Positive selection of senescence through increased evolvability: ageing is not a by-product of evolution.

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Abstract

For the past century, scientists have debated whether or not ageing is directly selected by evolution. Because ageing occurs, by definition, late in life - that is, after the organism's development is complete - many people believe that it cannot be actively selected for as a process. Furthermore, because it reduces an individual's fitness, it is thought unlikely to be selected for. In agreement with this viewpoint, numerous theories have been proposed in the last 75 years to explain the observation of its widespread presence in the realm of life. The bd model of ageing is based on a simple life-history trait model that we recently introduced.

Our model suggests that senescence can be positively selected through evolution due to the increased evolvability it confers on organisms, not through a specific mechanism but through a 'function ageing', limiting organismal maintenance and reproduction. It confirms the substrate for mutation accumulation and antagonistic pleiotropy theories while providing an elegant explanation for the apparent tradeoff between longevity and fertility that led to the disposable soma theory without requiring an energy tradeoff. Furthermore, it predicts that the Lansing effect will be present in organisms that exhibit rapid post-reproductive senescence. This formal and numerical modeling of the evolution of ageing also provides new hints for testing the validity of existing theories.

Introduction

Ageing is defined as the effect of elapsed time on an organism; it is also known as'senescence'. Depending on the organism studied, it manifests itself in a wide range of age-related patterns of mortality, ranging from negligible senescence to post-reproductive death via progressive or brutal age-dependent mortality increase (Jones et al., 2014). Numerous explanatory theories of ageing have been proposed in the past century (reviewed in Kirkwood and Holliday, 1979). Whether they are focusing on the molecular aspects that lead to the observed ageing phenomena or on the evolution of the process, one fundamental question about the selectability of ageing through evolution remains.

Soon after Charles Darwin published his theory of evolution, August Weismann proposed evolutionary arguments to explain ageing (Weismann, 1882). "His initial idea was that there exists a specific death-mechanism designed by natural selection to eliminate the old, and therefore worn-out, members of a population" (Gavrilov and Gavrilova, 2002). Since then, and probably partially due to Weismann's later changes of mind on his early theory, it is mostly accepted that "ageing is not adaptive since it reduces reproductive potential" (Kirkwood and Holliday, 1979) and hence, fitness. Two other arguments are usually used against the selection of ageing. First, that this would have required a group selection effect stronger than selection at the individual level, which is very seldom the case (Smith,

1976). Second, the mortality rate is so high in early life that little senility is observed in the wild (reviewed in (Nussey et al., 2013)). There would thus be little opportunity for a removal mechanism to evolve (reviewed in (Johnson et al., 2019)). Since the 1950s onwards, evolutionary theories are mainly building upon the idea that ageing is a byproduct of natural selection (Fabian, 2011). A first example is Peter Medawar's theory of mutation accumulation for which ageing is caused by the progressive accumulation of deleterious mutations with effects that manifest only late in life (Medawar, 1952). Williams' antagonistic pleiotropy theory goes a step further than Medawar's by assuming the existence of antagonistic genes and mutations: They would not be selected against for negative effects manifesting later in life if they were beneficial at a young age. Finally, the "disposable soma" theory of ageing proposed by Thomas Kirkwood, is based on the idea that individuals have a limited amount of energy to be split between reproductive functions and (non-reproductive) maintenance of the organism, the "soma". According to Kirkwood's theory, increasing an organism's longevity would thus be associated with a decrease in growth and reproduction rates, delaying death (Kirkwood, 1977). Later, evolutionary conserved genes involved in both the regulation of longevity and organismal growth were discovered in the model organism *C. elegans* (Kenyon et al., 1993), later shown to be conserved in flies (Clancy et al., 2001) , mice (Bluher et al., 2003) and humans (van Heemst et al., 2005). Thus, genetic modulators for longevity exist and manifest themselves through evolutionarily conserved physiological mechanisms.

Nevertheless, although "the evolutionary theories of aging are closely related to the genetics of aging because biological evolution is possible only for heritable manifestations of aging"(Gavrilov and Gavrilova, 2002) and we now have countless examples of evolutionarily conserved genes playing a role in ageing across species (Partridge and Gems, 2002), the subject is still a matter of vivid debate (Kowald and Kirkwood, 2016). In their 2016 review, Axel Kowald and Thomas Kirkwood state that the "idea that aging is a programmed trait that is beneficial for the species [...] is now generally accepted to be wrong". If ageing cannot be positively selected for through evolution, can it be, at least partially, programmed? This question raised no less vivid debates than the previous one in the past century (Austad, 2004; Bredesen, 2004a, 2004b; Gavrilov and Gavrilova, 2002; Kirkwood and Melov, 2011; Longo et al., 2005; Skulachev, 2011). Two good examples of these active debates can be found in (Blagosklonny, 2013) and (Longo et al., 2005), these two works showing dramatically opposed views. The first, affirming that ageing cannot be programmed, the second that it can and will occur as it brings a "kind of population-level selection" that can be explained by kin selection. One of the final arguments given by Kowald and Kirkwood is that if ageing were to be programmed, "it would be possible experimentally to identify the responsible genes and inhibit or block their action".

Programmed or not, ageing in unicellular organisms is associated with mechanisms that discriminate new components from older ones as individuals replicate (Henderson et al., 2014; Lai et al., 2002, p. 2; Nyström, 2007; Sinclair and Guarente, 1997; Steiner, 2021). In multicellular organisms, the Lansing effect is a good candidate for such a mechanism. It is the effect through which the "progeny of old parents do not live as long as those of young parents" in rotifers (Lansing, 1954, 1947). More recently, it has been shown that older drosophila females and to some extent males tend to produce shorter lived offspring (Priest et al., 2002), zebra finch males give birth to offspring with shorter telomere lengths and reduced lifespans (Noguera et al., 2018) and finally in humans, "Older father's children have lower evolutionary fitness across four centuries and in four populations" (Arslan et al., 2017)(Arslan et al., 2017). Despite the absence of consensus on the underlying mechanisms (Monaghan et al., 2020), the near-ubiquity of the Lansing effect is important for our understanding of the selective forces shaping the evolution of life histories. In a recent article (Méléard et al., 2019), we introduced an asexual and haploid age-structured population model implementing a strong Lansing effect, showing that this strong transgenerational effect of ageing could be maintained. Here, by extending this model to any system able to reproduce and maintain its homeostasis, we show that 1) ageing - i.e. non-infinite reproduction and homeostasis maintenance - is an adaptive force of evolution, 2)

such a system evolves towards a configuration where fertility exceeds homeostasis capabilities, 3) propitious for pro-senescence mechanisms to appear - i.e. Lansing effect - within a few dozen generations. 4) Individuals carrying such a transgenerational effect of ageing have a non-null probability to be selected for when competing with individuals deprived of it. In addition, this model 5) allows to explain longevity-fertility tradeoffs mathematically without the need for energy investment strategies, while 6) suggesting that the selection of ageing relies on the maximization of a meta-characteristic named evolvability, in the form of fitness gradient. Finally, the landscape of this fitness gradient shows how mutation accumulation can accompany the evolution of ageing.

Results

A generalized bd model

The model and its population dynamics is similar to those described in (Méléard et al., 2019). Briefly, the model describes an asexual and haploid population structured by a life-history trait that is defined by a pair of parameters - or genes - (x_b, x_d) where x_b is defining the duration of fertility and x_d the age at which mortality becomes non-null. Here we generalized the model to any intensities of birth and death denoted (i_b, i_d) as well as to populations without Lansing effect (Figure 1, see also Annex 1). The selective pressure is enforced by a logistic competition *c* mimicking a maximum carrying capacity of the environment, thus no explicit adaptive value is given to any particular trait and, for each reproduction event, a mutation (*h*) of probability *p* can affect both the genes x_b and x_d, independently, following a Gaussian distribution centered on the parental trait. In Figure 1, the different cases are explored, depending on the respective values of x_b and x_d. Individuals in the Figure 1b-c configuration (for $x_b \leq x_d$) will always give progeny with a genotype (x_b, x_d) $\mp$ (h_b or h_d). The case of individuals carrying a genotype with $x_d < x_b$ (Figure 1a) is subtler, depending on the parental age *a* and whether the parent carries the possibility for a Lansing effect or not (Figure 1d-f). If $a < x_d$ or if the parent does not carry a Lansing effect, the genotype of the progeny will be as previously described. But if $a > x_d$, and if the parent carries the Lansing effect, then the progeny inherits a dramatically reduced x_d (here x_d is set to 0), mimicking a strong Lansing effect.

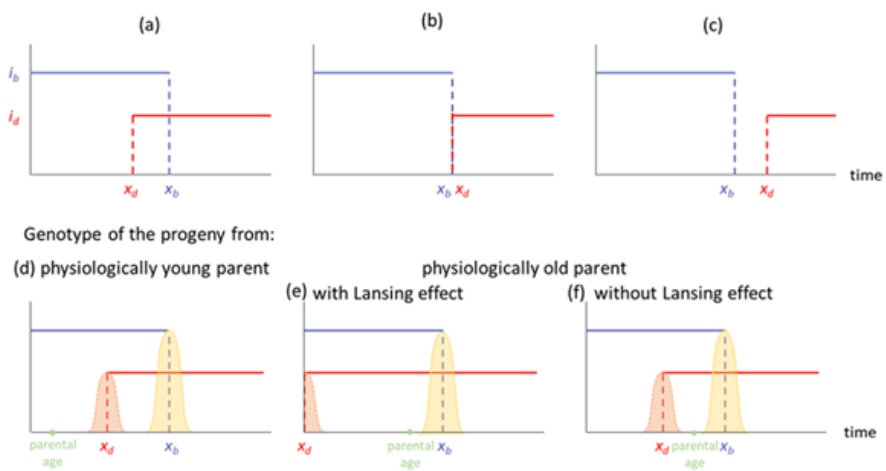

Figure 1: Three typical configurations of the model with $i_b > i_d$ and their effect on progeny's genotypes as a function of parental age. (upper panel) Each haploid individual is defined by a parameter x_b defining its fertility period of intensity i_b and a parameter x_d defining the time during which it will maintain itself, with an intensity i_d. These parameters can be positive or null. (a) 'Too young to die' : it corresponds to configurations satisfying $x_d < x_b$. (b) 'Now useless': it corresponds to configurations where $x_b = x_d$. (c) 'Menopause': it corresponds to configurations where $x_d > x_b$. (lower panel) Each individual may randomly produce a progeny during its fertility period [0; x_b]. (d) In the case of physiologically young parents ($a < x_d$), the progeny's genotype is that of its parent $\mp$ a Gaussian kernel of mutation centered on the parental gene. In the case of the reproduction event occurring after x_d, for configuration (a) above, two cases are observed, (e) if the organism carries a Lansing effect ability, the x_d of its progeny will be strongly decreased. (f) In the absence of the Lansing effect, the default rule applies.

In our previous work (Méléard et al., 2019), we formally and numerically showed the long-time evolution of the model to converge towards (x_b - x_d) = 0 in the case of individuals carrying a Lansing effect. To test whether this

convergence of (x_b - x_d) still occurred without this strong transgenerational effect of ageing, we implemented a new version of the model devoid of Lansing effect and simulated its evolution for a viable - i.e. allowing the production of at least one progeny - trait (x_b = 1.2, x_d = 1.6). Surprisingly, we still observe a convergence of (x_b - x_d). The dynamics of the trait (x_b, x_d) is described by the canonical equation of adaptive dynamics depending on the Malthusian parameter and its gradient (Annexe 1). The latter can be interpreted as the age-specific strength of selection in the sense of Hamilton. We observe that the evolution speed of x_b and x_d decreases with time as the previous - less general - form of the model did (Méléard et al., 2019). This allows us to recover the classical age-related decrease in the strength of selection (Hamilton, 1966; Haldane, 1941; Medawar, 1952).

Simulations of the generalized bd model presented here show that the x_b - x_d distance, i.e. the time separating the end of fertility from the increasing risk of death, converges - for any initial trait - towards a positive constant. Thus, it seems that the long term evolution of such a system is a configuration similar to Figure 2a (x_d < x_b). The formal analysis of the generalized bd model confirmed that the long-time limit of the traits (x_b - x_d) is the positive constant defined by the formula in Figure 2b (mathematical analysis Annexe 4), reached after a few dozen simulated generations, estimated by (time ≅ 75) / (average offspring) (Figure 2c). Although we formally demonstrate the long-time limit for any i_b and i_d, all our simulations are run using i_b = i_d = 1 in order to limit the number of conditions to assess and report.

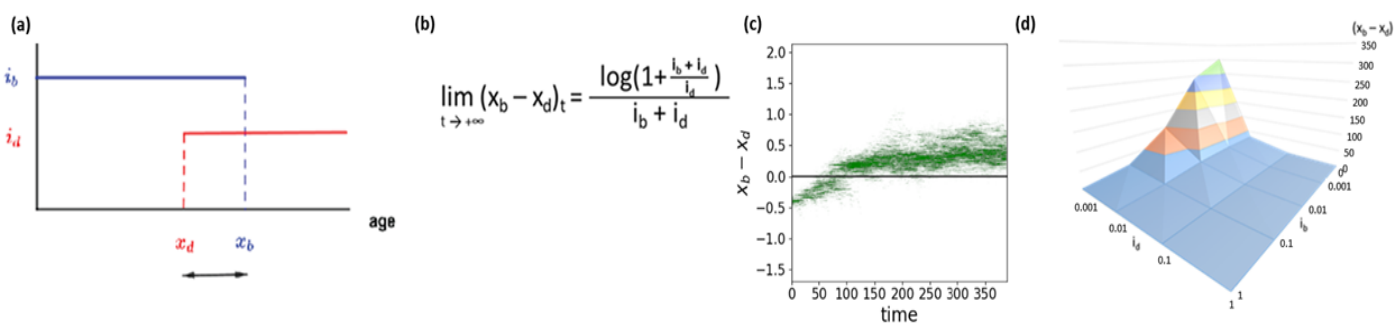

Figure 2: The bd model shows a convergence of x_b - x_d towards a positive value. Dynamics of the individual-based model shows a convergence of x_b - x_d towards a positive constant value in the absence of the Lansing effect. (a) The generalized b-d model shows a convergence of (x_b - x_d) for any i_b and i_d towards a positive value given by **(b) (cf. Annexe 4.3, figure 2). (c)** Simulation of 1000 individuals with initial trait (x_b = 1.2, x_d = 1.6) of intensities i_b = i_d = 1, a competition c = 0.0009 and a mutation kernel (p = 0.1, σ = 0.05) show that the two parameters co-evolve and maintain x_b - x_d ≅ 0 . **(d)** Landscape of solutions (x_b - x_d) as a function of i_b and i_d (colors separate ranges of 50 units on the z-axis).

Surprisingly, the limit value of the trait is not affected by x_b or x_d values - the fertility and organismal maintenance durations per se - but only by their respective intensities i_b and i_d. These intensities can be interpreted as the instant mortality risk i_d and the probability to give a progeny i_b. Interestingly, the long-time limit values for any i_b and i_d shows a significantly stronger sensitivity to the increasing mortality risk i_d than to reproduction by almost two orders of magnitude (Figure 2d). In addition, for extremely low values of i_b and i_d - i.e. below 0.01 - the apparent time correlation of the fertility and organismal integrity maintenance period is almost nonexistent since (x_b - x_d) is large. A biological manifestation of this would be a loss of organismal maintenance occurring long before the exhaustion of reproductive capacity. Such an organism would be thus characterized as having no significant fertility decrease during the ageing process. On the other end, for individuals showing either a high instant mortality risk or a high probability to give a progeny, the (x_b - x_d) trait is close to 0, meaning that fertility and organismal integrity maintenance are visibly correlated. Note that this mathematical study concerns individuals for which the mean number of descendants per individual is large enough, allowing us to define a viability set of traits (x_b, x_d) (see Annexe 2.3). Because of these mathematical properties, a tradeoff emerges between i_b, i_d, x_b and x_d. Let's consider an organism - for both the

Lansing and non-Lansing cases - with a low reproductive intensity $i_b = 0.01$ and $i_d = 1$. For it to be viable, the product $i_b * x_b$ has to be strictly superior to 1, hence here $x_b \geqslant 100$ (see Annexe 2.3). In this example, the long-time limit of the trait (x_b - x_d) is equal to ln(2), thus $x_b \cong x_d$. With the same reasoning, considering an organism significantly more fertile (with $i_b = 1$, $i_d = 1$), the long-time evolution lower limit of (x_b - x_d) is $1/\sqrt{3}$. This model thus allows an elegant explanation for the apparent negative correlation previously described between longevity and fertility without the need of implementing energy trade-offs or relative efficiency of energy allocation between maintenance and reproduction (see Annexe 2.3 - examples).

On the selection of Lansing effect

In our model, whatever the initial trait (x_b, x_d) in the viability set, evolution leads to a configuration of the trait such that the risk of mortality starts to increase before the fertility period is exhausted. Similar to biochemical reactions involved in a given pathway being evolutionarily optimized through tunneled reactions and gated electron transfers, we hypothesize here that such a configuration, caused by simple mathematical constraints, creates the conditions for the apparition, selection and maintenance of a molecular mechanism coupling x_b and x_d. Such a coupling mechanism could thus be the Lansing effect, the only described age-related decline in progeny's quality that seems to affect numerous iteroparous species (Lansing, 1947; Monaghan et al., 2020). More importantly, the vector of the Lansing effect could be as simple as a transgenerational transfer of maternal components known in yeast as asymmetrical inheritance, a mechanism of age-reset in *Saccharomyces cerevisiae* (Hill et al., 2016).

We calculated the chances of an organism with such a non-genetic pro-senescence mechanism surviving in competition with a population lacking such a mechanism. To do so, we looked at a population divided into two sub-populations: one made up of people who experienced the Lansing effect and the other made up of people who did not. As before, we assume that each individual is subject to the same competitive pressure. The Darwinian fitness of the two initial subpopulations is approximated by their Malthusian parameter (cf. Annexe 2, supplementary figure 2). Their traits are thus $(1.5; 1.3)_{Lansing}$ and $(1.5; 0.83)_{non\text{-}Lansing}$. In order to simplify the analysis, both the birth and death intensities are as follows: $i_b=i_d$ (the model is nevertheless generalized to any (i_b; i_d), see Annexe 5.1) and evolution was simulated for discrete pairs of mutation rate (**p**) and competition (**c**) parameters. Three indexes were calculated for each set of simulation: Table 1 a) the ratio of Lansing and non-Lansing populations that collapsed (a "-" indicates that all survived), Table 1 b) the ratio of total number of progenies produced during the simulation by each population and Table 1 c) the relative proportion of the Lansing population at the end of the simulation. Our 1200 simulations each of 2.10^5 birth-death events summarized in Table 1 show that the Lansing populations survive at least as well as non-Lansing ones (Table 1a) and show a significantly increased success for a moderate competition ($c = 9.10^{-4}$) and low (in our simulations) mutation rate ($p = 0.1$). With these parameters, Lansing populations show almost half the risk of disappearance of non-Lansing ones (Table 1a), producing nearly thrice as many descendants as non-Lansing populations (Table 1b) for up to a 20% faster growing population (Table 1c). Hence, although the Lansing effect leads to the production of a significant proportion of progeny with an extremely low fitness ($x_d = 0$), it decreases the risk of population collapse for organisms carrying it and seems to allow a slightly better growth of the population, whatever the magnitude of the Lansing effect (Sup. Figure 1).

	Mutation probability											
	0	0.1	0.5	1	0	0.1	0.5	1	0	0.1	0.5	1
	a) Lansing/non-Lansing collapsed population				b) Lansing/non-Lansing number of individuals				c) Lansing/total population size			
Competition 9.10^{-5}	-	-	-	-	1.30	1.38	1.39	1.35	0.57	0.64	0.62	0.59
9.10^{-4}	1.02	0.62	0.56	0.66	1.70	2.84	3.58	3.20	0.49	0.62	0.60	0.55
9.10^{-3}	1.00	1.05	1.13	1.03	1.05	1.31	1.56	1.84	-	0.43	0.44	0.49

Table 1: Populations with Lansing effect are favorably selected under logistic competition when the mutation rate is non-zero. *p* is the mutation rate and *c* the intensity of the logistic competition. For each couple (*p*, *c*), 100 independent simulations were run with 500 individuals per population at t_0 of which traits are $(1.5; 1.3)_{Lansing}$ and $(1.5; 0.83)_{non\text{-}Lansing}$ so that their respective Malthusian parameters are equal. Each simulation corresponds to 2.10^5 events of birth or death. Table **(a)** shows the ratio of Lansing and non-Lansing populations (out of 100 simulations in each case) that did collapse by the end of the simulation. For the lowest competition, none of the populations collapsed within the timeframe of simulations (-). For an intermediate value of competition, approximately half less Lansing populations disappear relative to non-Lansing ones. Table **(b)** shows the ratio of the number of individuals generated between Lansing and non-Lansing populations**.** On average, Lansing populations generate approximately twice as many individuals as non-Lansing ones. **(c)** On average, Lansing populations grow 20% more than the non-Lansing. Values highlighted in green are discussed further below.

The Lansing effect increases fitness in ageing populations by increasing their evolvability.

We focused on the Malthusian parameter to understand the evolutionary success of a characteristic that appears to reduce an organism's fitness - the genotypic rate of increase (Hairston et al., 1970) - in each population through time. Here we present the results for an intermediate set of **c** and **p** - highlighted in green Table 1 - that we identified as associated with the highest success rate of Lansing bearing populations. First, we observe that, on average, Lansing populations (blue) grow while non-Lansing ones (red) have a decreasing size (Figure 3a - blue and red curves represent deciles 1, 5 and 9). Nonetheless, in simulations where both populations coexist continuously, the Lansing population's higher fitness is marginal, with populations growing 20% faster than the non-Lansing population (Figure 3b). This higher success rate appears to be due to the Lansing population's faster and broader exploration of the Malthusian parameter space (Figure 3c). This maximization of the Malthusian parameter is not associated with any significant difference in either population's lifespan (time of death - time of birth) distributions (Figure 3d). Indeed, despite having the same mutation rate **p** and being subject to the same competition **c**, the distribution of non-Lansing progenies is essentially of the parental trait in the first 5 generations, whereas Lansing progenies (unaffected by the Lansing effect - we excluded progeny with $x_d = 0$ for the comparison) explore a broader part of the trait space (Figure 3e). Although their low fitness progeny ($x_d = 0$) represent up to 10% of the population for a significant amount of time, the Lansing-bearing population has significantly higher success (Figure 3f). As a result, Lansing populations reach the equilibrium trait faster than non-Lansing populations (Figure 3g). Thus, the relatively higher success of Lansing bearing populations appears to be associated with increased genotypic diversity, which leads to a broader range of fitness on which natural selection can act, namely evolvability.

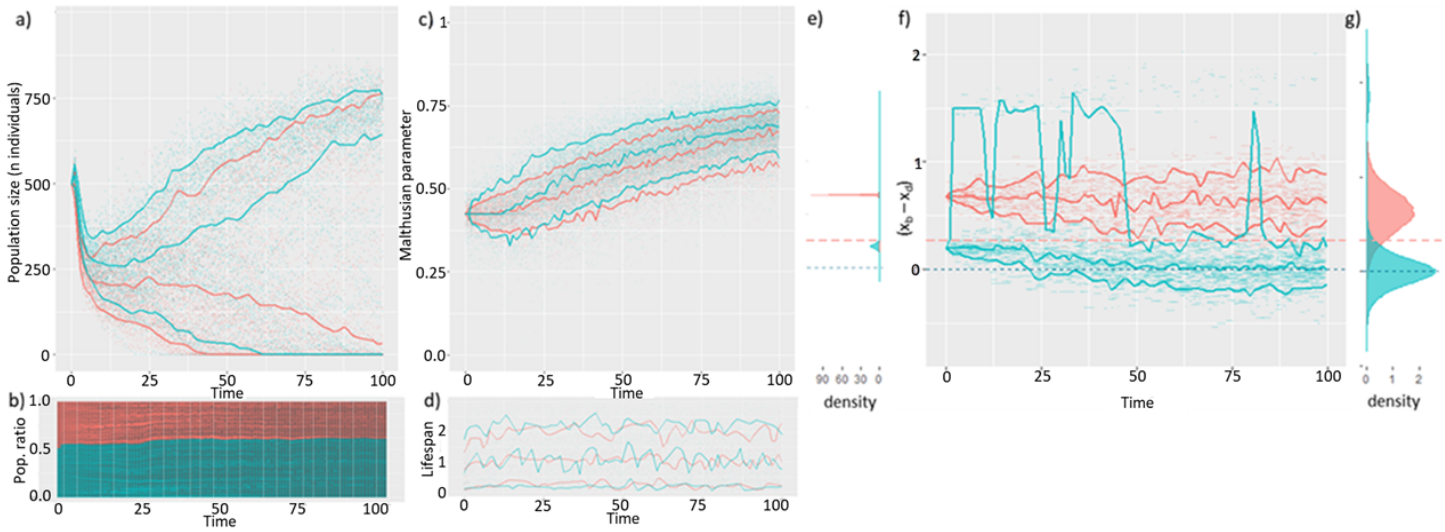

Figure 3: The Lansing effect maximizes populational survival by increasing its evolvability. 100 independent simulations were run with a competition intensity of 9.10^{-4} and a mutation rate p = 0.1 on a mixed population made of 500 non-Lansing individuals and 500 individuals subjected to such effect. At t_0, the population size exceeds the maximum load of the medium thus leading to a population decline at start. At t_0, all individuals are of age 0. Here, we plotted a subset of the 100.10^6 plus individuals generated during the simulations. Each individual is represented by a segment between its time of birth and its time of death. In each graph, blue and red curves represent deciles 1, 5 and 9 of the distribution at any time for each population type. **(a)** The higher success rate of Lansing bearing populations does not seem to be associated with a significantly faster population growth but with a lower risk of collapse. **(b)** For cohabitating populations, the Lansing bearing population (blue) is overgrowing by only 10% the non-Lansing one (red). **(c)** This higher success rate is associated with a faster and broader exploration of the Malthusian parameter - surrogate for fitness - space in Lansing bearing populations **(d)** that is not associated with significant changes in the lifespan distribution **(e)** but a faster increase in genotypic variability within the [0; 10] time interval. **(f)** This occurs although progeny from physiologically old parents can represent up to 10% of the Lansing bearing population and leads to it reaching the theoretical optimum within the timeframe of simulation **(g)** with the exception of Lansing progenies. **(e-g)** horizontal lines represent the theoretical limits for $(x_b - x_d)$ in Lansing (blue) and non-Lansing (red) populations.

The relative success of Lansing-bearing populations with randomly distributed traits

We have proposed a simple model that demonstrates the mathematical basis driving the evolutionary pressure that connects organismal maintenance and reproductive mechanisms. Nonetheless, our numerical investigation of our model's behavior has so far been limited to initial conditions in which the competing populations had equal Malthusian parameters. The low number of generations involved suggest that the conditions for the development, selection and maintenance of mechanisms of ageing (Lemoine, 2021) would have occurred early on, in a population of mixed individuals. As such, we decided to test the evolution of the trait $(x_b - x_d)$ in Lansing and non-Lansing bearing individuals of traits uniformly distributed on [-10; +10] (Figure 4 - left panel). We chose to plot one (Figure 4 - central panel) of the hundred simulations we made, that is representative of the general results. Simulations show, over 110 million individuals, an early counterselection of extreme trait values, typically $(x_b - x_d) > 4$. Interestingly, the whole space of $(x_b - x_d)$ trait is not explored evenly and the positive part of it represents approximately ⅔ of the individuals although the branched evolution process can lead a line on both the positive ('Too young to die' - Figure 1a) and negative ('Menopause' - Figure 1c) sides of the trait space. Both the Lansing and non-Lansing bearing populations manage to co-exist until the end of the simulation, each reaching a distribution centered on their respective theoretical solutions (Figure 4 - right panel), 0 for the Lansing (Méléard et al., 2019) and ln(3)/2 for the non-Lansing. When the initial condition does not restrict competition to populations with identical Malthusian parameters, the

Lansing bearing population is significantly less successful than the non-Lansing one, accounting for only one-third of the final population size. As such, the evolution of a mixed population of individuals with a trait (x_b - x_d) initially uniformly distributed on [-10; +10], bearing or not a strong inter-generational effect, will lead to a mixed solution of individuals carrying a trait that converged towards the theoretical solution such as $x_d \lesssim x_b$ thus allowing the maximization of fertility without cluttering the environment with individuals not producing descendants, very similar to Weismann's first intuition (Weismann, 1882). Nonetheless, this interpretation appears to be finalist and does not account for the relative success of each of our population types. We then investigate how ageing affects the evolvability of individuals who bear it, leading us to propose another interpretation of the fitness gain it brings.

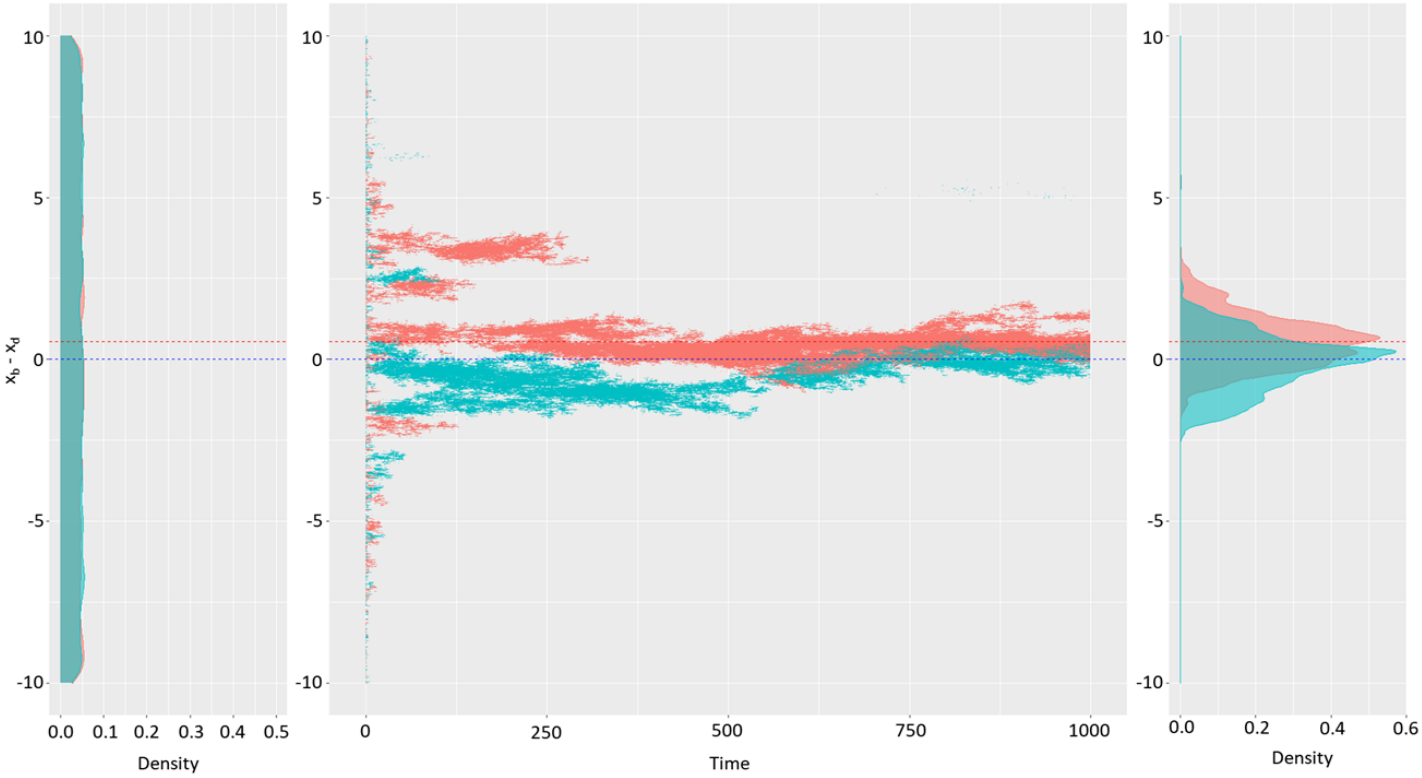

Figure 4: Mixed populations lead to (x_b - x_d) theoretical limit in a limited time and cohabitation of Lansing and non-Lansing populations. Starting with a homogenous population of 5000 Lansing bearing and 5000 non-Lansing individuals with traits uniformly distributed from -10 to +10 (left panel), we ran 100 independent simulations on time in [0; 1000]. (center panel) Plotting the trait (x_b - x_d) as a function of time for one simulation shows a rapid elimination of extreme traits and branching evolution. (right panel) The final distribution of traits in each population type is centered on the theoretical convergence limit for each. $N_{total} \cong 110$ million individuals, $c = 9.10^{-4}$, $p = 0.1$

The fitness gradient, a mediator of evolvability

We focused our attention on the differential landscape of the Malthusian parameters as a function of the trait (x_b, x_d) for both Lansing and non-Lansing populations to understand the origin of this relative success of individuals carrying the ability to transmit an ageing information to the next generation. We built this landscape numerically using the Newton method implemented in Annex 2. First of all, it is interesting to notice that we have derived from the equations that the maximum rate of increase for Malthusian parameters is $1/i_d$ with a maximum fitness value capped by i_b (Annex 2). Consistent with our previous characterization of the Trait Substitution Sequence in populations with Lansing effect (Méléard et al., 2019), Lansing individuals have a symmetrical fitness landscape (Figure 5, blue lines) centered on the diagonal $x_b = x_d$ (Figure 5, green diagonal). Along the latter, we can directly observe what is

responsible for the "selection shadow". As (x_b, x_d) increases, a mutation of same magnitude has smaller and smaller effects on the fitness, thus allowing for the accumulation of mutations (Figure 5, blue arrows). Non-Lansing individuals' cases are asymmetric, with symmetry breaking on the $x_b = x_d$ diagonal. For $x_d > x_b$ (Figure 5, upper diagonal), fitness isoclines fully overlap thus showing an equal response of both Lansing and non-Lansing fitness to mutations. In addition, as expected, the fitness of Lansing individuals is equal to that of non-Lansing ones for a given trait. On the lower part of the graph, corresponding to $x_d < x_b$, non-Lansing fitness isoclines separate from that of Lansing individuals, making the fitness of non-Lansing individuals higher to that of Lansing ones for a given trait. Nevertheless, the fitness gradient is significantly stronger for Lansing individuals as represented on Figure 5 by the yellow arrow and associated yellow area. For an individual of trait (x_b = 2.45; x_d = 1.05) a mutation making a non-Lansing individual gain 0.1 in fitness (isocline 0.7 to isocline 0.8) will make a Lansing individual increase its own by 0.42 (isocline 0.1 to above isocline 0.5). With a 4-fold difference, the Lansing population produces 4 times as many individuals as the non-Lansing ones for a given mutation probability. But this reasoning can be extended to any trait (x_b, x_d) with or without Lansing effect. Organisms ageing rapidly - i.e. with low x_b and x_d - will see their fitness significantly more affected by a given mutation *h* than individuals with slower ageing affected by the same mutation. As such, ageing favors the emergence of genetic variants, it increases an organism's evolvability.

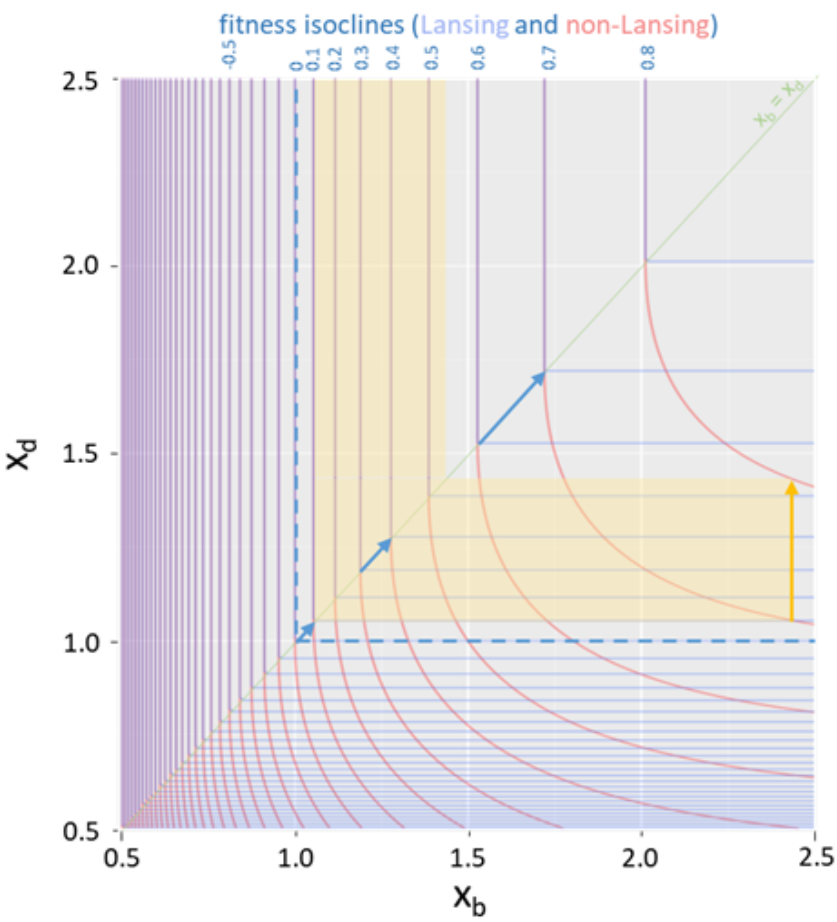

Figure 5: The Lansing effect is associated with an increased fitness gradient. We were able to derive Lansing and non-Lansing Malthusian parameters from the model's equations (see Annexe 1-2.3 and 1-5) and plot them as a function of the trait (x_b, x_d). The diagonal $x_b = x_d$ is drawn in light green. The corresponding isoclines are overlapping above the diagonal but significantly differ below, with non-Lansing fitness (red lines) being higher than that of Lansing's (light blue lines). In addition, the distance between two consecutive isoclines is significantly more important in the lower part of the graph for non-Lansing than Lansing bearing populations. As such, a mutation leading a non-Lansing individual's fitness going from 0.7 to 0.8 (yellow arrow) corresponds to a Lansing individual's fitness going from 0.1 to 0.52. Finally, Hamilton's decreasing force of selection with age can be observed along the diagonal with a growing distance between two consecutive fitness isoclines as x_b and x_d continue increasing.

Discussion

Ageing has a variety of effects on a wide range of organisms (Jones et al., 2014). However, its characteristics exhibit evolutionarily conserved so-called ageing hallmarks (Lopez-Otin et al., 2013), the most evolutionarily ancient of which is the loss of protein stability (Lemoine, 2021). For nearly a century and a half, researchers interested in understanding the evolutive role of ageing have been arguing about why ageing exists at all. Although early theories (Weismann, 1882) proposed a population-based adaptive role for it, the debate appears to have been settled in the twentieth century after seminal works demonstrating the time-dependent decline of selective pressure (Hamilton, 1966; Medawar, 1952) allowed for the existence of theories (Kirkwood, 1977; Medawar, 1952; Williams, 1957) proposing that ageing is nothing more than a by-product of evolution.

The model we presented here allows us to propose an alternative theory where ageing necessarily emerges for any system showing the two minimal properties of life, namely a) reproduction with variation (x_b) and b) organismal maintenance (x_d)(Trifonov, 2011). We formally show that a haploid and asexual organism with these two properties will rapidly evolve, within a few dozen generations, towards a solution such that (x_b - x_d) is strictly positive. More importantly, the time separating both parameters is independent of their absolute values and is solely determined by their respective rates, respectively i_b for x_b and i_d for x_d. This property enables us to explain the observations that fueled the disposable soma theory of ageing, which is based on an apparent trade-off between an organism's fertility and lifespan. Indeed, in our model, the lower limit condition for an individual's viability is $x_b * i_b > 1$. As such, an organism with a low fertility ($i_b << 1$) will require a long fertility time ($x_b >> 1$) to be viable. The formally demonstrated properties of our model imply that the duration for homeostasis maintenance (x_d) will rapidly evolve towards (x_b - x_d) equal to a positive constant, implying that $x_d >> 1$. A highly fertile organism, on the other hand, will evolve to its minimum viable condition, requiring only a small x_d. The apparent trade-off between fertility and longevity is thus solely a consequence of $x_b * i_b > 1$ and $\lim_{+\infty}(x_b - x_d)_t$, without the need to implement any constraint on resource allocations. By forcing xb and xd to converge, evolution creates the conditions for the emergence of a stage of life in which an individual's fertility declines while their risk of death increases. This time-coupling of the two properties would thus facilitate the selection of any molecular mechanism functionally coupling the two properties (Echave, 2021), and, contrary to what was proposed in (Stearns, 1989), we observe that two genes with no common genetic basis can be co-selected despite being unlinked by any direct tradeoff. By testing such a coupling mechanism, manifested as a strong Lansing effect, we demonstrated that not only is this seemingly fitness-decreasing mechanism capable of increasing fitness, but it also significantly increases the probability of a population bearing it to thrive when competing with a population of equal Malthusian parameter where the effect is absent. We found that a slight increase in fitness caused by the Lansing effect manifests itself numerically as an increase in genetic variability within the population. As a result, we propose that active mechanisms of ageing are chosen during evolution because of their ability to increase an organism's evolvability. The term refers to “an abstract, robust, dispositional property of populations, which captures the joint causal influence of their internal features upon the outcomes of evolution” (Brown, 2014). In other terms, it is “the capacity to generate heritable selectable phenotypic variation” (Kirschner and Gerhart, 1998). It is an interesting concept as it allows for a character that has no direct effect on fitness - or even a negative one (Maynard Smith, 1971) - to be under strong selection simply for its ability to bring the genetic-phenotypic variation that is the support of evolution. Furthermore, in a constantly changing environment, such a mechanism, triggered when age > x_d, would be extremely useful. Indeed, when environmental conditions become less favorable, x_d may be affected and individuals pushed to enter the [x_d; x_b] space earlier, increasing population evolvability. Our model predicts a high evolutionary conservation of the "function ageing" - ensuring that

an individual has a limited time to propagate its genes - but not necessarily a conservation of the underlying mechanisms, by constraining the long-term evolution of the trait (x_b - x_d) without any a priori on the underlying mechanism. This would lead to a layering of mechanisms through evolution as described recently in (Lemoine, 2021). Being able to derive Hamilton's result (Hamilton, 1966) from the mathematical analysis of our model (Méléard et al., 2019) confirms such evolving organisms to be sensitive to the accumulation of mutations (Medawar, 1952) while allowing antagonistic pleiotropy to occur (Williams, 1957). It is to note that this is, to our knowledge, the second model showing that the time-dependent decreasing pressure of natural selection derives from ageing not the other way around (Giaimo and Traulsen, 2022).

Although this simple model helps us to see ageing as an evolutionarily adaptive force for various ageing types, it is still a toy model. We are now developing more complex versions of it, notably to assess the interactions existing between i_b, i_d, x_b and x_d, but also to extend it to joint evolution of maturation, sex, ploidy and varying environmental conditions and ageing.

Materials and Methods

See Annex 2 for code, packages and the software used.

Authors' Contribution

RT wrote the Python code presented in Annexe 2 and developed the mathematical analysis presented in Annexe 1, JP translated the Python code into C and ran the broad trait simulations. MS verified the mathematical analysis from Annexe 1, developed the analysis presented in Annexe 2 and wrote the manuscript. RM designed the study, designed the figures and wrote the manuscript.

Acknowledgments

We would like to thank Dr. Sarah Kaakai for her help in transposing our initial simulation Python codes into the IBMPopSim framework, Dr. Allon Weiner for a few hours of "naive" discussion that helped explore the interpretations of this model's impact on our perception of ageing, Dr. André Klarsfeld for his numerous useful comments on the manuscript and Dr. Bastian Greshake Tsovaras for helping with setting up the mybinder.org implementations of the simulations' codes. This work was granted access to the GENCI-sponsored HPC resources of TGCC@CEA under allocation A0090607519. This work has been supported by the Chair "Modélisation Mathématique et Biodiversité" of Veolia Environnement-Ecole Polytechnique-Museum National d'Histoire Naturelle-Fondation X.

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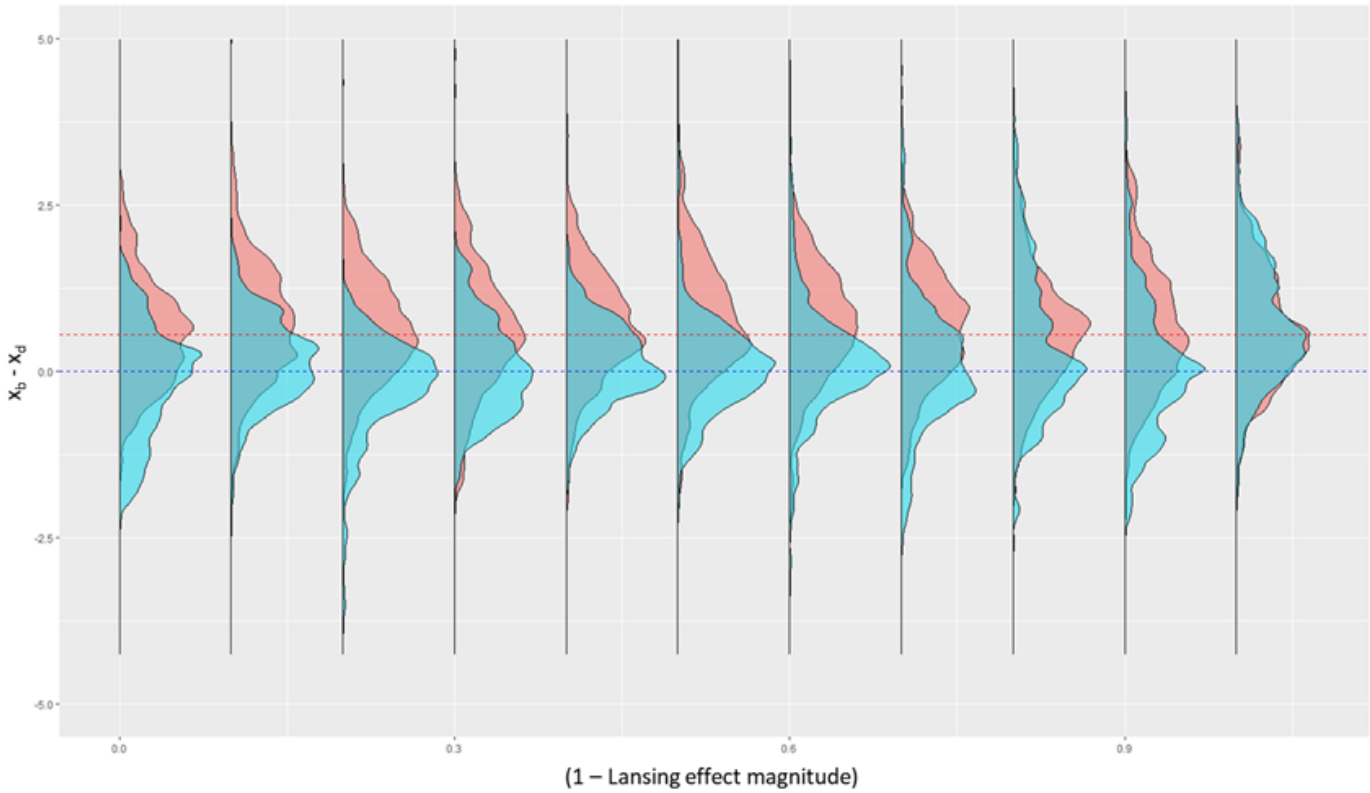
Annexe 1: mathematical proofs

Annexe 2: codes for simulations and data visualization

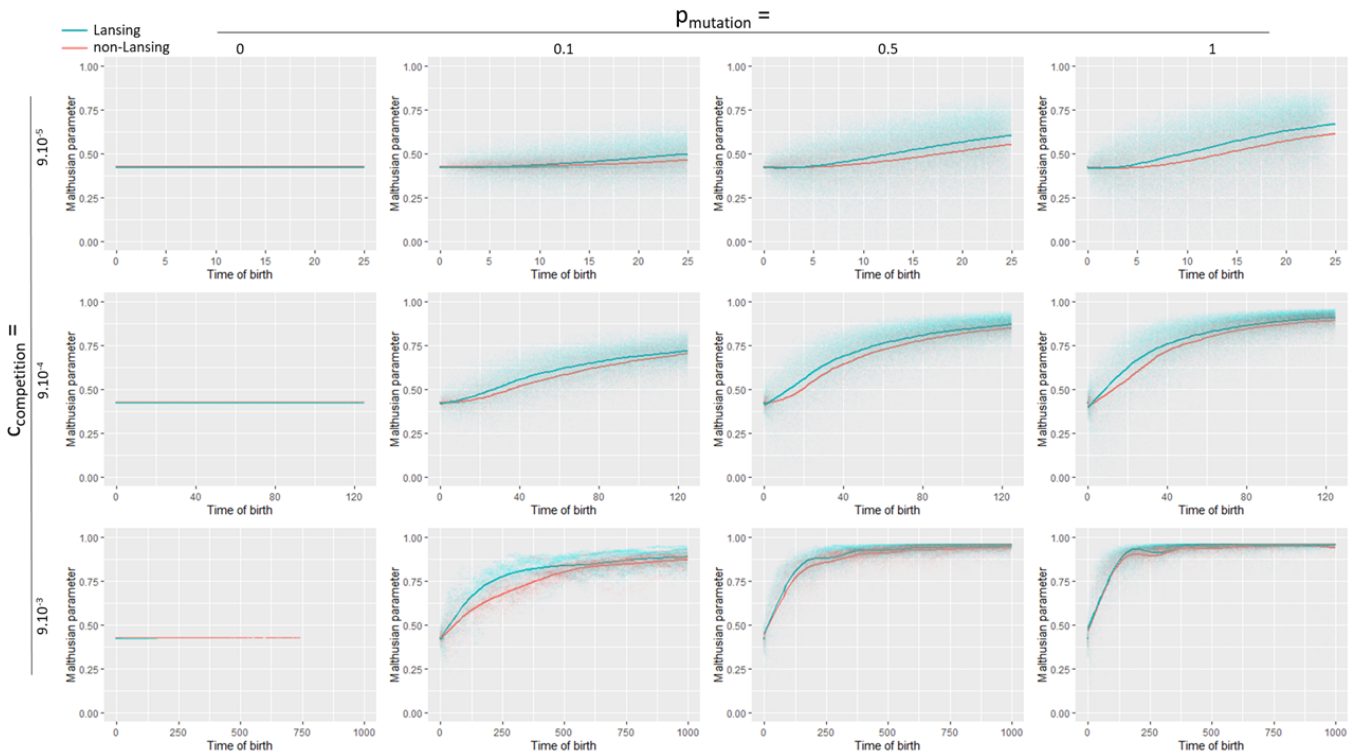
*Package IBMPopSim (R package IBMPopSim v0.3.1):
https://cran.r-project.org/web/packages/IBMPopSim/index.html
*Environment for simulations using IBMPopSim:
https://mybinder.org/v2/gh/MichaelRera/EvoAgeing/HEAD

.Exploring parameters for Lansing populations	Modele_Lansing_evo.ipynb
.Exploring parameters for non-Lansing populations	Modele_nonLansing_evo.ipynb
.Lansing / non-Lansing competition for equal Malthusian parameters	L_nL_compet_eqMalth.ipynb
.Lansing / non-Lansing competition (x_b-x_d) € [-10; 10]	L_nL_compet_heteroPop.ipynb

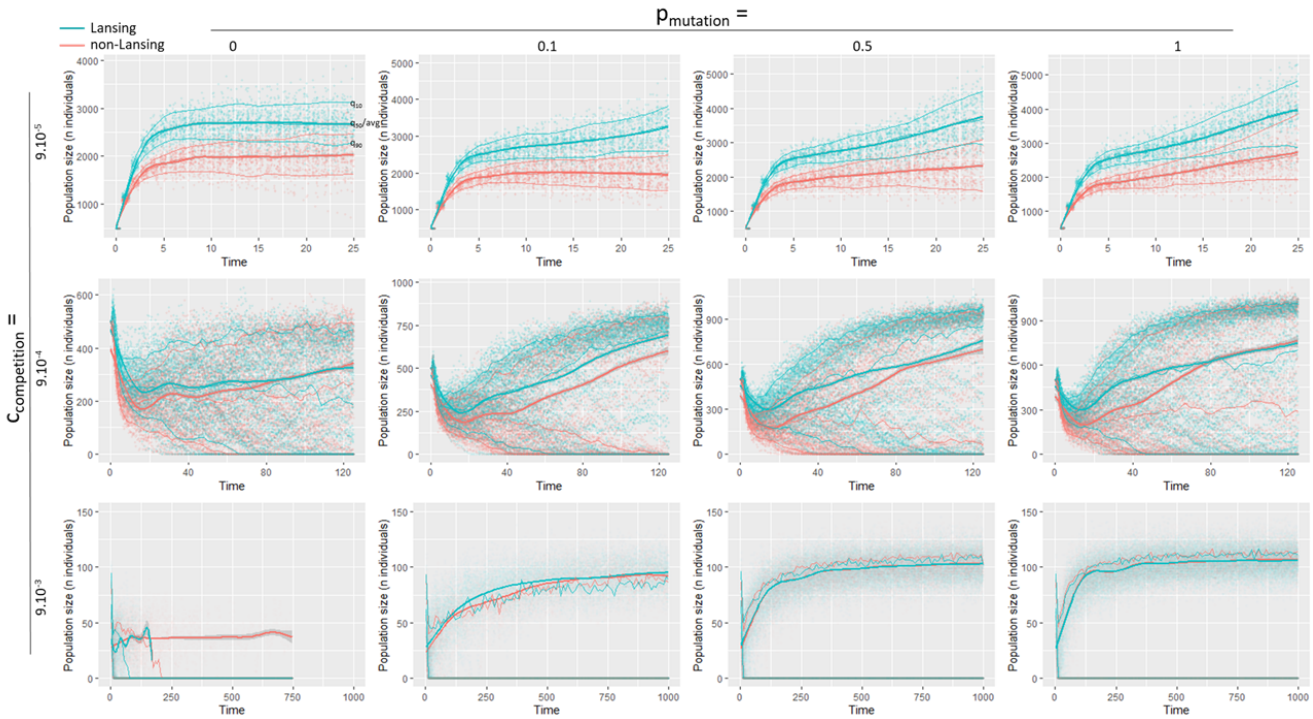
Supplementary figures



Supplementary figure 1: The magnitude of the Lansing effect does not influence the outcome of evolution. 100 independent simulations were run for each Lansing effect magnitude ranging from 0 (no Lansing effect) to 1 (progeny from parents age € [x_d; x_b] have $x_d = 0$), starting with 500 Lansing (1.5; 1.3) and 500 non-Lansing (1.5; 0.83) individuals. We plot here the distribution density of x_b - x_d at the end of the simulation (individuals born in the time interval [990; 1000]), for Lansing populations (blue) and non-Lansing ones (red). Surprisingly, the magnitude of the Lansing effect does not seem to affect the optimal x_b - x_d solution value.



Supplementary figure 2: Evolution of the average Malthusian parameter value in Lansing and non-Lansing populations as a function of time. *p* is the mutation rate and *c* is the logistic competition intensity. Individual values are plotted, the line represents the average value amongst populations. In all conditions with *p* > 0, the Malthusian parameter grows faster and remains slightly higher in the Lansing populations than in the non-Lansing ones.



Supplementary figure 2: Evolution of the Lansing and non-Lansing populations size as a function of time. *p* is the mutation rate and *c* is the logistic competition intensity.