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Parental age and offspring lifespan: the Lansing Effect and its underlying mechanisms

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**Abstract**

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*Introduction*

Biological ageing, or senescence, is characterized by the physiological deterioration of an organism, which negatively affects the reproductive capacity and fitness of an individual (Maklakov et al., 2015). The evolution of senescence is a central topic of evolutionary biology. The biological study of senescence typically focusses on the deterioration of the soma throughout the lifespan of an individual. However, also germline deterioration can have important consequences on senescence, and potentially lead to transgenerational senescence effects (Monaghan et al., 2020). A negative effect of parental age on offspring lifespan is known as the Lansing effect. In 1947, Albert Lansing investigated the relation between parental age and decline in offspring quality in rotifers, demonstrating that offspring die younger when their parents were older (Lansing, 1947; Monaghan et al., 2020). Following this seminal work, the Lansing effect has been studied in a range of organisms; though with highly inconsistent results. In European rabbits increasing maternal age results in reduced lifetime reproductive success, but increased survival (Rödel et al., 2009). In Asian elephants the opposite occurs; an increase in maternal age results in reduced survival but an increase in lifetime reproductive success (Reichert et al., 2020). Such an increase is also found in yellow-bellied Marmots (Kroeger et al., 2020). In both the common tern as well as in great tits a decrease in lifetime reproductive success with increasing maternal age has been demonstrated (Bouwhuis et al., 2010, 2015). In wild house sparrows increasing parental age results in a negative effect on lifetime fitness of the offspring (Schroeder et al., 2015). In *Drosophila* fruit flies, both positive (Krishna et al., 2012), negative (Hercus & Hoffmann, 2000; Kern et al., 2001; Price & Hansen, 1998; Priest et al., 2002), population-specific (Yılmaz et al., 2008) and strain-specific (Lee et al., 2019) relations between parental age and offspring lifespan have been found.

Parental age in relation to offspring lifespan has been thoroughly researched. It has been suggested that maternal effect senescence will decline more rapidly than fertility senescence (Moorad & Nussey, 2016). Meaning, an increase in maternal age has more effect on the quality of the offspring than on the maternal fertility. Demonstrating the importance of maternal age on the quality of the offspring and thus how important Lansing effect can be on the fitness of an individual. A generalized version of this model demonstrated the maternal effect senescence on age-specific survival and fertility throughout the life cycle in which the necessity of social interactions between mother and offspring is excluded. Hernádez *et al* demonstrate a decrease in age-specific survival and fertility with an increasing maternal age (Hernández et al., 2020). The life-history theory ‘terminal investment’ explains how an individual should invest more in reproduction at the end of its lifetime to prevent resources going to waste. This theory might have opposing consequences on the offspring quality as the Lansing effect. However, McNamara *et al* find the opposite is true: individuals show reproductive restraint later in life instead of an increase in reproductive effort (McNamara et al., 2009). Physiological changes can be explained by the organism its activity. If an organism can accumulate damage due to reproduction, it might be more beneficial to focus less on reproduction as it ages, to prevent its own death (McNamara et al., 2009). However, it is evolutionary advantageous to distribute more to reproduction (van den Heuvel et al., 2016). Not only maternal effect senescence might play a part in the Lansing effect, but paternal effect senescence as well. Sparks *et al* (2022) demonstrated a negative association between maternal age and female offspring life span over a long period of time. However, no negative association between paternal age and offspring of either sex was demonstrated.

Both maternal effect senescence affecting quality of the offspring, age-specific survival and fertility as well as the life-history theory ‘terminal investment’ could be possible mechanisms explaining the Lansing effect as is proposed by Monaghan *et al* (2020). It has been suggested that the Lansing effect could be explained by either intrinsic, genetic effects, the deterioration of the parents or their cells, or by indirect effects, changes in environment or investment from the parents. A direct effect possibly involved in the Lansing effect is a decline in gamete quality. Up until recently, it was thought that gametes were ageless however, this is not the case (Monaghan et al., 2020). Gametes are produced from a specific type of stem cell: the primordial germ cells. From the gonads, these cells differentiate into male or female gametes (Monaghan & Metcalfe, 2019). If the primordial germ cells become female, mitotic division results in the cells becoming oocytes. Next, the oocytes enter meiosis until this is halted, they are in meiotic arrest. During this long period of meiotic arrest, a decline in gamete quality might occur. For the male gametes, the primordial germ cells become undifferentiated spermatogonia before entering meiosis. During puberty, the spermatogonia enter proliferation in which they rapidly enter several mitotic divisions. Next, a meiotic division occurs which followed by the development of mature sperm. These steps occur through the life of the male as sperm is produced as required (Monaghan & Metcalfe, 2019). The number of divisions these stem cells go through, increase with age. Pohl *et al* (2021) demonstrate spermatogonia stem cell exhaustion with increasing paternal age. Thus, possibly explaining gamete decline in males.

A possible explanation the Lansing effect is a decline in gamete quality. Up until recently, it was thought that gametes were ageless however, this is not the case (Monaghan et al., 2020). Females produce their gametes early in development and store them for later use. During this storage damage accumulation can occur leading to a decline in gamete quality (Monaghan & Metcalfe, 2019). Males however, produce their gametes from stem cells as needed over their lifetime. A decline in gamete quality can occur during the cell divisions where mutations can accumulate.

Another proposed direct effect is a decline in quality of parental care; for instance, older parents might have lower foraging success and therefore provide less food to their offspring (Monaghan et al., 2020; Sparks et al., 2022). Another possibility is in accordance with the life-history theory. This entails that every individual invests a certain amount of resources into repair and the remainder into its reproductive effort. When an individual becomes a parent at a younger age, it will invest more resources into their offspring. When an individual becomes a parent at a later age, it will invest more resources into its own repair and maintenance than in its offspring (van den Heuvel et al., 2016). However, these mechanisms have either not been examined or only been researched independently. In order to understand why and how parental age can affect offspring quality and lifespan, the mechanisms need to be combined and examined more closely. Hence, the need for an individual-based model of the evolution of ageing with several possible mechanisms implemented.

Here, we present an evolutionary individual-based simulation model to examine which mechanisms contribute to the Lansing effect and to predict the importance of them. In our model, we implemented multiple mechanisms, such as a decline in gamete quality; a decline in parental care; an allocation of resources over repair and reproduction, which could play a part in generating a Lansing effect, to test whether these mechanisms lead to a Lansing effect and how they interact. We examined the effect of parental age on offspring lifespan both cross-sectional as well as longitudinal to gain a better understanding of how the data acquisition can influence Lansing effect.

*Methods*

**Individual-based simulation model**

We present an individual-based simulation model with ageing individuals and several mechanisms to explore the Lansing effect. The model consists of a population, containing females of size *N,* males of size *N* and of offspring of size *N* (the model parameters, the defaults and the explanation can be found in Table 1). The males, females and offspring are of type individual. Each individual has several intrinsic characteristics, age, maternal age, paternal age, and survival probability. The genetics of the individuals are represented by multiple gene arrays. An individual has binary genes, age-specific survival genes and age-specific resource allocation genes. Furthermore, an individual has gametes or stem cells depending on whether they are female or male.

Upon the start of the model, the population is initialized. The initialized population consists of males of size *N* and females of size *N* with the initial gene values as described in Table 1. Upon initialization, the population enters the time simulation which will continue until *tend* where every time step is considered a generation. The population first reproduces, every female picks a male, at random, and reproduces an number of offspring. The offspring become part of the population via the offspring vector. The next step in the simulation is the mortality round of the adult individuals, meaning the males and females. This depends on the genetically determined survival probability. Depending on which mechanisms are being examined and thus, which gene values should play a part in determining the individual its survival probability, the individual either ages one year or dies. If an individual reaches the maximum age *c*, they die as well. The next step is the maturing of the offspring. For every deceased individual from the preceding step, a random offspring is selected and included in the adult vector. Finally, the population enters the mutation round. During this step the gametes and stem cells mutate. Again, depending on which mechanisms are being examined in the simulation, determines which gene arrays mutate and which do not.

In order to estimate offspring lifespan over parental age, the population enters another simulation. This was done by a few extra steps after the time simulation had ended. The final population reproduces to generate *oN* offspring. These offspring become the new generation, and are equally distributed over males and females. The population enters a simulation loop. The population reproduces, this only happens as long as there are both males and females alive. The offspring are recorded on an individual level. Meaning every offspring a female and male produce is kept track of for both the male and female. Next, the mortality round is entered, which individuals die is determined by which mechanisms are enabled and which are disabled in the model. Finally, the population enters the mutation round, in which their stem cells and gametes mutate. In this simulation there is no step in which the population is filled to the original size by adding offspring. This loop continues for the maximum age, *c*, number of steps. At this point all individuals are either dead or have reached the maximum age after which they will die. After this simulation was finished, the recorded offspring per individual enter the mortality round until they have all died. The ages at death are gathered and written to an output file and we consider these the simulated offspring lifespans.

Table 1: Model parameters and the default values.

|  |  |  |  |
| --- | --- | --- | --- |
| *Parameter* | Value | Meaning | Name in model |
| *N* | 10.000 | Number of males and females in population | populationSize |
| *tend* | 100.000 | The end time of the simulation | tEnd |
| *c* | 40 | Maximum age | maximumAge |
|  | 3 | Number of offspring females get every generation | numOfOffspringPerFemale |
| *nsc* | 30 | Number of male stem cells | numOfStemCells |
| *mb* | 0.0024 | Mutation rate for the binary genes | mutationProb, mutationProbStemcell |
| *s* | -0.05 | The strength of the effect of the damaged binary genes on the survival probability | strengthOfSelection |
| *ma* | 0.002 | Mutation rate for the age-specific genes | mutationProbAgeSpecificGenes, mutationProbInvestmentGenes |
|  | -0.02 | Mutation bias for age-specific survival genes | meanMutationBias |
|  | 0 | Mutation bias for investment genes | meanMutationBiasInvestmentInRepair |
|  | 0.02 | Mutational effect size for age-specific genes | sdMutationalEffectSize, sdMutationalEffectInvestmentInRepair |
| *wi* | 0.3 | To scale how strict the investment in repair affects the survival probability | weightInvestment |
| *S* | 0.5 | Steepness of how the investment in reproduction affects offspring quality | steepnessAllocationToReproduce |
| *s* | 0.2 | Scaling investment genes | scalingStrengthOfAllocationToReproduce |

**Decline of gamete quality**

To simulate a decline in gamete quality, the binary genes of the stem cells and gametes are mutated every generation during the mutation round according to mutation probability *mb.* The binary genes are considered the gamete quality where a zero represents a healthy gene and an one represents a damaged gene. For every gene a random number between 0.0 and 1.0 is generated, this number is compared to the mutation probability. If a mutation were to occur, the gene becomes damaged. The survival probability for each *i*th individual based on the binary genes was calculated according to equation one.

Equation one describes the individual survival probability (*P*) which is dependent on the sum of damaged genes (*D*) and the strength of selection (*s*). The strength of selection determines how much the damaged genes affect the survival probability. If *s* = 0, the survival probability will be one, irrespective of the number of damaged genes. The individuals start with 10% of damaged genes.

**Age-specific survival**

Age-specific survival genes were included in the individual to simulate the lifespans evolving of the population. The genes were subsequently added to the gametes and stem cells of the individual as well. Each gene value is depicted by a survival probability ranging from 0.0 to 1.0. The genes were initialised with 10% damage as well, meaning the initial gene values were set to 0.9. Every generation during the mutation round, genes mutate with a mutation probability of *ma*, the mutation bias was determined by a normal distribution with a mean mutation bias of < 0 and a mutation effect size of . The bias was assumed to be negative to lower the survival probability of the individuals, in order to simulate deleterious mutation accumulation (Medawar, 1957). If the gene value falls below their lower limit of 0.0 or exceeds the upper limit of 1.0 due to a mutation, the gene value is cut off at the respective limit. Selection will occur for the younger age classes while the deleterious mutations will accumulate for the later age classes.

**Quality of parental care**

The quality of parental care is determined by the age-specific survival genes. Wherein the age of the parent at conception determines the parental care quality value. As these genes go through mutations, the deleterious mutations will accumulate for the older age-classes. Consequently, individuals becoming parents at later ages will have corresponding gene values that have undergone more rounds of mutation. The maternal and paternal parental quality have an equal weight in the effect on the offspring. The survival probability of the offspring is multiplied with the parental quality. Upon initialization of the population, the parental care quality is determined by the proportion of damage in the age-specific genes. Meaning, with 10% damage in the genes, the initial parental care quality will be 0.9.

*We assume intergenerational accumulative effect. If your parent is of lower quality, you yourself will be of lower quality but your own parental quality will be lower as well. Lansing assumed this as well. Good to mention somewhere.*

**Resource allocation between reproduction and repair**

We assume an individual can distribute resources over repair for its own survival or they can invest resources in reproduction. Initially we assume an equal division of resources. We implemented this by adding another set of age-specific genes to the individual, the gene values range between 0.0 and 1.0. These gene values correspond to the proportion of resources allocated to repair for its own survival. The remainder of this gene value subtracted from 1.0 represents the proportion of resources allocated to reproduction. Every generation during the mutation round, the age-specific genes mutate with a mutation probability *ma*. The mutation bias was determined by a normal distribution with a mean mutation bias of = 0, and a mutational effect size of . The mean mutation bias was set to zero to prevent any bias favouring allocation of resources to either repair or reproduction. If the gene value falls below their lower limit of 0.0 or exceeds the upper limit of 1.0 due to a mutation, the gene value is cut off at the respective limit, just as in the age-specific survival genes. The effect of the gene value for the survival of the individual was determined according to equation two.

Equation two describes how the proportion of resources allocated to repair () affect the survival probability (P) of each *i*th individual. The effect is scaled by a weight, *w* > 0, which determines the strength of the effect. If *w =* 0, then the survival probability will be one, irrespective of the proportion of resources allocated to repair. The bigger the weight, the more effect it has on the survival probability.

The proportion of resources allocated to reproduction affects the quality of the offspring at reproduction. It affects the quality according to equation three, with *z = 1.0 – x*, representing the proportion of resources allocated to reproduction.

Where the new intrinsic survival probability of the offspring () is determined by the old intrinsic survival probability (), multiplied by a logistic equation dependent on the steepness of the effect (*S*) and on the

**Reproduction**

*Explain how a new individual gets its genes and how the survival probability is affected by the different mechanisms. Maybe with figure?*

**Model analysis and statistics**

*This will be filled in later. After the results.*

*General*

*Explain, in words, generally how the model works. Use a figure to describe the flow of the model. This figure should explain, intuitively, how the model works, by beginning on biggest level and going down. Population consists of males, females and offspring. Every one of these groups consists of individuals. Every individual consists of three types of genes. Etc.*

*Next, explain the model step by step. Eg. for a beginning: The model starts by picking a seed for the random number generator. Next the parameter object is created containing all parameters necessary for the model to run. If a parameter file is received by the command line, the parameters within this file will be reset to these values instead of their defaults.*

*Gamete decline:*

*Explain how this is implemented. Include the formula in which the number of damaged genes is used to calculate the survival probability. Explain which genes are affected by gamete decline, and in what way. Name the parameters?*

*Introduction notes to self:*

*First paragraph: X.*

*Biological background about Lansing effect and parental age affecting the offspring lifespan.*

*Second paragraph: X.*

*What is currently known about Lansing effect according to literature.*

*Third paragraph: X.*

*Work towards what is missing in current literature. (only speculated – no real research). End with something like ‘… hence, the need for an individual-based model to research possible mechanisms explaining the Lansing effect.’ Include the mechanisms which might explain the Lansing effect.*

*Fourth paragraph: X.*

*Explain what my model/ research is. Begin with ‘Here, we present an evolutionary individual-based simulation model to research which mechanisms explain the Lansing effect. And to what extent.’. Very broadly explain the model. Quote from Jans paper: ‘The model represents a population of individuals whose lifespans evolve due to the accumulation of mutations with age-specific effects on survival, as in Medawar’s mutation accumulation theory of ageing (Medawar 1952).’*

*General > explain the Lansing effect. Name some organisms in which it occurs. Name how the mechanisms are only theoretically speculated about. Nothing is proven. Name some of the possible mechanisms. It needs to be clear to the reader why this research is relevant. Guide the reader towards the research question. In such a way that it makes complete sense why this is my research question/ topic.*

*To name in text, so, not in parameter table:*

* *Initial damage proportion at 10%.*
* *Weight maternal and paternal effect is equal for parental quality.*
* *Initial value for resource distribution is at 50/50 for reproduction/ repair.*
* *Initial damage in age-specific survival genes is at 10%.*
* *Number of female gametes. Maximum needed over a lifetime.*

Table : Model parameters and the default values.

|  |  |  |  |
| --- | --- | --- | --- |
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| *nsc* | 30 | Number of male stem cells | numOfStemCells |
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| *s* | -0.05 | The strength of the effect of the damaged binary genes on the survival probability | strengthOfSelection |
| *ma* | 0.002 | Mutation rate for the age-specific genes | mutationProbAgeSpecificGenes, mutationProbInvestmentGenes |
|  | -0.02 | Mutation bias for age-specific survival genes | meanMutationBias |
|  | 0 | Mutation bias for investment genes | meanMutationBiasInvestmentInRepair |
|  | 0.02 | Mutational effect size for age-specific genes | sdMutationalEffectSize, sdMutationalEffectInvestmentInRepair |
| *w* | 0.3 | To scale how strict the investment in repair affects the survival probability | weightInvestment |
| *S* | 0.5 | Steepness of how the investment in reproduction affects offspring quality | steepnessAllocationToReproduce |
| *s* | 0.2 | Scaling investment genes | scalingStrengthOfAllocationToReproduce |

**Results**

The first mechanisms to potentially explain the Lansing effect is a decline in gamete quality. Up until recently, it was thought that gametes were ageless (Monaghan P, 2020). However, this is not the case and therefore might be an explanation for the Lansing effect. Gametes are produced from a specific type of stem cell: the primordial germ cells (PGCs). In most sexually reproducing animals, these PGCs arise during embryogenesis and end up located in the gonads. In the gonads they differentiate into male or female gametes (Monaghan P, 2019).

If the PGCs become female, mitotic division were to occur rapidly. Afterwards some cells are lost, the remaining cells become the primary oocytes. The oocytes enter the first few stages of meiosis until this is halted. The primary oocytes are in meiotic arrest. This arrest continues up until ovulation, starting from the puberty and could end much later in life. In humans, the end of the arrest could last until 50 years, when women enter menopause. (Monaghan P, 2019). During this long period of meiotic arrest, a decline in gamete quality might occur.

This is implemented in the model by having the females generate the gamete stock at birth. Every time step a female survives; her gametes go through a mutation round. Meaning, if a woman survives to an older age, her gametes will have endured more mutations.

For the male gametes, the PGCs become undifferentiated spermatogonia. They will enter meiosis after birth. During puberty the germ cells become viable sperm. When a male enters puberty, the spermatogonia rapidly enter several mitotic divisions. Upon puberty, the number of male spermatogonia divisions drastically transcends the number of female oocytes divisions. After the mitotic proliferation, a meiotic division occurs, next mature sperm develops. These steps occur through the life of the male as sperm is produced as required (Monaghan P, 2019).

After these steps of proliferation, the sperm passes the epididymis, which might result in epigenetic changes to the sperm and can thus be an explanation for male gamete decline (Monaghan P, 2019). According to Goriely (2016), the replication errors occurring in stem cell division are the most likely explanation for more *de novo* mutations (DNMs) in children with an increased paternal age. These DNMs arise in the parental germ line, and they find that there is a strong correlation between the number of DNMs in a child and the age of the father. The number of divisions these stem cells go through, increase with age. Thus, possibly explaining gamete decline in males. The latter theory is examined as well in a research of Pohl et al (2021), in which they researched the effect of increasing paternal age on spermatogenesis. They focus, among others, on ageing-associated spermatogonial stem cell exhaustion. They explain that stem cell exhaustion could be explained by DNA damage, epigenetic changes or telomere shortening. They show that an increased age might result in hyperproliferation of the spermatogonia and a re-activation of quiescent spermatogonia. Both these processes could potentially explain a decline in the gamete quality of males.

This male decline is implemented in the model by mutating the stem cells of males for every time step. They generate several stem cells at birth, these will go through a mutation round every time step. Meaning, if a male survives to an old age, the stem cells will have endured more mutations. [Explain difference in implementation between males and females].

Upon running the simulation, for every time step the individuals underwent reproduction, mortality, offspring maturing and mutation. For every time step, the individuals that died were documented, including their own age at death as well as the age of their mother and father when they were born. Upon the end of the simulation, the surviving population was analysed. This was done by looking at their age at the end of the simulation and their survival probability. Based on these values, the remaining lifetime was determined, i.e., their expected age at death. The yearly probability of survival, *s*, can be calculated by taking the intrinsic survival probability (*x*) and multiplying this with the extrinsic survival probability (which can be calculated by subtracting the extrinsic mortality probability, *m*, from 1).

Next, based on this yearly survival probability, *s*, and the current age of the individual, *x*, the expected age at death, *y*, can be calculated based on the following:

When analysing these data, there seemed to be a decrease over an increasing parental age. However, when running the simulation multiple times the results differed, there would sometimes be an increase in expected age at death over an increasing paternal age. Another problem we encountered, there was not a lot of data available for the older ages. Since it is not very prevalent to get to the older age classes, some parental ages were not represented, or only by one or two offspring. Because of this, the results were not very reliable. The same simulation was run multiple times, and the output grouped together to try to circumvent this issue, however the same problem remained. Furthermore, to get to an older age, you would have to have a strong genome which meant that the offspring of these individuals would also inherit a stronger genome, balancing out the possible Lansing effect.

Therefore, we decided to research the individuals longitudinally, i.e., over their lifetime. We let the simulation run as was done previously. After reaching the final time step, a certain number of individuals were flagged. The remaining population, including the flagged individuals, again went through the simulation while keeping track of the offspring from the flagged individuals. When every flagged individual had died, the simulation stopped, and the offspring information of the flagged individuals was written to a file. This meant that for every individual we could compare the quality of the offspring in the beginning of their lifetime with the quality of the offspring in the end of their lifetime. Multiple statistical tests were performed over this data.

A linear mixed-effects model (LMM) was used to fit the data. For the first test, the expected age at death of the offspring of the flagged individuals were standardized. The slope of the fixed effect was significantly (p-value of 2.86 x 10-4) negative. Next, the standardized data was logit transformed. This new data was fitted by a linear mixed-effects model, again the slope was significantly (p-value of 1.28 x 10-6) negative. Next, a generalized linear mixed model with a beta distribution was used to fit the data. This resulted in a significantly (p-value of 6.91 x 10-5) negative slope as well. Finally, to perform a generalized additive model (GAM) a BAM function was used. A GAM is a linear model in which the beta coefficients are replaced by spline functions (Shafi, 2021). In our case, a separate spline for every ID, which represents every flagged individual, is fitted. This result can be seen in [*Figure 1*]. The relation between age of parent and expected age at death from their offspring decreases with an effective degrees of freedom value of 1.837, meaning weak non-linearity with a p-value of < 2 x 10-16.



Figure 1: expected age at death over the age of the flagged individuals. PLOT NEEDS FORMATTING.

**Conclusion and Discussion**