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 unpublished manuscript).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)

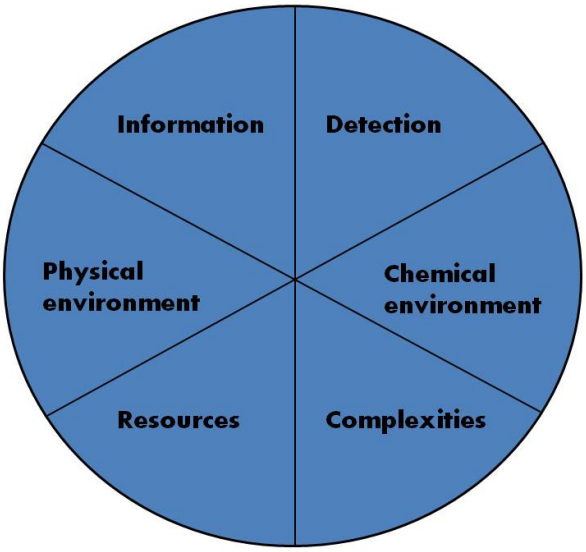

Figure 10.1: Following the causal pie model expounded Chapter 2, this figure shows the component causes that jointly constitute a sufficient cause for successful somatic repair: detection of damage, information on the desired state, resources for repair, physical and chemical circumstances that are compatible 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.