The Evolution of Ageing: Concepts, Causation and Calculus

Maarten Jan Wensink

The Evolution of Ageing: Concepts, Causation and Calculus
Proefschrift Leiden

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The Evolution of Ageing: Concepts, Causation and Calculus

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Part I

Introduction

Chapter 1

Preamble: Why and what

Why study the evolution of aging? Because evolutionary forces act on everything there is in life, including 'life histories'*. (An asterisk (*) indicates that a term is (more) fully developed in Appendix A.) A life history is a characterization of the life cycle by mortality and fecundity patterns, both timing and quantity. The central idea of life history theory is that life histories evolve the way organs evolve (standard textbooks are [1-3]). Like the environment may drive evolution of the beaks of Darwin finches by providing different kinds of nuts, it may also drive evolution of the length of the developmental period, leading to smaller, simpler organisms, or to more developed organisms, depending on which thrives better (development takes time). The way in which organisms age is a prominent part of the life history, and is subject to evolution. It is therefore *a priori* not unlikely that an exploration of evolutionary forces will yield important information about why and how we age. This information can potentially be used to guide intervention and prevention, while in turn - and this is a prominent element in this thesis - medical and/or epidemiological thinking informs the evolutionary analysis.

Life is a precarious phenomenon. The second law of thermodynamics declares that isolated systems evolve toward maximum entropy. With its rather strict organization, life is clearly not a maximum entropy (dynamic) state. Life therefore relies on a continuous intake of resources and a clever handling of those resources, to prevent a fall from this special state. The question is why the capability to prevent a fall from the ordered state would decrease over age, i.e. 'aging', or 'senescence'*. Aging can be defined at different levels. There is physiological aging, which means a gradual dysfunction of an organism's physiology over age. Examples are the loss in elasticity of blood vessels, the loss of grip strength with age, and the loss in the ability of the eye to accommodate and view things nearby. Demographic aging is characterized by increasing mortality and/or decreasing fecundity over age. For evolutionary purposes the only relevant definition of senescence is the demographic one: evolution is driven by births and deaths, no matter how births and deaths come about. Of course, demographic aging is not independent of physiological aging. Simply put, a beating heart is a prerequisite for survival and reproduction. The

translation of physiological aging into demographic aging is potentially delayed, indirect, and non-linear. We have no good idea of how it works. A concept that bears on this translation is given in Chapter 2. Uncertainty around this translation inspired the generality of the model in Chapter 7.

Senescence refers to change. It does not pertain to absolute values of mortality and fecundity rates. Baudisch [4] makes a distinction between 'pace' and 'shape'. Pace refers to the time scale at which some process takes place, for instance whether a typical lifespan is a matter of days, years or millennia. Shape refers to the nature (improvement, no change, deterioration) and extent of change that takes place over a 'unit of pace'. To give an example from [4], at the age at which survival is 1%, (swedisch female) humans experience 35 times their average mortality rate, while the shorter lived buffalo experiences 'only' 11 times average mortality. As life expectancy is the inverse of average mortality (Appendix B), this indicates a slower pace but steeper shape of senescence for humans relative to buffalos. It takes humans longer than buffalo's to complete an average lifespan, but humans change more in terms of mortality over that lifespan than buffalo's [4].

The patterns of pace and shape across the tree of life is diverse [5]. Some organisms, like humans, experience massive deterioration, while other organisms (for instance the sea tortoise) only improve with age. Hydra do not seem to experience change at all [6]. For further theory and application of the pace/shape distinction see [7-10].

Evolution happens. It has no purpose, conscience or higher design [11]. Evolutionary statements are of the form: if something with these and these properties exists in an environment with properties such and such, it will be so and so good at assuring the presence of itself and/or copies of itself in the future (propagation). It is this propensity of continued existence that the term 'fitness'* refers to in an evolutionary context. It depends on the combined effects of survival and reproduction (Appendix B).

Sometimes a distinction is made between proximate explanations (mechanisms) and ultimate explanations (evolution) of biological phenomena, such as aging [12]. This is a misconception. While it is entirely possible to *observe* mechanisms and evolution separately, *explanations* include an idea of the mechanistic (im)possibilities that drive evolution in the observed direction, while evolution selects amongst existing mechanisms and thus determines what mechanisms can be observed. Explanations concern the intersection of mechanistic and evolutionary considerations.

We could construct an evolutionary statement of the sort: 'Organisms that do not age would, ceteris paribus*, be better at propelling their heritable material into the future than organisms that do age, and hence invade against a background of organisms that age, eventually replacing the original, aging, population'. After all, aging means that mortality increases and/or fecundity decreases, which is not helpful for propagation. Then why does aging exist?

Mainstream theory has come up with two processes that could balance against the tendency of natural selection to eliminate aging. First, new genetic mutations* may arise

that lead to aging. These mutations are removed over evolutionary time because they decrease fitness of organisms that possess these mutations. In the mean time, new mutations arise that take the place of the mutations that are removed, and so on. Eventually, the rate at which such mutations occur could stabilize against the rate at which such mutations are removed by natural selection [13-15]. Some mutations that lead to aging are consequently always present, leading to the observation of the aging phenotype*. Under this theory, the result is a *loss* in Darwinian fitness.

In Chapter 3, I discuss some logical limitations on theories that invoke such mutations, which restricts any theory along these lines. The calculus presented in Chapter 5 is instrumental in evaluating this more restricted theory. The issue is further commented on in Chapter 2.

The second type of mainstream evolutionary theory is the theory that aging could be causally related to some other process that confers on an organism a fitness benefit greater than the cost of senescent deterioration, i.e. the 'trade-off'* explanation of aging. For instance, increased investment of resources in reproduction could leave fewer resources for somatic* maintenance, leading to increasing mortality over ages (conform the 'disposable soma theory' [16,17]). In some specific cases, cutting investments in maintenance and reallocating the saved resources to reproduction could increase fitness [18-20, Chapter 5]. Another, specifically genetic trade-off theory is 'antagonistic pleiotropy' [21,22]. 'Pleiotropy' means that a gene has more than one effect, while 'antagonistic' means that the effects are in opposite directions, in this case opposite effects on fitness through effects on mortality and/or fecundity. When (the expression of) some gene is necessary to achieve a phenotypic effect that increases fitness, a genetically correlated negative effect on fitness may come with it. This negative effect could be aging if the effects are felt predominantly at old age. Under trade-off theories, the collection of benefits and costs, including senescence, is selected for if the result is a *net gain* in Darwinian fitness.

A great number of modalities of trade-offs was listed by Stearns [1]. The models in this thesis, specifically Chapter 5 and Chapter 7, are not primarily concerned with the underlying trade-off mechanism, be it genetic or otherwise. The original theory of antagonistic pleiotropy as stated by G.C. Williams [21] was logically impossible, or at least incomplete ([16], Chapter 3). In general, a theory that relies on physiological limitations offers a more credible alternative than theories of individual genes (Chapters 3 and 10).

Whether a change in a set point under some trade-off leads to an increase in fitness depends on costs and benefits, and cannot be evaluated by means of verbal argument. There are two complementary approaches to formally evaluate evolution under trade-offs. There is 'direct optimization', which refers to finding the set point that leads to the highest absolute value of Darwinian fitness. The trade-off is captured in mathematical expressions that include a parameter that represents the set point. This parameter is then optimized, which means that fitness is maximized. The other approach uses selection gradients, evaluating *change* in fitness when varying a parameter under a trade-off. Obviously, the absolute value increases under a positive change, relating the approaches. A background to the demographic methods is given in Appendix B.

Hamilton [14] explored change by finding indicators of the sensitivity of fitness to an infinitesimal additive change (perturbation) in mortality or fecundity at a particular age. Hamilton's perturbation analysis was, and often still is, seen as something rather difficult and esoteric. However, Caswell [23,24] showed that Hamilton's indicators can be decomposed into demographic quantities that are well-known in stable population theory* [25]. This gives intuitive sense to these indicators, thus bringing them closer to home (discussed in Chapter 6). Using functional calculus*, Arthur [26] derived general expression of the sensitivities of scalar* demographic metrics, such as fitness, to changes in the patterns of mortality and fecundity *across all ages*. In Chapter 5, my co-authors and I show that Hamilton's indicators are a special case of Arthur's general approach, and we give a full analysis of the change in fitness as a result of changes in mortality and fecundity across ages.

In trade-off models aging is usually correlated only with increased fecundity at young ages (discussed in [27,28]). That is, an increased rate of reproduction at young ages comes with faster age-related deterioration of the vital rates, which is then supposed to explain aging. There are, however, other trade-offs that can lead to aging. Every individual aging organism would ceteris paribus live longer if it did not age. However, it is not true in general that organisms that age live shorter lives than organisms that do not age. Recall the pace and shape distinction discussed in the third paragraph: aging (shape) refers to change over the lifespan, while the length of the lifespan itself (pace) is something different. It is quite possible that aging has evolved because aging organisms live longer than non-aging organisms. This is the case if aging is associated with an *initially lower* mortality rate (that increases with age), such that average mortality is lower, and life expectancy higher. In this case, the 'ceteris paribus clause' is not fulfilled: if organisms did not age, they would not experience low mortality rates at young ages either. A mechanism that could lead to such a trade-off is discussed in Chapter 4. A formal demographic general model of this relatively neglected type of trade-off is proposed in Chapter 7, while also Chapter 5 touches on the issue. The hypothesis discussed in Chapter 4 is developed further in the general discussion of this thesis.

The evolution of aging, caused by newly arising deleterious mutations, trade-offs or both, is greatly facilitated by the fact that what happens to an organism late in life tends to have smaller effects on fitness than what happens early. These declining selection gradients limit the costs of senescence. Medawar [13] first stated explicitly and systematically that this might be the case, albeit for the wrong reasons (Chapter 6). Williams [21] followed up on this with a particular focus on genetic trade-offs, after which it was formalized by Hamilton [14] and further clarified by Caswell [23,24] (the selection gradients discussed two paragraphs ago). As mentioned, in Chapter 5 the selection gradients are embedded in Arthur's [26] more general approach.

Since declining selection gradients limit the evolutionary costs of aging, it is important to understand what causes this decline, and what may affect the pattern of decline. The probability of surviving to older ages is naturally lower than the probability of surviving

to younger ages. It is tempting to think that the age-related decline in selection gradients has its roots in the age-related decline in survival, and indeed such has been suggested many times [13,16,21,29-32]. This is not the case. Rather, the decline in selection gradients is a simple time effect: contributions to Darwinian fitness that lie in the past cannot be affected by later events. Since past contributions can only go up with age, selection gradients can only go down. This is true irrespective of any initial survival pattern, even if organisms just never die. Simply put: a population cannot be sustained if all organisms die before reproduction, but it can be sustained if all organisms die after many reproductive events. Chapter 6 digs deeply into this phenomenon, including its relation to the stable age-distribution, and demonstrates that declining survival does not drive the age-related decline in the force of selection, and why.

In evolutionary and demographic literature, mortality is sometimes classified as 'extrinsic' versus 'intrinsic' [33]. Apart from the question of its evolutionary effects (Chapter 6), it is questionable whether things like 'extrinsic mortality' or 'intrinsic mortality' even exist. To begin with, it is logically impossible to make such a partition, because extrinsic causes and intrinsic causes are not mutually exclusive (Chapter 2). The age-patterns of alleged intrinsic versus extrinsic mortality are tested empirically in Chapter 8, of which Koopman MD is the lead author. It is shown that alleged intrinsic versus extrinsic mortality have age-patterns alike. If 'extrinsic mortality' were really extrinsic, how could it have an age-pattern? The conclusion of the combined Chapters 2, 6 and 8 is that it is fruitless and confusing to refer to anything like 'extrinsic' or 'intrinsic mortality'. Rather, it is necessary to find or postulate all causes of mortality that are relevant, some extrinsic, some intrinsic, and to investigate their interaction. There is no role for 'extrinsic mortality' in the (evolutionary) theory of aging (Chapter 6), nor in the epidemiological literature (Chapter 8). I strongly recommend the term be banned.

Evolution and medicine have a lot to offer to each other. The causal pie model [34,35,Chapter 2] is one example of fruitful cross-fertilization. Another example, explored in the discussion of this thesis, is the limitations to repair. For instance the process of arteriosclerosis is instructive in showing how difficult it is to fully repair damage while maintaining function, and how existing mechanisms could have been used for new (repair) purposes, thus informing the evolutionary analysis (Chapter 10). Reversely, evolutionary analysis could provide medicine with ways of viewing (the functioning of) an organism, and consequently suggest intervention options. To understand human (patho-)physiology, we very much need a wholesale complexity interpretation of physiology and homeostasis*, including their evolutionary aspects. May this thesis be a small contribution towards such an account.

References

1. Stearns, S.C. (1992) The evolution of life histories. Oxford University Press, Oxford.

2. Charnov, E.L. (1993) Life history invariants. Oxford University Press, Oxford.

3. Roff, D.A. (2002) Life history evolution. Sinuaer Ass. Sunderland, MA.

4. Baudisch, A. (2011) The pace and shape of ageing. Methods in Ecology and Evolution 2:375-382.

5. Jones, O. R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C.G., Schaible, R., et al. (2014) Diversity of ageing across the tree of life. Nature 505:169-173.

6. Martínez, D.E. (1998) Mortality patterns suggest lack of senescence in hydra. Experimental Gerontology 33:217-225.

7. Wrycza, T.F. and A. Baudisch (2012) How life expectancy varies with perturbations in age-specific mortality. Demographic Research 27: 365-376.

8. Baudisch, A., Salguero-Gómez, R., Jones, O.R., Wrycza, T.F., Mbeau-Ache, C., Franco, M. and F. Colchero (2013) The pace and shape of senescence in angiosperms. Journal of ecology 101:596-606.

9. Wrycza, T.F. and A. Baudisch (2014) The pace of aging: intrinsic time scales in demography. Demographic Research 30: 1571-1590.

10. Wrycza, T.F., Baudisch, A. and T.I. Missov. Quantifying the shape of aging. Submitted manuscript.

11. Darwin, C. (1964) On the origin of species. A facsimile of the First Edition. Harvard University Press, Cambridge.

12. Gems, D. and L. Partridge (2013) Genetics of longevity in model organisms: debates and paradigm shifts. Annual Review of Physiology 75:25.1-25.24.

13. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London.

14. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology 12:12-45.

15. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge.

16. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

17. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of ageing and longevity. Proceedings of the Royal Society London B 205:531-546.

18. Sozou, P.D. and R.M. Seymour (2004) To age or not to age. Proceedings of the Royal Society B 271:457-463.

19. Baudisch, A. 2008. Optimization models. Pages 49-139 *in* Inevitable aging? Contributions to evolutionary-demographic theory. Demographic Research Monographs. Springer-Verlag Berlin, Heidelberg, Germany.

20. Baudisch, A. and J.W. Vaupel (2010) Senescence vs. sustenance: Evolutionary-demographic models of aging. Demographic Research 23:655-668.

21. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

22. Rose, M.R. (1991) Evolutionary Biology of Aging. Oxford University Press, New York.

23. Caswell, H. (1978) A general formula for the sensitivity of population growth rate to changes in life history parameters. Theoretical Population Biology 14:215-230.

24. Caswell, H. (2010) Reproductive value, the stable stage distribution, and the sensitivity of the population growth rate to changes in vital rates, Demographic Research 23:531-548.

25. Preston, S., Heuveline, P. and M. Guillot (2001) Demography. Blackwell, Oxford, UK.

26. Arthur, W.B. (1984) The analysis of linkages in demographic theory. Demography 21:109-128.

27. Kirkwood, T.B.L. and M.R. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London, B 332:15-24.

28. Baudisch, A. (2012) Birds do it, bees do it, we do it: contributions of theoretical modelling to understanding the shape of ageing across the tree of life. Gerontology 58:481-489.

29. Kirkwood, T.B.L. and S.N. Austad (2000) Why do we age? Nature 408:233-238.

30. Williams, P.D., Day, T., Fletcher, Q. and L. Rowe (2006) The shaping of senescence in the wild. Trends in Ecology and Evolution 21:458-463.

31. Monaghan, P., Charmantier, A., Nussey, D.H. and R.E. Ricklefs (2008) The evolutionary ecology of senescence. Functional Ecology 22:371-378.

32. Regan, J.C. and L. Partridge (2013) Gender and longevity: Why do men die earlier than women? Comparative and experimental evidence.
Best Practice & Research Clinical Endocrinology & Metabolism 27:467-479.

33. Carnes, B.A., Holden, L.R., Olshansky, S.J., Witten, T.M. and J.S. Siegel (2006) Mortality partitions and their relevance to research on senescence. Biogerontology 7:183-198.

34. Rothman, K.J. (1976) Causes. American Journal of Epidemiology 104:587-592.

35. Rothman, K.J. (2012) Epidemiology. An introduction, 2nd edn. Oxford University Press, New York.

Part II

Conceptual Papers

Chapter 2

The causal pie model: an epidemiological method applied to evolutionary biology and ecology

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Abstract

A general concept for thinking about causality facilitates swift comprehension of results, and the vocabulary that belongs to the concept is instrumental in cross-disciplinary communication. The causal pie model has fulfilled this role in epidemiology, and could be of similar value in evolutionary biology and ecology. In the causal pie model, outcomes result from sufficient causes. Each sufficient cause is made up of a 'causal pie' of 'component causes'. Several different causal pies may exist for the same outcome. If and only if all component causes for a sufficient cause are present, i.e. a causal pie is complete, does the outcome occur. The effect of a component cause hence depends on the presence of the other component causes that constitute some causal pie. Because all component causes are equally and fully causative for the outcome, the sum of causes for some outcome exceeds 100%. The causal pie model provides a way of thinking that maps into a number of recurrent themes in evolutionary biology and ecology: It charts when component causes have an effect and are subject to natural selection, and how component causes affect selection on other component causes; which partitions of outcomes with respect to causes are feasible and useful; and how to view the composition of a(n apparently homogeneous) population. The diversity of specific results that is directly understood from the causal pie model is a test for both the validity and the applicability of the model. The causal pie model provides a common language in which results across disciplines can be communicated, and serves as a template along which future causal analyses can be made.

Introduction

Life is all about cause and effect. A general concept for thinking about causality facilitates swift comprehension of results, while the vocabulary that belongs to the concept is instrumental in cross-disciplinary communication. Although in and of itself it does not lead to different results than those obtained with more specific models, a general model provides a quick grasp of the commonalities of seemingly diverse situations. Rothman's 'causal pie model' [1,2] has fulfilled this role in epidemiology, and we propose that it could be of similar value in biology, in particular in evolutionary biology and ecology. We introduce the model, discuss some generalities that derive from it, and show a wide-ranging sample of applications, from semi-neutral mutations to agents of selection.

The model

To paraphrase Rothman [2], the lights at home shine because they each have a light bulb, there is wire to the light bulbs, the switches are on, there is a power grid, and there is a power source. Take any of these factors away, and there is no light: The system contains 500% causality, for all five factors are 100% causative for the shining of the light. There is no limit to the sum of causes for some outcome [2].

The causal pie model, depicted in Figure 2.1 after Rothman's original [1], represents this way of conceptualizing causality. A sufficient cause is a constellation of component causes, the causal pie, that leads to an outcome. A component cause can be a component of more than one sufficient cause. If and only if all the component causes that make up a causal pie of some sufficient cause are present does the outcome occur. As a result, the effect of a component cause depends on the presence versus absence of the other component causes that make up some causal pie. These are called complementary component causes, which jointly make up the complementary set of a component cause. In absence of any one of the complementary component causes, a component cause in itself has no effect. Referring to the example above, if there is no connection to the power grid, varying the position of the switch does not alter the light being on or off.

This model is deterministic in the sufficient causes: If all component causes of some causal pie are present, then the sufficient cause is present and the outcome occurs. This does not prohibit the model from having statistical properties: If one (or more) of the component causes is described statistically, the (joint) distribution function of the (mixed) statistical model describes the outcome as a random variable.

The level of detail required for an analysis determines the biological outcome of interest, the number of sufficient causes that can exist for the same biological outcome, and what component causes make up the sufficient causes. For instance, a stroke that is caused by high blood pressure may be classified as an outcome different from a stroke that is not caused by high blood pressure. The latter clearly does not include sufficient causes that contain high blood pressure as a component cause, while the outcome 'any stroke' would.

As discussed above, causality adds up to more than 100%. Variation in the occurrence of an outcome due to variation in a specified component cause does add up to 100%. To illustrate this, consider another example [2]: The disease phenylketonuria (PKU) is characterized by abnormal metabolism of an amino acid, leading to severe symptoms such as mental retardation. PKU occurs only in people with a mutated gene. The various human diets on planet Earth include the amino acid, so that 100% of the occurrence versus non-occurrence of PKU on planet Earth is explained genetically. However, consider a hypothetical 'other planet', the inhabitants of which all have the genetic mutation, but do not all have a diet that contains the amino acid. On the other planet, 100% of the observed variation in the occurrence of PKU is explained by variation in the diet.

Variation explained is a matter of prevalence of component causes given some context. Although the percentage of variation explained might be of interest, of even greater interest are statements that are generally true, not just on planet Earth or on the other planet. Such a statement is that 100% of the incident cases of PKU is caused by a mutant gene, and 100% is caused by diet. On planet Earth, variation in the prevalence of PKU is explained by genes. Yet it is another component cause, diet, that is targeted as a treatment. This illustrates why general insights into causality are the more interesting kind of insights.

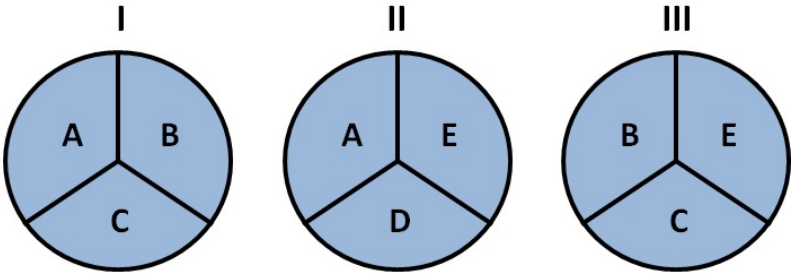

Figure 2.1: The causal pie model. *Component causes* A-E add up to *sufficient causes* I-III. Every sufficient cause consists of different component causes. If and only if all the component causes that constitute the *causal pie* of a sufficient cause are present, does the sufficient cause exist and does the *outcome* occur. Hence, the effect of a component cause depends on the presence of its *complementary component causes*, that is, its *complementary set*. I, II, and III can be sufficient causes for the same outcome, or for different outcomes, in which case the outcomes are correlated through the component causes. Examples are given throughout the text.

Application of the model to (evolutionary) biology and ecology

The causal pie model has a number of implications for (evolutionary) biology and ecology: it charts under what circumstances component causes have an effect and therefore can be subject to natural selection, and how component causes modulate the effect of and natural selection on other component causes; it shows which partitions of outcomes are useful, and which are not; and it provides a way of viewing the composition of a(n apparently homogeneous) population. Each of these points is developed below, and examples are given and framed in terms of the causal pie model.

Component causes, their effects, and the force of selection

The causal pie model explains when and why biological factors (component causes) have an effect. When component causes produce an effect, they could affect Darwinian fitness and hence become subject to natural selection. Component causes also influence whether other component causes have an effect and become subject to natural selection. We outline some generalities regarding this thinking, and give examples, which are framed in terms of the causal pie model.

The presence of all component causes of a causal pie constitutes a sufficient cause, which implies that the outcome occurs. Each of the component causes is then subject to the full force of natural selection on the outcome, for without any one of them, the outcome would not occur (Figure 2.2). The force of selection on the outcome is not partitioned over the component causes. Just like the sum of causes exceeds 100%, the force of selection on causes exceeds the force of selection on outcomes. Some component causes will not be determined intrinsically, such as the environment. These component causes will not be subject to natural selection. Still, it will usually be possible to define an intrinsic component cause that is subject to natural selection, such as avoidance of some environmental factor(s).

In the absence of any one of its complementary component causes, the emergence of a component cause has no effect and therefore is not subject to natural selection (barring effects through other sufficient causes). However, component causes are part of the complementary sets of all the other component causes in a causal pie. A component cause that does not give rise to an outcome immediately, does change the set of component causes against which yet other component causes arise (e.g. new mutations). It thus affects the chance that another component cause will arise in the context of its complementary set and hence make the outcome occur. In the long term, this gets picked up by evolution. Below we give a wide ranging sample of applications of these principles.

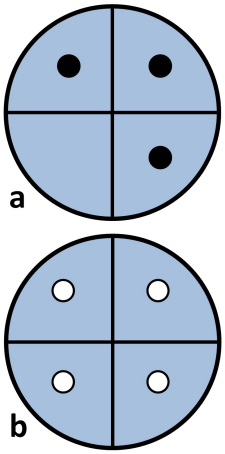

Figure 2.2: Natural selection in the causal pie model. Selection depends on the effect of presence versus absence of the component cause. (a) If one of the component causes is absent, the other component causes have no effect (barring effects through other causal pies) and are not subject to natural selection, as indicated by the dots being black. (b) If all the component causes are present, the outcome occurs, and all the component causes are subject to the force of selection on the outcome, because without any one of them, the outcome would not occur. If the component causes are A-D and the force of selection on the outcome is S_Ω, then the force of selection on every component cause, S_X, equals S_Ω: $S_A = S_B = S_C = S_D = S_\Omega$.

Example 1: Agents of selection

Wade and Kalisz [3] recognize that "the fitness of an individual is the result of the interaction of the phenotype with the environment and not an intrinsic feature of either one", the phenotype being caused by some gene of interest [3,p.1949]. In this context they discuss that the selection of a gene that gives a fitness (dis)advantage in a particular environment depends on whether that environment is indeed present. They call the environment the 'causal agent of selection' of the gene, since the environment causes the gene to be selected.

Wade and Kalisz's realization is a special case of the general principle that selection on a component cause depends on the presence or absence of its complementary set. The effect of the component cause 'gene' depends on its complementary component cause 'environment'. The complementary set can certainly be environmental, but can be essentially anything that completes a causal pie. If the interaction of many different genes is necessary to bring about some effect, as in the next example, genes act as each other's complementary component causes.

Example 2: Semi-neutral mutations

Genetic mutations can be semi-neutral: While they do not have an immediate phenotypic effect, they pave the way for non-neutral change over evolutionary time [4]. This happens when a number of mutations has to be acquired before causing phenotypic change. The order of occurrence and the way in which the mutations are generated may be completely random. Only the last mutation seems non-neutral and causes a change in the phenotype, but it is facilitated by the earlier, semi-neutral, mutations. The earlier changes are semi-neutral, because they seem neutral at first sight, but eventually get picked up by evolution.

In terms of the causal pie model, new mutations arise in the context of the existing mutations, which determine whether the complementary set is present. The first few mutations are insufficient to have a phenotypic effect, but they do change the context against which new mutations arise. At one point, the new mutation arises in the presence of the other mutations necessary for phenotypic change, i.e. its complementary set of a sufficient cause for phenotypic change. All of the mutations are equally causal to the outcome. Yet, all mutations before the one that leads to phenotypic change seem neutral, because their complementary set for phenotypic change is lacking.

Example 3: selection for versus selection of

Selection *of* refers to an empirical observation of what is selected, while selection *for* means that there is selection due to a causal effect of some trait on vital rates [5, discussed in 6]. These sorts of selection differ if traits are correlated, which is a well-established area of research [7-10]. As an example, consider a population of mice in which small mice have a selective advantage, for instance because they are not seen by predators. Suppose also that the same gene that controls body size causes large mice to have blue eyes, while it causes small mice to have green eyes. Finally, suppose that having blue eyes versus green eyes by itself does not affect mortality and fecundity. In this example there is selection for small body size, because this has a direct effect on the risk of predation. There is selection of not only small body size, but also of green eye color. Although the latter has no effect on fitness, selection results from the correlation of eye color with body size.

In the causal pie model, traits are correlated when they share one or more component cause(s). In Figure 2.1, A is a component cause for both sufficient cause I and II, leading to correlation. If one sufficient cause is subject to natural selection, the force of selection extends to all component causes. Some of these component causes can be component causes also of sufficient causes for neutral traits, leading to selection of. For instance, in Figure 2.1, selection on sufficient causes I and II leads to selection on component causes A-E. Sufficient cause III is not selected for (it is in itself a neutral trait). Still, there is selection of sufficient cause III, because there exists selection on all its component causes (B,C,E).

Example 4: Trade-offs

Correlated traits of particular interest are trade-offs [11,12]. For instance, an organism could have to balance the risk of starvation against the risk of being eaten by a predator while foraging. The preferred choice under this trade-off obviously depends on the presence of food versus the presence of predators. To give an example at a molecular level, consider the case in which a higher metabolic rate leads to higher short-term survival, for instance by higher vigilance, but also leads to increased damage accumulation due to oxygen radicals. This trade-off depends on the presence of scavengers for oxygen radicals, and on the vulnerability of the macromolecules to oxygen radicals.

A component cause has an effect only in the presence of its complementary set. This is true also for component causes that give rise to trade-offs. Therefore trade-offs depend on the presence or absence of complementary sets. In the first example above, predators and food (complementary component causes) may be distributed probabilistically over the habitat or over time. As the causal pie model is also probabilistic, it fits the examples above well. The probability distribution of either outcome depends on the probability distributions of the complementary component causes, which determine the preferred behavior.

Trade-offs depend on the presence of complementary component causes. There is selection toward optimal outcomes given the complementary component causes that are present: evolution will have the tendency to optimize within the limitations of the trade-off. For instance, in the molecular example in the first paragraph of this section, the trade-offs depend on the presence of scavengers for oxygen radicals, and on the vulnerability of the macromolecules to oxygen radicals. Given the vulnerability of macromolecules to oxygen radicals, and given a certain concentration of scavengers, evolution will optimize metabolism. At the same time, there is selection on the complementary component causes: evolution will have the tendency to push the boundaries of the trade-off, such that the trade-off becomes less restrictive. To stay with the example of oxidative damage, evolution will tend towards using less vulnerable macromolecules (if possible), and towards increasing scavenging capacity, thus changing the trade-off that it faces.

Example 5: The problem with age-specific genes

The evolutionary theory of aging is sometimes defined in terms of 'age-specific genes', genes that are active at a particular age or during a particular age-range and not before or after. The idea is that natural selection acts less forcefully against detrimental genes the later they are expressed [13-16]. However, age as such causes nothing, and cannot activate or deactivate genes [17-19]. At first sight, a way around this objection is to define a "substance S" (for senescence, deterioration with age), that is not in itself "deleterious in any normal sense" [20], in line with Williams's genes that "act differently in a different somatic environment" [14]. Some independent somatic change would trigger the expression of deleterious genes at high ages, thus making them 'age-specific'.

The causal pie model shows that it is not logically correct to say that substance S is not deleterious 'in any normal sense'. The causal pie is made up of two component causes - a certain concentration of substance S, and a substance S-sensitive gene - which together form a sufficient cause for deterioration and death. Completing the causal pie, substance S is as causal to the detrimental effect as is the substance S-sensitive gene. Without substance S, there would be no senescence, just like without the substance S-sensitive gene there would be no senescence. As a result, the force of natural selection on deterioration that results from the expression of the deleterious gene extends to both the gene and substance S [17]. Theories about age-specific genes are in fact theories about state-specific genes and some state-variable, in this case the concentration of substance S. Both are part of the evolutionary analysis.

Partitioning of outcomes

Generally speaking, partitions are useful only when they are based on qualities that are mutually exclusive. If this is not the case, something could belong to more than one partition. Because the whole point of partitioning is to divide things up, making partitions based on qualities that are not mutually exclusive should not be attempted, because it will fail.

In the causal pie model, multiple component causes need to interact for an outcome to occur. It is not useful to partition outcomes as caused by one versus the other component cause, since an outcome could be caused by both component causes at the same time. It can be useful, however, to make a partition between outcomes in which a particular component cause plays a role, versus outcomes in which it does not.

Example: Extrinsic mortality

Although they acknowledge a role for vulnerability of an organism to extrinsic threats, [21] set out to partition mortality "based on whether the primary cause of death does or does not originate from within the organism". Extrinsic mortality has been invoked at many points in evolution [13,14,19, but see 22].

Mortality, however, is a prime example in biology of interacting component causes, some extrinsic, some intrinsic to the organism. Therefore it is not possible to characterize mortality either extrinsic or intrinsic. A typical example is predation, where the presence of a predator (component cause 1) interacts with a state of vulnerability of the prey (component cause 2) and an environment that co-determines if prey and predator effectively meet, for instance a quality of vegetation (component cause 3). These three component causes could be partitioned in more detailed component causes if required, such as the cardiopulmonary capacity or fur color of predator and prey.

Component causes of mortality can be partitioned in extrinsic and intrinsic, but mortality itself cannot, for the simple reason that extrinsic and intrinsic mortality are not mutually exclusive. Acknowledging a role for vulnerability in 'extrinsic mortality' does not take away this objection. None of the component causes is more causative to the outcome, since without any one of them, the outcome would not occur. One could propose that there can be no predation without a predator, and that therefore the (extrinsic) presence of a predator must be the most causative cause for death by predation. However, neither is there predation without a prey. Being prey is something 'intrinsic'. There is no such thing as 'most causative cause'. A partitioning that could have some utility, is a partition of mortality in which an extrinsic component cause plays a role, versus mortality in which it does not. The term 'extrinsic mortality' retains some meaning in this respect, although one could wonder whether purely intrinsic mortality exists at all.

Population heterogeneity

Populations are heterogeneous, and an observation at the population level may be quite different from individual level processes [23]. A population may seem homogeneous, but below the surface, organism may differ greatly. Any change that may happen may have differential effects on each organism.

A way to look at heterogeneity in a population is to view all members of the population as different collections of causal pies that are sufficient causes for some outcome, for instance death. Some of those members will have many causal pies that are almost 'filled in', i.e. most component causes that make up the causal pie are present. Others will have mostly 'empty' causal pies. Yet others will have roughly equally filled causal pies, but the causal pies will be made up of different component causes. These individuals will be vulnerable to some types of stress, but robust to others, differing from individual to individual. How newly imposed stress affects each member of the population depends on the component causes that are yet present.

Example: Frailty along the life course

A physiological view of human aging proposed by Izaks and Westendorp [24] is that there exist multiple causal pies that form sufficient causes for deterioration and death which are slowly and steadily being filled in over the lifetime of an individual. Even apparently healthy older individuals are more vulnerable, because they have accumulated damages that in and of themselves do not cause disease or mortality, but that are part of causal pies that steadily have more component causes present. With more component causes already present, even if organisms appear healthy, it is easier to acquire the remaining component causes, leading to disability and death (Figure 2.3).

This view is by no means limited to humans, but applies to all living organisms. Vital rates may be improving during part of the life cycle, but causal pies of disability and death are being filled in concurrently, making the distance to disability and death shorter. While physiological markers of aging are already deteriorating, i.e. physiological aging, they may not yet lead to deterioration of mortality and fecundity, i.e. demographic aging. Yet, any addition stress will have a much larger chance of completing a causal pie in older individuals, leading to quick deterioration of vital rates later in life. This explains why demographic aging can trail physiological markers (component causes) with a delay, and why apparently healthy organisms may differ greatly in their vulnerability to stress. Together with trade-offs, causal pie models of aging may also contribute to explain the recently revealed diversity of aging patterns across the tree of life [25].

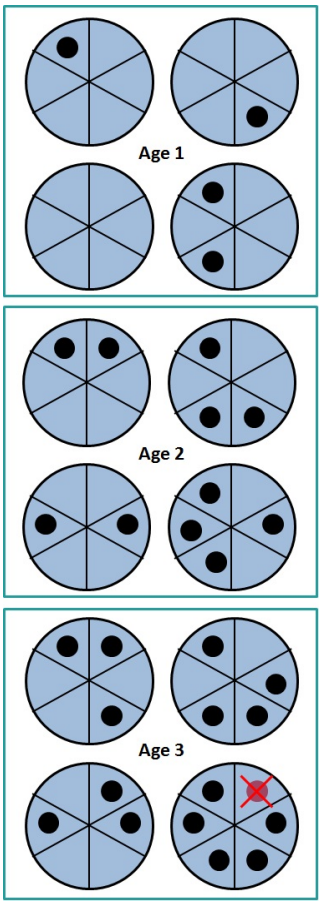

Figure 2.3: Frailty along the life course. An organism has a number of sufficient causes for mortality, that is, causal pies. A black dot in a part of a pie means that the component cause is present. Along the life course, more and more component causes become present, but the organism seems healthy when mortality and fecundity are considered. Yet, fewer and fewer additional damages are necessary to lead to death: The organism gets frailer. When the last component cause of some causal pie emerges, indicated by the cross at age 3, the deterioration becomes clearly manifest and the organism dies

Discussion

All the results discussed in this paper derive from one and the same principle: the causal pie model. Still, any and all of these results can be derived without reference to the causal pie model. For instance, no evolutionary biologist would be surprised to learn that if genetic variation in some respect is initially subject only to random drift, it can suddenly become subject to natural selection if the environment changes such that the genetic variation becomes relevant to Darwinian fitness. This is standard evolutionary theory; no causal pie model is needed to explain it. Then what is the utility of the causal pie model, in particular when compared to other models of causation?

In reality, science is subject to significant uncertainty. In a given natural system, not all causal pies may be known or identifiable, or the presence versus absence of (some of) the component causes may be ascertained only at a statistical level. More involved

models, such as structural equation modeling [26], are then necessary to discover the underlying causal relationships. Causation is then expressed in probabilistic terms, such that A causes B if the probability of B in the presence of A is greater than in the absence of A, i.e. $P(B|A)>P(B|\bar{A})$. As pointed out in section "The model", even though it is not itself a statistical model, the causal pie model is fully compatible with this probabilistic representation of causal relationships. The probability of the presence of all component causes of a pie chart is the product of the probabilities of the presence of each individual component cause, such that if A-D are all the component causes of causal pie I, it holds that $P(I)=P(A)P(B)P(C)P(D)$. If there are more than one sufficient causes I-III (causal pies) for outcome Ω, it holds that $P(\Omega)=P(I)+P(II)+P(III)$.

To reveal underlying causal relations in a data set, the causal pie model offers no alternative to the appropriate tools of data analysis, such as structural equation modeling ([27,28] are helpful references for such modeling in biology) or quantitative methods of natural selection [7]. However, we do not propose the causal pie model to take the place of these methods. Rather, it should be seen as a helpful tool of conceptualizing causation whenever this simplest model suffices. The causal pie model is a very simple model, perhaps the simplest, that captures the basic workings of causation. The model is instrumental in understanding a range of results, such as those discussed in this paper, and in avoiding common mistakes, such as partitions between non-mutually exclusive component causes and summing causes to 100%. In the meantime, it contains little jargon and no mathematics, so that the model is easily and intuitively accessible.

Although we use different words in various disciplines, we describe the same phenomena. The causal pie model can help to make bridges, so that various disciplines can draw on and be inspired by each other's finding. The range of examples that we give is a good demonstration of the utility of the causal pie model in this respect. We propose that the causal pie model provides an effective framework for thinking about causation, that it helps to avoid mistakes, and that it provides a simple common language in which results can be communicated across disciplines.

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References

1. Rothman, K.J. (1976) Causes. American Journal of Epidemiology 104:587-592.

2. Rothman, K.J. (2012) Epidemiology. An introduction, 2nd edn. Oxford University Press, New York.

3. Wade, M.J. and S. Kalisz (1990) The causes of natural selection. Evolution 44:1947-1955.

4. Wagner, A. (2011) The molecular origins of evolutionary innovations. Trends in genetics 27:397-410.

5. Sober, E. (1984) The nature of selection: a philosophical inquiry. Bradford/M.I.T. Press, Cambridge, Massachusetts.

6. Endler, J.E. (1986) Natural selection in the wild. Princeton University Press, Princeton.

7. Lande, R. (1982) A quantitative genetic theory of life history evolution. Ecology, 63:607-615.

8. Lande, R. and S.J. Arnold (1983) The measurement of selection on correlated characters. Evolution 37:1210-1226.

9. Arnold, S.J. and M.J. Wade (1984) On the measurement of natural and sexual selection: theory. Evolution, 38:709-719.

10. Mitchell-Olds, T. and R.G. Shaw (1987) Regression analysis of natural selection: statistical inference and biological interpretation. Evolution 41:1149-1161.

11. Stearns, S.C. (1989) Trade-offs in life history evolution. Functional Ecology 3:259-268.

12. Stearns, S.C. (1992) The evolution of life histories. Oxford University Press, Oxford.

13. Medawar, P.B. (1952) Uniqueness of the individual. Lewis, London.

14. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

15. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology, 12:12-43.

16. Charlesworth, B. (1994) Evolution in age-structured populations, 2nd edn. First edn 1980. Cambridge University Press, Cambridge.

17. Wensink, M.J. (2013) Age-specificity and the evolution of senescence: A discussion. Biogerontology 14: 99-105.

18. Kirkwood, T.B.L., and D.P. Shanley (2010) The connections between general and reproductive senescence and the evolutionary basis of menopause. Annals of the New York Academy of Science 1204:21-29.

19. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature, 270:301-304.

20. Dawkins, R. (2006) The selfish gene, 30th ed. First edn 1976. Oxford University Press, Oxford.

21. Carnes, B.A., Holden, L.R., Olshansky, S.J., Witten, T.M. and J.S. Siegel (2006) Mortality partitions and their relevance to research on senescence. Biogerontology 7:183-198.

22. Caswell, H. (2007) Extrinsic mortality and the evolution of senescence. Trends in Ecology and Evolution, 22:173-174.

23. Vaupel, J.W., Yashin, A.I. (1985) Heterogeneity's ruses: Some surprising effects of selection on population dynamics. The American Statistician 39:176-185.

24. Izaks, G.J. and R.G.J. Westendorp (2003) Ill or just old? Towards a conceptual framework of the relation between ageing and disease. BMC Geriatrics, 3:7-12.

25. Jones, O.R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C.G., Schaible, R. et al. (2014) Diversity of ageing across the tree of life. Nature 505:169-173.

26. Pearl, J. (2009) Causality, 2nd edn. Cambridge University Press, New York.

27. Shipley, B. (2000) Cause and Correlation in Biology, 1st paperback edn. Cambridge University Press, Cambridge.

28. Grace, J.B. (2006) Structural Equation Modeling and Natural Systems, 1st edn. Cambridge University Press, New York.

Chapter 3

Age-specificity and the evolution of senescence: a discussion

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Abstract

Senescence evolved because selection pressure declines with age. However, to explain senescence it does not suffice to demonstrate that selection pressure declines. It is also necessary to postulate biological mechanisms that lead to a deteriorated state of the organism at high ages, but not before. This has lead to the invocation of 'age-specific' genes or processes, a concept which is prone to be interpreted too freely. Events do not happen after a certain amount of time has passed. They need initiation, which means that senescence is required to be a continuous process. As a result, a change at a particular age cannot arise in isolation from changes at other ages, in particular not in isolation from changes at the ages nearby. These mechanistic constraints are not without consequence for the patterns of mortality and fecundity that can evolve. I conclude that from purely logical considerations, senescence is characterized as continuous rather than age-specific deterioration. These considerations guide (theoretical) research in the direction of investigating how continuous somatic change arises, rather than focusing on age-specific events.

Introduction: evolution of senescence and the meaning of age-specificity

The higher the age of an organism, the greater the organism's contribution to fitness that cannot be affected by any event happening at that age, because that contribution lies in the past. As a result, the state of an organism at high age is under less stringent selection than the state of the organism at low age, which promotes the evolution of 'senescence', the deterioration of the state of an organism over ages, which negatively affects 'vital rates' mortality and fecundity [1-3].

To explain aging, it does not suffice to conclude that selection pressure declines over ages. It is also necessary to define the processes that are hypothesized to lead to a deteriorated state at high ages, but not before. This has lead to the invocation of 'age-specific genes', thus giving a genetic basis to the deteriorated state [1-3]. However, this still allows for different interpretations. If 'age-specific' is to mean 'a gene that is expressed at some age but not before (or after)', there is a logical problem if such genes are taken as the source of senescence. As Kirkwood observed: "the time of action of a gene during adulthood is determined not by chronological time but by its biochemical environment", so that the "time-keeping process" or 'somatic change', a change in the biochemical environment that triggers a change in gene action, should be explained before age-specific alterations in gene action can be considered [4]. At this point it is necessary to specify what is meant by 'gene action'. If the expression of a gene would for example lead to the accumulation of damage (see below), the rate of accumulation of damage is the gene action. The result of this action is that over time there is an increase (change) in the amount of damage that has been accumulated, while the gene action has remained unchanged. A change in the gene action itself would mean that the expression of the gene leads to a different rate of accumulation, which can only occur if some somatic change occurs first. Thus, there can be change of the state of the organism without a change in gene action, but there can be no change in gene action without a somatic change that initiates this change in gene action [5]. Any change in gene action is state-specific rather than age-specific. This is a logical issue, unrelated to empirical evidence: events need initiation. They do not just happen because a sufficient amount of time has passed. Consequently, the process that causes senescence is necessarily continuous.

From the logical necessity that senescence is a continuous process there arises a natural alternative to the definition of age-specificity above. An 'age-specific process' could be defined as a process that leads to a certain state of an organism at a specific age, while actually taking place at all preceding (and subsequent) ages. The logical problem outlined above is then avoided, although it does not seem entirely correct to call such processes age-specific. From now on I refer to such processes as 'continuous'. The question then arises whether it is possible that a continuous process has a certain effect on vital rates at some isolated age, but no effect before or after that age.

To sum up, there exist two interpretations of age-specificity: One at high risk of circularity, because in order to have age-specificity at all, it requires the existence of the very change it set out to explain, and one that avoids this risk, but for which 'age-specificity' may not be the correct word. While some think about senescence in terms of the latter interpretation, others have tried to formulate theories of genes, causative for senescence, that do switch expression with age, or whose expression does lead to a different outcome at different ages, while avoiding the logical problem that Kirkwood pointed out. In this paper I show that these 'reparations' failed, and that if we wish to include genes that change their action or expression at some age(s) in an evolutionary theory of senescence, such state-specific genes play a role that is qualitatively different from the role that they are currently believed to play. Furthermore I discuss the difficulties of the idea that a continuous process has a certain effect on vital rates at some isolated age, but no effect before (or after) that age. I conclude that senescence should be considered as continuous somatic change, with continuous change in vital rates.

Age-specific deleterious effects derived from state-specific genes

Proposals to retain a place for 'age-specific', more correctly 'state-specific', genes in the evolutionary theory of senescence, appeal to (hypothetical) processes that have two characteristics. First, such processes are assumed to evolve independently of the presence of state-specific genes, so that potentially deleterious genes could measure the age of the organism from those processes. Second, such processes are postulated to have no direct effect on vital rates, so that the deleterious effect is mediated through state-specific genes, with the result that the deleterious effect takes place at some specific age. This idea is perhaps best articulated by Dawkins [6]. He discussed a "substance S" (S for senescence) which is innocuous in itself, but which accumulates in cells, and which triggers a change of gene action when its concentration reaches a certain threshold. Thus, substance S is seen as an independent time-keeper. A similar argument from the perspective of telomere length is sometimes raised in informal discussions. A telomere is a protective DNA-sequence at the end of the chromosome, the length of which is a decreasing function of age in humans [7]. The idea is that genes could sense the length of telomeres, and so could have age-specific effects. As discussed below, the presumed independence from state-specific genes of the somatic change cannot possibly be upheld, while the presumed innocuousness is doubtful at best.

There is no independent time-keeping mechanism

Even if substance S has no direct effect on vital rates, the triggering of deleterious age-specific genes is a far from innocuous activity. Accordingly, substance S is subject to natural selection, which means that the pace of accumulation of substance S can be manipulated by natural selection to postpone or forestall the action of potentially deleterious

state-specific genes (Figure 3.1). Deterioration of vital rates is caused by both substance S and the state-specific genes: Only if both factors are present does deterioration occur. The greater the number, severity, or sensitivity to somatic change of potentially deleterious state-specific genes ('state-specific load'), the greater the deterioration that results if the somatic change triggers those state-specific genes, and the stronger natural selection will act against this somatic change. Hence, the idea of a "substance S" as a somatic change that functions as a sort of clock, independently of the presence of state-specific genes, cannot be entertained. The same goes for telomere length: Whether contributing directly to the process of senescence or not (see below), an increase in state-specific load will increase selection on the activity of telomerase (an enzyme that reverses telomere shortening [7]). This viewpoint is quite different from the idea that state-specific genes can be superimposed on some existing change, which itself evolves independently.

That somatic change does not evolve independently is demonstrated by the following. Consider again that because substance S triggers genes to exert a detrimental effect, natural selection acts on the rate at which substance S is produced and on the rate at which it is cleared. In fact, the force of selection on substance S equals the force of selection on all individual state-specific genes that are triggered by substance S added up. Clearance of substance S could come at a cost, such as in cases in which the resources (energy, metabolites) that are used to clear substance S could otherwise have been used for reproduction. Alternatively, metabolism that involves a lower rate of production of substance S could require more resources.

Now consider what happens if only one state-specific gene is present, which gives a slight increase in mortality when activated at some threshold concentration of substance S. If there is some cost of clearing substance S, this could easily outweigh the cost of the slight increase in mortality at some age. Now increase the state-specific load. First, the rate of senescence will increase due to the higher state-specific load. However, at some point the mortality costs could outweigh the benefits of an alternative investment of resources. Instead of removing those state-specific genes with too detrimental an effect, natural selection may lead to clearance of substance S. As a result, the detrimental effect of all state-specific genes sensitive to substance S is forestalled, and the rate of senescence decreased. Of course, other somatic changes may still make the organism deteriorate. Also, if selection pressure on the potential action of state-specific genes is low enough, benefits of preventing this action may never outweigh cost. Nevertheless, the possibility that an increase in the state-specific load leads to a lower rate of senescence is notable. Although state-specific genes certainly act as a reinforcing factor given a certain pace of the somatic change, following the reasoning above a higher state-specific load does not necessarily lead to a(n) (proportional) increase in the rate of senescence. This effect emerges through the evolution of a slower somatic change in response to an increase in state-specific load.

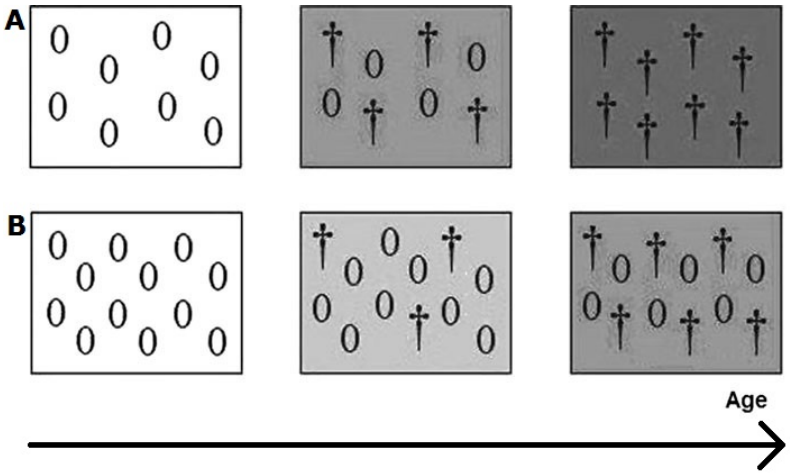

Figure 3.1: The interaction of somatic change and state-specific genes. Organisms are depicted as boxes, at different instants in time (arrow). State-specific genes (depicted as 0's) can have detrimental action (when they become daggers), depending on the somatic change (gray tint of the background). The somatic change is assumed to have no noxious effect other than activating detrimental state-specific gene action. The rate of senescence is then the rate at which gene action becomes detrimental. The relevance of the somatic change to the theory becomes abundantly clear when comparing organism a with organism b. Organism b has a higher state-specific load (higher number of 0's), but because of a slower somatic change, it has a lower rate of senescence

Are there innocuous time-keeping mechanisms?

Above it was demonstrated that the 'time-keeping' mechanism, or somatic change, does not evolve independently of the state-specific load. In addition, we might ask whether the second putative attribute of somatic change, the lack of a direct effect on the organism's vitality, is realistic. In the case of substance S, I suggest that it is unclear how an accumulating substance would not interfere with (cellular) signaling or the structural integrity of the organism. An effect may be expected even if some substance is chemically inactive, if only through the occupation of space, or through the addition of non-functional weight. If the somatic change is damage, as in the disposable soma theory, it is difficult to conceptualize how the damage would be free of any effect on vital rates. Indeed, central to the disposable soma theory is the idea that it is (the accumulation of) damage that leads to deterioration [4,8,9]. Similarly, changes that telomeres undergo over ages, such as loss of methylation, have been demonstrated to have direct effects on the vitality of the organism, while the shortening of telomeres with cell division is not universal [10]. I am not aware of any demonstration of a substance or other change that has no direct effect on vital rates, but that informs genes about the age of the organism, since Kirkwood [4] objected along similar lines.

In conclusion there are two objections to the concept that senescence is a result of age-specific deleterious effects derived from state-specific genes. First, there is no independent time-keeping mechanism, which means that potentially deleterious state-specific genes cannot be thought of as independent from the somatic change on which their activation relies. Second, because it is doubtful whether some somatic change can be without any effect on vital rates, an underlying continuous somatic change is expected to lead to a gradual deterioration of vital rates, rather than to age-specific deterioration.

Age-specific deleterious effects derived directly from continuous change

All the difficulties discussed above are avoided if the deterioration that characterizes senescence is viewed as the direct result of some continuous change, without mediation of some state-specific gene. With a continuous process directly causing senescence, the potential logical problem to explain what initiates deterioration does not exist. The question now arises to what extent it is possible that the deleterious effect of a continuous process takes place at some age, but not before or after. This seems to be even less likely than if the deleterious effect is mediated through a state-specific gene, in which case the somatic change is not directly harmful. As the somatic change takes place, it will likely give rise to some deterioration. There are, however, two reasons to expect that the bulk of the deleterious effect may be manifest only late. First, somatic change may be expected to be cumulative, for instance in case of cumulative damage, so that it may be expected that the higher the age, the greater the effect. Second, the amount of accumulated damage may translate into vital rates in a non-linear fashion. This could be the result of mechanisms that buffer, adapt, or remodel, leading to only a negligible decline of functioning initially [see, e.g., 11]. It could also be that a decline in functioning is translated into change in vital rates in a non-linear fashion, for instance exponentially. Consequently the continuum of change has the highest effect at high ages, so that the somatic change leads to a deterioration of vital rates at high ages, but not so much before, as is required to explain senescence.

The concept of gradual somatic change rather than age-specificity is corroborated by the evidence on the mechanistic, the physiological and the demographic level. At the molecular level, there is for instance a gradual increase in molecular damage and heterogeneity [11,12], gradual malfunctioning of the cellular control systems [13], and decline of the integrity of mitochondrial constituents [14]. At the physiological level, senescence is characterized by gradual loss of function, for instance in the case of grip strength [15,16]. At the demographic level, there is a gradual decline in fertility and a gradual increase in mortality. This is found in humans [17] and in wild animals, where senescence occurs in many natural populations, and in a gradual fashion, i.e. senescence does not suddenly happen at some age [18-21].

Discussion

It is possible (but theoretically superfluous) to postulate state-specific genes on top of, but not instead of, continuous somatic change. As discussed above, the evolution of somatic change is then not independent of the state-specific genes, and some direct effect of somatic change on vital rates may be expected. If senescence is caused by an accumulation of damage that leads to a changing state of the organism, as in the disposable soma theory, this changing state could trigger potentially deleterious genes in turn. Kirkwood [4,8] and later Zwaan [22] discussed this possibility, and concluded that if state-specific genes are triggered by somatic change, the process of senescence is reinforced. Certainly, cumulative damage may trigger state-specific genes. However, just as when state-specific genes are super-imposed on a substance S, an increase in the state-specific load does not necessarily increase the rate of senescence. If the accumulation of some type of damage could be prevented at low cost, an increase in the state-specific load to this damage may lead to slower accumulation of damage, with a lower rate of senescence as a result.

The conclusion that senescence is a continuous process, best characterized by decreasing deterioration over all ages, pertains to two contrasting ideas about the evolutionary theory of senescence that exist in parallel. First, there is the idea that senescence does not occur before some age at which selection pressure is virtually zero, called "essential lifespan" [23] or "warranty period" [24]. Second, there seems to be the idea that mortality is approximately inversely related to selection pressure, although quantitative statements are not made [25,26]. Neither of these takes seem entirely satisfactory in the context of the evolution of senescence, given the considerations in this paper. As for the concept of an 'essential lifespan' or a 'warranty period', selection pressure tends to decline in a gradual fashion. If we consider an iteroparous organism that does not senesce, the standard default situation in reasoning about the evolution of senescence, selection pressure is an exponentially declining function of age. As a result it is hard to pin down a specific lifespan that could be called 'essential'. Only after the evolution of senescence could such an age be approximated. As selection pressure declines gradually, it would be more natural to expect senescence to be a similar gradual process, happening at all ages with deterioration approximately inverse to selection pressure, i.e. the other concept mentioned above. However, this concept is unsatisfactory because only the gradual decline of selection pressure is considered, but not the fact that the state of the organism at one age is tied to the state of the organism at preceding and subsequent ages, which takes away degrees of freedom from the patterns of senescence that can evolve. As Kirkwood and Shanley [27] pointed out, this means that the age-pattern of selection pressure has only limited informative power, since a pattern approximately inverse to selection pressure may not be mechanistically allowed. Thus, there are two different gradual processes that interact to lead to the evolution of senescence. A straightforward way of modeling that follows from these considerations would be to trade the initial (meaning 'at maturity') value of the vital rates for their rate of change. An initial good performance (low mortality and/or high fecundity) then leads to faster decline (see for instance [9], appendix).

To summarize, there are two requirements that the mechanisms that are believed to give rise to senescence should fulfill. First, the bulk of the deterioration should happen late rather than early. In parallel, such processes are required to be continuous rather than age-specific, for otherwise no proper account of causality is given. Processes that fulfill these conditions, conditions that are derived purely on logical grounds, are prone to be cumulative and to translate into vital rates in a non-linear fashion, so that high ages are affected much more than early ages. This does not mean that early ages are not affected at all, which may be hard to achieve from a mechanistic perspective (see above). Senescence being a gradual process, theoretical research should focus on what causes the continuous somatic change [see, e.g., 28-31].

Conclusions

1. The process that underlies senescence is one that is continuous.
2. Whether this continuous process has effects other than those mediated through state-specific genes is irrelevant to the question whether it is subject to natural selection or not. It is, and this selection should be included in theories and models.
3. State-specific genes are part of the mechanism by which somatic change affects vital rates, and they may lead to a higher rate of senescence, but also to a lower rate of senescence because of the evolution of slower somatic change in response. An increase in the rate of somatic change, on the other hand, always leads to an increase in the rate of senescence.
4. Cumulative somatic change will have some effects at early ages, although these may be negligible.
5. The main evolutionary question about senescence is what drives continuous somatic change, rather than what age-specific genes exist.

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References

1. Medawar, P.B. (1952) Uniqueness of the individual. Lewis, London.

2. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

3. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology, 12:12-43.

4. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature, 270:301-304.

5. Kirkwood, T.B.L. and S. Melov (2011) On the programmed/non-programmed nature of ageing within the life history. Current Biology 21:R701-R707.

6. Dawkins, R. (2006) The selfish gene, 30th ed. First edn 1976. Oxford University Press, Oxford.

7. Blackburn, E.H. (1991) Structure and function of telomeres. Nature 350:569-573.

8. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of ageing and longevity. Proceedings of the Royal Society London B 205:531-546.

9. Kirkwood, T.B.L. and M.R. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society of London B 332:15-24.

10. Macieira-Coelho, A. (2011) Cell division and aging of the organism. Biogerontology 12:503-515.

11. Rattan S.I.S. (2006) Theories of biological aging: genes, proteins, and free radicals. Free Radical Research 40:1230-1238.

12. Rattan S.I.S. (2010) Synthesis, modification and turnover of proteins during aging. In: Nektarios Tavernarakis Protein metabolism and homeostasis in aging. Landes Bioscience and Springer Science + Business Media.

13. Hubbard, V.M., Valdor, R., Macian, F. and A.M. Cuervo (2012) Selective autophagy in the maintenance of cellular homeostasis in aging organisms. Biogerontology 13:21-35.

14. Passarino, G., Rose, G. and D. Bellizzi (2010) Mitochondrial function, mitochondrial DNA and ageing: a reappraisal. Biogerontology 11:575-588.

15. Kallman, D.A., Plato, C.C., Tobin, J.D. (1990) The role of muscle loss in the age-related decline of grip strength: cross-sectional and longitudinal perspectives. Journals of Gerontology 45:M82-M88.

16. Andersen-Ranberg, K., Petersen, I., Frederiksen H., Mackenbach, J.P. and K. Christensen (2009) Cross-national differences in grip strength among 50+ year-old Europeans: results from the SHARE study. European Journal of Ageing 6:227-236.

17. Vaupel, J.W. (2010) Biodemography of human ageing. Nature 464:536-542.

18. Finch, C.E. (1990) Longevity, senescence and the genome. University Chicago Press, Chicago.

19. Nussey, D.H., Kruuk, L.E.B., Donald, A., Fowlie, M. and T.H. Clutton-Brock (2006) The rate of senescence in maternal performance increases with early-life fecundity in red deer. Ecology Letters 9:1342-1350.

20. Jones, O.R., Gaillard, J-M., Tuljapurkar, S., Alho, J.S., Armitage, K.B. et al. (2008) Senescence rates are determined by ranking on the fast-slow life-history continuum. Ecology Letters 11:664-673.

21. Jones, O.R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C.G., Schaible, R. et al. (2014) Diversity of ageing across the tree of life. Nature 505:169-173.

22. Zwaan, B.J. (1999) The evolutionary genetics of ageing and longevity. Heredity 82:589-597.

23. Rattan, S.I.S. (2000) Biogerontology: the next step. Annals of the New York Academy of Sciences 908:282-290.

24. Carnes, B. (2011) What is lifespan regulation and why does it exist? Biogerontology 12:367-374.

25. Partridge, L. and N.H. Barton (1993) Optimality, mutation and the evolution of ageing. Nature 362:305-311.

26. Charlesworth, B. (1994) Evolution in age-structured populations, 2nd edn. First edn 1980. Cambridge University Press, Cambridge.

27. Kirkwood, T.B.L., and D.P. Shanley (2010) The connections between general and reproductive senescence and the evolutionary basis of menopause. Annals of the New York Academy of Sciences 1204:21-29.

28. Kozlowski, J. (1999) Adaptation: a life history perspective. Oikos 86:185-194.

29. Cichon, M., and J. Kozlowski (2000) Ageing and typical survivorship curves result from optimal resource allocation. Evolutionary Ecology Research 2:857-870.

30. Baudisch, A. (2008) Inevitable aging? Part II: optimization models. Demographic research monographs. Springer, Berlin.

31. Wensink, M.J., van Heemst, D., Rozing, M.P. and R.G.J. Westendorp (2012) The maintenance gap: a new theoretical perspective on the evolution of aging. Biogerontology 13:197-201.

Chapter 4

The maintenance gap: a new theoretical perspective on the evolution of aging

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Abstract

One of the prevailing theories of aging, the disposable soma theory, views aging as the result of the accumulation of damage through imperfect maintenance. Aging, then, is explained from an evolutionary perspective by asserting that this lack of maintenance exists because the required resources are better invested in reproduction. However, the amount of maintenance necessary to prevent aging, 'maintenance requirement' has so far been largely neglected and has certainly not been considered from an evolutionary perspective. To our knowledge we are the first to do so, and arrive at the conclusion that all maintenance requirement needs an evolutionary explanation. Increases in maintenance requirement can only be selected for if these are linked with either higher fecundity or better capabilities to cope with environmental challenges to the integrity of the organism. Several observations are suggestive of the latter kind of trade-off, the existence of which leads to the inevitable conclusion that the level of maintenance requirement is in principle unbound. Even the allocation of all available resources to maintenance could be unable to stop aging in some organisms. This has major implications for our understanding of the aging process on both the evolutionary and the mechanistic level. It means that the expected effect of measures to reallocate resources to maintenance from reproduction may be small in some species. We need to have an idea of how much maintenance is necessary in the first place. Our explorations of how natural selection is expected to act on the maintenance requirement provides the first step in understanding this.

Theoretical background

Aging is the fall of fecundity and/or the rise of mortality with chronological time [1,2]. This obviously being disadvantageous to evolutionary fitness, several attempts have been made to explain how evolution could allow aging to exist. The most notable theories include the mutation accumulation [3], antagonistic pleiotropy [4] and disposable soma [5] theories of aging. The first two regard aging the result of genetic side effects, while the disposable soma theory regards aging the result of damage that accumulates due to imperfect maintenance of the organism. According to the disposable soma theory the reason this happens is that resources allocated to maintenance that pays off at an age at which an individual is unlikely to be alive are better allocated to reproduction. Through optimization by natural selection, maintenance effort is believed to settle below the level that is required to prevent aging [5-8]. In this paper, 'maintenance effort' is defined according to the definition of Kirkwood and Rose [7] as investments to preserve functions, distinguishing these from investments that create functions, which are captured under the term 'growth'.

The maintenance requirement and the maintenance gap

With respect to aging most attention has been given to maintenance effort, while what we call the 'maintenance requirement', the level of maintenance effort required to prevent aging, has received little or no attention, especially not from an evolutionary perspective. Although overlooked, reducing the level of maintenance requirement would be an alternative strategy for the organism to prevent its aging. After all, it is the deficit of maintenance effort with respect to maintenance requirement at a point in time, we call this the 'maintenance gap', that causes aging. Any factor that would increase the maintenance gap would directly increase the rate of aging, be it increasing maintenance requirement or decreasing maintenance effort. All other things being equal, evolution will act to lower the maintenance requirement. It is the central question of this paper why an organism would let its maintenance requirement grow high, apparently defying this evolutionary incentive.

Evolutionary terminology

In a non-growing population the highest fitness is achieved by individuals that maximize lifetime reproductive output. This in turn is conventionally modelled as the sum of age specific fertilities multiplied by age specific survival probabilities. To increase lifetime reproductive success, fertility rate could be augmented, reproductive survival prolonged, or both. It is important here to make a clear distinction of terms. Several writers have suggested that there is a certain lifespan that the organism needs to make its reproductive contribution to the next generation. Rattan [9] calls this 'essential lifespan', while Carnes [10] has named it the 'warranty period'. It is important to realize that this 'essential lifespan'

has evolved, and thus is the product of evolution - we cannot assume it as a starting point in an evolutionary theory.

Where the maintenance requirement comes from and why it is important

Survival of the organism is the result of the capacity to withstand challenges from extrinsic and intrinsic sources; investments in both characteristics contribute to lower all cause mortality. Death from intrinsic causes is optimized to the level of extrinsic mortality through evolved limitations on maintenance efforts [5,7]. On the other hand, mortality from extrinsic causes is the outcome of the organisms capacity to respond to environmental challenges to the integrity of the organism, as well as of these challenges themselves. With incremental investments in such capacity, mortality from extrinsic causes is expected to fall. However, such capacity may be maintenance demanding, thus leading to a higher maintenance requirement and therefore to a higher rate of aging. A similar reasoning goes for reproductive capacities. We suggest that we thus have another optimization process that happens through natural selection: when growing characteristics that increase fecundity and the capacity to cope with extrinsic challenges, the maintenance requirement will increase due to the continuous investment that is necessary to maintain the soma. This higher maintenance requirement directly translates into a bigger maintenance gap. Consequently, the direct benefit of lower mortality from extrinsic causes (and higher fecundity) comes at a cost of lower intrinsic durability and aging in the long run. We show two hypothesized mortality trajectories of organisms that follow differing approaches to this trade-off (Figure 4.1). Organism A grows to a state in which it is more robust to extrinsic challenges than organism B, but its state succumbs under the weight of its maintenance requirement, so that in the longer run it faces a faster acceleration of mortality rate than organism B. From this trade-off it importantly follows that nothing restricts the extent of development of the described characteristics as long as there is a net benefit for fitness (see Box). Maintenance requirement may grow so high that a maintenance gap would remain even if all resources were to be allocated to maintenance, especially because age-independent mortality tends to obscure disadvantageous late-life consequences, as was suggested by Medawar [3]. Thus it is conceivable that some phenotypes are selected that attain characteristics they cannot possibly maintain.

Positioning our contribution in the existing literature

It has been uttered before, that bigger body size goes with a bigger maintenance requirement [11]. However, the adaptations we envision may comprise body size, but not necessarily do. Two equal masses of tissue may differ in their maintenance requirement.

Average adult mortality scales negatively with adult body size [12]. Aging, though, is a term that relates to change and not to absolute level [1,2]. Therefore, our hypothesis is in line with scaling theory. To prove or disprove the concept put forward in this paper would require a careful analysis of high quality long term individual data, correcting for

reproductive effort and the effect of size on food intake. The expected finding would be that mortality rates accelerate relatively faster in individuals with lower initial mortality rates. At least suggestive is that in the wild a bigger size is associated with a longer life [13], whereas in laboratory and domestic environment longevity of animals typically shows a negative correlation with mass [14,15]. After all, lifespan in a protected environment may predominantly reflect the force of mortality due to intrinsic causes (higher maintenance requirement for bigger individuals), whereas mortality in the wild may predominantly reflect death form extrinsic causes (lower mortality from extrinsic causes for bigger individuals).

Implications for mechanistic theories of aging - IGF-1

In aging research one can distinguish proximate (mechanistic) causes of aging [20-22], and ultimate (evolutionary) causes of aging. Possible mechanisms through which maintenance requirement may act include differences in metabolic rate and the associated production of reactive oxygen species, as well as differences in insulin/IGF-1 signalling. Insulin-IGF-1 signalling, a prime regulator of growth, is invariantly associated with lifespan regulation in mammals. The role of reduced insulin/insulin-like growth factor 1 (IGF-1) signalling in lifespan extension is well established in invertebrates [23]. IGF-1 and growth hormone (GH) primarily control growth and differentiation. In mice, genetic disruption of the GH/IGF-1 pathway is associated with reduced adult body size and major increases in lifespan under laboratory conditions [24]. It is tempting to speculate that survival probabilities and fitness of these animals are low under adverse environmental conditions. Also in humans, genetic variants associated with reduced IGF-1 signalling have been associated with reduced height and enhanced survival [25,26]; it seems that the human maintenance gap could be due to elevated maintenance requirement for a substantial part.

Box: Big brains

The rate of aging is determined by the amount of unperformed maintenance/unit of time, the 'maintenance gap'. For the size of this gap, how much maintenance is necessary is just as important as how much maintenance is actually done. Greater size and/or maintenance-heavy tissue imply a greater maintenance requirement. An example of maintenance-heavy tissue is the (human) brain, that, in addition to the cost of its growth (even after reaching adolescence), consumes a very substantial amount of energy for its maintenance [16,17]. All other things being equal the greater maintenance requirement will lead to faster aging. Nevertheless, on the whole the brain has a beneficial impact on survival [18] because it allows the organism to cope better with its environment. Also, the brain may facilitate better access to resources, and energy savings through more efficient behavior and physiology [19]. Therefore, the brain facilitates a greater maintenance effort and interestingly affects both sides of the maintenance gap. If the brain would not have all these immediate benefits, it would have been strongly selected against.

Discussion and conclusion

Baudisch [27] questions: "Early in life, when individuals develop and grow, mortality falls and reproductive potential increases. Why is it that these age patterns cannot persist (...)?" Our answer is that an organism may attain a state that ultimately is not sustainable, even if all its resources were allocated to maintenance. To this moment the disposable soma theory of aging has aimed to explain why organisms do not maintain themselves, while they are considered to be able to [8]. The important novel concept that this paper aims to deliver is that just as any maintenance effort, any maintenance requirement needs an evolutionary explanation. Hence, to understand the evolutionary cause of aging, research should focus on the maintenance gap as a whole. Taking this one step further leads to the conclusion that if there is sufficient selection on traits that favor a high maintenance requirement, this maintenance requirement is unbound. The scope for mathematical models as well as research addressing the underlying mechanisms of aging is thus broadened in exciting new directions. The mechanistic cause of aging perhaps cannot be found in merely monitoring the fluxes of resources within the organism; even if all resources are found to be allocated to maintenance, the organism may still age. What contributes most to the maintenance gap in a specific organism depends on the environmental niche an organism lives in, but both factors that contribute to the maintenance gap, maintenance requirement and maintenance effort, are complementary rather than mutually exclusive and are united in the concept of the maintenance gap. Thinking in terms of the maintenance gap, then, takes all important factors into consideration when it comes to maintenance and aging, so that all questions can be grouped in two overarching questions. Where does the maintenance gap in a particular species come from? How do we close it?

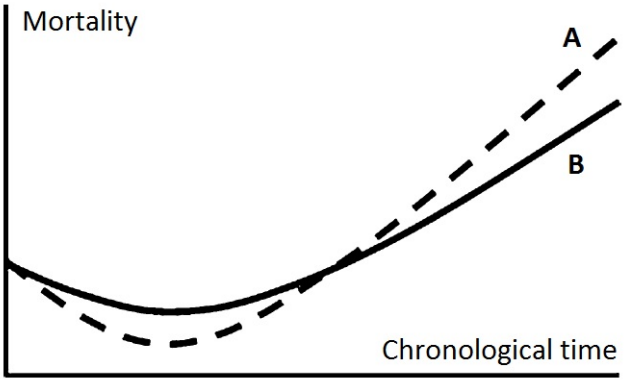

Figure 4.1: Hypothesized mortality trajectories; organism A (*dashed line*) gains lower midlife mortality than organism B (*solid line*) but pays the price of faster mortality acceleration later in life. For simplicity only mortality is considered, but a similar (inverse) graph could be drawn for fecundity

References

1. Finch, C.E. (1990) Longevity, senescence and the genome. University Chicago Press, Chicago

2. Baudisch, A. (2011) The pace and shape of ageing. Methods in Ecology and Evolution 2:375-382.

3. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London.

4. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

5. Kirkwood, T.B.L. (1977) Evolution of aging. Nature 270:301-304.

6. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of aging and longevity. Proceedings of the Royal Society B: Biological Sciences 205:531-546.

7. Kirkwood, T.B.L. and M.R. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London, B 332:15-24.

8. Drenos, F. and T.B.L. Kirkwood (2005) Modelling the disposable soma theory of aging. Mechanisms of Ageing and Development 126:99-103.

9. Rattan, S.I.S. (2000) Biogerontology: the next step. Annals of the New York Academy of Sciences 908:282-290.

10. Carnes, B.A. (2011) What is lifespan regulation and why does it exist? Biogerontology 12:367-374.

11. Munch, S.B. and M. Mangel (2006) Evaluation of mortality trajectories in evolutionary biodemography. Proceedings of the National Academy of Sciences USA 103:16604-16607.

12. Charnov, E.L. (1993) Life history invariants. Oxford University Press, Oxford.

13. Gaillard, J.M., Festa-Bianchet, M., Delorme, D. and J. Jorgenson (2000) Body mass and individual fitness in female ungulates: bigger is not always better. Proceedings of the Royal Society B: Biological Sciences 267:471-477.

14. Rollo, C.D. (2002) Growth negatively impacts the life span of mammals. Evolution & Development 4:55-61.

15. Miller, R.A., Harper, J.M., Galecki, A. and D.T. Burke (2002) Big mice die young: early life body weight predicts longevity in genetically heterogeneous mice. Aging Cell 1:22-29.

16. Mink, J.W., Blumenschine, R.J. and D.B. Adams DB (1981) Ratio of central nervous system to body metabolism in vertebrates: its constancy and functional basis. American Journal of Physiology 241: R203-R212.

17. Isler, K. and C.P. Van Schaik (2006) Metabolic costs of brain size evolution. Biology Letters 2:557-560.

18. González-Lagos, C., Sol, D. and S.M. Reader (2010) Large-brained mammals live longer. Journal of Evolutionary Biology 23:1064-1074.

19. Kaplan, H.S. and A.J. Robson (2002) The emergence of humans: the coevolution of intelligence and longevity with intergenerational transfers. Proceedings of the National Academy of Sciences USA 99:10221-10226.

20. Rattan, S.I.S. (2006) Theories of biological aging: genes, proteins, and free radicals. Free Radical Research 40:1230-1238.

21. Rattan, S.I.S. (2008) Minireview - increased molecular damage and heterogeneity as the basis of aging. Biological Chemistry 389:267-272.

22. Holliday, R. and S.I. Rattan (2010) Longevity mutants do not establish any "new science" of ageing. Biogerontology 11:507-511.

23. Kenyon, C.J. (2010) The genetics of ageing. Nature 464:504-512.

24. Bartke, A. (2005) Mini review: role of the growth hormone/insulin-like growth factor system in mammalian aging. Endocrinology 146:3718-3723.

25. van Heemst, D., Beekman, M., Mooijaart, S.P., Heijmans, B.T., Brandt, B.W., Zwaan, B.J., et al. (2005) Reduced insulin/IGF-1 signalling and human longevity. Aging Cell 4:79-85.

26. Suh, Y., Atzmon, G., Cho, M-O., Hwang, D., Liu, B., Leahy, D.J., et al. (2008) Functionally significant insulin-like growth factor I receptor mutations in centenarians. Proceedings of the National Academy of Sciences USA 105:3438-3442.

27. Baudisch, A. (2005) Hamilton's indicators of the force of selection. Proceedings of the National Academy of Sciences USA 102:8263-8268.

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Part III

Mathematical Papers

Chapter 5

No senescence despite declining selection pressure: Hamilton's result in broader perspective

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Abstract

Theory predicts that senescence should inevitably evolve because selection pressure declines with age. Yet, data show that senescence is not a universal phenomenon. How can these observations peacefully coexist? Evolution of any trait hinges on its impact on fitness. A complete mathematical description of change in fitness, the total fitness differential, involves selection pressure along with a perturbation function that describes how the vital rates, mortality and fecundity, are affected across ages. We propose that the perturbation function can be used to model trade-offs when vital rates are perturbed in different directions and magnitude at different ages. We find that for every trade-off we can identify parameter values for which senescence does evolve and others for which it does not. We argue that this reconciles the apparent contradiction between data and theory. The total fitness differential is also instrumental in deriving mathematical relationships between alternative indicators of selection pressure. We show examples and highlight that any indicator combined with the right perturbation function can be used to parameterize a specific biological change. Biological considerations should motivate what perturbation functions are used. We interpret the relevance of Hamilton's finding that selection pressure declines for the evolution of senescence: declining selection pressure is a necessary but not a sufficient condition.

Introduction

Higher ages are of less evolutionary importance than younger ages. As organisms go through their life course, more and more offspring are born, so more and more of the organism's contributions to the gene pool come to lie in the past. Since earlier contributions cannot be affected by later events, death of older individuals incurs less of a penalty to evolutionary fitness than death of younger individuals. In a nutshell, this declining selection pressure is the basis of evolutionary explanations of senescence, the deterioration of an organism's vital rates due to changes in its state as the organism gets chronologically older [1-3]. Selection pressure declines for any pattern of fecundity and survival [3], even for organisms that initially exhibit 'sustenance', unchanging rates of reproduction and survival with age (sensu [4]), or organisms that show 'negative senescence', defined by rising rates of reproduction declining rates of mortality with age (sensu [5]).

If declining selection pressure were a sufficient condition for the evolution of senescence, then evolution should mold any life course, even those that initially exhibit no or negative senescence, to the senescent phenotype after sufficient evolutionary time. Yet, patterns of sustenance and negative senescence can be observed in nature [5,6]. Therefore declining selection pressure alone cannot be the decisive argument, and something else must be at play [6].

Selection pressure expresses the sensitivity of fitness to some standard unit of change in a vital rate, mortality and fecundity, at a specific age. To know how fitness changes as a result of some real biological perturbation, it is necessary to know which vital rate(s) are affected, at which ages, and how strongly. These changes can be captured in a perturbation function, which describes the effects on mortality and fecundity as a function of age. The perturbation function completes the total fitness differential, which is the full and general analytical description of how fitness changes if mortality and/or fecundity change(s) [7,8]. Any effect on fitness can only be known if the total fitness differential is considered.

To find an appropriate perturbation function, one has to consider the underlying biology: if mortality is perturbed at one age, what would happen biologically at other ages, and what does that mean for the perturbation function? The complex causal pathways leading to changed gene expression, the accumulation of damage, loss of physiological control, but also growth and learning (all of which affect mortality and fecundity patterns), are likely to be tied in some more or less continuous trajectory of change. These cannot be reduced to independent age-specific changes [9,10]. Here, the perturbation function is helpful, since it describes such age-patterns.

The combination of selection pressure and perturbation is commonly studied in age-structured models [11,12], matrix population models [13, §9.1.6 of 14], and quantitative genetics [15]. Yet, studies of senescence typically invoke standard-unit changes at particular ages (or age-ranges), drawing conclusions from verbal comparison of 'early' (low ages) versus 'late' (high ages) [e.g. 1-3,16-18]. In the same vein, conclusions about the evolution of senescence are frequently drawn directly from patterns of selection pressure [e.g 19-24]. We exemplify biologically realistic perturbation functions and use those in combi-

nation with the associated selection pressure, thus completing the evolutionary analysis. This leads to results that are not evident from models based on selection pressure alone. Mathematical relationships between alternative indicators of selection pressure are clarified using the perturbation function. We conclude with showing that Hamilton's finding is a necessary but not a sufficient cause for the evolution of senescence.

Fitness consequences of changes in vital rates

Hamilton [3] used the intrinsic rate of increase 'r' as a measure of fitness, defined as the unique real root of the Euler-Lotka equation, within the framework of stable population theory [11,14,25]:

$$\int_0^\infty e^{-rx}\ell(x)m(x)dx = 1 \tag{5.1}$$

In this equation $\ell(x)$ denotes survival up to age x, and $m(x)$ denotes age-specific fecundity. Survival is related to the instantaneous mortality rate $\mu(x)$:

$$\ell(x) = e^{-\int_0^x \mu(t)dt} \tag{5.2}$$

By implicit differentiation of r with respect to an additive perturbation of mortality and fecundity respectively, Hamilton [3] derived indicators of selection pressure on age-specific additive perturbations of mortality and fecundity. These indicators are:

$$\frac{dr}{dF_a} = \frac{e^{-ra}\ell(a)}{T} \tag{5.3}$$

$$\frac{dr}{d\Delta_a} = -\frac{\int_a^\infty e^{-rx}\ell(x)m(x)dx}{T} \tag{5.4}$$

where

$$T = \int_0^\infty x e^{-rx}\ell(x)\,m(x)\,dx \tag{5.5}$$

which is the average age at reproduction in a population, i.e. generation time [11]. Furthermore, $d\Delta_a = d\mu(a)da$, an infinitesimal additive change in mortality multiplied by an infinitesimal neighborhood of the age at which this change takes place, and $dF_a = dm(a)da$, an infinitesimal additive change in fecundity multiplied by an infinitesimal neighborhood of the age at which this change takes place.

Using functional calculus, Arthur [7] derived a general analytical expression for the sensitivity of r to changes in the patterns (rather than age-specific values) of fecundity and survival, writing r in its differential form:

$$dr = \frac{1}{T}\left[\int_0^\infty e^{-ra}d\ell(a)m(a)da + \int_0^\infty e^{-ra}\ell(a)dm(a)da\right] \tag{5.6}$$

If the perturbation of survival is considered at the mortality level, the two being related through equation (5.2), applying the product rule to $d\ell(a)$ and integrating by parts, this

expression can be rewritten as:

$$\frac{dr}{d\varepsilon} = \int_0^\infty \left[\frac{e^{-ra}\ell(a)}{T} \frac{dm}{d\varepsilon}(a,\cdot) - \frac{\int_a^\infty e^{-rx}\ell(x)m(x)dx}{T} \frac{d\mu}{d\varepsilon}(a,\cdot) \right] da \tag{5.7}$$

Perturbation parameter ε captures small perturbations in fecundity ($dm/d\varepsilon(a,\cdot)$) and mortality ($d\mu/d\varepsilon(a,\cdot)$). These perturbations can be functions of age, and possibly other parameters, indicated by the dot. The two other elements can be recognized as Hamilton's indicators of selection pressure, equations (5.3) and (5.4). Writing H^* and $H^\dagger$ for Hamilton's indicators of selection pressure on additive changes in fecundity and mortality rate respectively, the general equation for change in r is:

$$\frac{dr}{d\varepsilon} = \int_0^\infty \left[H^*(a) \frac{dm}{d\varepsilon}(a,\cdot) + H^\dagger(a) \frac{d\mu}{d\varepsilon}(a,\cdot) \right] da \tag{5.8}$$

At every age, the effect of change in mortality and fertility on fitness is given by the product of fitness sensitivity (H^* or $H^\dagger$) and the perturbation in the vital rate ($dm/d\varepsilon$ and $d\mu/d\varepsilon$). Integration over all ages then yields the full fitness consequences. As an example of a perturbation function, mortality μ could equal some constant c in the baseline scenario, while perturbed mortality could be given by

$$\mu(a,\varepsilon) = c + \varepsilon(a-p)s \tag{5.9}$$

where age p is the one age at which the perturbed mortality function crosses the baseline (constant) mortality, $\varepsilon \geq 0$ is a perturbation parameter, while parameter $s > 0$ models the strength of the trade-off. Both s and ε are given in units of time^{-1}. Except for its dimensionality, parameter s is redundant in this case, but not in other perturbations (see below), and is included here for consistency. The perturbation function expresses how strongly mortality gets to deviate from the baseline scenario, which in the case of equation (5.9) is

$$\frac{d\mu}{d\varepsilon} = (a-p)s \tag{5.10}$$

Notice that this perturbation function involves changes at all ages.

Invasion study

Expression (5.8) can be analyzed for any perturbation functions $dm/d\varepsilon(a,\cdot)$ and $d\mu/d\varepsilon(a,\cdot)$ of interest, in the context of the life histories of a resident phenotype, which determine H^* and $H^\dagger$. Notice that selection pressure is "situational" (pg 34 of [26]): as soon as vital rates actually do change, selection pressure changes with them. As a result, the fitness differential can be used to indicate an initial direction of change, but for real-life, non-infinitesimal changes, it provides only a linear approximation (see [27-29] for methods to improve on this limitation). We need therefore to choose a phenotype for the resident population to be able to derive exact expressions for selection pressure.

We choose a *sustenant* resident phenotype. Although it is not evident that early organisms were sustenant, this assumption avoids presuming that senescence has evolved before explaining that very phenomenon, and has therefore often been taking as a starting point in previous approaches [e.g. 1,2,12,13,30].

The perturbation function, we propose, can be used to mimic trade-offs, since this function can express different direction and magnitude of perturbation of vital rates at each age, which is what happens under a trade-off. The perturbation functions are assumed to pertain to all organisms in a population. The environment is assumed to be constant.

Having thus obtained the ingredients for the fitness differential, the latter can be evaluated to determine whether invasion is possible. If and only if a positive fitness differential exists, i.e. $dr/d\varepsilon > 0$, improvement is possible locally, so that invasion will take place if the necessary variation exists. If $dr/d\varepsilon = 0$, there is no advantage of one phenotype over the other (neutral change can occur), while if $dr/d\varepsilon < 0$, improvement is not possible.

For a sustenant phenotype the life history is characterized by constant fecundity (m_0) and constant mortality (c). Solving equation (5.1) with $m(x) = m_0$ and $\mu(x) = c$ yields $r = m_0 - c$. Substitution of this result in equations (5.3) and (5.4), accounting for equation (5.2), and integrating by parts gives the following results:

$$H^* = m_0 e^{-m_0 a} \tag{5.11}$$

$$H^\dagger = -m_0 e^{-m_0 a} \tag{5.12}$$

In a sustenant phenotype, selection pressure is an exponentially declining function of age. These are the indicators of the force of selection on an age-specific additive change of mortality and fecundity respectively that determine whether a mutant phenotype can invade a resident sustenant phenotype under the trade-off of interest (similar to equation (6) in [12]).

Substitution of the results in equations (5.11) and (5.12) in equation (5.8) yields:

$$\frac{dr}{d\varepsilon} = m_0 \int_0^\infty e^{-m_0 a} \left(\frac{dm}{d\varepsilon}(a,\cdot) - \frac{d\mu}{d\varepsilon}(a,\cdot) \right) da \tag{5.13}$$

This equation can be evaluated for alternative perturbation functions. First, to demonstrate the principle, we consider a linear trade-off within the mortality function, such that the mortality rate is initially reduced, but increases linearly with age. Second, because this trade-off has received considerable attention, we evaluate a trade-off that involves both mortality and fecundity. In the disposable soma theory [30,31], fecundity is increased at a cost to repair. The perturbation function associated with this trade-off could be such that mortality increases linearly with age while reproductive rate is increased by a constant at all ages. Third, illustrating a case when negative senescence can evolve, we evaluate an exponential trade-off within mortality, such that the mortality rate is reduced at low ages but increases exponentially with age or vice versa.

Linear trade-off within mortality

This trade-off is characterized by perturbation function (5.10). Substitution in equation (5.13) yields:

$$\frac{dr}{d\varepsilon} = -m_0 s \int_0^\infty (a-p) e^{-m_0 a} da \tag{5.14}$$

Rearranging and integrating by parts gives:

$$\frac{dr}{d\varepsilon} = -m_0 s \left(\frac{1}{m_0^2} - \frac{p}{m_0} \right) = s \left(p - \frac{1}{m_0} \right) \tag{5.15}$$

Whether the derivative in equation (5.15) is greater than zero, so that the senescent phenotype can invade, depends on parameter p: the higher age p, the longer the mortality rate stays below its original constant level. Thus, high values of p should promote the evolution of senescence, while low values should not. Age p_0 marks the boundary between trade-offs that do (greater p) or do not (smaller p) favor the evolution of senescence. Substituting p_0 for p in equation (5.15), setting $dr/d\varepsilon = 0$, and solving for p_0 yields:

$$p_0 = \frac{1}{m_0} \tag{5.16}$$

Interestingly, $p_0 = 1/m_0 = T$. Thus, for all p greater than generation time T the senescent phenotype can invade, while for smaller values it cannot. Notice that this result holds only in a specific resident life history under a specific perturbation function.

Linear trade-off involving both mortality and fecundity

Another possibility is that a trade-off results in a linear increase in mortality and a higher constant reproductive rate. Mortality and fecundity then become:

$$\mu(a,\varepsilon) = c + \varepsilon a s \tag{5.17}$$

$$m(\varepsilon) = m_0 + \varepsilon \tag{5.18}$$

For mortality this is the same perturbation as in section 3.1 with $p = 0$. Whether the senescent phenotype can invade or not is now not a function of p (since $p \equiv 0$ from the nature of the trade-off), but of the rate at which mortality increases with some increase in reproductive rate, modeled by parameter s. Substituting $d\mu/d\varepsilon = as$ and $dm/d\varepsilon = 1$ (from equations (5.17) and (5.18) respectively) in equation (5.13) gives:

$$\frac{dr}{d\varepsilon} = m_0 \int_0^\infty e^{-m_0 a} da - m_0 s \int_0^\infty a e^{-m_0 a} da = 1 - s/m_0 \tag{5.19}$$

If $dr/d\varepsilon > 0$ the senescent phenotype can invade, which is the case if $s < m_0$. For greater values of s (when mortality increases faster for the same m) the senescent phenotype cannot invade.

Exponential trade-off within mortality

In the previous paragraph we evaluated whether a senescence phenotype could invade. Of equal interest is the question whether a negatively senescent phenotype, with improving vital rates over its adult lifespan, can invade the sustenant resident phenotype. The study of negative senescence versus sustenance requires care, since many functional forms of the perturbation function are biologically intractable. For instance, a continuous additive decline in mortality or fecundity would lead to negative mortality and fecundity at high ages, which is not biologically possible. There are two conceivable solutions to this problem. The first is to calculate $dr/d\varepsilon$ on some interval on which mortality and fecundity take strictly positive values. If the vital rates on that interval are biologically plausible, and $dr/d\varepsilon$ takes a negative value on that interval, it could well be argued that the negatively senescent, 'negasent', phenotype could invade. However, in this method implicit assumptions about vital rates after the interval of investigation are made, so that the vital rates remain strictly non-negative. A more elegant method is to limit the study of negative senescence to perturbations that do not lead to negative mortality and fecundity on the entire positive real domain, as in the following case.

Consider an exponential perturbation of the mortality function:

$$\mu(a,\varepsilon) = c + \varepsilon(e^{s(a-p)} - 1) \tag{5.20}$$

This gives $d\mu/d\varepsilon = e^{s(a-p)} - 1$. As before, p is the age at which there is no perturbation of mortality, while the farther away from p, the greater the perturbation is, but now in an exponential fashion. The strength of exponential increase is modeled by s. The greater s is, the more the mortality rate is reduced before age p, and the more it is increased after age p. Substitution of $d\mu/d\varepsilon$ from equation (5.20) in expression (5.13) yields:

$$\frac{dr}{d\varepsilon} = -m_0 \int_0^\infty \left(e^{s(a-p)} - 1\right) e^{-m_0 a} da \tag{5.21}$$

$$= -m_0 \left[\int_0^\infty e^{s(a-p)-m_0 a} da - \frac{1}{m_0}\right] \tag{5.22}$$

Since it is required that $dr/d\varepsilon > 0$ for the senescent phenotype to be able to invade, it is also required that:

$$\int_0^\infty e^{(s-m_0)a} da < \frac{e^{sp}}{m_0} \tag{5.23}$$

The integral in inequality (5.23) does not converge if $s \geq m_0$, irrespective of p, so that the inequality does not hold. The interpretation of this is that if, as the result of the trade-off, mortality increases faster than selection pressure declines, there is a growing, negative effect at higher ages, and the net effect on fitness will be deleterious. If $s < m_0$, the integral does converge and takes the value $\frac{1}{m_0 - s}$. Just as in the linear case, it is possible to find a $p_0(s)$, so that for $p > p_0$ the senescent phenotype can invade, while for $p < p_0$ it cannot.

This is done by substituting p_0 for p in equation (5.23), setting $dr/d\varepsilon = 0$, and solving for p_0:

$$p_0 = \frac{ln(\frac{m_0}{m_0 - s})}{s} \tag{5.24}$$

The exponential trade-off also facilitates an exponential decline in mortality from a higher initial level, while mortality takes strictly positive values, in which case we allow $i < 0$. The negasent phenotype can invade if $p < p_0$, with p_0 as in equation (5.24).

Alternative indicators of selection pressure

The perturbation function given by equation (5.7) can be used to show relationships between alternative indicators of selection pressure. Baudisch [32] derived several alternative indicators of selection pressure, for instance the sensitivity of fitness to an age-specific *proportional* perturbation of mortality. All these indicators [32,p.8264] consist of one of Hamilton's elementary indicators, expressions (5.4) and (5.3), scaled by some factor that depends on the actual value of mortality or fecundity. Considering Baudisch's alternative indicators, the same result can be derived by using Hamilton's elementary indicators, while scaling the perturbation function by the same mortality- or fecundity-dependent factor that is used to obtain the alternative indicator.

Hamilton [3] also derived the sensitivity of fitness to an additive perturbation of mortality from some age onwards (as opposed to *at* some age):

$$\frac{dr}{d\Delta_{a\ldots\infty}} = -\frac{\int_a^\infty (x-a)e^{-rx}\ell(x)m(x)dx}{T} \tag{5.25}$$

In a thorough discussion on the difference between $dr/d\Delta_a$ and $dr/d\Delta_{a\ldots\infty}$, Abrams [33] argued that a senescent change is best characterized by $dr/d\Delta_{a\ldots\infty}$, because an intrinsic deterioration (senescence) at age a will last throughout life, and will thus continue to affect mortality and fecundity.

If senescence is characterized as Abrams [33] argued, so that at some age mortality is increased for the rest of the lifespan of an organism, then the corresponding perturbation for $dr/d\Delta_a$ is:

$$\frac{d\mu}{d\varepsilon}(x) = \begin{cases} 0 & \text{if } x < a \\ 1 & \text{if } x \geq a \end{cases} \tag{5.26}$$

Substitution of this perturbation in equation (5.7) gives

$$\frac{dr}{d\varepsilon} = -\frac{1}{T}\int_a^\infty \int_z^\infty e^{-rx}\ell(x)m(x)dxdz \tag{5.27}$$

Using differentiation by parts, it can be shown that expression (5.27) equals $dr/d\Delta_{a\ldots\infty}$ (equation (5.25)).

A biological change has a unique fitness effect. The biological change is expressed in the *combination* of perturbation function and indicator of selection pressure, i.e. the

parameterization of the fitness differential. If the same perturbation function is combined with a different indicator of selection pressure, a different biological change is expressed. Any two parameterizations that express the same biological change always give the same result.

Discussion

If it is argued verbally that fitness increases under some trade-off given a (declining) pattern of selection pressure [e.g. 2,3,16,17], this is equivalent to the mathematical statement that under the trade-off there exists a positive fitness differential, i.e. $dr > 0$. Going beyond the verbal argument, we formally evaluate this fitness differential. The fitness differential depends on the indicators of selection pressure, defined by the life history of a resident phenotype, and on the perturbation function, defined by physiological mechanisms. So what are biologically realistic perturbation functions? Abrams [33] considered a stepwise perturbation that remains over the rest of the lifespan. He motivated this perturbation by considering a trade-off that results in increased fecundity at age a, at the cost of unrepaired molecular damage originating at age a. The resulting deteriorated state of the organism will remain, and will continue to affect mortality throughout the organism's lifespan. On the other hand, Wensink et al. [34] discuss the possibility that it may be evolutionary beneficial for an organism to grow to a state that is simply unmaintainable with the resources that it has at its disposal. In that case, other than in the case of resource allocation taking place at each age, attaining such a state at some age puts the organism on a trajectory of deterioration for the rest of its life. Thus, an initial improvement of vital rates results in further deterioration of these vital rates at all subsequent ages. A similar trajectory of accelerating deterioration rather than a stepwise increase may be expected if senescence is the result of dysregulation with age, or of loss of robustness [35]. There is evidence that suggests that the accumulation of damage with senescence may sometimes be a matter of correlation without causation [36,37], although damage accumulation will no doubt play a role. In both examples above, one inside and one outside the paradigm of senescence being caused by damage accumulation, the senescent change is not a one-time increase, but rather a continuous deterioration.

For the evolution of negative senescence, Vaupel et al. [5] hypothesize that organisms that do not stop growing upon reaching maturity may exhibit negative senescence, since for many species (for instance fish), growth results in higher fertility and lower mortality. If growth or learning are considered decisions taken at every age (whether to grow or not, whether to learn or not), they could be characterized by a perturbation that models a one-time improvement from some age onwards. If, on the other hand, negative senescence is characterized by continuous improvement (growth and learning is a character that is either part of the phenotype across ages, or not), there is a trajectory of improvement rather than a one-time increase, parameterized by a perturbation function such that mortality decreases monotonously and fecundity increases monotonously.

As briefly mentioned in the introduction to section 3, indicators of selection pressure are situational. Results obtained from indicators of selection pressure, i.e. the fitness

differential, indicate the initial direction of evolution, which is bound to change as the resident phenotype evolves. Hence, the results apply only locally; a global optimum is not demonstrated. This is a general limitation of such approaches [e.g. 16-24]. Still our point remains valid that perturbation functions can always be found which for some range of parameters lead to senescence and for another lead to negative senescence, which clarifies the relation between direct optimization models and models of selection pressure. Direct optimization models maximize fitness under a set of constraints defined at all ages. These models do not contain Hamilton's indicators of selection pressure explicitly, and can predict absence of senescence or even negative senescence to evolve [4,5,38-40]. Models of selection pressure calculate fitness sensitivities to changes in vital rates at specific ages and explore how the pattern of decline of selection pressure is affected by varying model parameters. No formal equation automatically ties together changes at particular ages, and the (pattern of) decline is often taken to directly predict the outcome of evolution [2,3,16-24]. Evaluating the fitness differential, this deficiency is fixed. Changes at particular ages are tied together by the perturbation function, and it turns out that the finding of sustenance or negative senescence as possible outcomes of evolution is not a peculiarity of optimization models: this result can equally well be derived from the calculus of selection pressure when the full fitness differential is considered, in line with the result of Charlesworth that quantitative genetics and optimization models should in principle lead to similar results [41].

The view that trade-offs only determine specifics of the pattern of senescence, while the evolution of senescence itself is inevitable because of declining selection pressure, needs to be adjusted. Trade-offs do more than just determine the details of senescence: they co-determine whether senescence evolves at all. If trade-off perturbation functions that promote sustenance or negative senescence capture biologically realistic conditions, then it follows that the evolution of senescence is not inevitable.

Why is it that some biological mechanisms (perturbation functions) defy the inevitability of senescence, and how does this work out mathematically? At high ages selection pressure may be low, but perturbations that grow over ages may have become large. An organism will have had a lot of time to learn and grow, so that improvement (higher fecundity, lower mortality) may be considerable. There exists no mathematical reason why improvement of vital rates would have a limit: mortality can continue to decline asymptotically to zero, while fecundity can continue to go up. In addition, the benefits of sustenance or even negative senescence remain over a potentially unlimited range of ages: there is no age beyond which survival is impossible *a priori*, and with dropping mortality, very high ages may be attained. As a result, possible loss of fitness by senescence is limited by fitness itself, but the possible gain in fitness by negative senescence has no mathematical limit.

In contrast to trade-off perturbations, the theory of mutation accumulation invokes perturbations with very small effects that are only deleterious. In the mutation accumulation theory, mutations with a late-acting deleterious effect on fitness are not removed by natural selection because their overall effect on fitness is small. As a result, such mutations accumulate over evolutionary time. The later the age at which they act, the less likely

they will be removed [1,3,11]. As trade-offs and mutation accumulation are not mutually exclusive, would it not be true that even if trade-offs lead to negative senescence, senescence still evolves because selection pressure declines, giving way to 'loss-only' processes under the mutation accumulation theory?

We do not think so. First, existing life histories will be a combination of both types of perturbations. The question would then be which process dominates, mutation accumulation or trade-offs [42]. If trade-offs lead to significant negative senescence, this could offset deterioration by mutation accumulation. Which process dominates the demographics is not necessarily the same at all ages. Perhaps the two effects together could explain why organisms that show protracted negative senescence throughout their lifespan could still show a little upswing in their mortality function at very high ages [5]. Second, since the mechanisms of senescence are likely to lead to sustained or increasing deterioration rather than age-specific effects, the costs of senescence are much higher than Hamilton's age-specific indicators may suggest (see also [9,33]). Consequently the evolution of senescence by mutation accumulation may be rare. In any event, the empirical finding of protracted improvement during adult lifespan is strongly suggestive of trade-offs playing an important if not decisive role in the evolution of senescence[6].

Then what, if not the inevitability of senescence, does Hamilton's finding that selection pressure universally declines really mean? If selection pressure did not decline, any cost of senescence would be infinite, i.e. equation (5.8) would not converge, so that senescence could not possibly evolve. We propose that declining selection pressure is a necessary but not a sufficient condition for the evolution of senescence.

Conclusion

To study selection pressure alone does not suffice for drawing conclusions about the evolution of senescence; the actual perturbation needs to be considered as well. This completes the total fitness differential, which is the full description of change in fitness. Different combinations of alternative indicators of selection pressure and perturbation functions (parameterizations of the total fitness differential) can capture the same pattern of change in vital rates, predicting the exact same effect on fitness. At high ages selection pressure may be low, but perturbations that grow over ages may have become large, defying the inevitability of the evolution of senescence. For a complete understanding of aging, we recommend including the total fitness differential in discussions of senescence, rather than Hamilton's indicators of selection pressure alone.

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References

1. Medawar, P.B. (1952) An unsolved problem of biology. P. 3-24 in: Uniqueness of the individual. Lewis, London, UK.

2. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

3. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology 12:12-45.

4. Baudisch, A. (2008) Part II: optimization models. In: Inevitable aging? Contributions to evolutionary-demographic theory. Demographic Research Monographs. Springer-Verlag Berlin, Heidelberg.

5. Vaupel, J.W., Baudisch,A., Dölling, M., Roach, D.A. and J. Gampe (2004) The case for negative senescence. Theoretical population biology 65:339-351.

6. Baudisch, A. and J.W. Vaupel (2012) Getting to the root of aging. Science 338:618-619.

7. Arthur, W.B. (1984) The analysis of linkages in demographic theory. Demography 21:109-128.

8. Caswell, H. (2010) Reproductive value, the stable stage distribution, and the sensitivity of the population growth rate to changes in vital rates. Demographic Research 23:531-548.

9. Wensink, M.J. (2013) Age-specificity and the evolution of senescence: A discussion. Biogerontology 14: 99-105.

10. Kirkwood, T.B.L., and D.P. Shanley (2010) The connections between general and reproductive senescence and the evolutionary basis of menopause. Annals of the New York Academy of Sciences 1204:21-29.

11. Charlesworth, B. (1994) Evolution in age-structured populations, second edition. Cambridge University Press, Cambridge, UK.

12. Charlesworth, B. (2001) Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. Journal of Theoretical Biology 210:47-65.

13. Caswell, H. (1982) Optimal life histories and the age-specific costs of reproduction. Journal of Theoretical Biology 98:519-529.

14. Caswell, H. (2001) Matrix population models. Construction, analysis, and interpretation. Sinauer, Sunderland, MA.

15. Falconer, D.S. and T.F.C. Mackay (1996) Introduction to quantitative genetics, fourth edition. Longman, Essex, England.

16. Kirkwood, T.B.L. and M.R. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London, B 332:15-24.

17. Partridge,L. and N.H. Barton (1993) Optimality, mutation and the evolution of ageing. Nature 362:305-311.

18. Abrams, P.A. (1993) Does increased mortality favor the evolution of more rapid senescence? Evolution 47:877-887.

19. Partridge,L. and D. Gems (2006) Beyond the evolutionary theory of ageing, from functional genomics to evo-gero. Trends in ecology and evolution 21:334-340.

20. Martin, G. (2007) Modalities of gene action predicted by the classical evolutionary biological theory of aging. Annals of the New York Academy of Sciences 1100:14-20.

21. Metcalf, C.J. and S. Pavard (2007) Why evolutionary biologists should be demographers. Trends in ecology and evolution 22:205-212.

22. Monaghan, P., Charmantier, A., Nussey, D.H. and R.E. Ricklefs (2008) The evolutionary ecology of senescence. Functional Ecology 22:371-378.

23. Kirkwood, T.B.L. and S. Melov (2011) On the programmed/non-programmed nature of ageing within the life history. Current Biology 21:R701-R707.

24. Shahrestani, P., Quach,J., Mueller,L.D., and M.R. Rose (2012) Paradoxical physiological transitions from aging to late life in Drosophila. Rejuvenation research 15:49-58.

25. Lotka, A. (1924) Elements of mathematical biology, first edition. Reprinted 1956 Dover Publications Inc., New York, USA.

26. Stearns, S.C. (1992) The evolution of life histories. Oxford University Press, Oxford.

27. Caswell, H. (1996) Second derivatives of population growth rate: calculation and applications. Ecology 77:870-879.

28. Steinsaltz,D., Evans,S.N. and K.W. Wachter (2005) A generalized model of mutation-selection balance with applications to aging. Advances in applied mathematics 35:16-33.

29. Wachter, K.W., Evans, S.N. and D. Steinsaltz (2013) The age-specific force of natural selection and biodemographic walls of death. Proceedings of the National Academy of Sciences USA 110:10141-10146.

30. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

31. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of aging and longevity. Proceedings of the Royal Society B: Biological Sciences 205:531-546.

32. Baudisch, A. (2005) Hamilton's indicators of the force of selection. Proceedings of the National Academy of Sciences USA 102:8263-8268.

33. Abrams, P.A. (1991) The fitness costs of senescence: the evolutionary importance of events in early adult life. Evolutionary Ecology 5:343-360.

34. Wensink, M.J., van Heemst, D., Rozing, M.P. and R.G.J. Westendorp (2012) The maintenance gap: a new theoretical perspective on the evolution of aging. Biogerontology 13:197-201.

35. Kriete, A. (2013) Robustness and aging - a systems-level perspective. BioSystems 112:37-48.

36. Doonan, R., McElwee, J.J., Matthijssens, F., Walker, G.A., Houthoofd, K., Back, P., et al. (2008) Against the oxidative damage theory of aging: superoxide dismutases protect against oxidative stress but have little or no effect on life span in Caenorhabditis elegans. Genes and Development 22:3236-3241.

37. Gems, D. and R. Doonan (2009) Antioxidant defense and aging in *C. elegans*. Cell Cycle 8:1681-1687.

38. Sozou, P.D. and R.M. Seymour (2004) To age or not to age. Proceedings of the Royal Society B 271:457-463.

39. Baudisch, A. and J.W. Vaupel (2010) Senescence vs. sustenance: evolutionary-demographic models of aging. Demographic Research 23:655-668.

40. Baudisch, A. (2012) Birds do it, bees do it, we do it: contributions of theoretical modelling to understanding the shape of ageing across the tree of life. Gerontology 58:481-489.

41. Charlesworth, B. (1990) Optimization models, quantitative genetics, and mutation. Evolution 44:520-538.

42. Dañko, M.J., Kozlowski, J., Vaupel, J.W. and A. Baudisch (2012) Mutation accumulation may be a minor force in shaping life history traits. PloSOne 7:e34146.

Chapter 6

‘Extrinsic mortality’ does not drive the evolution of senescence

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Abstract

The evolution of senescence is often explained by arguing that, in nature, few individuals survive to be old and that therefore it is evolutionarily unimportant what happens to organisms when they are old. A corollary to this explanation is that extrinsically imposed mortality, because it reduces the chance of living to be old, favors the evolution of senescence. These ideas, although incorrect, are widespread. We show that selection gradients are not proportional to survivorship, but to the stable age-distribution, and we highlight the difference. We also show that selection gradients decline with age even in the hypothetical case of zero mortality. We analyze age-independent perturbations of mortality, and show that they affect neither selection gradients nor the solution of optimal life history models. We propose correct verbal explanations of the reason that selection gradients decline with age, and discuss other relevant factors such as density effects and interaction mortality.

Introduction

The evolution of senescence is often explained by arguing that, in nature, only few individuals survive to be old and that therefore it is evolutionarily unimportant what happens to organisms when they are old. A corollary to this explanation is that extrinsically imposed mortality, because it reduces the chance of living to be old, favors the evolution of senescence.

Although both of these ideas have been refuted in the technical literature, they persist, and it is easy to find statements of them:

> "(...) The decline in the proportion of individuals remaining alive at progressively older ages, as a consequence of extrinsic mortality factors, provides sufficient explanation for the decline in the strength of selection with age" [1].

> "(...) the force of selection will show a monotonic decline (...), whether or not the organism experiences intrinsic ageing, being a consequence only of mortality" [2].

> "Extrinsic hazards (such as predation, infection and the physical environment) leave progressively fewer individuals alive, so that mutations affecting only older age classes experience a declining force of natural selection" [3].

Similar statements are found, e.g., in [4–7].

Thus, the claim is that since survivorship (the probability of survival from birth to a given age, $\ell(x)$ in life table notation) declines with age, it is relatively unimportant to evolution what happens to organisms when they are old. A natural consequence of this idea is that a steeper decline in survivorship should lead to higher rates of senescence, while a more gradual decline should lead to lower rates of senescence:

> "The central prediction of classic theory is that high extrinsic mortality leads to accelerated aging" [8].

In practice, it is difficult to define 'extrinsic mortality'. Intrinsic and extrinsic causes may interact to produce mortality, while only the latter are factors over which the organism has no control. Studies have compared populations with high and low levels of predation [e.g. 9], or compared populations with different habitats [e.g. 10] as ways to compare levels of extrinsic mortality. The level of internal control over the resulting mortality, however, may vary. Extrinsic mortality needs specification before its (evolutionary) effects can be discussed.

The issue that we wish to address, however, is not definitions of extrinsic mortality, but the role that extrinsic mortality has been ascribed in evolutionary theories of senescence in general. Selection gradients certainly decline with age, and that decline implies the relative unimportance of advanced ages, which does indeed facilitate the evolution of senescence. But declining survivorship does not drive the decline. We demonstrate

this by referring to Caswell's [11-13] decomposition of the selection gradients on mortality and fertility, by showing that selection gradients would decline even if mortality were zero at all ages (which is admittedly hypothetical, but proves the point), and by showing that selection gradients are not affected by the simplest representation of extrinsic mortality: age-independent mortality.

Once we have established that selection gradients decline, and why, we explore whether extrinsic mortality may affect the pattern of decline of the selection gradients, given some specific definitions of the term. Relevant findings in this respect are discussed.

Why senescence can evolve: selection gradients decline with age

The action of selection on a trait depends on how fitness changes in response to a change in that trait. This response is called the selection gradient.[1] It expresses by how much fitness changes if some trait changes, i.e. the sensitivity of fitness to changes in the trait.

Senescence can evolve because the selection gradients on mortality and fertility decline with age. The absolute value of these selection gradients goes down with age for all life histories.

The mathematics are as follows. Darwinian fitness is given by r [14-17], the unique real root of the Euler-Lotka equation [18]:

$$\int_0^\infty e^{-rx}\ell(x)m(x)dx = 1 \tag{6.1}$$

Here, $m(x)$ is the reproductive rate at age x, while $\ell(x)$ denotes survivorship up to age x, which is a function of the mortality rate $\mu(x)$:

$$\ell(x) = e^{-\int_0^x \mu(t)dt} \tag{6.2}$$

The differential of r is

$$\delta r = \int_0^\infty \left[H^*(a)\delta m(a) + H^\dagger(a)\delta\mu(a)\right] da \tag{6.3}$$

where

$$H^*(a) = \frac{1}{T}e^{-ra}\ell(a) \tag{6.4}$$

$$H^\dagger(a) = -\frac{1}{T}\int_a^\infty e^{-rx}\ell(x)m(x)dx \tag{6.5}$$

[1] In earlier literature, terms like 'force of selection' [e.g. 19] or 'selection pressure' [e.g. 44] were used for this quantity. Analogies to forces, or pressures, however, obscure the nature of the term as the slope, or gradient, of fitness as a function of the trait. The term was carefully defined by Lande [15] and Arnold and Wade [45], and is fundamental to quantitative genetics. It also appears in the formalism of the canonical equation of Adaptive Dynamics [e.g. 46].

with

$$T = \int_0^\infty x e^{-rx} \ell(x) m(x) dx \tag{6.6}$$

$H^*(a)$ and $H^\dagger(a)$ are the selection gradients on age-specific fecundity and mortality respectively, discovered by Hamilton [19]. Together with the description of some biological perturbation $dm(a)$ and $d\mu(a)$, the selection gradients describe how fitness changes, i.e. dr (see [20,21] for discussion and application). The absolute values of (6.4) and (6.5) decline with age for all life histories[2]

Declining selection gradients with age reduce the evolutionary disadvantage of late-life deterioration, i.e. senescence [22]. Senescence may evolve because over age, selection becomes progressively inept to counterbalance the accumulation of deleterious mutations [17,22], or because selection may favor early-life benefits that are correlated with negative effects at later ages [22-24]. It should be noted that declining selection gradients are a necessary but not a sufficient condition for the evolution of senescence, and that selection gradients are only part of a complete description of evolutionary change (equation (6.3), [20]). The response to the selection gradients depends on the genetic (co)variance structure of the traits involved [e.g. 15].

Why the selection gradient declines with age

To understand what determines the selection gradients, it is helpful to decompose Hamilton's indicators into well-known demographic quantities within the framework of stable population theory [24], to consider the case when mortality is zero for all ages, and to evaluate the result of an age-independent perturbation of mortality.

Survivorship versus the stable age-distribution

Let $v(a)$ be the reproductive value, which expresses the value of the expected reproductive output of an organism given that it is alive and of age a:

$$v(a) = \frac{e^{ra}}{\ell(a)} \int_a^\infty e^{-rx} \ell(x) m(x) dx \tag{6.7}$$

Let $c(a)$ be the stable age-distribution, which gives the proportional composition of the population by age:

$$c(a) = \frac{e^{-ra} \ell(a)}{\int_0^\infty e^{-rx} \ell(x) dx} \tag{6.8}$$

[2]One special exception must be mentioned. Unlike the gradient on mortality, the selection gradient on fertility can *increase* with age in a declining population. If r is sufficiently negative relative to survival probability [47-49], the stable age distribution, and thus the selection gradient on fertility, will increase with age. It is unlikely that a population would persist in such a negative growth phase for long enough for evolution to act. However, Mertz [47] suggested that the delayed onset of reproduction in the California condor (*Gymnogyps californianus*) might reflect millenia of population decline from a distribution over all of North America to the species current restricted range in central California. Caswell [49] proposed that selection gradients while declining could be important for nonequilibrium populations.

Finally, let b be the birth rate:

$$b = \left[\int_0^\infty e^{-rx}\ell(x)dx\right]^{-1} \tag{6.9}$$

With T as in equation (6.6), Hamilton's indicators of selection pressure can be decomposed as follows[11,13]:

$$H^*(a) = \frac{c(a)}{bT} \tag{6.10}$$

$$H^\dagger(a) = \frac{-c(a)v(a)}{bT} \tag{6.11}$$

Of both indicators, the denominator is just a scalar. The numerator of each indicator consists of the proportional abundance of organisms in some age class, $c(a)$, and the value of its expected reproductive output in the subsequent age-class. In case of reproduction, the 'subsequent' age-class is age zero, in which the value of the expected reproductive output is one ($v(0) = 1$, since equation (6.1) holds). Hence equation (6.10). In case of survival, the value in the next age-class is $v(a)$. Hence equation (6.11). Because $H^\dagger$ refers to mortality rather than survival, $H^\dagger$ is negative.

The decomposition above clarifies why the suggestion that "potential contributions to fitness by individuals of a given age must be weighted by the probability of surviving up to that point" [26] is incorrect. Rather, it must be weighed by the proportional abundance of organisms of some age, i.e. the stable age-distribution $c(a)$ (equation (6.8)).

Survivorship and the proportional abundance of organisms in each age class are not the same. Survivorship at age a is the proportion of a cohort that dies after age a. Survivorship is a function of mortality only (equation (6.2)); no organisms are added to the population that is considered (a cohort). The stable age-distribution on the other hand is a function not only of mortality, but also of reproduction, because organisms are added to the population that is considered. In age-classified models, newborns are zero-year-olds, which next become one-year-olds while more zero-year-olds are born, and so forth. In this way, reproduction affects the distribution of the population over age-classes. The term e^{-rx} in the stable age-distribution (equation (6.8)) models this effect.

Why would impact on individual fitness (H^* and $H^\dagger$) be a function of the population growth rate r through e^{-rx}? The answer lies in the use of r as a measure of fitness. Although fitness is an attribute of individuals, high fitness results in a growing population that descends from the focal organism. It is this "population growth rate of the individual" that r refers to if it is used as a measure of fitness [27]. Reproduction adds zero-year-olds to that population. As a result, the proportion of that population that is of high ages is reduced, as modeled by e^{-rx} in equation (6.8), so that an event at higher ages is experienced by a reduced proportion of the population. This mechanism also causes the decrease in the proportion of older test tubes in Medawar's [22] famous thought experiment, and not, as Medawar thought, extrinsic mortality. The survivorship function does not model this phenomenon.

Although evolutionary impact is proportional to the stable age-distribution, survivorship is part of the formal description of the stable age-distribution. To understand fully why the selection gradients decline with age, we now consider the case in which mortality is zero for all ages, and evaluate what happens if mortality is perturbed in an age-independent way.

If mortality is zero for all ages

Consider the extreme case of zero mortality at all ages. Then survivorship remains constant at 100% and does not decline with age:

$$\ell(a)\,|_{\mu=0} \;=\; 1 \qquad \text{for all } a \tag{6.12}$$

The stable age-distribution, in contrast, still changes with age and becomes:

$$c(a)\,|_{\mu=0} \;=\; \frac{e^{-ra}}{\int_0^\infty e^{-rx}dx} \tag{6.13}$$

As long as there is some reproduction, r is necessarily greater than zero, which makes $c(a)$ a declining function of age. Since births add zero-year-olds to the population, this age-class will always be the largest compared to progressively older ages. The stable age-distribution declines with age as a result.

Hamilton's selection gradients for the case of zero mortality yield:

$$H^*(a)\,|_{\mu=0} \;=\; \frac{e^{-ra}}{T} \tag{6.14}$$

$$H^\dagger(a)\,\big|_{\mu=0} \;=\; -\frac{1}{T}\int_a^\infty e^{-rx}m(x)dx \tag{6.15}$$

Again, $r > 0$ given that there is some reproduction, so $H^*(a)$ and $H^\dagger(a)$ decline with age even if survivorship does not.

If mortality changes in an age-independent way

It is frequently claimed that an evolutionary effect of additional extrinsic mortality is that it exacerbates senescence. However, it has been shown that this is not true if extrinsic mortality is independent of age: in this case it has no effect on the (pattern of decline in the) selection gradients [28,29]. A unit increase in an age-independent mortality term leads, per definition, to a unit decrease of the population growth rate. While such extrinsic mortality reduces survivorship at older ages, thus reducing the abundance of this age class in the overall population, the reduced population growth rate means that fewer organisms will be present in lower age classes too, canceling the effect of reduced survivorship on the stable age-distribution or the reproductive value. The selection gradients are therefore essentially insensitive to age-independent mortality.

Imposing an age-independent extrinsic mortality is equivalent to disregarding part of the population. Nothing except for the population size, implying a greater role for stochasticity, would be different if partitions of a population are considered rather than the population as a whole:

> "Imagine that we take a population with a huge number of individuals into a sufficiently large laboratory such that there is no density dependence. We allow the population to reach a stable equilibrium with respect to age-structure and gene frequencies. Now we take that population and apply extra mortality by removing half the individuals at random, regardless of age. After this extrinsic mortality event, absolutely nothing will have changed that can affect selection: the environment, reproductive output of survivors, age-distribution, phenotypes, and gene frequencies all stay the same" [30].

The mathematics, in line with the results of Abrams [28] and Caswell [29], are as follows. Survivorship (equation (6.2)) can be written as the product of two exponentials, one that contains a constant that represents the age-independent extrinsic mortality γ, and one that contains all age-dependent mortality terms, $\mu_0(x)$:

$$\ell(x) = e^{-\gamma x} e^{-\int_0^x \mu_0(t)dt} \tag{6.16}$$

Plugging this expression in the Euler-Lotka equation and merging e^{-rx} with $e^{-\gamma x}$ yields

$$\int_0^\infty e^{-(r+\gamma)x} e^{-\int_0^x \mu_0(t)dt} m(x)dx = 1 \tag{6.17}$$

For any specified pattern of reproduction $m(x)$ and age-dependent mortality $\mu_0(x)$ there exists one and only one real $r+\gamma$ that satisfies equation (6.17). This implies, r being the dependent variable, that:

$$\frac{\partial r}{\partial \gamma} = -1 \tag{6.18}$$

As a result, the outcome is invariant under a change in γ wherever survivorship and e^{-rx} appear together. This is true for the stable age-distribution $c(a)$, reproductive value $v(a)$, generation time T and the birth rate b, i.e. for all components of Hamilton's indicators of selection pressure (see decompositions (6.10) and (6.11)). Thus, Hamilton's selection gradients as a whole are insensitive to γ:

$$\frac{\partial H^*(a)}{\partial \gamma} = 0 \tag{6.19}$$

$$\frac{\partial H^\dagger(a)}{\partial \gamma} = 0 \tag{6.20}$$

Survivorship declines more steeply with age if γ is increased; the selection gradients do not.

In this section we have demonstrated three points: 1. The selection gradients at each age are proportional to the stable age-distribution at that age, not to survivorship (equations (6.10) and (6.11)). The stable age-distribution is quite distinct from survivorship, and we have highlighted the difference. 2. Even if survivorship did not decline with age ($\mu = 0$), the stable age-distribution and the selection gradients would still go down with age. 3. An age-independent perturbation of mortality does not affect any of the components of the selection gradients, even though it clearly does affect survivorship. These three things combined unequivocally demonstrate that declining survivorship does not drive the age-related decline in the selection gradients.

A correct verbal expression of the basic reason for the decline of the selection gradients with age could be as follows. If an organism is older, it has accumulated more reproduction during its past life course than when it was young. Current events do not change past reproduction. The offspring that have been produced started life as zero-year-olds that contribute to a population that descents from the focal organism. A progressively smaller proportion of that population is affected by anything that affects only the old. Since past contributions to fitness can only go up with age, the selection gradients can only go down with age.

An equivalent verbal intuition is given by Flatt and Promislow [31]:

> "If the effects of [a] mutation are confined to some late age, individuals carrying the mutation will likely have already passed it on to their offspring by the time it is expressed, and natural selection will be relatively ineffective in eliminating it."

These verbal explanations are straightforward and in line with evolutionary theory.

Optimization models

Our considerations so far have focused on changes of fitness (dr): selection gradients indicate how fitness would respond if some trait value were changed. Evolutionary theory uses this to predict changes in the traits, given patterns of genetic variance and covariance [15]. An alternative approach is optimization: given mechanistic considerations, what strategy maximizes fitness? For example, in the disposable soma theory it is posited that organisms allocate their resources, for instance energy, between the competing demands of reproduction and somatic maintenance [24,32,33]. There are two places to invest: 1. keep your own entity going. 2. create more copies of your entity. Resources invested in one function cannot be invested in the other. Depending on the return on each investment, some allocation strategy will maximize fitness, i.e. be optimal. Proposed models of such trade-offs (reviewed in [33]) apply direct optimization rather than relying on selection gradients, although the trade-offs certainly can be modeled in terms of selection gradients [12,20].

If an investment is made in either the organism itself or in its offspring, and both die of purely extrinsic mortality at the same rate, then nothing is gained by making one allocation rather than the other. Alternatives are equally bad, no organism does better

than the other, so no evolutionary response to natural selection may be expected. As a result, optimality is not affected by age-independent mortality. Additional information is necessary to decide what is optimal, such as how mortality would increase over age if an organism were to forego somatic maintenance. This intuition is formalized below, in line with earlier results [35-37].

Trade-offs between or within the mortality and fecundity functions are subject to some lower level parameter θ that is optimized so as to maximize r. In addition to θ, r depends on the age-independent mortality γ, which is independent of θ. Given relationship (6.18), which is a general result of the Euler-Lotka equation (equation (6.1)), it follows that

$$r(\theta,\gamma) = r(\theta,0) - \gamma \tag{6.21}$$

As a result of this independence, it holds that

$$\frac{dr(\theta,\gamma)}{d\theta} = \frac{dr(\theta,0)}{d\theta} \tag{6.22}$$

Thus, if $\hat{\theta}$ satisfies the optimality condition

$$dr = \left.\frac{\partial r(\theta,0)}{d\theta}\right|_{\theta=\hat{\theta}} = 0 \tag{6.23}$$

it also satisfies the optimality condition

$$dr = \left.\frac{\partial r(\theta,\gamma)}{d\theta}\right|_{\theta=\hat{\theta}} = 0 \tag{6.24}$$

The optimal value of θ is thus independent of (a change in) age-independent mortality γ.

Discussion

The ghost of extrinsic mortality continues to haunt the evolutionary theory of senescence. It does so in two ways. First, as the quotes in the introduction exemplify, it is still widely believed that extrinsic mortality causes senescence, because it reduces the chances of survival to advanced ages. If few organisms survive to old age, it is argued, old ages are less evolutionarily important. This idea is admittedly intuitive, but wrong, and leads to a second error: the idea that higher extrinsic mortality should lead to a higher rate of senescence.

As we show, evolutionary impact is not proportional to survivorship, but to the proportion of the population that is of some age, i.e. the stable age-distribution. We have demonstrated the differences between these quantities and shown that selection gradients would decline with age even in the hypothetical case of zero mortality at all ages. We have shown that the decline in survivorship that results from age-independent mortality does not affect the selection gradients.

Our analysis holds for r as a measure of fitness, within the context of stable population theory. However, the basic reason why state- and age-independent mortality should

not matter to evolution is much more general, and unrelated to the choice of the measure of fitness: If mortality is purely extrinsic and age-independent, no strategy will allow the organism to avoid this mortality.

Selection gradients decline with age because reproduction accumulated up to a given age, which is unaffected by events after that age, contributes to the population and reduces the fraction of the population that is affected by events at higher ages. Since past reproduction can only go up with age, the selection gradients can only go down with age.

Our analysis of age-independent mortality shows that extrinsic mortality *per se* has no effect on the evolution of senescence. Age-dependent mortality, and age-dependent density effects, by contrast, can have such effects [28,29].

Abrams [28] suggested that extrinsic mortality could affect the rate of senescence through age-dependent density effects, even if the mortality is the same for organisms of any age and state. This occurs when organisms of different age respond differently to population density. He concluded that, depending on the age dependence of the density effects, anything is possible [28]; no universal evolutionary result, such as promotion of senescence, can be expected from an increase in extrinsic mortality.

In the case of density-independent models, Caswell [29] suggested from preliminary results that extrinsic mortality focused on young individuals would reduce the evolution of senescence, while extrinsic mortality focused on old individuals would increase the evolution of senescence. Indeed, a role for extrinsic factors in some death event does not exclude a role for intrinsic factors in the same event [38,39]. In fact, it is hard to think of mortality that is determined exclusively extrinsically. For instance, predation certainly needs an extrinsic factor, the predator, but it also needs an intrinsic factor, the prey. What about abiotic factors, such as being hit by lighting? Surely, few forms of life may reasonably be expected to withstand a 30kA lightning discharge. But even if vulnerability is independent of age, exposure may not be, because behavioral patterns will determine which individuals are in locations with high probability of lightning strikes. These behavioral factors may well vary with age, leading to age-dependence of the interaction mortality.

What would be the evolutionary consequences of changing an extrinsic cause (of all the causes that are required to cause the death event), for instance the density of predators? The general answer is that depending on the interactions, anything goes[29]. Natural selection will tend to shift life histories so as to avoid spending time in vulnerable states, depending on the costs and the alternatives [39]. For instance, experiments have shown that if only adults are subject to 'extrinsic mortality', a higher rate of senescence can evolve [8,40]. In this case, organisms can increase reproduction at a cost to survival, so that resources are concentrated in organisms of less vulnerable state. On the other hand, if weaker organisms are targeted by predators, it is evolutionary beneficial to remain a strong and vigilant adult, and 'extrinsic mortality' will work counter-senescence (a possible explanation for the findings of Reznick et al. [9]). Notice that such age-dependent density effects are only feasible if organisms of different ages have different physiological states, for otherwise there is no good reason why extrinsic factors would affect organisms in an age-dependent way: age-specificity can only exist if it is in fact (hidden) state-specificity [41].

The arguments laid out in this paper have theoretical and practical consequences. Empirical research has shown little support for the "central prediction" of the evolutionary theory of senescence [8] that a higher level of extrinsic mortality (predators, environment, laboratory) should lead to a higher rate of senescence [9,26]. A number of authors have concluded that hence there is a need for a more involved theory of senescence, in which mortality is state dependent, and/or in which density effects play a prominent role [8,9,26]. Given the results derived in this paper, it becomes clear why there is little support for the central prediction. It is not that this prediction happens not to predict biological reality; life history theory simply makes no such prediction. After decades of theoretical work, we are still challenged to develop theory that provides more than an incidental match with the data. Our results corroborate the need for theory that is more involved; it may include combinations of age- and stage-specific mortality [42], density effects, and/or interaction mortality. Such a theory should involve mechanisms of senescence, as evolutionary pressures alone are only half the story [20,43].

Conclusion

1. Selection gradients on mortality and fertility decline with age because accumulated reproduction from earlier ages, that remains unaffected by later events, contributes to the population, reducing the share of the population that is subject to any events specific for higher ages.
2. The age-related decline of selection gradients can be explained without reference to mortality.
3. An age-independent change in mortality does not affect the selection gradients.
4. Since it is unlikely that purely extrinsically determined mortality even exists, (supposed) causes of mortality and their (supposed) interactions must be specified before any conclusions about evolutionary effects of the mortality can be drawn.
5. The evolutionary response to age-dependent mortality and/or age-dependent density regulation depends on how different age groups are affected; no general statement can be made about how density effects and interaction mortality mold the evolution of age-patterns.
6. There is need for more involved theory that includes not only density effects and age-dependent mortality, but also an account of the mechanisms and their interaction with the environment that shape the evolution of senescence.

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References

1. Monaghan, P., Charmantier, A., Nussey, D.H. and R.E. Ricklefs (2008) The evolutionary ecology of senescence. Functional Ecology 22:371-378.

2. Kirkwood, T.B.L. and S. Melov (2011) On the programmed/non-programmed nature of ageing within the life history. Current Biology 21:R701-R707.

3. Regan, J.C. and L. Partridge (2013) Gender and longevity: Why do men die earlier than women? Comparative and experimental evidence. Best Practice & Research Clinical Endocrinology & Metabolism 27:467-479.

4. Gems, D., and L. Partridge (2013) Genetics of longevity in model organisms: debates and paradigm shifts. Annual Review of Physiology 75:25.1-25.24.

5. Fabian, D. and T. Flatt (2011) The evolution of aging. Nature Education Knowledge 2:9.

6. Fabian, D. and T. Flatt. (2012) Life history evolution. Nature Education Knowledge 3:24.

7. Vijg, J. and J. Campisi (2008) Puzzles, promises and a cure for ageing. Nature 454:1065-1071.

8. Chen, H. and A.A. Maklakov (2012) Longer life span evolves under high rates of condition-dependent mortality. Current Biology 22:2140-2143.

9. Reznick, D.N., Bryant M.J., Roff, D., Ghalambor, C.K. and D.E. Ghalambor (2004) Effect of extrinsic mortality on the evolution of senescence in guppies. Nature 431:1095-1099.

10. Austad, S.N. (1993) Retarded senescence in an insular population of Virginia opossums (*Didelphis virginiana*). Journal of Zoology 229:695-708.

11. Caswell, H. (1978) A general formula for the sensitivity of population growth rate to changes in life history parameters. Theoretical Population Biology 14:215-230.

12. Caswell, H. (2001) Matrix population models. Construction, Analysis, and Interpretation. Sinauer, Sunderland, MA, USA.

13. Caswell, H. (2010) Reproductive value, the stable stage distribution, and the sensitivity of the population growth rate to changes in vital rates, Demographic Research 23:531-548.

14. Fisher, R.A. (1930) The fundamental theorem of natural selection. Pages 25-30 *in* The Genetical Theory of Natural Selection. Clarendon Press, Oxford, UK. (Reprinted and revised, 1958. New York: Dover).

15. Lande, L. (1982) A quantitative genetic theory of life history evolution. Ecology 63:607-615.

16. Metz, J.A.J., Nisbet, R.M. and S.A.H. Geritz (1992) How should we define 'fitness' for general ecological scenarios? TREE 7:198-202.

17. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge, UK.

18. Lotka, A. (1924) Elements of Mathematical Biology. Reprinted 1956 by Dover Publications Inc., New York, USA.

19. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology 12:12-45.

20. Wensink, M.J., Wrycza, T.F. and A. Baudisch (2014) No senescence despite declining selection pressure: Hamilton's result in broader perspective. Journal of Theoretical Biology 347:176-181.

21. Arthur, W.B. (1984) The analysis of linkages in demographic theory. Demography 21:109-128.

22. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London, UK.

23. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

24. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

25. Preston, S., Heuveline, P. and M. Guillot (2001) Demography. Blackwell, Oxford, UK.

26. Williams, P.D., Day, T., Fletcher, Q. and L. Rowe (2006) The shaping of senescence in the wild. Trends in Ecology and Evolution. 21:458-463.

27. McGraw, J.B. and H. Caswell (1996) Estimation of individual fitness from life-history data. The American Naturalist 147:47-64.

28. Abrams, P.A. (1993) Does increased mortality favor the evolution of more rapid senescence? Evolution 47:877-887.

29. Caswell, H. (2007) Extrinsic mortality and the evolution of senescence. Trends in Ecology and Evolution 22:173-174.

30. Moorad, J.A. and D.E.L. Promislow (2010) Evolution: aging up a tree? Current Biology 20:R406-R408.

31. Flatt, T. and D.E.L. Promislow (2007) Still pondering an age-old question. Science 318:1255-1256.

32. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of ageing and longevity. Proceedings of the Royal Society London B 205:531-546.

33. Kirkwood, T.B.L. and M. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London, B 332:15-24.

34. Baudisch, A. (2012) Birds do it, bees do it, we do it: Contributions of theoretical modelling to understanding the shape of ageing across the tree of life. Gerontology 58:481-489.

35. Gadgil, M. and W.H. Bossert (1970) Life historical consequences of natural selection. The American Naturalist 104:1-24.

36. Taylor, H.M., Gourley, R.S., Lawrence, C.E. and R.S. Kaplan (1974) Natural selection of life history tributes: an analytical approach. Theoretical Population Biology 5:104-122.

37. Law, R. (1979) Optimal life histories under age-specific predation. The American Naturalist 114:399-417.

38. Wensink, M.J., Westendorp, R.G.J. and A. Baudisch (2014) The causal pie model: an epidemiological method applied to evolutionary biology and ecology. Ecology and Evolution 4:1924-1930.

39. Williams, P.D. and T. Day (2003) Antagonistic pleiotropy, mortality source interactions, and the evolutionary theory of senescence. Evolution 57:1478-1488.

40. Stearns, S.C., Ackermann, M., Doebeli, M. and M. Kaiser (2000) Experimental evolution of aging, growth, and reproduction in fruit flies. Proceedings of the National Academy of Sciences of the USA 97:3309-3313.

41. Wensink, M.J. (2013) Age-specificity and the evolution of senescence - a discussion. Biogerontology 14:99-105.

42. Caswell, H. and R. Salguero-Gómez (2013) Age, stage and senescence in plants. Journal of Ecology 101:585-595.

43. Baudisch, A. and J.W. Vaupel (2012) Getting to the root of aging. Science 338:618-619.

44. Emlen, J.M. (1970) Age specificity and ecological theory. Ecology 51:588-601.

45. Arnold, S.J. and M.J. Wade (1984) On the measurement of natural and sexual selection: theory. Evolution 38:709-719.

46. Doebeli, M. (2011) Adaptive Diversification. Princeton University Press, Princeton, New Jersey, USA.

47. Mertz, D.B. (1971) Life history phenomena in increasing and decreasing populations. Pages 361-400 *in* G.P. Patil, E.C. Pielou, and W.E. Waters, eds. Spatial ecology, volume 2: Sampling and monitoring biological populations and population dynamics. Pennsylvania State University Press.

48. Caswell, H. and A. Hastings (1980) Fecundity, developmental time, and population growth rate: an analytical solution. Theoretical Population Biology 17:71-79.

49. Caswell, H. (1982) Life history theory and the equilibrium status of populations. American Naturalist 120:317-339.

Chapter 7

Interaction mortality: senescence may have evolved because it increases lifespan

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Abstract

Given an extrinsic challenge, an organism may die or not depending on how the threat interacts with the organism's physiological state. To date, such interaction mortality has been only a minor factor in theoretical modeling of senescence. We describe a model of interaction mortality that does not involve specific functions, making only modest assumptions. Our model distinguishes explicitly between the physiological state of an organism and potential extrinsic, age-independent threats. The resulting mortality may change with age, depending on whether the organism's state changes with age. We find that depending on the physiological constraints, any outcome, be it 'no senescence' or 'high rate of senescence', can be found in any environment; that the highest optimal rate of senescence emerges for an intermediate physiological constraint, i.e. intermediate strength of trade-off; and that the optimal rate of senescence as a function of the environment is driven by the way the environment changes the effect of the organism's state on mortality. We conclude that knowledge about the environment, physiology and their interaction is necessary before reasonable predictions about the evolution of senescence can be made.

Introduction

The effect of extrinsically imposed mortality on the evolution of senescence has received considerable attention [1-6]. Initially, it was advocated that extrinsically imposed mortality should accelerate, and even cause senescence [1-4], an idea that survives to date [7]. This view has been refuted by rigorous modeling [8,9]. In general, it holds that mortality does not affect evolution if it affects all organisms equally [8-10]. The intuitive reason for this is that evolution favors a phenotype (strategy) if it is better at propagation than other strategies. If all strategies are affected equally, no strategy improves relative to others, and selection gradients remain unchanged.

Mortality that does not distinguish between individuals is often called 'extrinsic mortality' and modeled as an age-independent parameter in the mortality function of age-structured models [8,9,11-13]. In these models, extrinsic mortality is a discounting factor in the survival function that cannot be molded in any way by the (fictitious) organism that is studied. However, whether environmental threats result in mortality depends on the interaction of those threats with an organism's physiological state [11,14,15]. By adjusting its state, an organism can influence death from environmental causes. In this respect, we highlight that age-independence does not imply state-independence: the relevant state parameters might just happen not to change over age. Indeed, the level of an age-independent term in the mortality function can be molded by the organism's state, and this molding is subject to natural selection.

To investigate mortality-environment interactions from a theoretical perspective, we model a trade-off between an age-independent and an age-dependent mortality term. As an example of a biological rationale for such a model, Wensink et al. [16] have suggested that it could be beneficial from an evolutionary standpoint to attain a state that is unmaintainable by its very nature, causing mortality to be low at young ages, but to increase over time. As a result, death can be postponed to later ages, depending on the magnitude of initial reduction relative to the ensuing increase in mortality with age.

Many of the theoretical models of senescence that have been proposed depend on particular functions [13,17-19]. This suffices for a proof of principle, but leaves one wondering what the result would have been had a different function been used. We postulate general mathematical conditions that characterize the trade-off. As a result, the model does not predict exact patterns of mortality, but rather charts the range of outcomes that can be obtained with specific models that fulfill the formal conditions.

We find that depending on the physiological constraints, any outcome is possible in any environment, be it 'no senescence' or 'high rate of senescence'; that the highest optimal rate of senescence emerges for an intermediate physiological constraint; and that the optimal rate of senescence as a function of the environment is driven by the way the environment changes the effect of the organism's state on mortality. We conclude that predicting the outcome requires knowledge about the interaction of the environment and the organismal physiology: separately, these have little predictive power. We propose, perhaps paradoxically, that senescence may have evolved because it extends lifespan.

Analysis

Consider the mortality function

$$\mu(x;k,s,E) = e^{ksx} + E/(k+1). \tag{7.1}$$

Variable x denotes age. Separated from the variable by a semi-colon are the age-independent parameters k, s and E. E models the environment, higher values indicating a more challenging environment, k is a trade-off parameter that reduces death through the term $E/(k+1)$ but gives rise to an increase of mortality over age through the term e^{ksx}, modified by s, which models the 'severity' of the trade-off (high s leads to fast increase in mortality with age for any specified $k > 0$). For $k = 0$ mortality is initially higher than for $k > 0$, but does not rise further with age, while any increase in k reduces mortality initially, but leads to a faster age-related increase in mortality, depending on s.

Because there is no strong theoretical basis on which to assume mortality function (7.1), we define a set of general formal conditions for the mortality function that describes the trade-off. We refer to Appendix S1 for the complete formal description of the model, but the general idea is straightforward. The model has two additive components, $A(x;k,s)$ and $B(k)$. Component A depends on age, while component B does not. Responsible for the trade-off is parameter k. It reduces component B, but increases the rate at which A increases with age, depending on yet another parameter, s. Thus, k reduces mortality initially, but gives rise to an age related increase of mortality. The steepness of this increase depends on s. Parameters k and s and variable x act in a multiplicative manner, i.e. ksx, so that if the organism deteriorates γ times as fast ($k\gamma$), or if deterioration impacts mortality γ times as much ($s\gamma$), or if γ times as much time has passed ($x\gamma$), this all has the same effect. For the analysis of the effect of the environment, we consider that component B co-depends on a parameter E, which models the environmental challenge: $B(k,E)$.

To find k^*, the optimal k, we maximize Darwinian fitness subject to the constraints as formalized. Fitness is given by r as the unique real root of the Euler-Lotka equation [20-23]:

$$\int_0^\infty e^{-rx}\ell(x)m(x)dx = 1. \tag{7.2}$$

Survival is denoted by $\ell(x)$; the reproductive rate is denoted by $m(x)$; and r is the intrinsic rate of increase, or the unique real root of equation 7.2. Survival and the mortality rate are related through

$$\ell(x) = e^{-\int_0^x \mu(t)dt}. \tag{7.3}$$

The derivative of r with respect to k is [19,24]:

$$\frac{\partial r}{\partial k} = -\frac{\int_0^\infty \left(\int_0^x \frac{\partial \mu}{\partial k}(t)dt\right) e^{-rx} l(x)m(x)dx}{\int_0^\infty x e^{-rx} l(x)m(x)dx}. \tag{7.4}$$

This equation is used to evaluate whether r can increase by an increase in k under specified circumstances.

For discussions on how to measure the rate of senescence, see [25,26]. However measured, the rate of senescence will be zero if $k^*s = 0$. We use only this property to obtain our results, hence not relying on a particular measure.

Results

Given our model assumptions, the highest optimal rate of senescence occurs for an intermediate value of s, i.e. an intermediate severity of the trade-off. No senescence occurs if k^* or s equals zero. Hence it follows that the optimal rate of senescence is zero if s is zero. It can also be proven that the optimal rate of senescence is greater than zero for at least one $s > 0$. In addition, the optimal rate of senescence is zero if s is large. This, then, charts the general pattern, proven in Appendix S1: the highest rate of senescence is found for an intermediate physiological constraint s. In Figure 1 we present simulations for several specific functions, varying parameter s. The optimal rate of senescence starts at zero, increases, and then drops back to zero for large enough s. Figure 1 illustrates that there exists a variety of exact patterns, depending on function specifics, that all conform to the general pattern proven in Appendix S1. Whether the optimal rate of senescence is a continuous function of s or not, the location of the peak, and other specifics do depend on the exact trade-off equation and on the age-pattern of reproduction, $m(x)$.

A formal proof of this result is given in Appendix S1, but can be broadly understood from the way k and s interact. A value of $k = 0$ makes r insensitive to s, whereas values of $k > 0$ imply that larger s reduces fitness without bound. Smaller values of s imply a slower increase in mortality over age for a specified $k > 0$, so that, if s is small enough, the initial reduction in mortality outweighs the costs of mortality increasing with age for some $k > 0$.

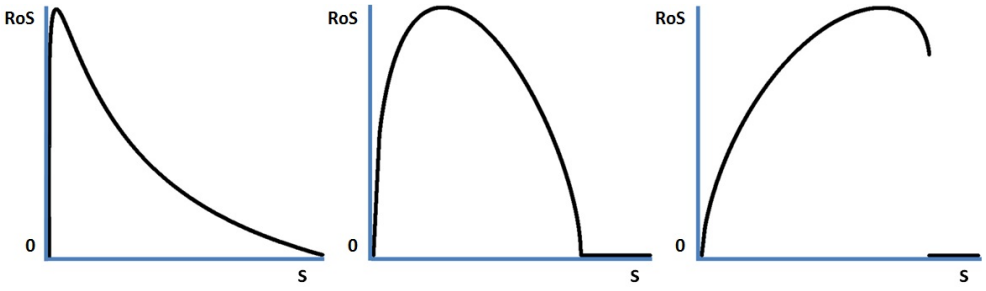

Figure 7.1: The optimal rate of senescence as a function of s for a variety of functions. The rate of senescence 'RoS' calculated as k^*s is given as a function of s for a fixed value of E given three specific trade-off functions. These graphs demonstrate that a variety of patterns may exist, that may have discontinuities and/or points at which the function is not differentiable. Yet these graphs all have in common that the optimal rate of senescence is zero for $s = 0$, then increases, and then returns to zero for large values of s (Appendix S1).

The optimal rate of senescence as a function of the environment is less straightforward (Appendix S1). If $|dB/dk|$ is a monotonously increasing function of the environment, as in equation (7.1), a harsher environment allows for a larger perturbation of mortality. In this case, a harsher environment would work pro-senescence. If, on the other hand, $|dB/dk|$ is not a function of the environment, or a decreasing function of the environment, such an effect is not expected. In Figure 2 we present simulations for several specific functions, for all of which $|dB/dk|$ is a monotonously increasing function of E. These simulations, while demonstrating a distinct possibility, do not follow from the model as a general result. Whether they apply or not depends on how exactly the environment interacts with organismal physiology.

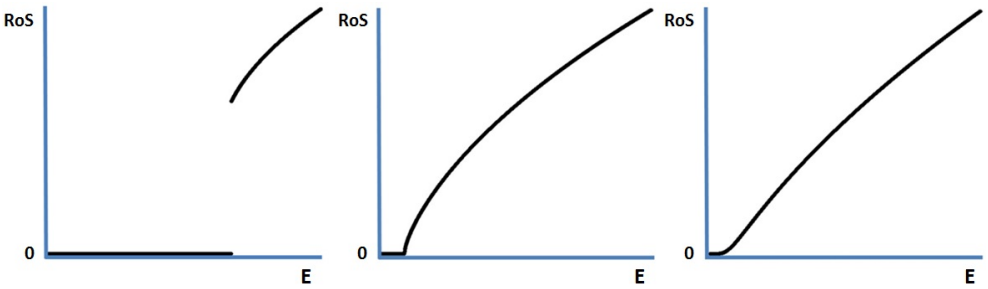

Figure 7.2: The optimal rate of senescence as a function of E for a variety of functions. The rate of senescence 'RoS' calculated as k^*s is given as a function of E for a fixed value of s given three specific trade-off functions. All these functions have in common that a harsher environment allows for a more favorable perturbation of mortality. This, however, may not be the case in general; these simulations are not a general result (Appendix S1). Notice how discontinuities can be introduced by changing the function specifics.

Discussion

There are many ways to model the impact of environmental threats on mortality as a function of an organism's state. We have focused on a term that is a function of ksx versus an age-independent term, because age-independent mortality by default does not effect evolution [8-10]. We show that if an age-independent term of the mortality function is a function of an organism's state, this term can nevertheless be related to senescence, by allowing a trade-off between the mortality rate at age zero versus the rate at which mortality increases with age. Yet, other models may be equally valid representations for environment-state interactions. However, we argue that our model is at least *reasonable*: the interactions may play out the way we have outlined. Rejecting our results for specific circumstances, then, requires the knowledge that the interactions are *not* the way we have modeled them: it requires knowledge of environment-state interactions. Therefore it holds in general that no predictions can be made without knowledge of these interactions.

We found that if $|dB/dk|$ is a monotonously increasing function of E, a harsher environment can be pro-senescence, contrary to elementary evolutionary theory, that states that mortality does not affect evolution if it affects all organisms equally [8-10]. Alongside other plausible explanations such as density effects [8], this finding could explain why a harsher environment was positively correlated with senescence in particular studies, e.g. [27].

Life history models are as general as their assumptions are minimal. The choice of a parametric function for the purpose of theoretical modeling is itself an assumption. It limits a model's predictive power. For instance, if mortality in a life history optimization model is captured by the (parametric) Gompertz function [28,29], one is left wondering what the result would be if mortality were captured by a different function. Detailed prediction of a mortality trajectory requires a deep understanding of its underlying determinants. In life history models, it is rarely the case that exact mortality trajectories can be predicted on the basis of known physiological and molecular mechanisms, their interactions with each other, and their interactions with the environment. Hence, the challenge lies in making models as general as possible without loosing sight of what the model is designed to explore. We have aimed to retain generality by making modest assumptions, yet keeping the focus on the envisioned trade-offs.

A model's value is also limited if that what the model aims to explore cannot be found within the model. For instance, a resource allocation model that does not contain enough resources to fulfill some task will unsurprisingly predict that that task is not fulfilled. If the aim of the model was to find out whether that task will be fulfilled or not, the model does not give any additional insight. The sought after limitation was imposed on the model, and an explanation of why the task is not fulfilled cannot be found by studying the model: the model is "inappropriately constrained" [30]. Our model does not include the possibility of negative senescence [19,30]. Hence, it should be kept in mind that the model does not inform us about the circumstances under which negative senescence could evolve, and that the model in no way excludes this possibility.

When two factors are jointly responsible for affecting fitness, both factors are subject to natural selection [15,31]. In the model presented here, we imposed s and searched for k^*. Assuming that there is variation in k, k will tend to evolve in the direction of k^*. If there is variation in s, s evolves as well. Organisms with lower s will be able to enjoy the benefits of a higher k while avoiding some of the costs, and thus enjoy a selective advantage. Although we analyze k^* as a function of s, we do not chart selection on s.

Most studies on adaptive explanations for the evolution of senescence focus on trade-offs between mortality and reproduction [13,32]. Our study of trade-offs within mortality widens the scope of current modeling of senescence. If a trade-off exists within the mortality function, an increase in fitness derives mostly from lifespan extension. There will be a 'timing effect' as well: survival is more evolutionary rewarding if reproduction during the survived ages is high. Yet, notice that the global results that we present here do not depend on the particular pattern of $m(x)$, but rather on the existence of a trade-off within the mortality function. Our model indicates the global behavior of the model, which depends on the *lifespan extension* achieved if k is increased. Thus, we derive the

hypothesis that senescence may have evolved because senescent organisms outlive non-senescent organisms. This may be counter-intuitive, but the matter becomes clear when the pace of life is distinguished from the shape of senescence [26]. Pace refers to the amount of time in which a process takes place, for instance the time it takes to live a life. Shape refers to the amount and sort of change that happens during that time, for instance if and how mortality and fecundity change during a lifespan. Lifespan is equal to the inverse of average mortality. If mortality increases over age, but starts off from a much lower level than would otherwise be the case, average mortality may go down, implying lifespan extension.

Conclusions

1. In the class of trade-offs that we model, the presence as well as the absence of senescence can be predicted by life history optimization, irrespective of function specifics.
2. The highest optimal rate of senescence occurs for trade-offs that entail costs of intermediate severity in terms of senescence.
3. Optimality of senescence depends on the interaction of environment and physiology. Predictions of optimality cannot be derived from either of them alone.

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References

1. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London.

2. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

3. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

4. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of ageing and longevity. Proceedings of the Royal Society London B 205:531-546.

5. Monaghan, P., Charmantier, A., Nussey, D.H. and R.E. Ricklefs (2008) The evolutionary ecology of senescence. Functional Ecology 22:371-378.

6. Chen, H. and A.A. Maklakov (2012) Longer life span evolves under high rates of condition-dependent mortality. Current Biology 22:2140-2143.

7. Gems, D. and L. Partridge (2013) Genetics of longevity in model organisms: debates and paradigm shifts. Annual Review of Physiology 75:25.1-25.24.

8. Abrams, P.A. (1993) Does increased mortality favor the evolution of more rapid senescence? Evolution 47:877-887.

9. Caswell, H. (2007) Extrinsic mortality and the evolution of senescence. Trends in Ecology and Evolution, 22:173-174.

10. Moorad, J.A. and D.E.L. Promislow (2010) Evolution: aging up a tree? Current Biology 20:R406-R408.

11. Sozou, P.D. and R.M. Seymour (2004) To age or not to age. Proceedings of the Royal Society B 271:457-463.

12. Charlesworth, B. (2001) Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. Journal of Theoretical Biology 210:47-65.

13. Kirkwood, T.B.L. and M.R. Rose (1991) Evolution of senescence: late survival sacrificed for reproduction. Philosophical Transactions of the Royal Society London, B 332:15-24.

14. Williams, P.D. and T. Day (2003) Antagonistic pleiotropy, mortality source interactions, and the evolutionary theory of senescence. Evolution 57:1478-1488.

15. Wensink, M.J., Westendorp, R.G.J. and A. Baudisch (2014) The causal pie model: an epidemiological method applied to evolutionary biology and ecology. Ecology and Evolution 4:1924-1930.

16. Wensink, M.J., van Heemst, D., Rozing, M.P. and R.G.J. Westendorp (2012) The maintenance gap: a new theoretical perspective on the evolution of aging. Biogerontology 13:197-201.

17. Drenos, F. and T.B.L. Kirkwood (2005) Modelling the disposable soma theory of aging. Mechanisms of Ageing and Development 126:99-103.

18. Bonsall, M. (2006) Longevity and ageing: appraising the evolutionary consequences of growing old. Philosophical Transactions of the Royal Society London, B 361:119-135.

19. Wensink, M.J., Wrycza, T.F. and A. Baudisch (2014) No senescence despite declining selection pressure: Hamilton's result in broader perspective. Journal of Theoretical Biology 347:176-181.

20. Caswell, H. (2001) Matrix population models. Construction, Analysis, and Interpretation. Sinauer, Sunderland, MA, USA.

21. McGraw, J.B., and H. Caswell. (1996) Estimation of individual fitness from life-history data. The American Naturalist 147:47-64.

22. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge.

23. Lotka, A. (1924) Elements of mathematical biology, first edition. Reprinted 1956 Dover Publications Inc., New York, USA.

24. Arthur, W.B. (1984) The analysis of linkages in demographic theory. Demography 21:109-128.

25. Rozing, M.P. and R.G.J. Westendorp (2008) Parallel lines: nothing has changed? Aging Cell 7:924-927.

26. Baudisch, A. (2011) The pace and shape of ageing. Methods in Ecology and Evolution 2:375-382.

27. Austad, S.N. (1993) Retarded senescence in an insular population of Virginia opossums (*Didelphis virginiana*). Journal of Zoology 229:695-708.

28. Gompertz, B. (1825) On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Philosophical Transactions of the Royal Society of London 115:513-585.

29. Lenart, A. (2014) The moments of the Gompertz distribution and maximum likelihood estimation of its parameters. Scandinavian Actuarial Journal 2014:255-277.

30. Vaupel, J.W., Baudisch, A., Dolling, M., Roach, D.A., Gampe, J. (2004) The case for negative senescence. Theoretical Population Biology 65:339-351.

31. Wensink, M.J. (2013) Age-specificity and the evolution of senescence: a discussion. Biogerontology 14:99-105.

32. Baudisch, A. (2012) Birds do it, bees do it, we do it: Contributions of theoretical modelling to understanding the shape of ageing across the tree of life. Gerontology 58:481-489.

Appendix S1: proof of global result

Formal description of the model

There are two parameters, k and s, and one variable, x, that interact in a multiplicative manner: ksx. Parameter k sets the organism up for deterioration over age x, while parameter s indicates the impact of deterioration on mortality. Let

$$y(x;k,s) = ksx. \tag{7.5}$$

To create the trade-off, mortality is split into two components, A and B. Component $A(y(x;k,s))$ is age-dependent, while $B(k)$ is age-independent:

$$\mu(x;k,s) = A(y(x;k,s)) + B(k). \tag{7.6}$$

We also assume that mortality is a smooth function.

Parameters k and s are age-independent. The severity of the trade-off is modeled by $s \geq 0$, i.e. s affects the change in component A that results from a given reduction of B by k. Affecting both mortality components, parameter $k \geq 0$ mediates the trade-off:

$$\frac{\partial B}{\partial k} < 0 \; \forall k, \tag{7.7}$$

and

$$\frac{dA}{dy} > 0 \; \forall y, \tag{7.8}$$

i.e., if any of x, k and s is increased while the others are non-zero, component A increases.

Mortality cannot be zero or negative. Hence we postulate that

$$B \geq 0 \; \forall k, \tag{7.9}$$

while

$$A(0) = C > 0. \tag{7.10}$$

This makes biological sense, because if no deterioration with age occurs ($k = 0$), if deterioration does not lead to age-related increase in mortality ($s = 0$), or if no time has past ($x = 0$), mortality will not (have) change(d), so it will be some constant, C.

Also, the increase in mortality component A should be unbounded:

$$y \to \infty \; \Rightarrow \; A(y) \to \infty. \tag{7.11}$$

This again makes biological sense, because if the combined effect of the passage of time, deterioration over time, and deterioration affecting mortality goes to infinity, so does mortality.

Finally, let

$$B(0) = E. \tag{7.12}$$

Thus, the model is defined.

The senescence phenotype is modeled by the parameter settings $[k > 0 \wedge s > 0]$, for if either k or s is zero, $[y = 0\ \forall x] \Rightarrow [A(y) = C\ \forall x]$: $s = 0$ makes mortality insensitive to k (and x) and vica versa.

The physiological constraint s

Lemma 1: $\exists s_z > 0 : k^* > 0$**.**

Set $r_0 = r_{|k=0}$. For $k = 0$, the effect of a perturbation in k on r is (equation (4) *of the main text*)

$$\frac{\partial r}{\partial k}\Big|_{k=0} = -\frac{\int_0^\infty \left(\int_0^x \frac{\partial \mu}{\partial k}\Big|_{k=0}(t)dt\right) e^{-(r_0+E+C)x} m(x)dx}{\int_0^\infty x e^{-(r_0+E+C)x} m(x)dx}. \tag{7.13}$$

Element $\frac{\partial \mu}{\partial k}(x)$ of equation (7.13) can be written as

$$\frac{\partial \mu}{\partial k}(x) = \frac{dB}{dk} + sx\frac{dA}{dy}(y(x)). \tag{7.14}$$

Note that $y(x; k = 0, s) = 0 \cdot sx = 0$ for all x, s. Hence, with $w_1 = \frac{dB}{dk}|_{k=0} < 0$, $w_2 = \frac{dA}{dy}|_{y=0} > 0$ it holds that

$$\int_0^x \frac{\partial \mu}{\partial k}\Big|_{k=0}(t)dt = w_1 x + s\frac{w_2}{2}x^2. \tag{7.15}$$

Plugging result (7.15) back into equation (7.13) yields

$$\frac{\partial r}{\partial k}\Big|_{k=0} = -w_1 - s\frac{w_2}{2}\frac{\int_0^\infty x^2 e^{-(r_0+E+C)x} m(x)dx}{\int_0^\infty x e^{-(r_0+E+C)x} m(x)dx}. \tag{7.16}$$

With $-w_1$ strictly positive, it is always possible to pick

$$s_z > 0 : \frac{\partial r}{\partial k}\Big|_{k=0, s=s_z} > 0, \tag{7.17}$$

implying that

$$\exists s_z > 0 : k^* > 0, \tag{7.18}$$

which is what we set out to prove.

Lemma 2: $\exists s_M > 0 : \forall s \geq s_M : k^* = 0$**.**

Suppose $\tilde{\mu} = A$ (mortality supposing there were no B). Then $\tilde{\mu}$ gives $\tilde{r}(k, s)$. Since $\mu(x) \geq \tilde{\mu}(x)$ and $l(x) \leq \tilde{l}(x)\ \forall x > 0$, it holds that

$$r(k, s) \leq \tilde{r}(k, s)\ \forall k, s. \tag{7.19}$$

Given $s > 0$, any increase in k increases $\tilde{\mu}$ at all ages except age 0, which implies

$$\forall s > 0 \forall k : \frac{\partial \tilde{r}}{\partial k} < 0 \; \forall k \; . \tag{7.20}$$

Given $k > 0$, any increase in s increases μ and $\tilde{\mu}$ at all ages except age 0, so that

$$\forall k > 0 \forall s : \frac{\partial r}{\partial s} < 0 \text{ and } \frac{\partial \tilde{r}}{\partial s} < 0. \tag{7.21}$$

Condition (7.11) implies that

$$\forall k > 0 : \lim_{s \to \infty} \tilde{r}(k,s) = -\infty. \tag{7.22}$$

Given equation (7.16), one can choose s big enough so that $\frac{\partial r}{\partial k}|_{k=0}$ is negative:

$$\exists s_1 : \frac{\partial r}{\partial k}\Big|_{k=0} < 0. \tag{7.23}$$

Together with (7.21), this implies

$$\exists k_1 \; \forall s \geq s_1 : \forall 0 < k \leq k_1 : r(k,s) \leq r(k,s_1) < r_0. \tag{7.24}$$

Properties (7.21) and (7.22) imply that

$$\exists s_2 : \forall s \geq s_2 : \tilde{r}(k_1,s) \leq \tilde{r}(k_1,s_2) < r_0. \tag{7.25}$$

Now choose

$$s_M = \max\{s_1, s_2\}. \tag{7.26}$$

Then $\forall s > s_M$:

$$(i) \quad 0 < k \leq k_1 : r(k,s) < r_0 \text{ (because of (7.24))} \tag{7.27}$$

$$(ii) \quad k > k_1 : r(k,s) < \tilde{r}(k,s) \leq \tilde{r}(k_1,s) < r_0 \text{ (because of (7.25))}, \tag{7.28}$$

implying that

$$[\forall s \geq s_M : \forall k > 0 : r(k,s) < r_0] \Rightarrow k^*(s) = 0. \tag{7.29}$$

This completes the proof.

The environment

How would variation in the environment affect the results? Referring to equations (7.13) and (7.14), the general answer is that this depends on how dB/dk depends on the environment. For instance, let

$$B(k,E) = E/(k+1), \tag{7.30}$$

so that

$$\frac{\partial}{\partial E}\left(\frac{\partial B}{\partial k}\right) < 0, \tag{7.31}$$

$$E \to \infty \Rightarrow \frac{\partial B}{\partial k} \to -\infty. \tag{7.32}$$

This implies (equation (7.16)) that for every specified $s > 0$

$$\left[\exists E : \left.\frac{\partial r}{\partial k}\right|_{k=0} = -w_1 - s\frac{w_2}{2}\frac{\int_0^\infty x^2 e^{-(r_0+E+C)x} m(x)dx}{\int_0^\infty x e^{-(r_0+E+C)x} m(x)dx} > 0\right] \Rightarrow k^* s > 0, \tag{7.33}$$

so that the environment can always be harsh enough to lead to senescence. If, on the other hand,

$$B(k,E) = E - k, \tag{7.34}$$

with $k < E$, it holds that

$$\forall E\ \forall k : dB/dk = -1, \tag{7.35}$$

in which case E does not affect k^*.

Part IV

Data Paper

Chapter 8

Intrinsic and extrinsic mortality reunited

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**These authors contributed equally to this publication*

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Abstract

Intrinsic and extrinsic mortality are often separated in order to understand and measure aging. Here we show that the age patterns of allegedly intrinsic and extrinsic mortality are similar. We argue that aging and death can be better explained by the interaction of intrinsic and extrinsic risk factors than by classifying mortality itself as being either intrinsic or extrinsic. Therefore, scientific methods, clinical reasoning, and public health policies should not be founded on the partitioning of intrinsic and extrinsic mortality, but account for the tight interaction between intrinsic and extrinsic risk factors.

Introduction

To understand and measure how ageing leads to an increase in the rate of mortality, many clinicians and scholars separate intrinsic and extrinsic mortality. They envision intrinsic mortality as the result of processes of physical and functional degradation originating within the human body. As these processes arise with increasing age, intrinsic mortality would represent ageing. Extrinsic mortality is seen as the result of hazards from the environment. As the human body is exposed to these hazards uniformly across ages, extrinsic mortality would not represent ageing[1-3]. This assumption is often made implicitly. However, while the separation of intrinsic and extrinsic mortality has far-reaching consequences for biomedical research, clinical practice, and public health, we challenge that this separation has a scientific basis.

It is a fundamental theorem in biology that every phenomenon is explained by the interaction of genes and environments. From this point of view, it is a misconception to equate genes with causal factors within the body and the environment with those outside it[4]. Rather, the effects of genes are moderated by the environment and vice versa[5]. Disease and death are not either genetic or environmental, but of mixed genetic and environmental origin[6]. Yet, little attention is given to gene-environment interaction in the context of ageing[4]. Biomedical disciplines are in need of a likewise fundamental understanding of the interaction between intrinsic and extrinsic causes of ageing.

Different classifications of intrinsic and extrinsic mortality have been proposed[1-3], but the separation of intrinsic and extrinsic mortality itself has never been submitted to formal testing. As an empirical test, we compare the age patterns of typical examples of allegedly intrinsic and extrinsic mortality over age. If a distinction can be made, the risk of intrinsic mortality due to ageing is expected to increase over age, while the risk of extrinsic mortality due to environmental hazards is expected to be largely constant over age.

Intrinsic and extrinsic mortality display similar age patterns

We derived age- and cause-specific mortality rates from the European Detailed Mortality Database of the World Health Organization for 31 European countries and Israel in 2009 or 2010. As our focus is on the ageing process, we excluded ages below 10 years, at which congenital, birth-related, and developmental disorders are dominant. According to usual classifications[1-3] we included as typical examples of intrinsic mortality death due to ischaemic heart disease (ICD-10 codes I20-I25), diabetes mellitus (E10-E14), and cancer (C00-C97) and included as typical examples of extrinsic mortality death due to infectious diseases (A00-B99), due to accidents such as transport accidents, falls, drowning, and exposure to mechanical forces (V01-X29), and due to natural disasters such as excessive heat or cold, lightning, earthquakes, storms, and floods (X30-X39).

Figure 1 shows the age patterns of mortality rates for allegedly intrinsic and extrinsic mortality. Rates of intrinsic mortality increase over age to a maximum at the highest age (left panels). Rates of extrinsic mortality increase over age in a similar manner (right panels).

Because disease is a major risk factor of death, we compare the age patterns of incidence rates for the same typical examples of allegedly intrinsic and extrinsic disorders. For this, we derived age- and cause-specific hospital discharge rates from the European Hospital Morbidity Database of the World Health Organization for 26 European countries and Israel in 2008, 2009, or 2010.

Figure 2 shows the age patterns of incidence rates of allegedly intrinsic and extrinsic disorders. Incidence rates of intrinsic disorders increase over age to a maximum at the near-highest age (left panels). Incidence rates of extrinsic disorders increase similarly over age to a maximum at the highest age (right panels).

Gene-environment interaction in the causation of ageing

The human body is exposed to various stressors that originate within and outside the body. During life, the repetitive exposure to these stressors leads to accumulation of permanent damage, which leads to dysfunction, disease, and ultimately death[6,7]. The various damages that have been acquired at younger ages increase the body's vulnerability to be subsequently damaged by stressors from its genome or environment. As ageing amounts to the increasing risk of disease and death, ageing is a consequence of the accumulation of damages from genetic as well as environmental sources[7,8]. For example, ageing is partly attributed to mutations of the DNA, which are induced by spontaneous chemical reactions, replication errors, metabolic waste products, radiation, and viruses. These mutations impair the DNA's repair function, decrease its resistance to further mutations caused by intrinsic and extrinsic stressors, and increase the risk of disease and death[9]. Ageing depends on the interaction between a genetic susceptibility to damage and the damage caused by genetic and environmental stressors, leading to an increase in susceptibility to further damage from both genetic and environmental stressors. This is reflected by our finding of similar increases over age for different types of mortality and morbidity.

Epidemiological and biological data support that ageing is a result of the interaction between intrinsic and extrinsic stressors. Ischaemic heart disease, diabetes mellitus, and cancer are typically regarded as determined by intrinsic ageing, but are meanwhile largely attributable to hazards that originate in the environment, including tobacco and alcohol use, sunlight, pollution, an excessive dietary composition, and a minimal necessity of physical activity[10]. These environmental hazards affect the structure and functioning of the genome and are required for the development of disease[8,9]. Even the accelerated bodily deterioration caused by well-defined genetic substrates as in Huntington's disease is influenced by the environment[11]. As a consequence, environmental interventions can prevent or postpone ischaemic heart disease, diabetes mellitus, and cancer[12-14].

Infectious diseases, accidents, and natural disasters require environmental risk factors, but cannot be uncoupled from the body's vulnerability that increases over age. Ageing of the immune system increases the risk of infectious diseases[15]. The immune system is influenced by microorganisms and other environmental factors, like smoking, sunlight, and dietary components and meanwhile plays an essential role in the pathogenesis of cardiovascular disease and cancer[8,16]. Commensal and infectious microorganisms

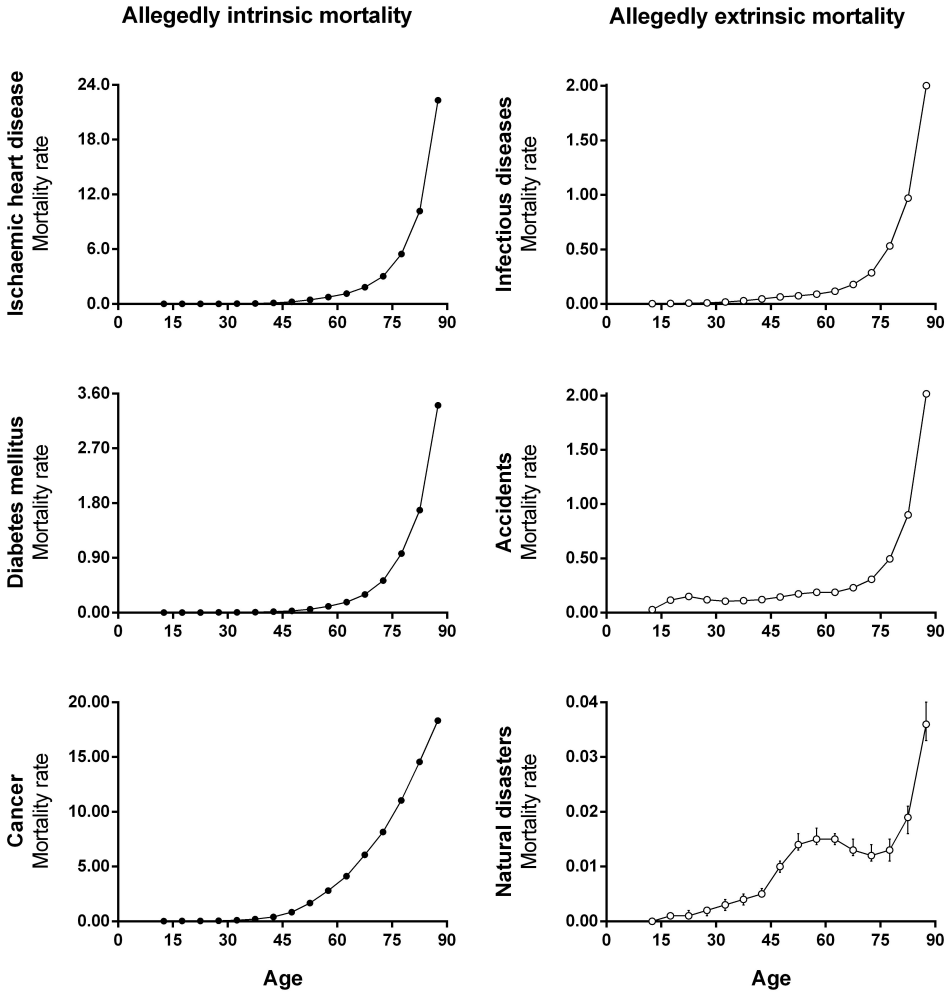

Figure 8.1: **Age patterns of mortality rates for typical examples of allegedly intrinsic mortality due to ageing and extrinsic mortality due to the environment.** Mortality rates are given as number of deaths per 1000 person-years; ages are given as years.

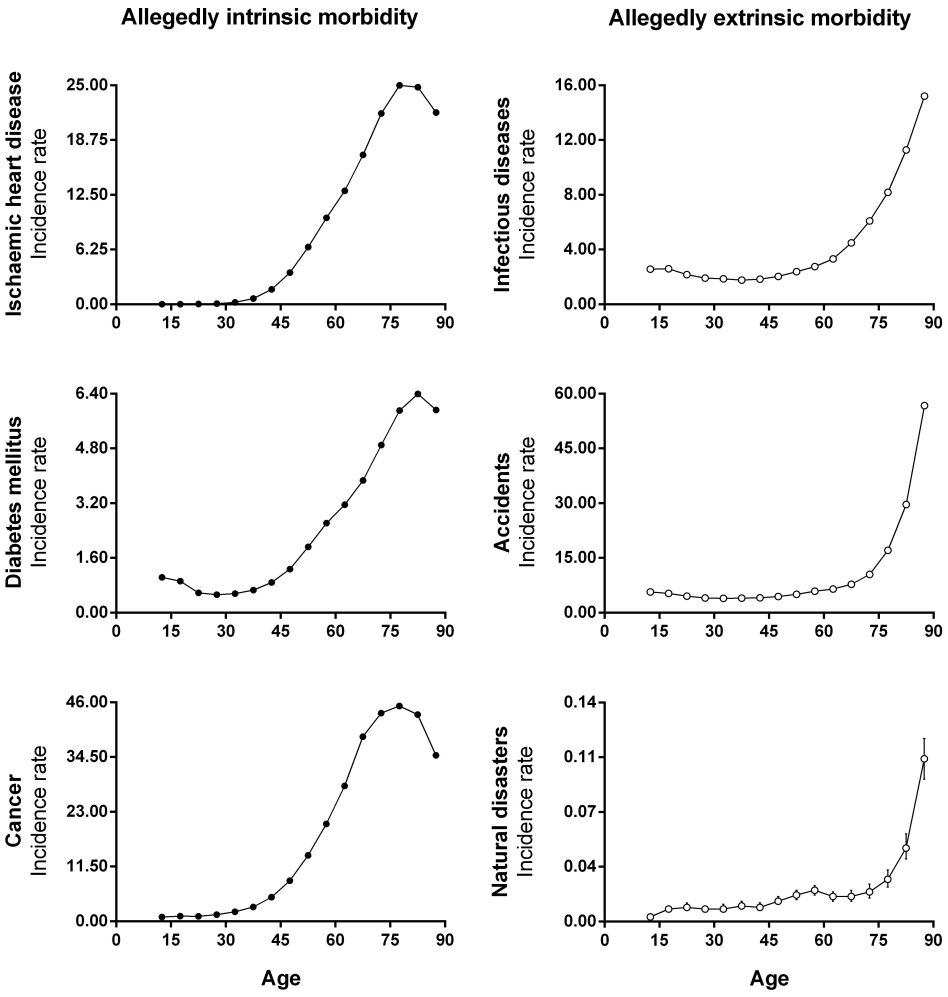

Figure 8.2: **Age patterns of incidence rates for typical examples of allegedly intrinsic disorders due to ageing and extrinsic disorders due to the environment.** Incidence rates are given as number of hospital discharges per 1000 person-years; ages are given as years.

can induce or prevent diseases attributed to ageing, including autoimmune disease, cardiovascular disease, neuropsychiatric disease, and cancer[16]. Even the risk of being affected by seemingly fully stochastic hazards is age-dependent. Sensory, cognitive, and executive dysfunctions, disability, and multimorbidity that accumulate over age predispose to burns, chokes, falls, traffic accidents, and other environmental hazards[17-19].

Relevance to biomedical research, clinical practice, and public health

In biomedical research, intrinsic and extrinsic mortality are separated when measuring the ageing process. Mathematical models are used in such a manner that distinct parameters account for intrinsic and extrinsic mortality[20]. The intrinsic parameter describes an increase in mortality over age that adds to an age-independent risk of dying described by the extrinsic parameter. These models are applied to interpret the effects of experimental interventions as affecting either the rate of ageing or the age-independent risk of dying[21]. Previously, such a biological interpretation of the mathematical parameters has been criticised[22]. The present study reinforces this critique, demonstrating that such a mathematical separation of intrinsic and extrinsic mortality is biologically unfounded. As the measurement of the rate of ageing is essential for research on ageing, alternative approaches are needed to measure this rate correctly by taking into account both allegedly intrinsic and extrinsic mortality as components of ageing[22].

In clinical reasoning, disease and death are classified as intrinsic or extrinsic in an attempt to better understand the ageing process. Disorders such as cardiovascular disease, diabetes mellitus, and cancer are considered as intrinsically progressing with increasing age, while disorders such as infectious diseases, accidents, and natural disasters are considered as environmental. The underlying pathogenic processes are sorted similarly. In dermatology, for example, the deteriorating synthesis of interstitial proteins is attributed to intrinsic ageing, while sun-induced damage is thought to constitute extrinsic environmental damage[23]. However, the damage in the skin that is accrued with increasing age is due to both the deteriorating protein synthesis and sunshine.

When intrinsic mortality due to ageing and extrinsic mortality due to the environment are separated, ageing is accepted as an inevitable side effect of increasing age while environmental hazards are taken as bad luck. In contrast, when genetic and environmental are acknowledged to interact tightly in the causation of ageing, disease, and death, new perspectives arise with both a bad and a good outlook. The bad news is: all mortality is related to ageing. The risk of allegedly extrinsic mortality increases over age similarly as compared with allegedly intrinsic mortality, because they are equally attributable to degeneration of the human body's structures and functions. Consequently, older people are most vulnerable to be struck by environmental hazards. Prevention of mortality due to infectious diseases, accidents, and natural disasters should particularly aim at protecting the frail elderly. Alike, the aged skin should be protected as it is easily bruised or sunburnt.

The good news is: all mortality is related to the environment. The risk of allegedly intrinsic mortality increases over age, but is just as well dependent on environmental hazards. A proper understanding of the tight interaction between the intrinsic and extrinsic components recognises that ageing is not inevitable, but malleable through the environment. Especially lifestyle interventions seem effective, such as limiting sun exposure to delay ageing of the skin. Knowledge on this interaction leads the way to identify other environmental risk factors that cause ageing and can be targeted to prevent ageing[24]. To reach this goal, intrinsic and extrinsic mortality should not be separated in mathematical models when measuring ageing, in clinical reasoning when explaining ageing, and in public health when allocating prevention and intervention.

Key messages

1. Mortality is often partitioned into intrinsic mortality due to ageing and extrinsic mortality due to environmental hazards.
2. This classification of intrinsic and extrinsic mortality is ill-defined and misleading.
3. Empirical data show that the risks of intrinsic and extrinsic mortality increase similarly over age.
4. Genetic and environmental stressors interact to cause ageing and death.
5. The separation of intrinsic and extrinsic mortality should not be incorporated in mathematical models when measuring ageing, should not be applied in clinical reasoning when explaining ageing, and should not be used in public health when allocating prevention and intervention.

Contributors and sources

The authors have extensively investigated and written on the causative mechanisms underlying ageing and on the measurement of ageing by age patterns of mortality. JJEK and MJW study these themes as PhD students. JJEK conceived this study. JJEK, MJW, DvB, and RGJW designed this study. JJEK collected and analysed the data. JJEK, MJW, and DvB drafted the manuscript. All authors contributed to the interpretation of the data and to the intellectual content and revision of the manuscript. All authors approved the final manuscript. RGJW is the guarantor. Data were derived from the European Detailed Mortality Database and the European Hospital Morbidity Database, both provided by the World Health Organization's Regional Office for Europe through:
http://data.euro.who.int/en/data-and-evidence/databases.

References

1. Gurven, M. and A. Fenelon (2009) Has actuarial aging "slowed" over the past 250 years? A comparison of small-scale subsistence populations and European cohorts. Evolution 2009:1017-1035.

2. Carnes, B.A., Holden, L.R., Olshansky, S.J., Witten, T.M. and J.S. Siegel (2006) Mortality partitions and their relevance to research on senescence. Biogerontology 7:183-198.

3. Carnes, B.A. and S.J. Olshansky (1997) A biologically motivated partitioning of mortality. Experimental Gerontology 32:615-631.

4. Grigorenko, E.L. (2005) The inherent complexities of gene-environment interactions. Journals of Gerontology Series B Psychological Sciences and Social Sciences 60:53-64.

5. Hunter, D.J. (2005) Gene-environment interactions in human diseases. Nature Reviews Genetics 6:287-298.

6. Rothman, K.J. and S. Greenland (2005) Causation and causal inference in epidemiology. American Journal of Public Health 95 Suppl 1:S144-S150.

7. Izaks, G.J. and R.G.J. Westendorp (2003) Ill or just old? Towards a conceptual framework of the relation between ageing and disease. BMC Geriatrics 3:7.

8. López-Otín, C., Blasco, M.A., Partridge, L., Serrano, M. and G Kroemer (2013) The hallmarks of aging. Cell 153:1194-1217.

9. Freitas, A.A. and J.P. de Magalhães (2011) A review and appraisal of the DNA damage theory of ageing. Mutation Research 728:12-22.

10. Lim, S.S., Vos, T., Flaxman, A.D., Danaei, G., Shibuya, K., Adair-Rohani, H., et al. (2012) A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2224-2260.

11. Wexler, N.S., Lorimer, J., Porter, J., Gomez, F., Moskowitz, C., Shackell, E., et al. (2004) Venezuelan kindreds reveal that genetic and environmental factors modulate Huntington's disease age of onset. Proceedings of the National Academy of Sciences of the USA 101:3498-3503.

12. Rasmussen-Torvik, L.J., Shay, C.M., Abramson, J.G., Friedrich, C.A., Nettleton, J.A., Prizment, A.E., et al. (2013) Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk in Communities Study. Circulation 127:1270-1275.

13. Estruch, R., Ros, E., Salas-Salvadó, J., Covas, M.I., Corella, D., Arós, F., et al. (2013) Primary prevention of cardiovascular disease with a Mediterranean diet. New England Journal of Medicine 368:1279-1290.

14. Lindström, J., Ilanne-Parikka, P., Peltonen, M., Aunola, S., Eriksson, J.G., Hemiö, K., et al. (2006) Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. Lancet 368:1673-1679.

15. DiCarlo, A.L., Kaminski, J., Kovacs, E.J., Sempowski, G.D. and D.B. Palmer (2009) Immune senescence. Trends in Immunology 30:293-382.

16. Wahren-Herlenius, M. and V. Kuchroo (2011) Gene-environment interaction in induction of autoimmunity. Seminars in Immunology 23:65-154.

17. Damián, J., Pastor-Barriuso, R., Valderrama-Gama, E. and J. de Pedro-Cuesta (2013) Factors associated with falls among older adults living in institutions. BMC Geriatrics 13:6.

18. Lavallière, M., Handrigan, G.A., Teasdale, N. and P. Corbeil (2012) Obesity, where is it driving us? Journal of transportation safety and security 4:83-93.

19. Peck, M.D. (2011) Epidemiology of burns throughout the world. Part I: distribution and risk factors. Burns 37:1087-1100.

20. Ricklefs, R.E. and A. Scheuerlein (2002) Biological implications of the Weibull and Gompertz models of aging. Journals of Gerontology Series A: Biological Sciences and Medical Sciences 57:B69-76.

21. Mair, W., Goymer, P., Pletcher, S.D. and L. Partridge (2003) Demography of dietary restriction and death in Drosophila. Science 301:1731-1733.

22. Koopman, J.J.E., Rozing, M.P., Kramer, A., de Jager, D.J., Ansell, D., De Meester, J.M.J., et al. (2011) Senescence rates in patients with end-stage renal disease: a critical appraisal of the Gompertz model. Aging Cell 10:233-238.

23. Jackson, R. (2001) Elderly and sun-affected skin: distinguishing between changes caused by aging and changes caused by habitual exposure to sun. Canadian Family Physician 47:1236-1243.

24. Khoury, M.J., Davis, R., Gwinn, M., Lindegren, L. and P. Yoon (2005) Do we need genomic research for the prevention of common diseases with environmental causes? American Journal of Epidemiology 161:799-805.

Part V

General Discussion

In this thesis, my various co-authors and I have explored the limitations of evolutionary theories of aging, and have tried to overcome those limitations or to find a way of viewing and formalizing the matter in a (more) proper and complete way. Theories and models are characterized by what they *do not* take into account, their limitations, as much as by what they *do* take into account. A few limitations of the theories and models discussed in this thesis deserve special mentioning. Not all limitations have been mentioned so far, and not all are overcome in this thesis. Both these limitations and the new insights that I hope this thesis contains lead the way to future areas of research, outlined at the end of this discussion.

Chapter 9

Limitations

Calculus and biology

Calculus is the branch of mathematics that is built on the premise that values and changes in those values can be divided up in ever smaller, indeed infinitely small (infinitesimal) pieces. Hamilton used calculus to devise models of infinitesimal age-specific changes, which is biologically unrealistic (Chapter 3). In Chapter 5, my co-authors and I have tried to improve on Hamilton's method by showing how Hamilton's indicators fit in Arthur's more general framework of perturbation analysis of scalar demographic metrics. The method calculates the change in fitness if mortality and fecundity are perturbed *across all ages*, rather than age-specifically. Also, we show how trade-offs can be modeled within this framework. Yet, it remains calculus applied to biology. Although the entire life history is perturbed at once in Chapter 5, i.e. all ages are affected, it is still done so in an infinitesimal manner: the perturbation function that we use is an infinite vector of age-specific changes that have some magnitude relative to each other, but are all infinitely small nevertheless. It is unlikely that this is the character of real biological perturbations, if only because living beings have a finite number of genes that together produce a very non-infinitesimal effect. Yet, Chapter 5 is instrumental in rejecting unjustified claims that have been made with reference to calculus, and as a linear approximation of real perturbations of life histories.

Age-structuring

Populations can be structured in many ways, both in empirical studies and in theoretical models [1]. Age is probably the only variable used for classification that in and of itself has absolutely no effect on anything at all. Without doubt, and without exception, age causes nothing. Its explanatory power results only from its correlation with yet-to-be-discovered underlying causal pathways. Still, it is intuitive to structure populations by age, specifically when one is interested in aging. Hamilton [2] showed how mathematically

convenient it is to derive sensitivities of fitness to age-specific changes. Theories of aging have largely been postulated in terms of age-specific changes [e.g.3,4,5, but see 6 and Chapters 3 and 4]. Still, in the end, age is just a 'parameterization': a way to describe a pattern. The parameterized pattern is independent of the parameterization, as is any calculation done on the pattern. Readers with mathematical background may liken this parameterization to the parameterization of a line integral: the result does not depend on the parameterization chosen to describe the line.

If one is not continuously aware of the fact that age is in principle irrelevant, analyzing age-structured models is playing with fire. It is easy to come up with some age-specific mathematical equation, but accounting for it biologically is much more challenging. One cannot freely dream up age-specific changes in vital rates without thinking about how these should come about, and about how changes in vital rates at different ages are related (Chapter 3). Books on age-structured population models [e.g.7] should come with a big warning that age-classification is essentially beside the point.

Models identify only sufficient conditions

Typically, evolutionary models of aging ask the question: suppose that the mechanistic constraints can be mimicked by these (relatively simple) equations, what mortality and fecundity patterns emerge? Would aging evolve, or not? When the model is good, it gives a set of parameters for which aging is predicted to evolve, and a set of parameters for which it is not. This means that *if* such equations and such parameter settings indeed mimicked real world phenomena, they could explain these phenomena. Or not. In terms of predicting real world phenomena, theoretical models construct only a *sufficient* condition for the predicted outcome (I am grateful to Dr. Giaimo for stating this so clearly). They are an instrument for conceptualizing thinking, and for assuring that reasoning is self-consistent. They do not, however prove anything about reality. Specifically, they do not produce a *necessary* condition. Sometimes it is tested whether models are 'consistent' with observed data [e.g. 8]. That is better than nothing, but it is also little more than nothing. What is shown is that the model can produce a pattern such as the one observed, but this is often trivial due to a great number of free parameters. It is risky to claim any 'success' of optimization models in explaining patterns [3], as many mechanisms, including many trade-offs, can produce the same pattern. This warning pertains also to the model in Chapter 7. It is unlikely that the mechanism that inspired the model, proposed in Chapter 4, is the only mechanism at play, and that all pattern like the patterns produced in Chapter 7 find their roots in the mechanisms laid out in Chapter 4.

References

1. Caswell, H. (2001) Matrix population models. Construction, analysis, and interpretation. Sinauer, Sunderland, MA.

2. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology 12:12-45.

3. Partridge, L. and N.H. Barton (1993) Optimality, mutation and the evolution of ageing. Nature 362:305-311.

4. Partridge, L. and N.H. Barton (1996) On measuring the rate of ageing. Proceedings of the Royal Society London B 263:1365-1371.

5. Charlesworth, B. (2001) Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. Journal of Theoretical Biology 210:47-65.

6. Kirkwood, T.B.L., and D.P. Shanley (2010) The connections between general and reproductive senescence and the evolutionary basis of menopause. Annals of the New York Academy of Science 1204:21-29.

7. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge.

8. Abrams, P.A. and Ludwig, D. (1995) Optimality theory, Gompertz' law, and the disposable soma theory of senescence. Evolution 49:1055-1066.

Chapter 10

Future directions

There are two future directions that I would like to highlight in this section. The first is the description of life histories by statistical analysis of Hamilton's indicators of the force of selection. The second is a more wholesale and imaginative perspective on (the evolution of) aging than that provided by the classic theories of aging.

Statistical analysis of Hamilton's indicators

Although selection gradients are by themselves no *predictor* for evolution (Chapter 5), the rate at which they decline could be a good *descriptor* of life histories. This rate depends on both mortality and fertility, the combination of which maps into measures of Darwinian fitness, so that it is preferred to a separate description of mortality and fertility patterns. Furthermore, the rate at which the selection gradient on mortality declines is constant if mortality and fecundity are constant, increases if mortality and fecundity exhibit a combined deterioration (senescence), and decreases if organisms improve their vital rates (negative senescence). Hamilton's indicators are mutually exclusive with respect to age, i.e. they always add up to the same value, so that a high value at one age limits the value at other ages (Wensink et al. unpublished manuscript). Hence they could be evaluated as random variables using standard statistics.

Particular attention as an indicator of aging deserves the rate of decline in the force of selection over age, specifically relative to the age-pattern of reproductive value (proposed by [1]). Caswell [2,3] showed that the selection gradient on age-specific perturbations of mortality equals the proportional abundance of organisms in that age-class ('stable age-distribution') multiplied by 'reproductive value', which is the value of reproductive output *given* that an organism is in some age-class (discussed in Chapter 6). Thus, while reproductive value could be a good indicator of senescence on the individual level, the selection gradient on mortality could be a good estimate of evolutionary impact of changes at the individual level. This observation hints at a potentially promising line of further research.

Is aging an 'evolutionary thing'?

I started this thesis stating that aging is a problem that can be approached from an evolutionary angle. But all considered, is this true? I argue that aging *is* an evolutionary question (everything is an evolutionary question on some level), but of a quite different kind than currently conceived. I set out future directions for aging research that better fit the likely evolutionary background.

Evolution tends to select organisms in possession of traits that improve the organisms' capability of propagation relative to organisms not in possession of those traits. Without variation in the possession of heritable traits that affect an organism's capability of propagation, there would be no evolution by natural selection. Hence, every observation of the possession of a trait by some organism is a function of variation that may or may not have existed at an earlier point in time. If it is found that some trait, e.g. (absence of) aging does not exist, it can mean that the trait is not beneficial for fitness: variation has existed, but the trait has been selected against. Second, it can mean that in the past there has been no variation in the trait: the trait could be beneficial, but has never emerged, and so has never been subject to natural selection. If the trait has never emerged, this can be due to random effects, i.e. the necessary variation could exist, but it so happens that it has never come about. Alternatively, the lack of variation is due to mechanistic constraints that cannot be overcome, i.e. the necessary variation could not possibly exist. To sum up: 1. variation did exist; 2. variation did not exist, but could have existed; 3. variation did not exist because it cannot exist. Aging is usually approached from the first angle, whereas I argue that to a large extent it should be addressed from the third angle. If there exist constraints with respect to aging that cannot be overcome within a particular form of life, the existence of aging is still an evolutionary question, but the question becomes why that form of life has evolved, rather why aging has evolved within that form of life.

What are the constraints that lead to aging in complex organisms like humans? Classic theories of aging suggest that there is a number of genes in absence of which we would not age [e.g. 5-9], and/or that if our physiology were such that more resources were allocated to somatic maintenance, we would not age [e.g. 10,11]. For instance, Stearns [7, pg. 200] writes: "aging (...) [is] caused by many genes of relatively small effect that produce ageing as a by-product. (...) Ageing caused by major genes with large effects is not ruled out but is not expected to be the usual case." In the same vein, explanations of the evolutionary theory of aging invariably start with a statement to the effect that the force of selection declines with age, after which the mechanisms are discussed [e.g. 12-15]: 'What happens late in life does not matter so much, therefore aging evolves', that is the rhythm. This implies that if that what happens late in life mattered *more*, aging would not occur.

I do not think that either of these statements is true. Consider again the balance between damage and repair. Think of what the necessary ingredients are for successful repair of damage. As Figure 10.1 shows, the list is demanding. Certainly some resources (building blocks, energy) are necessary, conform the disposable soma theory [11,16]. Yet,

the availability of resources alone is not enough. Damage must first be detected, otherwise no repair can even be attempted (I am grateful to Dr. van Heemst for drawing my attention to this fact). What is also needed is information that directs the way resources are employed, so as to recover the original situation (I am grateful to Dr. Baudisch for drawing my attention to this fact). The resources and repair machinery need to have access to the location where the damage has occurred, and need to be able to operate there. This requires physical space, and a chemical environment that is compatible with the operation of the repair machinery and with the structural integrity of the building blocks. Even if the repair machinery is in principle compatible with the target site in the sense that it by itself does not lead to failure of cells or organs, it can lead to unwanted interactions that makes the repair evolutionarily unfavorable, as chemical by-products of the repair process may give false instructions to nearby cells or organs. The function of the damaged soma will often need to be retained during repair. Shutting down the heart, the brain or most blood vessels would lead to immediate death, thus restricting repair (Boris Kramer has pointed this restriction out to me). Finally, and of the utmost importance, since natural selection acts upon existing variation, it is unlikely that repair is the only function of the repair machinery. Repair machinery, in whatever form, has evolved. This simple fact means that repair machinery will often have other functions in an organism's physiology, because this could explain the existence of the necessary variation in the evolutionary past that lead to the evolution of the repair machinery. Repair machinery could have come about by random effects, but this is far less likely than the alternative scenario that repair machinery was already there in some other function, and got picked up by evolution for repair purposes. In this scenario, repair machinery has other functions to service, so that the effectiveness of repair is likely to be limited. Repair mechanisms may be all rounders rather than specialists. All rounders do many things reasonably well, but seldom anything perfect.

To give a medically inspired example, arteriosclerosis is a complex disease process that starts with a fat deposit in arterial walls, which can already be observed in adolescents ('fatty streaks', [17]). But arteriosclerosis is not a process only of fat (cholesterol and triglycerides). Essentially, it is an inflammatory process that interacts with and is modulated by cardiovascular risk factors like blood lipid levels and blood pressure [18]. What would it take to 'repair' an artery that is 'damaged' by a fat deposit? Is inflammation damage, repair, or both? How could the original artery be recovered? First, it needs sensing that the arterial wall has been damaged. Resources will be necessary, certainly. Information on how the resources should be used are necessary as well: how should the arterial wall be structured? Any repair machinery should not interfere with the function of the artery (transportation of nutrients and oxygen through the flow of blood), since otherwise vital organs (brain, muscle) could be compromised. Hence, the repair machinery needs to be able to function in small space, in the presence of shear stress by the blood flow, and in the chemical environment of blood. The repair process, even if it is in principle compatible with the physical and chemical environment of an artery, is further restricted by the requirement that it does not lead to any by-products that could cause unwanted interactions downstream, for instance chemicals that give wrong signals to the target organ(s)

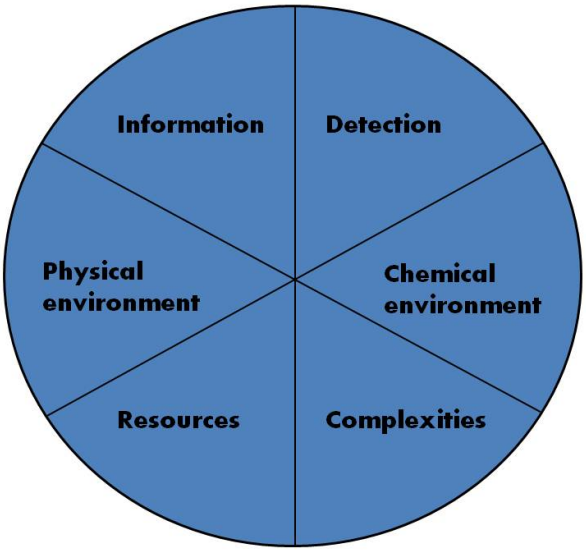

Figure 10.1: Following the causal pie model expounded Chapter 2, this figure shows the component causes that jointly constitute a sufficient cause for successful somatic repair: detection of damage, information on the desired state, resources for repair, physical and chemical circumstances that are compatible with repair, and lack of forbidding complexities that may arise as a consequence of the repair process. Without any one of these component causes, repair does not occur. The exact requirements in terms of these six factors are further explained in the text.

of the artery. Finally, the repair machinery used is likely to be required for other purposes as well. Inflammation has a clear other function, namely the response to infection. Inflammation is closely related to the maintenance of structural integrity: the inflammatory process initiates tissue repair processes. Dr. van Heemst hypothesizes that the formation of a plaque could be an attempt to encapsulate the damage by overgrowth, so as to create a microenvironment in which repair can take place (personal communication). Thus, perhaps the inflammatory component of arteriosclerosis could be seen as an attempt to use existing mechanisms (inflammation) to prevent uncontrolled growth of arterial fat deposits. This imperfect repair may work well on the short term, but cause problems in the long run, and elements of the inflammatory process may be counter productive as a result of their evolutionary history, which may be one of the reasons why the doctor considers it part of a disease process [18]. In this example it is not fruitful to wonder why sufficient resources have not been allocated to the repair process, or to try find the bad gene that causes cells of the immune system to invade the arterial wall. The example shows that in terms of 'repair', the *absolute best* that life can do might just be to put a patch. Aging is then characterized not so much by 'damage and repair', but rather by 'damage and patching'.

This view on aging is far removed from the classic theory of aging. There are no "many genes of relatively small effect" [7] that lead to aging, nor is the allocation of re-

sources [11,16] the most important determinant of the aging process. Of the classic theories of aging, the disposable soma theory probably gets closest to reality. It does not depend on problematic and highly theoretical 'age-specific genes' (Chapter 3). Instead, it postulates a strong, realistic mechanism of aging, of which experiments have shown that it plays at least *some* role [19,20]. Yet, it should be acknowledged that resource allocation is certainly not all that matters, that the role of 'extrinsic mortality' and survival has been misunderstood in the disposable soma theory (Chapter 6), and that the namesake postulate of the theory, i.e. that the soma is 'disposable', is incorrect.

The take on aging set out above also reflects on the question of negative senescence. Of course, I fully agree with Vaupel et al. [21] that if vital rates improve over most of the lifespan, it makes sense to characterize the overall life history as negative senescent. Yet, 'damage and patching' rather than 'damage and repair' means that in the end demographic aging will yield to physiological aging (see Chapter 1), even though the data do not show this, which might be due to the unavoidable scarcity of data on old age survival [22]. Even if continued survival were optimal from the evolutionary viewpoint, it may just be impossible on mechanistic grounds. The results of Chapter 5, show that there are no evolutionary grounds on which to declare aging a universal phenomenon. But as the problem of aging is much more difficult mechanistically than usually assumed, real life events may differ materially from the predictions of simple evolutionary models, especially at high ages.

Aging is a 'state-thing'. The state that an organism has determines whether the organism can be maintained and/or repaired. Some states are more difficult to maintain than others. Only if this 'higher state' in terms of maintenance requirement yields benefits that outweigh the costly maintenance and/or more rapid deterioration is it evolutionary beneficial to attain such a state. A good example of the relevance of state is that of the *dauer* state of some worms, "an alternative developmental stage of nematode worms, particularly Caenorhabditis elegans, whereby the larva goes into a type of stasis and can survive harsh conditions" (Wikipedia, 'dauer-larva', accessed 2-28-14). By assuming the dauer state, the larva lasts magnitudes of its normal lifespan longer than the non-dauer larva. The larvae assume a 'low' state, which incurs little damage (conform Chapter 4), probably with a low information content, and which lasts much longer and better than 'higher' states. Humans do not have such plasticity, but this shows the impact of state. The enhanced survival is clearly not a matter of a different set of 'age-specific genes' or of resource allocation.

Considering the outlined restrictions on the repair process and theories based on age-specific genes, I suggest that the evolutionary theory of aging, at least as much as it pertains to complex organisms like ourselves, should be moved from "variation has existed, from which natural selection produced the aging phenotype" to "given our complex form of life, no variation could exist such that it produces organisms that do not age". Of course evolutionary forces do act on the aging pattern, but in the light of such mechanistic considerations, it is very unlikely that aging could be limited to a significant extent, or even eliminated, had Hamilton's selection gradients been different. The moment at which our

form of life evolved, then, is the moment at which aging evolved. Perhaps we might have escaped aging as simple organisms. However, the benefits that came with our form of life (low mortality, high throughput of resources, leading to many offspring) may have outweighed the disadvantages (aging). This fits the 'trade-off explanation' of aging, but not in the form in which the trade-off explanation is put in the classic writings [1,7-16]. It is a materially different way of thinking, and informs medicine in a different way. It becomes meaningless to search for specific genes of small effect that give rise to trade-offs and aging, or to ask why we do not allocate more resources to repair than we do. Certainly, it is good to know that evolutionary forces act on the aging process, and that in a universe much unlike ours trade-offs and new mutations may balance against the tendency of evolution to eliminate aging. But this is not going to help us other than as intellectual entertainment. Instead, I propose a research program on 'the evolution of unretainability': what are, in different forms of life, the structural and informational limitations that lead to the inevitability of aging? This is the concept that my co-authors and I have started to entertain in Chapter 4, and this is the concept that I believe will bring us further. Aging is in the blueprint of our complex form of life.

References

1. Partridge, L. and N.H. Barton (1996) On measuring the rate of ageing. Proceedings of the Royal Society London B 263:1365-1371.

2. Caswell, H. (1978) A general formula for the sensitivity of population growth rate to changes in life history parameters. Theoretical Population Biology 14:215-230.

3. Caswell, H. (2010) Reproductive value, the stable stage distribution, and the sensitivity of the population growth rate to changes in vital rates, Demographic Research 23:531-548.

4. Lande, R. (1982) A quantitative genetic theory of life history evolution. Ecology, 63:607-615.

5. Leroi, A.M., Bartke, A., De Benedictis, G., Franceschid, C., Gartnere, A., Gonosf, E., et al. (2005) What evidence is there for the existence of individual genes with antagonistic pleiotropic effects? Mechanisms of Ageing and Development 126:421-429.

6. Charlesworth, B. (2001) Patterns of age-specific means and genetic variances of mortality rates predicted by the mutation-accumulation theory of ageing. Journal of Theoretical Biology 210:47-65.

7. Stearns, S.C. (1992) The evolution of life histories. Oxford University Press, Oxford.

8. Williams, G.C. (1957) Pleiotropy, natural selection, and the evolution of senescence. Evolution 11:398-411.

9. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London.

10. Kirkwood, T.B.L., and D.P. Shanley (2010) The connections between general and reproductive senescence and the evolutionary basis of menopause. Annals of the New York Academy of Science 1204:21-29.

11. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

12. Abrams, P.A. (1993) Does increased mortality favor the evolution of more rapid senescence? Evolution 47:877-887.

13. Kirkwood, T.B.L. and S.N. Austad (2000) Why do we age? Nature 408:233-238.

14. Partridge, L. and D. Gems (2002) Mechanisms of ageing: public or private? Nature Reviews Genetics 3:165-75.

15. Monaghan, P., Charmantier, A., Nussey, D.H. and R.E. Ricklefs (2008) The evolutionary ecology of senescence. Functional Ecology 22:371-378.

16. Kirkwood, T.B.L. and R. Holliday (1979) The evolution of ageing and longevity. Proceedings of the Royal Society London B 205:531-546.

17. Levy, M.N., Koeppen, B.M. and B.A. Stanton (2006) Berne and Levy - Principles of Physiology, Fourth Edition. Mosby, New York.

18. Lusis, A.J. (2000) Atherosclerosis. Nature 407:233-41.

19. Diderich, K. Alanazi, M. and J.H.J. Hoeijmakers (2011) Premature aging and cancer in nucleotide excision repair-disorders. DNA Repair 10:772-780.

20. Boesch, P., Weber-Lotfi, F., Ibrahim, N., Tarasenko, V., Cosset, A., Paulus, F., et al. (2011) DNA repair in organelles: Pathways, organization, regulation, relevance in disease and aging. Biochimica et Biophysica Acta 1813:186-200.

21. Vaupel, J.W., Baudisch,A., Dölling, M., Roach, D.A. and J. Gampe (2004) The case for negative senescence. Theoretical Population Biology 65:339-351.

22. Jones, O. R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C.G., Schaible, R., et al. (2014) Diversity of ageing across the tree of life. Nature 505:169-173.

Part VI

Appendices

A. Glossary of terminology.

Aging: Has been used to refer to two phenomena. One is the mere passage of time, without reference to any change. The other is deterioration with the passage of chronological time. I use it in the latter sense, with the exception of some particular chapters, in which it is explicitly stated otherwise. Compare with: Senescence.

Ceteris paribus: All other things being equal. A clause used across sciences, particularly in economics, indicating that a situation is considered in which only one element is different. It allows isolation, at least locally, of the effect of the element under discussion.

(Darwinian) fitness: The propensity to assure and increase the presence of an entity's heritable material over time.

Functional: A 'function of a function' that takes a function as input and returns a scalar*.

Functional calculus: The calculus that pertains to functionals*.

Gene: The molecular unit of heredity, made up from DNA. To my knowledge, a good word for 'unit of heredity' as a general concept, not restricted to DNA, is missing. Hence, I stick to 'gene' also at places where the modality of heredity should not necessarily be DNA.

Genotype: The genetic composition of an organism.

Germ cells: Cells form which a next generation derives. Compare with: Soma.

Homeostatis: The property of a system that internal conditions are kept stable, in particular in physiology.

Life history: The collective of timing and magnitude of life events, such as age at maturity, lifespan, number of reproductive bouts, and aging. The central proposition of life history theory is that like organs and the color of a butterfly, life history evolves.

Mutation: A change in a sequence of DNA. In general, it has been found that only a limited number of DNA sequences have a specific effect; most sequences just do not have any noticeable biological activity. Hence, most random mutations lead to loss of function.

Phenotype: The collective of physiological properties of an organism. Depends on genotype, other mechanisms of heredity, the current environment, and an the complete past of environment-phenotype interaction.

Scalar: A quantity that is described by a single value, such as life expectancy. As opposed to quantities that are described by a collection of values, such as age-specific survival.

Senescence: Refers to deterioration with age. Compare with: Aging. Note: various authors have made a distinction between aging as the passage of time versus senescence as deterioration with that time. The propensity to make such a distinction is not widespread. Unless indicated otherwise, I do not adhere to this distinction.

Soma: Sanskrit for 'body'. Used to refer to that what does not form the basis of a next generation. Compare with: Germ cells.

Stable population theory: Specified, time invariant birth and death rates as a function of age asymptotically lead to a stable distribution of organisms over age groups, and fixed reproductive values for each age group. It is these distributions and functions that stable population theory refers to.

Survival: The state of being alive or not. Sometimes a difference is made between survival as the probability of surviving a *period*, versus survivorship as the probability of surviving from age zero to a specified age.

Trade-off: Two objectives cannot be realized at the same time, at least not to the same extent. A common trade-off in life history theory is a trade-off between reproduction and survival. It is believed that high fertility comes at a cost to survival. Notice that the existence of a trade-off does not prohibit that some organisms are just better at everything: Bill Gates can buy more apples, houses, cars and what not than all of us together (barring the off chance that the readership of this thesis includes Bill Gates), but still, even for Bill Gates it is true that he can spend every Dollar only once.

B. Survival analysis and Darwinian fitness

Survival* analysis is based on analyzing survival time X as a random variable [1], survivorship at age x, $\ell(x)$, being

$$\ell(x) = P(X \geq x). \tag{10.1}$$

The age-derivative of $\ell(x)$, $\ell'(x)$, is the additive inverse of the probability density function of the survival times, $f(x)$:

$$\ell'(x) = -f(x). \tag{10.2}$$

The mortality rate $\mu(x)$ is the change in survivorship conditioned on survivorship itself:

$$\mu(x) = -\frac{\ell'(x)}{\ell(x)}. \tag{10.3}$$

The rationale for analyzing the mortality rate is that the change in survivorship at age x comes down on those who survive up to age x, so that it expresses the change that pertains to survivors. Survivorship is directly related to the mortality rate through

$$\ell(x) = e^{-\int_0^x \mu(t)dt}. \tag{10.4}$$

Life expectancy from some age x onwards is calculated from $\ell(x)$ as

$$e(x) = \frac{1}{\ell(x)} \int_x^\infty \ell(t)dt, \tag{10.5}$$

with $e(0)$ life expectancy at birth. To die at age x, one has to survive to age x, and then die. Hence, $f(x)$ can be expressed as

$$f(x) = \ell(x)\mu(x). \tag{10.6}$$

Taking the integral over $f(x)$ yields

$$\int_0^\infty f(x)dx = 1. \tag{10.7}$$

The result of equation (10.7) makes sense. In intuitive terms, the chance of dying at some point in a lifetime is exactly one. In mathematical terms, $f(x)$ is a probability density function, integrating over which yields 1. This total mortality is incurred over $e(0)$ units of time. Hence, average mortality per time unit ($\bar{\mu}$) is $1/e(0)$, and vica versa:

$$e(0) = 1/\bar{\mu}. \tag{10.8}$$

Life expectancy and average mortality per time unit are inversely related. More generally, $\bar{\mu}(x)$ being average mortality from age x onwards,

$$\bar{\mu}(x) = \frac{\int_x^\infty \ell(t)\mu(t)dt}{\int_x^\infty \ell(t)dt}. \tag{10.9}$$

Knowing any one of the functions $\mu(x)$, $\ell(x)$ or $f(x)$, all others can be calculated.

Darwinian fitness is clearly a function of survival. The survivorship function indicates how long entities last, which is an indicator of future presence of the heritable material. Darwinian fitness is evenly clearly a function of reproduction. Reproduction leads to the creation of new entities, which contribute to the future presence of the heritable material. Reproduction and survivorship interact, in the sense that they determine each other's utility: The longer newly produced organisms survive, the greater their impact on the heritable material 'being there' in the future. Reversely, only organisms that are alive can reproduce, so survivorship augments reproductive output. Consequently, a measure of Darwinian fitness will depend on the product of survivorship and reproduction.

We can consider the instantaneous 'replacement rate' of organisms. To reproduce, an organism has to be alive. To die, it has to be alive as well. So at any moment, the instantaneous replacement rate is:

$$\ell(x)m(x) - \ell(x)\mu(x). \tag{10.10}$$

This is the rate at which new life is produced minus the rate at which life is lost, at an instance in time. However, organisms may defer reproduction and survival to later moments. For instance, during the first decade or so, humans do not reproduce, but do suffer mortality, so that the instantaneous replacement rate is negative. Early life processes, however, can have a large impact on later performance. Organisms grow and develop, which increases the vital rates at later points. This is not captured in equation 10.10, which is why equation 10.10 should be evaluated over all ages:

$$\int_0^\infty \left(\ell(x)m(x) - \ell(x)\mu(x)\right) dx = \int_0^\infty \ell(x)m(x)dx - \int_0^\infty \ell(x)\mu(x)dx. \tag{10.11}$$

Of the far right integral of equation (10.11) we know exactly what it is. It is the probability of an organism's death at some point during its lifetime, which is one per definition. There is therefore no surprise in this integral, and it can be left out of evolutionary considerations. The first integral on the right hand side of equation (10.11) is called the net reproductive

rate, which is the expected value of number of offspring produced over an organism's lifespan [2,3].

The net reproductive rate has been used as a measure of fitness. It is, however, imperfect, because it does not account for *timing* of reproduction. An organism that replaces itself twice has a net reproductive rate of two. However, an organism that replaces itself twice every year will establish a population that grows much faster than a population established by an organism that replaces itself twice every ten years. Thus, it is necessary to extract a per time growth rate from a schedule of mortality and fecundity. This growth rate is conventionally indicated by r, and is called the intrinsic rate of increase, or the population growth rate. In the latter case, it should be kept in mind that the population that is referred to is the population established by the organism under study. Although a fitness measure should be an individual measure, otherwise competition cannot be accounted for, high individual fitness leads to a growing population of copies of that individual, so that we speak of "the population growth rate of the individual" [4]. The way to extract this population growth rate is to solve for r as the unique real root of the Euler-Lotka equation [2,3,5,6]:

$$\int_0^\infty e^{-rx}\ell(x)m(x)dx = 1. \tag{10.12}$$

The equation has many complex solutions, signifying potentially great oscillations initially. However, under some age-pattern of mortality and fecundity, eventually a stable population emerges, with asymptotic growth rate r. Lotka [5] was attentive enough to take ρ as a symbol for the unique real root of the equation, but it has become conventional to use r, keeping in mind that this is meant to refer to the unique real root of the equation.

Thus, we have obtained a valuable measure of Darwinian fitness, r, which passes the 'evolutionary stable strategy' (ESS) test [3]. This means that no organism that maximizes r under some constraints can be out-competed by organisms that choose a different strategy under the same constraints.

References

1. Collett, D. (2003) Modelling survival data in medical research, second edn. Chapman & Hall/CRC

2. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge, UK.

3. Caswell, H. (2001) Matrix population models. Construction, analysis, and interpretation. Sinauer, Sunderland, MA.

4. McGraw, J.B., and H. Caswell. (1996) Estimation of individual fitness from life-history data. The American Naturalist 147:47-64.

5. Lotka, A. (1924) Elements of Mathematical Biology. Reprinted 1956 by Dover Publications Inc., New York, USA.

6. Preston, S., Heuveline, P. and M. Guillot (2001) Demography. Blackwell, Oxford, UK.

C. Nederlandse samenvatting / Summary in Dutch

Introductie

Waarom worden we minder vitaal als we ouder worden? En hoe gebeurt dat precies? Welke veranderingen treden er op en kunnen we die veranderingen vatten in een begrijpelijk patroon? Begrijpen we die veranderingen goed genoeg om te kunnen interveniëren? Dit zijn belangrijke vraagstukken waar het de volksgezondheid betreft. Op de levensloop werken evolutionaire krachten, net zoals die werken op de kleuren van de vleugels van vlinders of de snavels van vogels [1]. Daarom is het in beginsel niet onwaarschijnlijk dat een goede evolutionaire analyse van veroudering bij zou kunnen dragen aan ons begrip van het (menselijk) verouderingsproces en aan onze mogelijkheden om daarin te interveniëren. Andersom, en dat komt nogal eens terug in dit proefschrift, verrijkt het medisch/epidemiologisch denken de evolutionaire analyse.

Veroudering is evolutionair nadelig. 'Nadelig' is hier geen uitdrukking van waarde. Evolutie is iets dat gebeurt; het heeft geen bewustzijn, ontwerp of doel [2]. Een evolutionaire kwestie kan altijd als volgt geformuleerd worden: 'als iets met deze en deze eigenschappen bestaat in een omgeving zus en zo, dan is het vermogen om te zorgen voor het toekomstige bestaan van het organisme zelf en/of kopieën van zichzelf zo en zo groot'. Aan dit vermogen, dat altijd afhangt van de omgeving, refereert de term 'fitness' in een evolutionaire context. Fitness hangt af van een combinatie van overleving en voortplanting, ongeacht hoe deze overleving en voortplanting bereikt worden. Een elementaire maat van fitness, die ook gebruikt wordt in de meer wiskundige hoofdstukken, wordt besproken in Appendix B. Als het hebben van een bepaalde eigenschap grote gevolgen heeft voor de fitness, dan wordt ook wel gezegd dat de selectiedruk groot is. Als bijvoorbeeld mensen met rood haar zich twee keer zo snel en veel zouden voortplanten als mensen zonder rood haar, dan is de selectiedruk op haarkleur hoog, en mag een sterke toename van het aantal mensen met rood haar verwacht worden. Als haarkleur weinig uitmaakt voor de fitness, dan is de selectiedruk op haarkleur laag. Voor de term 'selectiedruk' bestaan meer strikte wiskundige beschrijvingen, maar voor een relatief eenvoudige uitleg volstaat deze term.

Wat is nodig voor een gedegen evolutionaire analyse? Zoals de titel van dit proefschrift doet vermoeden zijn hiervoor in elk geval nodig: biologische concepten, met name vanuit de fysiologie (hoe werkt een lichaam), evenals een goed model van oorzakelijkheid en wis-kundige modellen. Deze laatste dienen om met meer zekerheid te kunnen zeggen tot welke voorspellingen de concepten leiden. Omdat voor het conceptualiseren en modelleren een goed begrip van oorzakelijkheid nodig is, wordt de lezer allereerst een eenvoudig concept hiervan aangereikt. Daaropvolgend wordt een aantal andere concepten uiteengezet, waarna de belangrijkste conclusies van het modelleren worden aangestipt (met de aantekening dat de wiskundige evaluatie terugkoppelt naar wat conceptueel voor mogelijk mag worden gehouden). Gaandeweg zal blijken welke onvolkomenheden of hiaten de oude theorieën hebben. Afgesloten wordt met een verkenning van eventuele vervolgstappen.

Oorzakelijkheid: *the causal pie model*

Het *causal pie model* (de oorzakelijke taart) is een geheugensteuntje waarmee misverstanden voorkomen kunnen worden, en waarmee schijnbaar volstrekt verschillende resultaten vanuit hetzelfde concept begrepen kunnen worden. In **hoofdstuk 2** wordt dan ook voorgesteld dit model altijd in het achterhoofd te houden, en passeert een verscheidenheid aan vindingen binnen de (evolutie)biologie de revue vanuit deze invalshoek.

Stelt u zich een taart voor die is opgedeeld in taartpunten. Elke taartpunt is een deeloorzaak, en alleen wanneer alle deeloorzaken (*component causes*) aanwezig zijn, is sprake van een voldoende oorzaak en treedt de bijbehorende uitkomst op (Figuur 2.1 op pagina 13). Een voorbeeld: waarom brandt thuis het licht? Is dat omdat er een peertje in de fitting zit? Is dat omdat de lichtknop op de 'aan'-stand staat? Is het omdat er ergens een elektriciteitscentrale staat? Overduidelijk brandt het licht vanwege al deze deeloorzaken: neem één van deze deeloorzaken weg, en u zult zien dat het licht niet brandt. Alleen als alle deeloorzaken samenkomen brandt het licht. Dit geldt ook voor biologische verschijnselen; het gaat om deeloorzaken die samenkomen [3].

Dit model is zo eenvoudig dat weleens aan het nut ervan getwijfeld is. Echter, als tegelijkertijd wetenschappelijk gezien vele zaken fout gaan die met dit model voorkomen kunnen worden, moeten we toch concluderen dat het model een functie heeft. Het model is inderdaad geen hogere wiskunde, maar juist daarom zeer nuttig als geheugensteuntje. In de nu volgende tekst wordt hier dan ook regelmatig aan gerefereerd.

Concepten

Het leven is een precaire balans tussen orde en wanorde. De tweede wet van de thermodynamica zegt dat entropie (wanorde) nooit afneemt in een gesloten systeem. Leven behelst een bepaalde ordening, die mogelijk is omdat levende organismen geen gesloten systemen zijn. Er is een voortdurende inname van grondstoffen, niet in het minst ten behoeve van energie, die volgens bepaalde voorschriften worden gebruikt, zodat de toe-

name van entropie in het organisme wordt tegengegaan. De centrale vraag is waarom het vermogen om te voorkomen dat de geordende staat (leven) wordt opgegeven af zou nemen met de leeftijd van een organisme. Dit verouderingsproces uit zich in demografische maten, voortplanting en sterfte, maar hier ligt een fysiologisch verouderingsproces aan ten grondslag. Voorbeelden zijn het verlies van elasticiteit van de bloedvaten, het afnemen van het vermogen van de ogen om te accommoderen, en het verlies van kracht. Evolutie draait om geboorte en sterfte, ongeacht hoe die geboorte en sterfte bereikt worden. Voor evolutionaire vragen moeten we daarom uiteindelijk altijd kijken naar de demografische maten, maar zonder het onderliggende fysiologische proces te vergeten. Dit is het **eerste concept**: vergeet de fysiologie niet.

Veroudering gaat over verandering. Als iedereen in het lichaam van een tachtigjarige geboren zou worden, en zijn/haar leven lang zo zou blijven, dan zouden wij niet verouderen, en zelfs niet 'altijd oud zijn'. Het is omdat een oud mens minder makkelijk uit een stoel opstaat en trager denkt bij een spelletje domino dan een jong mens dat wij veroudering kennen. Het gaat om een vergelijking tussen jong en oud; niet om absolute maten. Deze verandering kan fysiologisch beschouwd worden (wat zijn de verschillen tussen een jong en een oud lichaam?), maar ook demografisch: hoe, bijvoorbeeld, verschilt de sterftekans per tijdseenheid tussen oude en jonge mensen? Dit is het **tweede concept**: veroudering gaat over verandering, bijvoorbeeld over de toename van de sterfte met het ouder worden. De gemiddelde sterfte staat hier los van; het gaat erom hoe de sterfte verandert.

Dit concept is ook wel verwoord als *pace* en *shape* [4]. De eerste term refereert aan de tijdspanne waarin een proces, een leven plaatsvindt, bijvoorbeeld de gemiddelde levensverwachting. De levensverwachting is het omgekeerde van de gemiddelde sterfte (Appendix B). Als het leven kort is, is de *pace* snel. Maar dit zegt niets over de vraag of er überhaupt verandering plaatsvindt tijdens de levensloop, of dat een verbetering of verslechtering betreft, en hoe sterk die verandering dan is. Vandaar de tweede term, *shape*. Bijvoorbeeld, oude mensen hebben maar liefst 35 maal de gemiddelde sterfte per tijdseenheid. Vanaf het laagste punt (rond twaalfjarige leeftijd) is de toename in de sterfte per tijdseenheid maar liefst duizendvoudig. Dit is een dramatische verandering. Er bestaan een heleboel dieren en planten die korter leven dan mensen, maar een veel minder sterk uitgesproken verandering ondergaan tijdens dat kortere leven: een snellere *pace*, maar minder uitgesproken *shape*. Er bestaan zelfs soorten die het overgrote deel van hun leven verbetering lijken te laten zien [5].

We hebben veroudering nu geconceptualiseerd als een verandering, waarbij we ons blijvend bewust moeten zijn van het fysiologische proces dat hieraan ten grondslag ligt. Dit laatste wordt nog weleens vergeten, vanwege iets dat 'de wiskundige verleiding' genoemd zou kunnen worden. Met een beetje wiskunde is het namelijk goed te doen om de evolutionaire consequenties te beschrijven van leeftijdspecifieke veranderingen. Zo kan bijvoorbeeld berekend worden hoe de groei van de populatie afneemt indien de sterfte op een bepaalde, geïsoleerde leeftijd toeneemt. Dit is wiskundig eenvoudig, waardoor het verleidelijk is steeds modellen te maken waarvan je je af kunt vragen welke relatie deze

nog hebben met de realiteit. Welk biologisch/fysiologisch proces zou precies op die ene leeftijd de sterfte moeten verhogen, maar niet op andere leeftijden? In de realiteit is de gezondheid op leeftijd x niet onafhankelijk van de gezondheid op de leeftijden x-1 en x+1. Dit is een belangrijk punt, want modellen die dit verband in aanmerking nemen geven aanmerkelijk andere resultaten dan modellen die dat niet doen. Dit is het **derde concept**: veroudering is een continu proces. In **hoofdstuk 3** worden de overwegingen uitgebreid uiteengezet. In de (wiskundige) **hoofdstukken 5 en 7** blijkt dat de realiteit van continue veranderingen tot significant andere voorspellingen leidt dan modellen die uitgaan van leeftijdspecifieke veranderingen.

Één van de verschijnselen die bij de toepassing van het model van het *causal pie model* (**hoofdstuk 2**) aan bod komt is het vermeende verschijnsel van 'extrinsieke sterfte'. In sterfteonderzoek wordt nogal eens een onderscheid gemaakt tussen sterfte veroorzaakt door extrinsieke (van buiten het organisme) versus sterfte veroorzaakt door intrinsieke (van binnen het organisme) factoren. Als sterfte (voornamelijk) komt door extrinsieke factoren wordt deze sterfte ingedeeld bij de *extrinsieke mortaliteit*, terwijl sterfte (voornamelijk) veroorzaakt door interne factoren als *intrinsieke mortaliteit* in de boeken wordt gezet. Natuurlijk kan dit onderscheid in werkelijkheid niet gemaakt worden, omdat een externe deeloorzaak een interne deel-oorzaak niet uitsluit. Bijvoorbeeld, een ongeluk hangt af van een onveilige omgeving (externe factor), maar alleen gecombineerd met onoplettendheid, gebrek aan lenigheid, en kwetsbaarheid (interne factoren) leidt een potentieel gevaarlijke situatie tot de dood. In de paragraaf over het *causal pie model* werd besproken dat verschillende deeloorzaken allemaal aanwezig moeten zijn voordat het bijbehorende effect optreedt. Dit betekent dat het niet zo is dat de ene deeloorzaak belangrijker is dan de andere: er is geen 'meest oorzakelijke oorzaak'.

Het idee van extrinsieke mortaliteit is opmerkelijk hardnekkig. Zelfs wanneer erkend wordt dat zowel interne als externe factoren een rol spelen, wordt soms toch nog gepoogd het onderscheid intrinsiek/extrinsiek te maken. In **hoofdstuk 8** wordt aan de hand van data gedemonstreerd dat dit toch echt niet kan. Zogenaamde extrinsieke en intrinsieke mortaliteit hebben ongeveer hetzelfde patroon over de leeftijd. Hoe zou dat kunnen als extrinsieke mortaliteit vooral extern bepaald wordt?

Het is in dit geval beter te luisteren naar de wiskunde. In de verzamelingenleer behoort het tot de definitie van een 'partitie' (opdeling) dat er geen overlap is tussen de onderdelen van de verzameling. Dat lijkt inderdaad de enige zinnige definitie. In sterfteonderzoek zou dit een opdeling in oorzaken *met* versus oorzaken *zonder* extrinsieke deeloorzaken kunnen zijn. De vraag is of dat de wetenschap verder helpt. Er zullen altijd zowel extrinsieke als intrinsieke oorzaken aan te wijzen zijn voor sterfte. Dit is het **vierde concept**: intrinsiek versus extrinsiek kan niet.

Soms wordt onderscheid gemaakt tussen 'onmiddelijke verklaringen' (mechanismen) en 'ultieme verklaringen' (evolutie) van biologische verschijnselen, bijvoorbeeld van veroudering. De onmiddelijke verklaring brengt dan de mechanismen aan het licht: wat gebeurt er precies, hoe werkt het? Bijvoorbeeld, welke moleculen spelen een rol? De ultieme verklaring gaat in op het 'waarom': wat zijn de evolutionaire voor- en nadelen van

wat er gebeurt? Het maken van dit onderscheid is een misvatting. Zoals ook de modellen in dit proefschrift (de **hoofdstukken 5 en 7**) laten zien komen verklaringen altijd en overal voort uit het snijpunt van mechanismen en evolutionaire krachten. Mechanismen en evolutionaire krachten kunnen wel apart geobserveerd worden, maar een verklaring behelst *juist* de interactie van deze twee factoren. Mechanistische (on)mogelijkheden bepalen het domein waarbinnen evolutie haar werk kan doen. Als gevolg van dat werk kunnen de evolutionair minder productieve mechanismen niet langer worden geobserveerd. Immers, we nemen aan dat deze mechanismen door de eeuwen heen verdwenen zijn. Evolutie en mechanismen moeten daarom altijd in samenhang worden bezien (**vijfde concept**). Juist deze interactie maakt het onderwerp zo interessant!

Veroudering leidt tot meer sterfte en minder voortplanting dan anders het geval geweest zou zijn. We zouden aldus een evolutionaire uitspraak kunnen doen die als volgt gaat: 'Organismen die niet verouderen zouden, *ceteris paribus*, beter zijn in het doen voortbestaan van hun erfelijk materiaal dan organismen die wel verouderen, en het daarom beter doen dan een populatie van organismen die *wel* verouderen. Veroudering zou dus door evolutie moeten verdwijnen: niet-verouderende dieren doen het beter. Waarom bestaat veroudering dan toch?

Hier komen we bij de twee bestaande lijnen waarlangs de theorieën van veroudering kunnen worden gekenschetst. Beide lijnen gaan uit van evolutionaire druk tegen veroudering, maar pogen hier een andere druk tegenover te stellen. De lijnen verschillen van elkaar in hetgeen ze er tegenover zetten.

De eerste lijn stelt dat nieuwe (genetische) veranderingen ('mutaties') die veroudering veroorzaken spontaan blijven voorkomen. De mate waarin die mutaties nieuw ontstaan stabiliseert dan tegen de mate waarin evolutie die mutaties weer laat verdwijnen [6,7]. Op die manier zijn er altijd wat mutaties aanwezig die veroudering veroorzaken. Onder deze theorie ontstaat een *verlies* aan fitness. Hier wordt opgemerkt dat deze theorie uitgaat van een manier van werken van leeftijdspecifieke genen waarvan we weten dat deze onjuist is, en dat deze theorie ook wordt tegengesproken door de data.

De tweede lijn is de *trade-off* verklaring [6,8]. Afhankelijk van de voor- en nadelen van veroudering, kan veroudering ontstaan. Of niet. Een mogelijk voordeel waar traditioneel naar gekeken wordt is voortplanting. Meer voortplanting zou ten koste kunnen gaan van het onderhoud van het eigen lichaam, met veroudering als gevolg [8]. Veroudering dus, maar gecompenseerd door een toename in de voortplanting. Afhankelijk van hoe sterk dat verouderingsproces is versus hoeveel extra voortplanting op die manier gegenereerd zou kunnen worden kan het geheel aan *trade-off* voordelen bieden of niet. Onder de *trade-off* theorie ontstaat netto een *winst*, of in elk geval geen verlies, aan fitness. Deze theorie is niet in tegenspraak met de data. Trade-offs zijn daarom het **zesde concept** dat nodig is voor een goede evolutionaire analyse (zie ook de discussie). Er zijn zelfs onderzoeken waaruit inderdaad een zekere mate van *trade-off* blijkt, maar hier moet wel bijgezegd worden dat ons begrip van het trade-off-mechanisme zeer beperkt is.

Beide lijnen van evolutionaire verklaringen van veroudering, zoals hierboven uiteengezet, zijn zeer geholpen door de observatie dat de selectiedruk afneemt met de leeftijd [9]. Selectiedruk, technisch de 'selectie gradiënt', drukt uit hoezeer fitness verandert met een toename van sterfte of voortplanting. Deze grootheid neemt af met de leeftijd: hoe ouder een organisme is, hoe kleiner de gevolgen van een standaard verandering in sterfte of voortplanting voor de fitness. Dit betekent dat gebeurtenissen laat in het leven onder minder stringente evolutionaire controle staan, en dat er dus 'meer kan'. Zo kan veroudering ontstaan langs de lijnen zoals hierboven geschetst, in aanmerking genomen de beperkingen en mogelijkheden zoals uiteengezet in dit proefschrift.

Dat de selectiedruk afneemt met de leeftijd is een belangrijke constatering waar het de evolutie van veroudering betreft. De evolutionaire gevolgen van veroudering worden hierdoor immers gelimiteerd. Maar waardoor komt nou die afnemende selectiedruk? Een veelgehoorde verklaring is dat dit komt omdat we toch weinig kans hebben oud te worden [10]. Dit is onjuist. De selectiedruk neemt af ook als de sterfte nul is voor alle leeftijden, en elk organisme dus volledige zekerheid heeft elke willekeurige leeftijd te bereiken. Afnemende selectiedruk heeft daarom in eerste aanleg niets met sterfte te maken. In plaats daarvan is het een tijdeffect. Op het moment dat een organisme zich voortplant stelt het een gedeelte van zijn fitness zeker. Toekomstige gebeurtenissen kunnen deze bijdrage aan fitness niet raken, waardoor de selectiedruk afneemt. Bijvoorbeeld, als mensen op twaalfjarige leeftijd zouden overlijden zouden ze geen kans zien om zich voort te planten. De populatie zou dan uitsterven, en een gen dat zorgt voor dood op zulk een vroege leeftijd zou rap weer verdwijnen. Maar nu, wat gebeurt er als mensen op vijftigjarige leeftijd zouden overlijden? Er is ruim kans geweest voor voortplanting, en een gen dat zorgt voor overlijden op vijftigjarige leeftijd zou worden doorgegeven aan de volgende generatie, en dus niet zo rap verdwijnen. En let wel: deze redenering werkt ook als er initieel helemaal geen sterfte is, i.e. als iedereen overleeft tot 50-jarige leeftijd.

Het gaat er dus om wat er zou gebeuren als de sterfte opeens toe zou nemen op een bepaalde leeftijd: dit is wat de selectiedruk uitdrukt. Dat is puur theoretisch, omdat gezondheid op verschillende leeftijden met elkaar verbonden is: de gezondheid op leeftijd x is niet onafhankelijk van de gezondheid op leeftijd x-1 en leeftijd x+1. Wiskundige modellen, het volgende onderwerp van deze samenvatting, zullen dus rekening moeten houden met deze beperking. **Hoofdstuk 6** bevat een uitgebreide uitleg en analyse aangaande de afnemende selectiedruk (**zevende concept**).

Een andere misconceptie is dat tijd en energie beter besteed kunnen worden aan het maken van en zorgen voor nakomelingen dan aan het onderhoud van het eigen lichaam [8]. De denkfout zit hem dáárin dat elke investering - in onszelf, in nakomelingen, of in elk anderszins aan ons gerelateerde organisme - een investering is in een organisme dat in leven is op het moment waarop die investering plaats vindt, en zal overlijden in de toekomst. Er is dus geen verschil tussen de betreffende organismen in deze zin: alle organismen zijn op het moment waarop de afweging gemaakt wordt in leven, en als er geen verandering in sterfte optreedt over de leeftijd, bijvoorbeeld door veroudering (en dit mag niet bij voorbaat verondersteld worden!), dan hebben alle organismen op enig

moment in de toekomst dezelfde kans om dood te zijn. Ook hier doet het toevoegen van leeftijdsonafhankelijke sterfte in principe niets: het beïnvloedt alle alternatieven precies evenzeer, en in het algemeen is het niet per se beter in het ene organisme te investeren dan in het andere. Let wel: natuurlijk, zolang er sterfte is, zal er ook geboorte moeten zijn, anders volgt uitsterving. Maar de vraag is of die geboorte ook gunstig is wanneer dat ten koste gaat van het zich voortplantende organisme. Het antwoord is: zou kunnen, afhankelijk van hoeveel er te winnen valt met elke investering. Hier is niets algemeens over te zeggen: dit hangt af van de kosten en baten van elke optie (**hoofdstuk 5**), en die hangen op hun beurt weer af van de fysiologie in brede zin, en van de interactie van de fysiologie met de omgeving (**hoofdstuk 7**). Vaak zijn juist jonge en oude dieren het doelwit van roofdieren, en valt er juist veel meer voor te zeggen om vooral een sterk en vitaal organisme goed te onderhouden. Als dat niet blijkt te gebeuren, zou dat ook kunnen komen doordat dit gewoonweg onmogelijk is in deze vorm van leven, en we moeten redenen bedenken waarom dat zo zou zijn.

We hebben gezien dat sterfte het resultaat is van de manier waarop en de mate waarin de fysiologische staat van een organisme het organisme in staat stelt te reageren op de omgeving. Hieruit kan een interessante hypothese worden gesmeed, namelijk dat een organisme zich 'groter' zou kunnen maken dan het op lange termijn vol kan houden, om op korte termijn sterfte te ontlopen (**hoofdstuk 4**). 'Groter' moet niet te letterlijk worden genomen. Het gaat erom dat een bepaalde (complexe) staat op korte termijn voordelen kan bieden in de vorm van verhoogde overleving, maar dat veroudering het gevolg kan zijn omdat deze staat te complex, te 'groot' is om te onderhouden. Sterfte wordt uitgesteld, overleving wordt naar voren gehaald. Of dit uiteindelijk voordelen biedt hangt af van de snelheid en kracht van het verouderingsproces in verhouding tot de vroege verbetering in overlevingskansen: wordt de *pace* vertraagd (langer leven) als gevolg van een andere *shape* (meer veroudering)? Deze hypothese is interessant, omdat een sterke focus altijd gelegen heeft op *trade-offs* tussen overleving versus voortplanting. Het idee is dat veroudering het resultaat is van investeringen in voortplanting die ten koste gaan van het onderhoud van het eigen lichaam. Dit kan, maar het is evenzeer mogelijk dat er binnen de sterftefunctie zelf geschoven kan worden door een lichaam te ontwikkelen dat te 'groot', te complex is om te onderhouden. Dit lichaam bezwijkt dan als het ware onder zijn eigen gewicht. Deze hypothese is het onderwerp van **hoofdstuk 4** en wordt gemodelleerd in **hoofdstuk 7**.

Wiskundige modellen

Om voor- en nadelen tegen elkaar af te wegen, en om exacte resultaten te bereiken, volstaan woorden meestal niet. Soms is het inzichtelijker om processen in kaart te brengen met behulp van een berekening. De **hoofdstukken 5-7** bevatten zulke berekeningen. De ideeën achter deze berekeningen zijn als volgt. Allereerst is er een maat nodig van evolutionaire prestatie. Evolutie gaat over het verspreiden en verbreiden van erfelijk materiaal. Hiervoor is overleving en voortplanting nodig. Als we aannemen dat er enige sterfte is, hetgeen redelijk lijkt, is een organisme op enig moment niet meer. Het enige overblijvende

erfelijk materiaal van het organisme bestaat dan in zijn nakomelingen. We kunnen dus, en dit is makkelijker gezegd dan gedaan, het (verwachte) aantal nakomelingen tellen. Echter, dit is niet genoeg. Stel dat er twee soorten organismen zijn, die elk twee nakomelingen per ouder maken gedurende hun leven. Het aantal nakomelingen per ouder over het leven is dus twee voor allebei de soorten, hetgeen betekent dat de populatie zich per generatie verdubbelt. Maar stel nu dat dit alles zich voor het ene organisme in twee keer zoveel tijd afspeelt als voor het andere. Dat zou betekenen dat het ene organisme zich twee keer zo snel verdubbelt als het andere, en daarom een veel sneller groeiende populatie vestigt. De langzaam groeiende variant wordt dan weggeconcurreerd. Daarom wordt er een wiskundige methode gebruikt om de groeisnelheid per tijdseenheid te berekenen voor elk gegeven patroon van overleving en voortplanting. Dat werkt net als rente op een spaarrekening: hoe hoger de rente, hoe sneller het vermogen groeit (zie **Appendix B**, [11]). Op deze maat valt nog steeds van alles aan te merken, maar het is vaak de beste die we hebben. Bovendien werkt alles wat in de **hoofdstukken 5 tot 7** gesteld wordt in principe ook voor aangepaste maten van fitness.

Er zijn twee, complementaire, soorten van berekeningen van belang om *trade-offs* te modelleren. De eerste methode zoekt direct naar de hoogste mate van fitness die bereikt kan worden onder een gegeven *trade-off* [12,13]. De tweede methode is het zoeken of de fitness verbeterd kan worden onder een gegeven *trade-off* (**hoofdstuk 5**). De methoden zijn natuurlijk gerelateerd: indien een toename van fitness mogelijk is betekent dit immers dat er een hogere waarde van fitness bestaat. Beide methoden hebben zo hun nut. Het zoeken naar een mogelijke toename is waarschijnlijk hetgeen waar evolutie het zelf mee moet doen. Evolutie berekent geen optima; evolutie zet stapjes [13,14]. Toch kan het ook interessant zijn optima te weten te komen, simpelweg omdat het je vertelt dat veel beters er niet inzit, tenminste niet als je model klopt.

In **hoofdstuk 5** wordt vroeger werk [e.g. 9] op het gebied van het zoeken naar een mogelijke verandering van fitness in een meer algemeen demografisch kader [15] ingebed, en worden vervolgens verschillende *trade-offs* onderzocht onder dit algemeen demografische model. **Hoofdstuk 7** is gebaseerd op directe optimalisering: wat is de hoogst bereikbare fitness, en wat is de bijbehorende strategie onder de *trade-off*? De modellen in de **hoofdstukken 5 en 7** gaan uit van continue veranderingen in plaats van leeftijdspecifieke veranderingen. En dit geeft verrassende resultaten. Waar bijvoorbeeld een analyse met leeftijdspecifieke veranderingen lijkt te suggereren dat de evolutie van veroudering onvermijdelijk is, zo blijkt dat het aan elkaar schakelen van leeftijdspecifieke veranderingen in een biologisch plausibel patroon deze conclusie onderuit haalt.

De belangrijkste resultaten van dit modelleren zijn als volgt:

- De selectiedruk neemt af met het toenemen van de leeftijd, ook wanneer de sterfte nul is voor alle leeftijden. **(Hoofdstuk 6)**
- De manier waarop en de mate waarin de selectiedruk afneemt met de leeftijd is in principe niet gerelateerd aan *leeftijdonafhankelijke* sterfte. **(Hoofdstuk 6)**
- De evolutie van veroudering is niet onvermijdelijk, zelfs niet wanneer de afnemende selectiedruk expliciet gemodelleerd wordt. **(Hoofdstuk 5)**

- Of veroudering kan evolueren of niet hangt af van de fysiologische mogelijkheden en beper-kingen die een rol spelen bij veroudering. **(Hoofdstukken 5 en 7)**
- De sterkste mate van veroudering wordt gevonden voor een gemiddelde sterkte van een *trade-off*. Hier wordt mee bedoeld dat de veroudering, het nadeel, gemiddeld sterk is ten opzichte van het voordeel. De intuïtie hierachter is als volgt. Als het nadeel heel klein is (veroudering niet sterk is), dan is de veroudering nu eenmaal niet sterk. Het is dan vaker evolutionair optimaal om dit beetje veroudering toe te laten in ruil voor het voordeel. Als de veroudering erg sterk is in verhouding tot het voordeel, dan moet het voordeel achterwege worden gelaten, en treedt de veroudering niet op. Alleen bij gemiddelde mate van veroudering is de mate van veroudering redelijk sterk *en* kan het optimaal zijn om veroudering toe te laten. **(Hoofdstuk 7)**
- Om te kunnen zeggen of veroudering optimaal is of niet kan niet gekeken worden naar de omgeving alleen of naar de fysiologie van het organisme alleen; dit wordt volledig bepaald door de interactie van beide factoren. Dit betekent dat veroudering, maar ook afwezigheid van veroudering, kan voorkomen in zowel een zeer vijandige omgeving als in een zeer vriendelijke omgeving. **(Hoofdstuk 7)**

Discussie: Gevolgtrekkingen uit dit proefschrift

In dit manuscript heb ik getracht een gedegen evolutionaire analyse van veroudering te geven. Daarvoor waren biologische concepten, een model van oorzakelijkheid en wiskundige modellen noodzakelijk. Tot op zekere hoogte bouwde ik daarbij voort op de bestaande 'klassieke' theorie. Echter, het kader van deze bestaande theorie komt steeds meer onder druk. In de literatuur wordt gerefereerd aan "veel genen met een klein effect die veroudering veroorzaken" [1] of de "allocatie van middelen naar lichamelijk onderhoud" [8] als de veroorzakers van veroudering. Het beeld dat hierbij geschetst wordt is dat het menselijk lichaam zoals wij dat kennen mogelijk niet zou verouderen, ware het maar dat een beperkt aantal genen overboord kon worden gezet, of dat een grotere hoeveelheid middelen kon worden ingezet voor lichamelijk onderhoud. Het idee is dan dat dit niet gebeurt vanwege de met de leeftijd afnemende selectiedruk. Deze zienswijze is te beperkt, en daarmee wordt voorbijgegaan aan een groot aantal mechanistische restricties die het niet-verouderen een precaire, zo niet onmogelijke exercitie maken. Er zijn veel meer beperkingen op lichamelijk onderhoud dan grondstoffen alleen. Er is informatie nodig over hoe het lichaam idealiter zou moeten werken. Er is detectie nodig van schade. Een eventueel reparatie- of beschermingsproces neemt ruimte in en kan alleen onder bepaalde chemische omstandigheden plaatsvinden. Ook komen bij zo een proces bijproducten vrij die verkeerde signalen zouden kunnen geven aan nabijgelegen organen of cellen, of juiste signalen verstoren. En bovendien mag de lichamelijke functie niet onderbroken worden tijdens al deze taken. Zou dat allemaal kunnen binnen complexe vormen van leven zoals wij die kennen, bijvoorbeeld binnen het menselijk lichaam? Kan het niet zo zijn dat het menselijk lichaam zo gebouwd is dat onderhoud op het niveau van het geheel tot stilstand brengen van het verouderingsproces gewoon onmogelijk is? We verouderen gewoon!

Bij de eerder genoemde restricties op lichamelijk onderhoud komt nog dat een onderhoudsproces geëvolueerd zou moeten zijn, en in evolutie speelt de geschiedenis altijd een rol: evolutie ontwerpt geen organismen, maar prutst met wat er voorhanden is [13]. Dit betekent dat enig onderhoudsproces, uitzonderingen daargelaten, waarschijnlijk plaatsvindt met componenten die ook een andere rol hebben in het lichaam, omdat dit zou kunnen verklaren waarom deze componenten beschikbaar waren voor het evolutionaire proces. Deze andere rol beperkt hoezeer deze componenten geschikt zijn voor hun taak als onderhoudsmachinerie. Lichamelijk onderhoud zou wel eens meer kunnen lijken op het met duct tape weer vastplakken van de uitlaat die op straat lag dan op het netjes installeren van een nieuwe. Een van de conclusies c.q. stellingen van mijn proefschrift is dan ook dat we toe moeten naar de vraag waarom ononderhoudbare levensvormen ontstaan zijn, in plaats van ons af te vragen waarom een onderhoudbaar lichaam niet onderhouden wordt.

Dit leidt tot de vraag of veroudering wel een evolutionaire kwestie is, en zo ja op welk niveau. Alles is wel een evolutionaire kwestie op de een of andere manier, maar niet precies zoals er nu naar gekeken wordt. De huidige evolutionaire modellen gaan uit van een organisme dat mogelijk niet veroudert, en mixen daar wat losse genen in, of veranderen wat aan de allocatie van middelen tussen de verschillende lichamelijke functies, waardoor een organisme veroudert. Zoals betoogd zou veroudering wel eens inherent kunnen zijn aan hoe ons lichaam in elkaar zit. Als we niet zouden verouderen, dan zou ons lichaam er heel anders uitzien. We zouden dan geen mensen zijn, maar, wie weet, Barbapappa's. Veroudering blijft dan een evolutionaire vraag, maar deze vraag krijgt een andere invalshoek. In plaats van ons af te vragen waarom veroudering bestaat binnen ons lichaam en te zoeken naar een handvol genen die voor die veroudering verantwoordelijk kunnen worden gehouden, zullen we ons af moeten vragen waarom onze vorm van leven geëvolueerd is. Er zijn dan mechanistische beperkingen waardoor de niet-verouderende mens nooit geëvolueerd kan zijn. Blijkbaar zitten er daar dan tóch bepaalde voordelen aan deze vorm van leven, anders zou de menselijke vorm van leven immers uitgestorven zijn. Maar het heeft dan geen zin om te kijken naar bepaalde individuele genen, en te vragen waarom die geselecteerd zijn of niet. Of om te zoeken naar punten waar het lichamelijk onderhoud te kort schiet. In plaats daarvan zit de *trade-off* in het ontstaan en bestaan van onze vorm van leven.

Veroudering zit in onze blauwdruk, en *binnen* deze vorm van leven kunnen we niet vrijelijk dromen over wel versus niet verouderen. De beperkingen op lichamelijk onderhoud die hierboven aan bod kwamen zijn een krachtig argument vóór deze manier van denken. Moge dit proefschrift een goede start betekenen van een meer mechanistisch geïnspireerde theorie van (de evolutie van) veroudering.

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Referenties

1. Stearns, S.C. (1992) The evolution of life histories. Oxford University Press, Oxford.

2. Darwin, C. (1964) On the origin of species. A facsimile of the First Edition. Harvard University Press, Cambridge.

3. Rothman, K.J. (2012) Epidemiology. An introduction, 2nd edn. Oxford University Press, New York.

4. Baudisch, A. (2011) The pace and shape of ageing. Methods in Ecology and Evolution 2:375-382.

5. Jones, O. R., Scheuerlein, A., Salguero-Gómez, R., Camarda, C.G., Schaible, R., et al. (2014) Diversity of ageing across the tree of life. Nature 505:169-173.

6. Medawar, P.B. (1952) An unsolved problem of biology. Pages 3-24 *in* Uniqueness of the individual, Lewis, London.

7. Charlesworth, B. (1994) Evolution in age-structured populations, second edn. Cambridge University Press, Cambridge.

8. Kirkwood, T.B.L. (1977) Evolution of ageing. Nature 270:301-304.

9. Hamilton, W.D. (1966) The moulding of senescence by natural selection. Journal of Theoretical Biology 12:12-45.

10. Kirkwood, T.B.L. and S.N. Austad (2000) Why do we age? Nature 408:233-238.

11. McGraw, J.B. and H. Caswell (1996) Estimation of individual fitness from life-history data. The American Naturalist 147:47-64.

12. Baudisch, A. (2012) Birds do it, bees do it, we do it: contributions of theoretical modelling to understanding the shape of ageing across the tree of life. Gerontology 58:481-489.

13. Maynard Smith, J. (1978) Optimization theory in evolution. Annual review of ecology, evolution, and systematics 9:31-56.

14. Jacob, F. (1977) Evolution and tinkering. Science 196:1161-1166.

15. Arthur, W.B. (1984) The analysis of linkages in demographic theory. Demography 21:109-128.

D. List of publications

Koopman JJE, Wensink MJ, Rozing MP, van Bodegom D, Westendorp RGJ. *Intrinsic and extrinsic mortality reunited.* Under review: Experimental Gerontology.

Wensink MJ, Caswell H, Baudisch A. *The rarity of survival to old age does not drive the evolution of senescence.* First revision: American Naturalist.

Wensink MJ, Wrycza TF, Baudisch A (2014) *Interaction mortality: senescence may have evolved because it increases lifespan.* PLoS One 9:e109638

Wensink MJ, Westendorp RGJ, Baudisch A (2014)*The causal pie model: an epidemiological method applied to evolutionary biology and ecology.* Ecology and Evolution 4:1924-1930.

Wensink MJ, Wrycza TF, Baudisch A (2014) *No senescence despite declining selection pressure: Hamilton's result in broader perspective.* Journal of Theoretical Biology 347:176-181.

Wensink MJ (2013) *Age-specificity and the evolution of senescence: a discussion.* Biogerontology 14:99-105.

Wensink MJ, van Heemst D, Rozing MP, Westendorp RGJ (2012) *The maintenance gap: a new theoretical perspective on the evolution of aging.* Biogerontology 13:197-201.

Alizadeh Dehnavi R, de Roos A, Rabelink TJ, van Pelt J, Wensink MJ, Romijn JA, Tamsma JT (2008) *Elevated CRP levels are associated with increased carotid atherosclerosis independent of visceral obesity.* Atherosclerosis 200: 417-23.

E. Curriculum vitae

Maarten Jan Wensink was born October 3rd 1984 in Amstelveen, the Netherlands. He attended primary school at 'Het Kompas' in Voorschoten, the Netherlands, and secondary school at subsequently 'Vlietland College' in Leiden and 'Sint Antonius College' in Gouda. After using a gap year to travel to France, Ireland and Spain, he studied Medicine at Leiden University between 2003 and 2010, acquiring his title as medical doctor in June 2010. In addition, he attended a number of additional courses, such as Moral Philosophy and Special Relativity Theory. Intrigued by the theories of aging during his studies, he decided to start his PhD research at the Max Planck Institute for Demographic Research in Rostock, Germany, in cooperation with the Leyden Academy on Vitality and Ageing in Leiden. Maarten is an enthusiast sailor and a certified sailing instructor.

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