn at random to replace it. Further
 113 demographic stochasticity occurred through a Poisson breeding process with fecundity rate
 114 $F(a_i, \mathbf{G}_i)$. I ignored on the other hand the effect of the population size on the expression of recessive
 115 mutations, and instead assumed that all mutations were dominant. The effect of the population size

116 on the rate of homozygosity would likely reinforce the conclusion of this paper by allowing more
 117 recessive mutations to be expressed in small than large populations (Hartl and Clark, 2007).

118 Table 1: Model parameters

Notation	Biological meaning	Value
Parameters for survival		
S_0	Baseline survival probability	0.65
s_S	Selection coefficient on survival	0.025
b	Coefficient of density-dependence in survival	Island: 0.001 Mainland: 0.00001
Parameters for fecundity		
F_0	Baseline fecundity rate	3
s_F	Selection coefficient on fecundity	0.05
K	Number of territories	Island: 100 Mainland: 10,000
Parameters for mutations		
U	New mutations per reproduction	0.01
ε	Probability of beneficial mutation	0.01
Parameters for migrations		
n_0	Seed size	10
T	Time in years between seeding events	1000
Tuning parameter		
α	Intensity of antagonistic pleiotropy	0.05 (MA) to 5 (AP)

119

120 To simulate MA, each mutation was assigned an age a below which the mutation had no effect. The
 121 individual genotype functions $G_i^{(S)}(a)$ and $G_i^{(F)}(a)$ gave the number of mutations whose deleterious
 122 effect on survival and fecundity respectively started at age a for individual i (and subsequently lasted
 123 until death). At each reproduction event, new mutations occurred with rate U . Upon the occurrence
 124 of a new mutation, the age a was drawn at random and the genotype of the resulting offspring was
 125 updated using $G_i^{(\theta)}(a) = 1/2 \left(G_m^{(\theta)}(a) + G_f^{(\theta)}(a) \right) + 1$, where $\theta=S$ or F , and m and f denoted the
 126 two parents of individual i . A proportion ε of the mutations had a beneficial effect (Goyal et al.,
 127 2012), in which case the update was $G_i^{(\theta)}(a) = 1/2 \left(G_m^{(\theta)}(a) + G_f^{(\theta)}(a) \right) - 1$. Since the mutations
 128 were effectively neutral if the individual died before age a , the strength of selection decreased with
 129 age as per classic models of the evolution of senescence.

130 To simulate AP, I added a beneficial effect of $G_i^{(\theta)}(a)$ before age a (Eq. 1), that counteracted the
 131 deleterious effect of $G_i^{(\theta)}(a)$ after age a . In other words, senescence-inducing mutations now had a
 132 positive effect during early life. That effect was modulated by parameter α . When α was near 0, MA
 133 dominated, and when α tended towards large values, AP dominated. The parameter α itself was not
 134 subject to selection, but instead represented an extrinsic constraint on the strength and shape of
 135 selection on $G_i^{(\theta)}(a)$.

Eq. 1	$S(a_i, \mathbf{G}_i, N_t) = S_0 \cdot \overbrace{(1 - bN_t)}^{\text{density-dependence}} \overbrace{-s_S \cdot \sum_{u \leq a_i} G_i^{(S)}(u)}^{\text{deleterious late-life effects}} \overbrace{+\alpha \cdot s_S \cdot \sum_{u > a_i} G_i^{(S)}(u)}^{\text{beneficial early-life effects}}$ $F(a_i, \mathbf{G}_i) = F_0 \overbrace{-s_F \cdot \sum_{u \leq a_i} G_i^{(F)}(u)}^{\text{deleterious late-life effects}} \overbrace{+\alpha \cdot s_F \cdot \sum_{u > a_i} G_i^{(F)}(u)}^{\text{beneficial early-life effects}}$
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136 At time $t=0$, the populations were made of identical individuals that had not accumulated any
 137 mutation yet and did not exhibit senescence. I immediately separated two populations: one in the
 138 mainland with $K = 10,000$ territories, starting with an initial population size of 10,000 individuals, and
 139 one in an island with $K = 100$ territories, starting with an initial population size of 10 individuals (Fig.
 140 1). I then proceeded with the mutation-selection process for $T=1000$ years. At the end of that first
 141 period of 1000 years, I seeded a second island population by randomly selecting 10 individuals from
 142 the mainland source (Fig. 1), and then I let the mutation-selection process operate for another 1000
 143 years. I did not allow for gene flow between populations other than during the seeding events. I also
 144 ignored competition between the island populations, e.g., the number of territories K did not depend
 145 on the number of island populations. Next, at the end of the second period of 1000 years, I seeded a
 146 third and last island population, and let the mutation-selection process operate for a final 1000 years
 147 (Fig. 1). At each new seeding event, the populations took less than 30 years to reach their asymptotic
 148 population size as determined by the number of available breeding territories K and the demographic
 149 parameters in Eq. 1. This model thereby also illustrated the difference between the demographic
 150 balance (the equilibrium between births and deaths when the population is near carrying capacity)
 151 and the mutation-selection balance (the equilibrium between the rate of apparition of new
 152 deleterious mutations and the rate at which they are eliminated by natural selection), which indeed
 153 happened at different time scales as expected. The script to reproduce the simulation is provided in
 154 Appendix S1.

155 **Statistical analysis**

156 I compared the rates of senescence across the four populations at the end of the simulation. For this
 157 purpose, I used Eq. 1 to compute the age-specific survival and fecundity rates of all the individuals
 158 that were alive at the end of the simulation. Then I fitted the Gompertz's model of survival and a log-
 159 linear model of fecundity for each individual (results were qualitatively similar if using the Weibull's
 160 model instead of Gompertz's) (Ricklefs, 1998). From these models, I obtained the Gompertz' rates of
 161 actuarial senescence and the log-linear rates of reproductive senescence. I applied generalized linear
 162 models with the individual rates of senescence as dependent variable, and the population age and
 163 parameter α as predictor variables.

164 **Ranking on the pace of life continuum**

165 The generation time, the average age difference between mothers and daughters (Charlesworth,
166 1994) correlates negatively with the intensity of senescence across vertebrates (Jones et al., 2008;
167 Péron et al., 2010, and references therein). Slow-breeding, long-lived species usually exhibit slow and
168 delayed senescence, whereas fast-breeding, short-lived species exhibit fast and early senescence.

169 For each individual at the end of my simulation, I computed its theoretical generation time as the
170 average age difference between mothers and daughters in a population made entirely of the
171 genotype of the focal individual. I then looked for any departure from the general rule that the
172 generation time should correlate negatively with the rate of senescence.

173 **Results and Discussion**

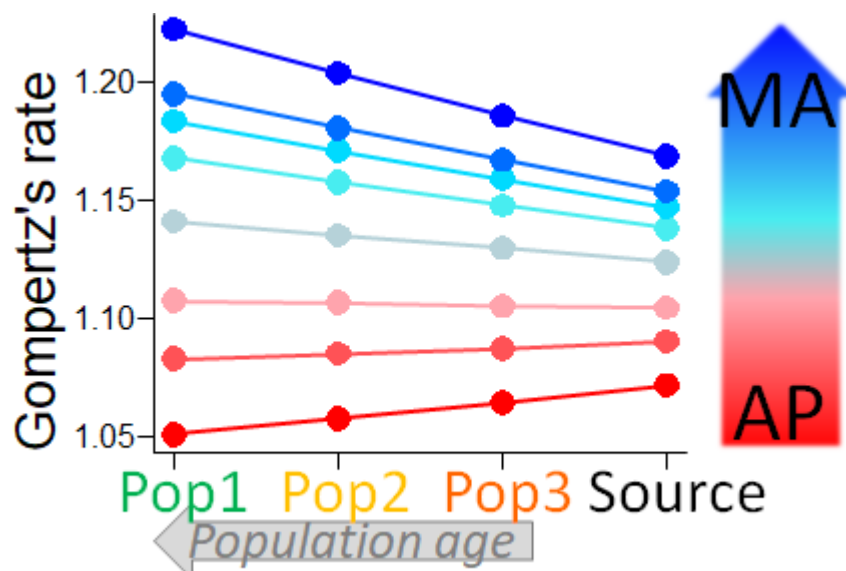
174 **Actuarial senescence at the end of the simulation**

175 As predicted, at the end of the simulation, the rate of actuarial (survival) senescence covaried with
176 the population age (the time since the populations had been small) across populations. Furthermore,
177 also as predicted, the direction of that correlation changed between the mutation accumulation
178 theory (MA) and the antagonistic pleiotropy theory (AP) (Fig. 2). Under MA (blue curves in Fig. 2), old
179 island populations (populations that had been small for a long time) exhibited more senescence than
180 young island populations (populations that had been small for a short time), and than the source
181 population. Under AP (red curves), old populations exhibited less senescence than young
182 populations, and than the source population. Therefore, this simulation exercise confirmed that,
183 everything else being equal, the demographic history predicted the contemporary rate of senescence
184 and could be used to test evolutionary theories of senescence. The difference between the
185 populations was however small (Fig. 2; Table 2a), which I attributed to the design of the experiment,
186 and especially the fact that, to save on computing time, the populations had only 3000 years to
187 evolve.

188

189 Fig. 2: Change in the Gompertz's rate of actuarial (survival) senescence with the time since the
 190 divergence from the large source population (population age: x-axis) and with the intensity of
 191 antagonistic pleiotropy (red for antagonistic pleiotropy AP, blue for mutation accumulation MA).

192



193

194

195 Table 2: Linear model of individual rate of senescence depending on the population age and on the
 196 intensity of antagonistic pleiotropy α . The populations age was rescaled from 1 (oldest island
 197 population) to 4 (source population).

	Estimate	S.E.	df	deviance	ANOVA P-value
(a) Gompertz' rate of actuarial (survival) senescence					
(Intercept)	0.10	0.01			
Population age	-0.001	0.003	1	0.2	0.78
$\log(1/\alpha)$	0.04	0.01	1	514	<0.001
Population age \times $\log(1/\alpha)$	-0.005	0.002	1	4.1	0.07
(b) Log-linear rate of reproductive senescence					
(Intercept)	-3.21	0.002			
Population age	0.049	0.0005	1	0.7	<0.001
$\log(1/\alpha)$	-0.70	0.001	1	18205.1	<0.001
Population age \times $\log(1/\alpha)$	0.026	0.0003	1	3.1	<0.001

198

199

200 These results build on previous studies in two major ways. First, previous authors documented the
 201 role of the population size under MA (Lohr et al., 2014 and references therein), but did not fully
 202 articulate its role under AP. Thus the fact that MA and AP lead to mutually exclusive predictions was
 203 not explicit in previous works. Second, previous works assumed mutation-selection balance, and did
 204 not address the potential effect of the demographic history, i.e., the time since populations have

205 been small and large. By relaxing the equilibrium assumption using a fully numerical approach, I
206 opened a new avenue for empirical tests based on the variation in demographic history across
207 sympatric populations, when at least one of the populations can be assumed to not have reached the
208 mutation-selection balance yet (e.g., recent introduction).

209 **Ranking on the pace of life continuum**

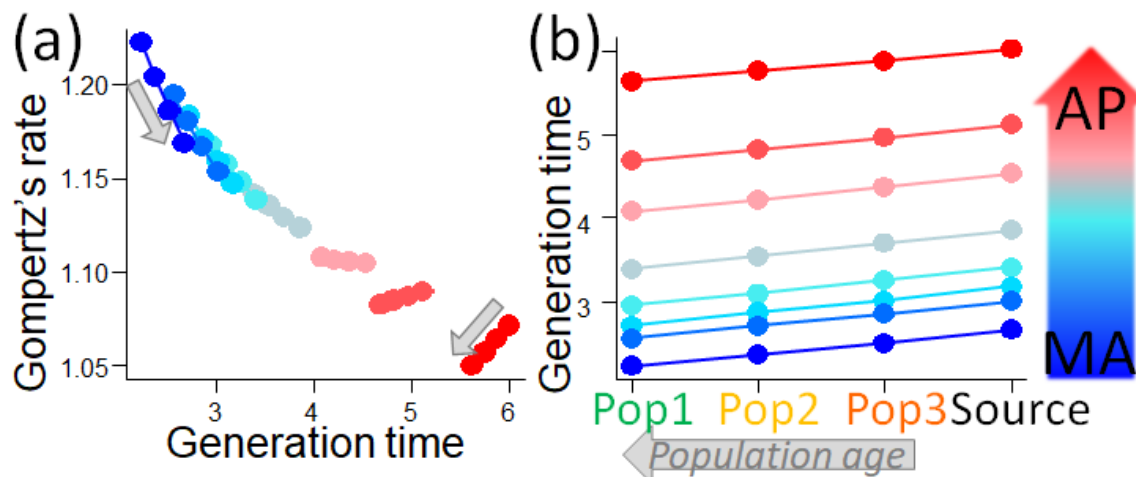
210 The generation time at the end of the simulation increased with the parameter α (Fig. 3). This result
211 stemmed in the model formulation; when α was low, evolution could only yield a decrease in
212 lifespan, whereas when α was high, the lifespan instead increased when mutations accumulated (Eq.
213 1) (Péron et al., 2019). However, irrespective of the parameter α , the generation time always
214 decreased across populations with the population age at the end of the simulation (the time since
215 they had been small; Fig. 3b). This was because, under both MA and AP, the selection on early life
216 performance and fecundity was more efficient in large than small populations. Overall, the
217 parameter α thus empirically mediated a negative correlation between the generation time and the
218 rate of senescence (Fig. 3a). This result corroborated the general pattern observed in comparative
219 analyses across vertebrate species (Jones et al., 2008; Péron et al., 2010).

220 By contrast, for a large α , the correlation between the generation time and the rate of senescence
221 across populations of different population ages became positive instead of negative (red curves in
222 Fig. 3a). In other words, I generated a departure from the expectation that slow species should
223 exhibit slow senescence. If observed in empirical data, such a departure would constitute evidence
224 for AP. In addition, this result indicated that in order to use the demographic history as a basis for
225 empirical tests of evolutionary theories of senescence, researchers will first need to account for the
226 variation in the generation time. Lastly, this result helped explain the residual variance in the
227 aforementioned comparative analyses. Indeed, the relative contribution of MA and AP to the
228 evolution of senescence could be species-specific, and different species also expectedly have
229 experienced different demographic histories.

230

231

232 Fig. 3: Relationship between the generation time and the rate of actuarial senescence when the
 233 contribution of antagonistic pleiotropy to the evolution of senescence increases (shade turns to red)
 234 and when the population age increases (time since the divergence from the large source population:
 235 grey arrow).

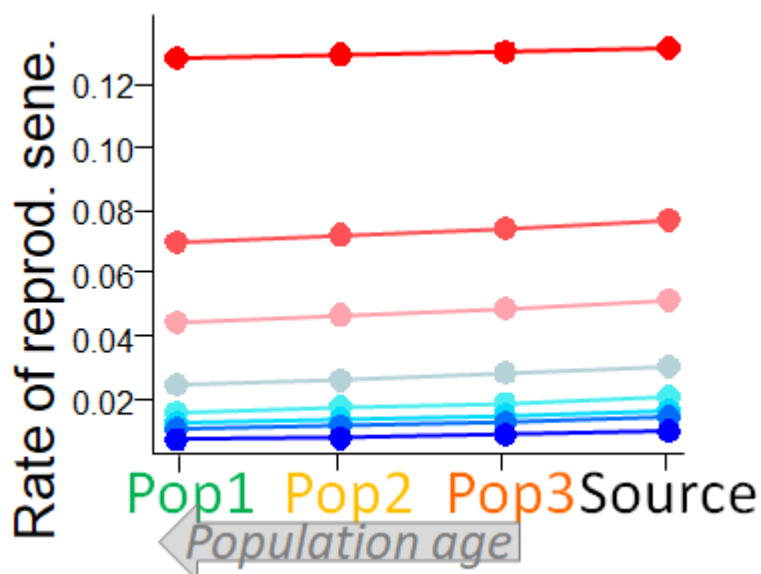


236

237 Asynchronous senescence

238 The rate of reproductive senescence did not verify the prediction (Fig. 4; Table 2b). This result could
 239 have been expected under the theory of asynchronous or asymmetric senescence (Moorad and
 240 Ravindran, 2022). Indeed, individuals needed to wait and survive several years before they reached
 241 breeding status, thereby maintaining a strong selection on late-life fecundity and in other words
 242 preventing the strength of selection on fecundity to decline with age as fast as it did for survival. This
 243 aspect of the model mimicked the delayed access to reproduction in some island species, such as the
 244 Seychelles warbler *Acrocephalus sechellensis* (Komdeur, 1992). This mechanism explained why
 245 reproductive senescence was eventually weak (less than 10% decline in fecundity at age 10) and why
 246 the rate of reproductive senescence did not verify the prediction. This aspect of the model was
 247 unlikely to correspond to the general case, as indeed even the Seychelles warbler does not exhibit
 248 the level of asynchronous senescence that my model predicted (Brown et al., 2022).

249 Fig. 4: Change in the rate of reproductive senescence with the time since the divergence from the
 250 large source population (populations age: x-axis) and with the intensity of antagonistic pleiotropy α .
 251 Legend as in Figs. 2 and 3.



252

253

254 Conclusion

255 I provided the first piece of *in silico* support for the use of the demographic history as a basis for
 256 empirical tests of the evolutionary theories of senescence, making it possible to decipher the
 257 mutation accumulation theory of senescence (MA) from the antagonistic pleiotropy theory (AP).
 258 Precisely, I predicted that the correlation between the time since a population had been small and its
 259 rate of senescence should be positive under MA and negative under AP. In practice, such
 260 comparisons could be performed in island systems that have been colonized multiple times by the
 261 same lineage, yielding sets of populations of different “population age” as defined above. One could
 262 also use the now widely available sequentially Markovian coalescent methods (Drummond et al.,
 263 2005) to estimate the demographic history from genomic data in sympatric species (Cornetti et al.,
 264 2015). One of the advantages of such a framework is that the alternative of comparing populations
 265 from different locations is more likely to be confounded by environmental factors (Péron and Vollot,
 266 2024).

267 Importantly, in order for the predictions of the present study to hold, at least one of the populations
 268 being compared must not have reached the mutation-selection balance yet. There are at least two
 269 real-life systems in which this condition could be verified. First, the island of São Tomé in the Gulf of
 270 Guinea harbors three species in the bird genus *Ploceus*, one of them a recent man-assisted
 271 introduction from the African mainland (Winkler et al., 2020). Second, the island of Lifou in New
 272 Caledonia was colonized three independent times by the bird genus *Zosterops*, the last time about

273 0.5Ma ago (Cornetti et al., 2015). A particular feature of Lifou compared to the typical small island
274 system is the abundance of avian predators; on Lifou, “extrinsic mortality” factors could be similar to
275 those on the mainland.

276 Other tests of MA require either cross-breeding experiments with age-specific fitness monitoring
277 (Escobar et al., 2008; Hughes et al., 2002), which would be challenging to implement in long-lived
278 species outside of the lab; or the systematic identification of genes or alleles with an age-specific
279 effect that matches the assumption of MA and contradicts the assumptions of AP, which has only
280 ever been unambiguously achieved in humans to my knowledge (Johnson et al., 2017; Rubinsztein
281 and Carmichael, 2003; but see Yuan et al., 2024). Thus, the framework being proposed in the present
282 study represents an opportunity to test the contribution of MA to the evolution of senescence in a
283 wider variety of taxa across the tree of life than currently possible.

Supplementary material

Appendix S1: R scripts to reproduce the simulation.

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