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Mosaic Ageing

Bachelor Thesis

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version 1.0

Groningen, March 2017

Abstract

The idea that traits should age synchronously stems from the classical evolutionary theories of Williams and Smith. Recent empirical data, both in lab and in the wild, has however not confirmed this hypothesis. Here, I will shed some light on recent research conducted on the ageing of different traits in animals in nature. These results are – if possible – explained from an evolutionary aspect, by means of viewing the ageing process as asynchronous or *mosaic*. This theory of mosaic ageing stresses the complexity and how interconnected different processes of the ageing process are. I propose mosaic ageing not as a replacement but as an extension to the classical theories of ageing and suggest to focus on longitudinal research to further investigate the complex process of ageing.

Contents

Chapter 1

Introduction

With the steady increasing life expectancy, the last fifty or so years the interest in ageing and ageing research has increased considerably. A good example of this is the Healthy Ageing research program of the RUG, focusing on the medical aspect of ageing. Another, maybe underexposed component is the evolution of senescence.

What is ageing? Ageing or senescence has been described as a process of deterioration in body components over age, increasing the susceptibility to death. This is mostly observed as a physiological decline, such as loss in organ function or cellular processes.

The main question of evolutionary relevance about ageing is: how could senescence develop in populations, since ageing comes with higher mortality and thus is selected against? To answer this and other questions, and possibly provide insights in the complex process of ageing, evolutionary thinkers such as Medawar, Williams and Smith have laid the theoretical foundation (see also 2.1). A hypothesis fitting in this framework was postulated by Williams and Smith, namely that the ageing of different traits should happen in synchrony. The evolutionary explanation is simple: if the lifespan of an individual is limited by the ageing of a single organ, natural selection would favour any genetic changes to make this organ more durable, resulting in synchrony among organ wear.

However, studies so far have given close to no indication that this is happening, both in humans or laboratory model organisms (Herndon et al. 2002, Bansal et al. 2015, Lahdenperä et al. 2004). Also in populations in nature it is shown that traits age asynchronously (Hayward et al. 2015). Since the ageing process might be seen as a complex process, highly subject to environmental influences and with high individual variation, the difference in rates of senescence between traits may thus be viewed as *mosaic* (Walker & Herndon 2010). Indications of mosaic ageing are contrasting trait trajectories over age (see figure 1.1). But are these mosaic ageing patterns visible in populations in the wild? In this thesis, differences between traits found in research will be analysed from an evolutionary approach and with these results the view of ageing as a mosaic process is discussed.

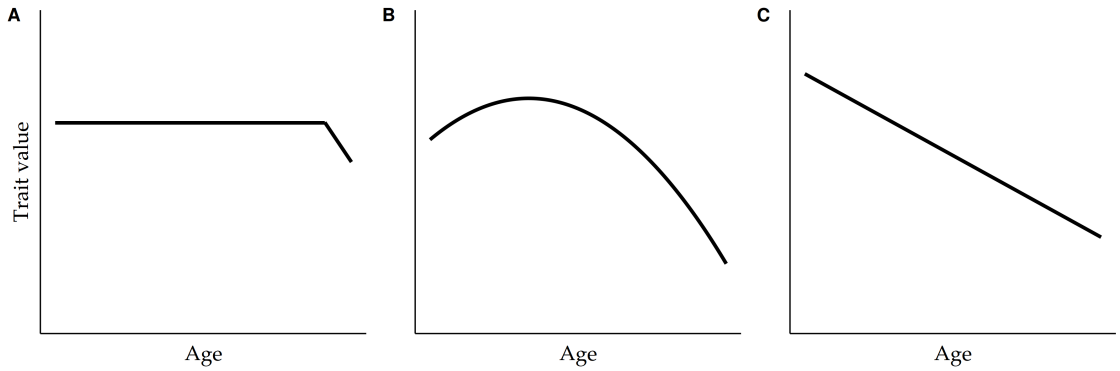

Figure 1.1: An example of different ageing trajectories between traits, showing A) *a terminal decline*, B) *an increase followed by a exponential decrease*, C) *a linear decrease* in a trait over age.

Chapter 2

Evolutionary theories of ageing

2.1 Classical evolutionary ageing theories

The increasing interest for ageing in the second half of last century, along with progress in the cellular and molecular disciplines of biology, gave birth to over 300 theories of ageing (Medvedev 1990). However, here the focus will primarily be on the evolutionary aspect.

Weismann was the first evolutionary biologist come up with a theory of senescence. His theory was that ageing is a mechanism of natural selection to sort out the worn out and thus weaker individuals from a population so they would not compete with their offspring for food and space. The elimination of individuals would be necessary for evolution to take place (Weismann 1882). There are however several fallacies in his reasoning. For example, Weismann lacks the explanation of how natural selection could bring forth such an ageing mechanism. Also, he does not explain the rarity of individuals in a wild population to become old enough to die of natural causes. Mortality in nature consists mainly of extrinsic factors such as diseases, starvation or predation. Besides, if animals in the wild would survive to the point where ageing negatively influences the survivability, such a trait would be disadvantageous and thus would be selected against.

This last argument also forms the basis of modern evolutionary theories: a high extrinsic (external) mortality rate makes that there are less old individuals and natural selection weakens further with increasing age. Thus, a selective disadvantage for a hereditary factor that expresses later in life is relatively smaller than in early life (Medawar 1952). This may account for a large range of alleles with later deleterious effects, resulting in the *mutation accumulation theory*.

Expanding this theory the *antagonistic pleiotropy theory* is posted by Williams (1957). He argues that, even though senescence has a relative small effect on the fitness of an individual, it can still be selected against. Thus, a positive fitness benefit must be attached to this negative senescence effect. Thus, he assumes that genes of some sort have opposite effects on fitness at different ages, so called pleiotropy, where late-in-life deleterious effects are coupled to early-in-life benefits. As a hypothetical example he mentions a mutation that has a positive effect on calcification of bone – making an individual stronger in early life – with the same calcification effect of connective artery tissue later in life, causing higher mortality. Such a mutation is evolutionary favourable since the amount of young individuals is much larger, resulting in overall higher fitness. This means that even a small early-in-life benefit with larger – even mortal – health consequences later in life can be evolutionary favourable.

Another theory of ageing is the *disposable soma theory*, in a sense a special case of Williams' pleiotropy theory. Having a more physiological approach, in this theory the assumption is made that an individual has a limited supply of energy (food) at its disposal. Thus, not all body functions, e.g. reproduction, thermoregulation or repair and maintenance of somatic (non-reproductive) cells, are optimally invested in and a compromise must be made to allocate these limited resources. As pointed out in the theories above, an individual's death in nature is more likely to be caused by extrinsic than intrinsic factors. Thus, there is less reason of allocating

metabolic resources to somatic cell maintenance as long as the individual can last until death by extrinsic causes. This way, resources are committed to functions that have evolutionary benefits early in life such as reducing energy needs or reproduction, resulting in the faster ageing of cells. The mortal effect of the latter affects not enough individuals to outweigh the selection benefit of the former (Kirkwood & Holliday 1979). An example mentioned by Kirkwood (2002):

> *Metabolic resources are scarce, as is evidenced by the fact that the major cause of mortality for wild mice is cold, due to failure to maintain thermogenesis. From a genetic point of view, the mouse will benefit by investing any spare resource into thermogenesis or reproduction rather than into better DNA repair capacity than it requires.*

The name "disposable soma theory" stems from the analogy with the disposable goods, in which no money is spent on making the product durable since its lifetime is limited anyway. This is similar to the low expenditure of metabolic resources to somatic cell maintenance.

2.2 (A)synchronous and mosaic ageing

Williams accompanied his theory of pleiotropy (see above) with several deductions. One of this was that 'senescence should be a generalized deterioration' (Williams 1957). Reiterated in 1962 by John Maynard Smith, with the then recent evolutionary theories of Medawar and Williams as basis, he argued that multiple physiologically independent traits should age in synchrony. An example given by Smith:

> *Suppose that ageing in mice is in fact multiple, each organ system ages according to its own programme. Then if one organ system, say the vascular system, wore out sooner than any other, natural selection would favour any genetic changes tending to make the vascular system more durable, but would not oppose changes tending to make, say, the nervous system deteriorate more rapidly. The result would be the synchrony of physiologically independent ageing processes.*

Thus, by natural selection acting on a trait that ages relatively quick, eventually synchrony of senescence among traits will be reached in evolutionary time. This theory of synchronous development of traits is subject to a few conditions:

1. The extrinsic (or external) mortality should be substantial – neither too low or non-existent, nor too high
2. The environment of a population must be plenty stable

The first condition is fundamental for evolutionary theory of ageing (as described in 2.1) for deleterious effects to be able to develop at later age without being selected against too much. If the extrinsic mortality is too high however, no selection will take place at all because death is not caused by ageing. Lastly, the environment is of impact on the life-trajectories of quite some traits, where under different circumstances the rate of ageing for a trait can vary (see 3.5 for examples). If there is a lot of fluctuation in the environment over multiple generations, the influence of different ageing traits on death might vary a lot, where natural selection has 'not enough time' to balance out these effects and synchronise ageing. Thus, over evolutionary time for selection to act on ageing traits, the environment should stay relatively stable for synchrony between trait senescence to occur.

Mosaic Ageing Almost no studies over the last few decades have confirmed the synchronous ageing of traits, not in model organisms (Herndon et al. 2002, Bansal et al. 2015), humans (Christensen et al. 2009, Lahdenperä et al. 2004) and even animals in the wild (Hayward et al. 2015, Hammers et al. 2015). These results support the consideration that the process of ageing in individuals is (almost) never under the circumstances as described above. It seems that ageing is no unitary phenomenon but a multi-component complex with mechanisms reacting

differently depending on the time and setting. The recently formulated term for this is *Mosaic ageing* (Walker & Herndon 2010, Cevenini et al. 2008).

The idea behind this phenomenon is that multiple traits can senesce at different rates – even when not influenced by e.g. environmental factors, behavioural dynamics or density dependence – because of the varying impact of a trait on the fitness, where fitness is optimally described by lifetime reproductive success (LRS). An example: If two traits have an equal effect on reproductive success, take for example offspring size and percentage of offspring alive, the ageing pattern of these traits will expected to be similar. If litter size would decline significantly over age and litter success wouldn't, the former would decrease fitness and unnecessary resources are invested in the latter.

Thus, ageing patterns of traits can be ascribed to the trait's effect on LRS and therefore their ageing rate and trajectory will vary. This also means that these ageing patterns can give in indication on the influence a trait has on the lifetime reproductive success.

Chapter 3

Findings in recent literature

Although a lot of research has been done on the subject of ageing (in vitro as well as in nature), not many scientists have focused on the aspect of ageing of multiple traits. Despite that Williams's and Smith's hypothesises stem from mid-twentieth century, only in the recent years the relation between multiple traits over age have been investigated, though in between researches the variation of the examined traits is high. Thus, before discussing the findings on senescence of multiple physiological properties, a more general prediction of the evolutionary theories – with a greater amount of evidence – is described. This is the relationship between reproduction and fecundity (fertility). This might give some insights to the dynamics in trait senescence.

3.1 Fecundity–longevity relationship

One of the main predictions of the disposable soma and antagonistic pleiotropy theories is that increase in early reproductive effort is paired with the decrease of longevity or vice versa. This is observed in laboratory when using mutations in model organisms to test the effects of life-lengthening genetic modifications. In the nematode (*Caenorhabditis elegans*), modifications such as influencing electron transport chain in mitochondria, reducing respiration and metabolic activity and manipulation of the *insulin-like growth factor* (IGF) receptor all cause substantial higher longevity, up to twice as long life expectation (Jenkins et al. 2004). In all cases, this is paired with a substantial decrease in reproductive performance (Rea et al. 2007, Chen et al. 2007). In the widely used *Drosophila melanogaster* (fruit fly), similar techniques for life elongation are used: decreasing metabolic rate and influencing the insulin signal pathway. These show a similar strong negative correlation between livespan and fecundity (Stearns et al. 2000, Clancy 2001, Tatar et al. 2001, Marden et al. 2003). Even in small mammals (lab mouses) used in the labs this relation is visible (Bartke 2005).

However, while these trade-offs are found in multiple lab studies, the same expectations are not as much confirmed for populations in the wild. This might be caused by the high amount of environmental change such as temperature or density-dependence causing different life-history strategies, giving too much variance in the result. Another factor is a (often) much higher external/extrinsic mortality in wild populations, in which a strategy with higher longevity is not viable for maximizing fitness relative to a strategy with higher fecundity. This will cause to evolute to a high-fecundity strategy only and thus results of the trade-off between longevity and fecundity will probably not be found in nature.

Some recent, both cross-sectional and longitudinal based results do however confirm the prediction of this trade-off. An example can be found in common lizards, where a decline in survivability over age only occurs in individuals that have invested more in the initial offspring attempt, measured by the relative size of the offspring to the mother (Massot et al. 2011) See figure 3.1. Another example is to be found in a study with turtles, where body size (plastron length) determines relative investment in eggs in early or late life. Smaller turtles invest relatively more in eggs (measured in weight) than do heavier turtles (Warner et al. 2016). This is

another example of a trade-off of higher terminal fitness investment versus earlier growth (body weight).

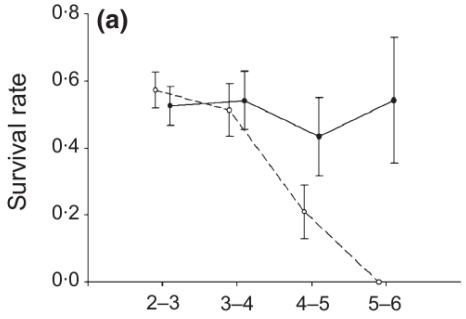

Figure 3.1: A possible relationship between fecundity and longevity. The dashed line and continuous lines show individuals with higher and lower investment in first reproduction attempt respectively (Massot et al. 2011).

3.2 Determining instances of mosaic ageing

Mosaic ageing, as explained in 2.2, is a similar term to 'asynchronous' or 'differential' ageing. It is used to describe the often varying senescence rates of components in complex organisms. Signs of this phenomenon occurring are great or significant differences in ageing trajectories over traits. Next, a few researches are reviewed to look for such ageing patterns between traits or between studies and how these traits relate to fitness or lifetime reproductive success.

An important element to consider when comparing ageing patterns is the high variety in how traits are measured and in what species. A distinction can be made between shape and pace (Baudisch 2011). To account for different ages of maturity and death between species, only the shape of ageing is discussed in this piece (see also figure 1.1). The pace of ageing, whilst informative when measuring trait values in similar systems (e.g. B- and T-cell mediated immunity), is not well fit to compare between different systems and species. Thus, ageing is mosaic when patterns – or shape – between the ageing of traits differs.

3.3 Physiological traits

Even though the pace of ageing of a trait is strongly dependant on environmental factors, as discussed in section 3.5, an attempt is made to sort out senescence patterns of these traits and, if possible, find relations between them, trends in their effect on general ageing and their relation to fitness.

What is a trait? The predicted synchrony among traits in the evolutionary theory of Williams and Smith is mostly about organ systems. However, a trait might also be of a behavioural aspect (such as cooperative breeding), molecular aspect (such as the amount of reactive oxygen metabolites), or immune-related (for example T-lymphocyte cell mediated immunity). All these traits might be susceptible to ageing, but act very differently on the fitness of an individual. This once again emphasises the complexity of ageing in different traits.

In this piece, a distinction is made between traits with a direct impact on lifetime reproductive success (fitness), such as offspring size or survivability, and traits with a lesser or unknown effect on the LRS, e.g. resting metabolism, blood carotenoid concentration or ungulate horn length.

3.3.1 Direct fitness components

One of the most measured properties in senescence studies in the wild is reproductive success, because of its direct effect on fitness. This includes a broad range of measurements, e.g. egg mass, hatchling mass, clutch size, clutch frequency and total egg output in nonmammalian species, or offspring birth weight and survival.

Examples In a study with *Alces Alces*, a free-ranging moose, the reproductive efforts are explored over age. The resulting ageing patterns of litter size is increasing up until approximately 11 years of age, after which a steep decline is observed. This terminal decline is an ageing effect suggesting the examined trait has a high impact on lifetime reproductive success (Ericsson et al. 2001).

In other species, similar patterns appear. In both the Seychelles warbler and the Tree swallow, the patterns of reproductive output (measured as number of fledglings of an age group relative to the average) are similar, when their relative ages are taken into account. This means that up until intermediate age the reproductive output increases, and then declines again at later ages. (Hammers et al. 2015, Vleck et al. 2011). Another property, survivability, is measured as well in both these species. These traits also share a similar age trajectory; stability in mortality/survivability in early age and a steady decline after intermediate ages (relative to the average age). These between both traits and both species are quite similar, one could say in synchrony. The similarity between age trajectories can be explained by the large impact these both traits have on the fitness.

3.3.2 Indirect fitness components and non-reproductive traits

Not much research has been done on the ageing of components or processes that have less influence on the lifetime reproductive success of individuals. A few examples are given.

Examples In a cross-sectional study on *Lacerta vivipara* (common lizard), measurement of the resting metabolic rate shows an increase over age (Massot et al. 2011) in one year and no variations with age in another year. This is not similar to earlier reptile ageing studies where resting metabolic rate declines with age in early life (Patnaik, 1994). Because the result found by Massot et al. is not consistent over different years, multiple metabolic ageing patterns seem to exist in reptiles. The authors themselves suspect linkage to the immune response invoked in the test subjects. The expectation from an evolutionary perspective would be that the resting metabolic rate would increase over age, to cope with e.g. increased resources used for late-life investment in other senescing body parts.

In a comparison between two ungulate species, differences are found in the length and the circumference of the horns and antlers in respectively Soay sheep and red deer. While in the deer both antler circumference and length increase at young ages and stabilize in older individuals, the Soay sheep horns keep growing in length over age until death while circumference declines with age after reaching half of the maximum age (Hayward et al. 2015, Nussey et al. 2009). According to evolutionary theory, an explanation for this might be that deer profit from having not only longer but also stronger antlers, since this positively affects the amount of offspring, in contrary to sheep, thus increasing impact on lifetime reproductive success and thus fitness.

In another species, Zebra finches, different life trajectories were found for two metabolism-related traits. The two traits are the standard metabolic rate (SMR) and the basal metabolic rate (BMR). These are the minimum energy expenditures of an adult measured during the rest phase. The former differs from the latter only in the ambient temperature the values were measured in; the BMR was measured at thermoneutral temperature and the SMR at an ambient temperature below this. Thus, the SMR includes energy used in thermoregulation of the body. The SMR increases over age with a stabilization in the terminal year, while the BMR decreases linearly over age until death (Briga 2016). The age trajectory of another trait, bill colour, has is stable until the terminal decline in the last year the birds are alive (Simons et al. 2016). These results

are not explained by the classical theories of ageing, since they do not senesce synchronously and have considerably different trajectories.

3.4 Immunosenescence

Since the immune system is one of the most important defence systems in animals and humans, it is widely studied. The impact of ageing of one or more immune systems components (immunosenescence) could have a great effect on longevity and thus lifetime reproductive success.

Though immunosenescence has mostly been studied in humans and lab animals, multiple studies are carried out on other species, especially birds. Multiple components of the immune system are tested, both acquired and innate immune responses. The former is tested in Tree swallows, Zebra finches[1] and Storm petrel, where the skin swelling response to test with PHA is tested. This induces a proliferation of the T-lymphocytes (cell-mediated immunity), and the resulting amount of swelling can be used as an index for the immune response. In all three species there was a negative correlation between immune response and age, thus providing evidence of immunosenescence (Haussmann et al. 2005), as well as in another study with Tree swallows (Palacios et al. 2007).

3.5 Environmental impact on ageing

The effect of the environment is important when studying senescence in the wild. The various ageing processes are dependant on lots of factors which can not always be controlled in populations in nature.

Examples An extensive research has been done on *Thamnophis elegans*, the western terrestrial garter snake, in which a broad range of traits and their corresponding age-trajectory is explored. This is done with two so called ecotypes, which stem from a common ancestor but differentiated into two (genetically) divergent populations. One is from lakeshore, grows fast, dies on an early age and dedicates much resources to reproduction. The other ecotype is from a meadow environment and is long-lived, growing slowly and producing less offspring. Results: the mitochondria in the long-lived meadow ecotype were more efficient, producing more ATP per amount of oxygen, also generating less reactive oxygen (harmful by-product of ATP production) at similar ATP production rates. Lastly, the DNA of long-lived ecotypes was – though damaged more – found to be repaired more efficiently. Since the lakeshore environment is a high-predation and mortality garter snake habitat, these findings are in accordance to the classical evolution theories posted by Williams, that populations of low-risk environments age slower and invest less in offspring. Another selective pressure that could have contributed to the slow-ageing phenotype in the meadow snakes, based on long-term data, is low food availability (Robert & Bronikowski 2010).

Another example is given by a study on guppies, where two populations were taken from both a high- and low-predation environment and placed in the latter. The females from the environment with high (external) mortality were found to have an earlier onset of senescence (Bryant & Reznick 2004). This result is as expected by the classical theories of ageing, since higher predation would – by natural selection – cause more investment in reproduction and therefore less in somatic maintenance (see 2.1). However, in a second experiment, the guppies were placed in a non-predation environment and the exact opposite was observed: guppies from a high-predation location have *lower* senescence of mortality and reproduction than those from low-predation environments. The explanation given by the authors is that although a higher amount of predators increases general mortality rates, this may cause a increase in food availability. If older individuals benefit more, this may cause evolution of slower ageing. In

[1] The Zebra finch colony was in captivity, with food available at pleasure, lack of predation and low chance of illness. The appearance of immunosenescence is thus more remarkable, since a terminal investment of resources to the immune system is expected.

short, predation also effects density and this density-dependence has effect on senescence as well.

From these results can be concluded that as per the predictions of classic theories of ageing, high extrinsic mortality causes selection for reproduction and growth, with corresponding increase in senescence. However, not only this environmental factor can influence the ageing patterns; other factors such as the density dependence or food availability can have great effects on the course and onset of senescence as well. This once again emphasizes the ageing process of being mosaic, as a complex structure of interacting processes.

Chapter 4

Discussion

Most examples displayed in the previous chapter show a trend of asynchrony between the ageing trajectories of different traits. This is in contradiction to the evolutionary theory of synchronous ageing proposed by Smith (1962) and Williams (1957). One of the possible reasons for the variety in the senescence of different components is the influence a trait or process has on the lifetime reproductive success (and thus fitness) of an individual; when this differs between two traits, the rate of senescence of these traits can differ as well.

Another factor in the diverse rates and trajectories of senescence is the environment, which is of great influence on the life-history decisions made in individuals. Not only predation or food availability, but also differences in e.g. density dependence can influence the onset and rate of senescence.

To view the ageing process as mosaic, it is important to not only find bivariate relationships between traits; more complex interactions between multiple traits – which age simultaneously – shape an individual's senescence, as Hammers et al. illustrates in the Seychelles warbler (Figure 4.1).

Proposal for future research Since senescence is a process within individuals, cross-sectional studies only tell part of the story. Longitudinal research is needed, marking individuals and measuring traits over time. In addition, to get insight in the complex process of ageing, it is of importance to not find correlation between two traits but to extend the research to multiple traits and their interactions.

Personal view Though the support and evidence for viewing evolutionary theory as mosaic seems broad, I think that Smith (1962)'s theory still stands; although under specific and stable circumstances. One of the important conditions to observe synchronous ageing is to have non-changing relationships between traits, as well as a relatively stable environment (meaning none or small variance in external mortality). Besides, the one theory does not exclude the other, so mosaic ageing might be observed as an *evolution* to the theory of synchronous senescence.

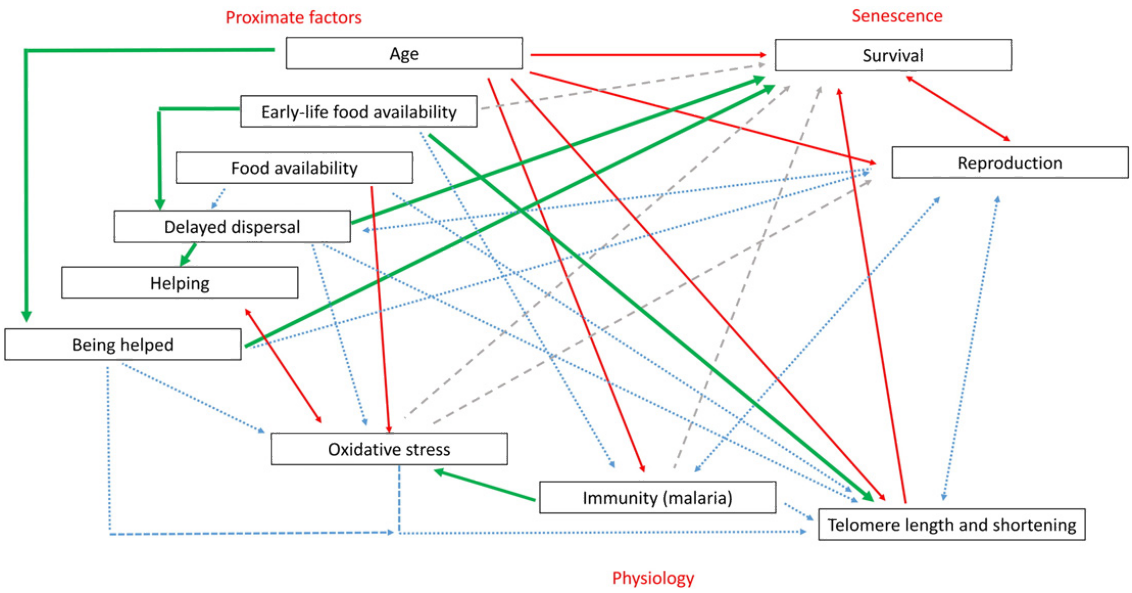

Figure 4.1: Possible relations between factors determining senescence in the Seychelles Warbler (Hammers et al. 2015).

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