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.

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