Targeting environmental and genetic aspects affecting life history traits

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General Introduction

General Introduction

In my thesis I start with a very broad view on the essence of life, what is it and what causes it to exist in the way it does. I will explain that, in my view, maintaining energetic states is all there is to sustaining life. This thesis revolves around the question of which strategy, for lack of a better word, an organism chooses to maintain itself for as long as possible through evolutionary time under different circumstances. Maintenance is here defined as “kept in evolutionary existence” and includes growth, reproduction, healing, etc. This has everything to do with energy and how it is allocated, how it is stored and at what rate it is used. The following chapter is abstract and philosophical, yet I think it is important to set a broad scale picture of life to portray the scientific account I have written over the past few years. I hope this will put my research in the wider context of life in general.

Life, entropy and everything

A living individual is in its essence “a part of the world with some identity that tends to become independent of the uncertainty of the rest of the world” (Wagensberg 2000). In this definition we find the marked difference between the living and non-living world[1]. The living world ends where the uncertainty of the rest of the non-living world begins. To be “certain”, one needs to be in control. To be in control requires power, which in itself requires energy. Energy is what is needed to maintain order in chaos, or, to put it in other words, maintain low local entropy. “Local” means lower entropy as a body, or a somatic unit. The second law of thermodynamics states that the total entropy of a system has to become higher with every change in the system. Yet, entropy is lowered by processes that counteract chaos by putting things in order, such as growth. Following the second law of thermodynamics this would not be possible, unless when the total entropy becomes much higher. This means that for entropy lowering processes such as growth, maintenance and reproduction, the entropy of the entire system the organism lives in has to become higher. This is because lowering the local entropy without elevating the entropy of the total system would violate the second law of thermodynamics. The energy required to lower local entropy has to come from the total system and this subsequently elevates the total entropy. In order that they gain lower entropy, living organisms have to breakdown substances or redistribute energy in a way that entropy of the total system becomes higher. Seen from this point of view, life is in its essence destructive.

Lowered entropy is not an aim in itself, because it does not require life; a salt crystal is a form of locally lowered entropy. Lowered entropy is a means, but not to an end, rather to a non-end, and the same applies to the organism. There is no such thing as a purpose or target in the process of survival. There is only the continuation of an entity that has the ability to replicate itself. The form of the entity we call the

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[1] T*he living world is regarded as the biotic realm, as contrasted with the non-living or abiotic world. We use the terms biotic and a-biotic or living and non-living here instead of the contrast between living and death. Dead things by definition used to live, otherwise they are not dead but lifeless. In short, death is inherent to life.*

phenotype. This entity survives when it produces a phenotype that is adapted to its environment in such a way that it can lower local entropy, which biologically means that it is able to grow, survive and replicate. To do so, the entity must efficiently transfer energy into growth, maintenance and reproduction in the environment it lives in.

The constant factor of life is that it has maintained itself through time, both through evolutionary time and during the time the organism is physically present. When an organism is not capable of reproducing, it only lives to die eventually, because of stochastic events, like for example a volcano eruption, predation or cardiac arrest. Dying without adding to procreation through time in the broad sense[2] is what I call an evolutionary dead end. This reasoning is an extrapolation of the selfish gene hypothesis (Dawkins 1976), where the only thing that matters for genes is to copy themselves into a next generation. Again, this process is not a function or a purpose in itself. It is the only way life is possible: it sustains itself or dies out. Thus, life can be approached as a self-replicating anomaly in entropy that remains present by its power to avoid uncertainty through time by the transfer of energy and the subsequent increase of total systemic entropy. The driving force behind the self-replicators is that the ones that are best adapted to their environment survive to live over evolutionary time. The fittest individuals are regarded as such always in hindsight. Because fitness can only be determined afterwards and no organism is consciously selecting itself, we should regard the evolutionary process as purposeless. The actual reproducing unit of an entity is always the essence of the entity, because the entity would be lost if it wasn't. The information on how to cope with the environment, reduce local entropy and maintain one's lineage should always be the part that is reproduced of the entity. In our world this happens because of a replication of nucleic acids, coding for the information to successfully reproduce nucleic acids into a next generation. A successful combination of nucleic acids encoding a product is called a gene. A gene encodes a product and thus a certain way of dealing with a situation. When several genes encoding several products are optimized for one or a few purposes, they may enhance the survival capacity of the total set of genes they belong to. Together these genes encode a more complex entity; the organism. The ultimate goal of the organism is to maintain the entity through time and reproduce. The exterior organism, the phenotype, is thus only a way of dealing with the environment as efficiently as possible.

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[2] *Adding to procreation can be done in a number of ways and it does not necessarily involve reproduction itself. For example, the provisioning of science, education or food, can enhance the well-being and survival capacities of youngsters of family or the community one lives in. As all humans are related to a certain extent, adding to someone else's survival is thus adding to the survival of a bit of oneself. In popular scientific literature this fact is not often acknowledged and mere redundancy of non-reproducing entities is proclaimed. I think this is rather shortsighted, because as stated this form of altruism is mere selfishness. As is everything, Nietzsche would say.*

Intermezzo

I have been writing in an extremely abstract way about biological phenomena. The rest of my thesis will be focussing on more pragmatic biological issues that have their own terminology. Because I think it is necessary for the sake of briefness to talk in jargon about science, I will shift from the philosophical terminology used in the first subparagraph to biological terms. For example, instead of using the noun "entity" I will turn to the word "organism". I will also start to use the term "evolution" more often and will then mean "the process that an organismal lineage changes over time and adapts to the environment it faces". The first paragraph discussed the most elementary principles of life. Further in this thesis, I will revert to these basic principles sometimes to illustrate how everything in biology eventually comes back to these and most of the time to show how close to the basics of life the work of this thesis comes. Also, for the sake of easy communication, I will use language that implies purpose in life, though there is no such thing.

Acquisition of energy

In the first part I explained why energy is vital to life. Here, I will explain what the importance of energy acquisition is.

In the time of physical presence of an organism, for its growth and maintenance, it needs to put energy into several mechanisms. To be able to do so, the required energy must be acquired. To do this efficiently, without having to wait for what accidentally comes along, energy acquisition systems have by definition a huge advantage in becoming more and more independent of the environment. Such systems may come into existence by chance and as a result of selective pressure then develop further to become the highly efficient energy acquisition machinery that can be observed in nature, such as catabolic enzymes, photo systems, guts etc. Arguably, systems with other features that are adaptive to new situations may come into existence in the ages that will follow. Energy acquisition via feeding, as happens in animals, requires a lot of extra structures to facilitate that the animal ends up with enough energy to be able to survive. Developing these structures and maintaining them has to cost less than it yields in terms of energy.

The environment

Acquiring energy is done in a large number of ways throughout life and has arisen as a result of positive selection pressure. The diversity varying from photosynthetic plants and chemotrophic crayfish to ants that practice agriculture indicates that there is a wide diversity of selection pressures in different systems. The environment is a very strong factor driving selective pressure. Here I explain how energy resources must be used to acquire new energy and how the organism that tries to escape environmental dependence ironically has to adapt to it.

It has been mentioned earlier in passing that the environment is everything the organism has as a reference point in terms of the "choices" that it makes[3]. Animals are forced to function in their environment as a consequence of the legacy of natural selection. The environment sets the scene in which the organism must function in order to survive and reproduce. The organism therefore has genes that are the result of the selective pressure on a viable form. Also, epigenetic regulation, such as methylation, is important in determining the phenotype. Such epigenetic factors may be seen as the way the genome can be fine-tuned to the environment without meddling with the genetics and may be involved in the basis for adaptive plasticity (Brakefield et al. 2005). Seen from this point of view, the organism is no longer the mere carrier of genes; the entropic anomaly that keeps on replicating itself by reducing uncertainty. It is a dynamic process, in which the entropic genetic entity has to adapt to external selective pressure in order to be able to compete for resources that are needed to avoid uncertainty. In other words, the environment is not only the sometimes dangerous set of conditions the organism has to escape, it also is the music to which it dances.

Allocation and trade offs

Once energy has been acquired it can be used for several purposes. The surplus energy that was gained by feeding structures gives the organism the potential to develop traits. The term 'traits' comprises many different categories, varying from developmental, physiological and behavioural to cognitive traits. In this part I will debate what underlies energy allocation to different traits.

One constant for an animal lineage is that the individuals of the lineage are eventually going to die. This implies that there can be no such thing as a Darwinian Demon[4]. It is impossible to be a Darwinian Demon because living organisms are always constrained in terms of the amount of energy that is available with which they can reduce local entropy. While it would be convenient to invest maximally in all processes[5], this is not feasible because of the limited resources one has.[6] Choices

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[3] *This is true for both the long-term ultimate evolutionary 'choices' that are shaped by natural selection, and the short-term proximate physiological mechanisms that the animal uses to respond quickly to a particular environment. In both cases the environment sets the standard the animals have to live up to.*

[4] *Darwinian Demon; i.e. an ever-living immensely reproducing unit. This Demon would need to spread fast, absorb resources and be resistant to everything that threathens it. This would, in theory, be the ideal organism towards which all selective pressure should lead (so there is a sort of end after all). Some organisms approach this situation more closely than others, the species Homo sapiens is making a good attempt to use up as many resources as possible, live long and reproduce exponentially.*

[5] *All processes an individual can invest in can be categorised as either maintenance, growth or reproduction. The most basic of these is maintenance, and the other two can be categorised in the factor maintenance as well. Maintenance should be*

have to be made; investing in growth, in reproductive output or in maintenance? These choices are not made consciously, most of the time because the organism has no such thing as a conscience, but also because consciousness, if present, has little influence on these processes[7]. Physiological and genetic constraints will make the ‘choices’ for you, no matter whether one’s consciousness agrees or not. Because the division of energy is important and comes close to the essence of the organism, the selection process favours organisms that allocate their energy in the most efficient way. Also, because an organism has to function as a whole and not as a collection of parts (Stearns 1992), sometimes the conflict between two traits may form a constraint on the evolution of one of the two traits (for a good overview of evolutionary constraints, see Zijlstra 2002, for one on trade offs and correlated traits, see Ricklefs and Wikelski 2002). The way resources are allocated is shaped by the environment the organism lives in, because this is the major determinant of fitness. When two mechanisms are in competition for the same resource and choices have to be made, we speak of a trade off. Essential to the Darwinian Demon is that it is not constrained by a fixed amount of energy, it therefore has no trade offs. Because energy can be distributed only once and resources are limiting, there are a lot of known trade offs in organisms. The best known one will be the trade off between longevity and reproduction, which we will discuss in the next paragraph.

Life history evolution

The allocation of resources as a result of environmental selection pressure leads to favouring one trait over the other in a trade off situation. Some of these traits are very basic to life, for example development time, reproductive output and life span

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defined as “preventing yourself from becoming extinct”. Growth will enable an individual to become less vulnerable, more powerful etc. which can all be seen as a way of maintenance. Reproduction can be viewed as a way of evolutionary maintenance, as is described earlier in the first chapter. Nevertheless, they are regarded as separate investments here because these are the elementary trade offs. For example, finding food should be categorised as maintenance, and once food is found it can be allocated to either of the processes categorised here.

[6] *This understanding lead the famous Thomas Malthus (Essay on the principle of population, 1798) to the theory that the struggle for existence will always lead to shortage. Both Charles Darwin and Alfred Russel Wallace picked up this theory to state that favourable features must thus have an advantage over unfavourable ones and thus that natural selection must be ubiquitous. This concept forms the basis of evolutionary biology as a discipline.*

[7] *There can be a lot of debate about this remark, it is meant to say that animals without a central nervous system that are not complex enough to make up their own minds, have little to think about. Apart from that, conscious individuals are not capable of determining the way their physiology works as well. If that were so, then obesity would not be a problem in this society. (Arguably, people can actively choose whether to become obese or avoid it.)*

(Stearns 1992). Many of these life history traits trade off or correlate with one another. When two life history traits depend on largely the same genes, selection on one will take the other along and the genetic correlation, positive or negative, becomes apparent. On the other hand, when two life history traits both require a lot of resources, they trade off and counteract one another.

Longevity, starvation resistance and reproduction.

Starvation resistance and longevity are found to be closely correlated in a number of studies (e.g. Borash and Ho 2001; Chippindale et al. 1996; Harshman et al. 1999a, 1999b; Leroi et al. 1994; Rose et al. 1992; Zwaan et al. 1991). It is often thought that longevity and starvation resistance are therefore dependent on the same genetic mechanism. However, other studies have shown that this relationship is present but hardly as straightforward as was thought earlier (Force et al. 1995; Archer et al. 2003; Phelan et al. 2003; Baldal et al. 2005). Apparently, the strong correlations found can degrade over time due to certain selection pressures, or be changed by a change in environmental conditions. This makes the supposition that both life history traits fully result from one mechanism unlikely. Thus, though starvation resistance and longevity are closely related in terms of their genetics, differences between their underlying mechanisms remain present. In Chapter 3 I present work concerning selection for increased starvation resistance. There, I also find that such selection on starvation resistance may, but does not necessarily, lead to increased longevity.

Starvation resistance and longevity are both found to trade off with reproduction in a similar way (Chippindale et al. 1993). This thus reflects the elementary trade off between maintenance and reproduction already mentioned briefly in footnote 4. The processes that underlie this trade off between maintenance and reproduction are formulated in the Disposable Soma theory (Kirkwood 1977; Kirkwood and Holliday 1979). This theory states that when the individual is in a position to procreate successfully, the individual itself becomes redundant and its offspring more important. It assumes that within the organism there is a conflict between the somatic and germ line tissues. The state of the trade off in this conflict is driven by the selection process. The trade off between starvation resistance and reproduction is very direct since they compete for precisely the same resource; fat. Depending on the evolutionary history and the environment, the allocation of fat is determined and the individual will ‘bet’ on one of the options.

Thrifty genes and phenes

That the environment is important in determining allocation models is illustrated by the fact that obesity is a serious problem in the Western society. One would expect that every lineage of organism should change towards a Darwinian Demon because of selection pressures towards infinitive life span and number of offspring. So, in theory affluent conditions in society should lead to a good allocation of the surplus energy. In practice, it is observed that our current affluence leads to a very high incidence of obesity and thus of sub-optimal usage of the energy acquired. So, I have to conclude that our allocation model is not set up for the abundant food conditions in current society.[8] Due to adverse conditions during our evolutionary history, our genotype has adapted to poor conditions relative to present-day life in the western world. This was first observed by Neel (1962) who studied the incidence of diabetes type II in the human population. The genotypes that have adapted to adversity are very economical with their energy and are therefore called thrifty.

An illustration

The people of the island of Nauru have gone through serious bottlenecks and have become adapted to adverse food conditions. During evolution, when food conditions were more limiting, the Nauruans transition of food to reserves has been optimized. In the presence of food the Nauruan is likely to allocate energy to reserves to be able to survive more adverse times. A sudden increase in wealth gave them the opportunity to import large quantities of very fat food. This resulted in a large incidence of mortally obese people in this population where the thrifty genotype has a very high frequency (Diamond 2003)[9]. All this can be explained by the insulin signalling pathway, which is the intermediate step from food presence to phenotypic response. In this molecular pathway, the allocation is determined and insulin signalling in people adapted to adversity will lead to storage of fat. A similar trend can be observed in American Indians, non-western immigrants and Europeans. In Europeans, this problem is of a smaller magnitude because the overall food quantity in Europe has increased gradually over the ages. Apparently, a difference in evolutionary history may have lead to a difference in response to environmental challenges. These lineage specific effects are thus basically differences between genotypes. In Chapter 1, we treated three species of *Drosophila* experimentally by rearing them under different larval densities, and then examined their responses in the amount of fat, body size, longevity and starvation resistance. Different species allocate their resources in a different way because of differences in their evolutionary background. Such lineage specific effects may thus be in part responsible for differences in life history traits.

In a time of scarcity, the individual is faced with a lack of resources and will then respond in a way that has proven its worth in evolutionary history. Sometimes this

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[8] *Taking into account that we, as humans, are still under the influence of natural selection, it is to be expected that in time humans in western world civilisations will adapt to the contiuous presence of large amounts of food. Evolutionary processes take time and the present situation of affluence is very young, in terms of evolutionary timescales.*

[9] *It could be argued that the Nauruans, with their preference for fat meals, fat-bodied partners and a sedentary life-style, are not only hindered by their genetic background but also by their culture. The frequency of the mortally obese genotype has dropped throughout recent years because of various reasons, one of them being the strongly reduced reproductive output of these obese individuals. Since the Nauruan culture increases the chance of becoming so obese, culture should be regarded an important factor shaping the genetic make-up of the human population.*

may prevent the individual from incurring damage and prove to be adaptive plasticity, in other cases, this defence will not be strong enough and the individual either dies or suffers serious damage, which I would call scar. In Chapter 2 I test a theory based on the observation that in the human population individuals that have suffered from adverse conditions in the womb, had a higher incidence of metabolic syndrome as adults as found by Hales and Barker (1992; 2001). Metabolic syndrome is the common name for a group of disease types such as diabetes type II and obesity. Altered insulin signalling is hypothesised to lead to this group of diseases. The prediction that adverse pre-adult conditions lead to increased risk in adults is called the thrifty phenotype hypothesis which is also called the Barker hypothesis. I have to note here that it is important to observe that in both the thrifty genotype and thrifty phenotype hypotheses, altered insulin signalling leads to increased risk of metabolic disease. It is, thus, very easy to confound these theories.[10] Testing the Barker hypothesis could reveal an effect of nutritional conditions on life history traits.

In summary, the life history traits of an individual are a manifestation of physiological trade offs, genetic constraints and past and present environmental selection pressures. Apart from the evolutionary consequences of selection on a certain strategy, the allocation problem also applies to the individual. It has to cope with the amount of energy it can spend. The issue of how to spend energy and on what, is dependent on the environment the individual is in.

Quality and quantity of diet

Life has to a varying extent escaped the environment by becoming more and more independent from it, yet life is not possible without the environment and thus the environment is important for two things; the first one is to ensure escaping it in terms of damage, the second one as a food source. Life history characteristics have been shaped by natural selection for the successful exploitation of the environment. A change in the environment to which the lineage had no opportunity to evolve an adaptive response is an interesting test case for the processes underlying the life history configuration and potential differences among lines. In this thesis I explain how food, as an environmental condition, may affect life history traits.

Food has a very direct effect on an organisms, homeostasis and slightly different products evoke different responses, as has been found for chocolate in humans (Serafini et al. 2003). Mair et al.'s (2005) study makes it clear that in *Drosophila* it is not the number of available calories that decrease longevity. Yeast removal from the media has a substantially larger beneficial effect on longevity than does the removal of exactly the same calorific amount of sugars. Yeast, therefore, represents not only a source of energy to the fruit fly, but must also induce physiological responses

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[10] The cause of the theories is, however, fundamentally different. Where the thrifty genotype hypothesis has an evolutionary, ultimate cause, the thrifty phenotype hypothesis has a physiological, proximate cause. Clear distinguishing and thoughtful experimentation are required to obtain the proper data. We aim at this in Chapter 2.

related to the allocation of resources. This probably has to do with the induction of the reproduction process in fruit flies.

The quantity of the diet is important for inducing responses. When an animal can acquire little food, it has a smaller amount of energy available than when it can eat *ad libitum*. The amount of energy available to an animal determines its allocation, therewith inducing responses in life history traits. In addition, the amount of food taken up also poses problems to the organism that need to be solved at the same time. More food, means more build-up of resources and if an animal eats too much it may encounter negative effects of affluence. Coronary heart disease in man is, in many cases, such an effect (Anonymus 1972). In a number of animal taxa, dietary restriction leads to an increase in lifespan and thus there is a negative effect of eating *ad libitum* (Lin et al. 2002; Merry 2002; Anderson et al. 2003; Houthoofd et al. 2003; Mair et al. 2003; Fontana et al. 2004; Kaeberlein et al. 2004; Mair et al. 2004). These studies show that animals in laboratories are largely over-fed and so longevity-enhancing dietary restriction is an important process in these cases. Actually, the response curve of longevity as a function of adult diet has an intermediate maximum. Both the poor and affluent diet result in a shortened life span relative to the intermediate diet. Thus, calorie restriction leads to elevated longevity, but only up to a certain point where longevity is maximal. When calorie restriction is so harsh that the organism experiences shortage, life span will not be enhanced but rather shortened. Because dietary restriction is only used in the positive sense of the word, we use another term for the negative effect of reducing calories, namely starvation.

All chapters of this thesis are about the effect of food on the individual. In Chapters 1 and 2, I changed pre-adult environmental conditions and observe the patterns that arise. In Chapter 3, I examine the genetic effects of selection for increased survival of starvation. In Chapter 4, 5 and 6, I compare genetically different lines under different nutritional states and other environments. The next section will discuss this.

Genotype-by-environment interactions

Thus far I have discussed the effects of the environment and of genetics on life histories separately. In the very first part of this introduction I already indicated that there is a firm dependence of the individual on the environment. Because the environment can be defined as the entropic state life has to escape from and take advantage of, the organism is bound to be in contact with the environment to acknowledge changes that may affect its survival. Therefore, the individual adapts to a specific environment. Here I explain how individuals that have adapted to a certain environment respond to a different environment and how these responses may vary among different genotypes.

The organism is thus intimately dependent on the environment. With its genes as causal factors and useful tools at the same time, the organism should manage to cope with the environment in order to take advantage of the opportunities that are feasible within its genetic and physical-chemical constraints. The effects that are observed in clonal individuals in different environments are thus always the responses of a single genotype to that environment.[11] Here, when I mention the response among different environments I speak of the reaction norm of this genotype. However, if more than one genotype is examined in these environments, one often sees the reaction norms cross. Take the example of individuals with genotype A or B that have an average longevity of 50 days in environment 1. In environment 2, A has an average longevity of 75, and B of 34. We see that the genotypes describe a different pattern across the two environments; Genotype A improves its longevity whereas B's longevity degenerates with a shift from environment 1 to 2. That is what we call genotype-by-environment interaction (see also Stearns 1992).

When species, populations, selection lines, or single gene mutants are compared in a range of different environments, or for a range of different traits, we can discover genotype-by-environment interactions. Genotype-by-environment interactions are central in my thesis.

Down to a more practical level

I have pointed out the driving forces behind life and the processes that underlie it. I have also identified which chapter is about which subject. Now I move on to a more practical level where we can implement the issues we have covered thus far. This level will be the research in *Drosophila melanogaster*, the fruit fly.

Since food is one of the major factors affecting an animal, there is likely to be plasticity in the response to certain food conditions, as has been shown by Carlson and Harshman (1999) for egg yolk mRNA. Adult fruit flies are post-mitotic in the sense that they do not grow any more after they have eclosed from the pupae (see Bhui-Kaur et al. 1998 for a more in depth study on maintenance consequences). The only thing they can do is store additional compounds as reserves. Fruit flies show plasticity in their longevity and it has been shown that reproduction and longevity trade off in fruit flies (Chippindale et al. 1993). Also, molecular signals are thought to underlie these trade offs rather than physiological resource allocation alone (Leroi 2001; Patel et al. 2002; Tu et al. 2002). Both mechanisms fit the Disposable Soma theory of ageing (Kirkwood 1977; Kirkwood and Holliday 1979).

The advantages of performing research on *Drosophila melanogaster* are numerous, but for me the following are most important: 1. *Drosophila* has a short generation time, making it easy to rear, 2. the flies are easy to handle and require conditions that are easily standardised, 3. much is known about its genetics, metabolism, physiology and life history, making it an organism with high reference potential, 4. all this gives the researcher the opportunity to do precise, in depth studies of specific well-developed fields. *Drosophila* provides us with a system where the precise effects of

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[11] *I am aware of the possibility of epigenetic factors that may cause clonal individuals to produce distinctly different phenotypes (e.g. Smith and Murphy 2004). For the sake of brevity I will not go into these any further.*

genetics and physiology can be examined. Combining the advantages of the laboratory with those of *Drosophila melanogaster* has proved to be a strong model system to make experimental manipulations in either genetics or environments, and examine their effects on the phenotype of the individual.

Outline of the thesis

During this project a cross fertilisation was present between the gerontologists, epidemiologists, animal ecologists, evolutionary biologists and industry, which proved to be highly productive. In this thesis Chapters 1, 2, 4 and 5 arose in close collaboration with people from various departments. Therefore, this thesis does not only invoke evolutionary paradigms but benefits from the strength of thought from many people from various backgrounds. I think this pragmatic paradigmatic plasticity added to the robustness of the thesis.

This thesis ranges from species and selection lines to single gene mutants, covering the effects of genetics, environments and genotype-by-environment interactions on life history traits. The mechanisms underlying these traits are examined by environmental manipulation, selection and state of the art expression analysis. The aim of this thesis is to identify aspects affecting life history traits at a number of different levels.

My first two Chapters deal with environmental manipulation effects on adult life history. In Chapter 3, I report on an artificial selection experiment for increased starvation resistance and an exploration of the associated correlated responses to selection in other life history and physiological traits. Chapters 4 and 5 continue with the data derived from the third Chapter. In Chapter 4, we focus on genotype-by-environment interactions among lines that are expected to show similar results on basis of earlier findings. Chapter 5 is a state of the art experiment showing the potential of micro-array studies for life history and genotype-by-environment research. In Chapter 6, the supposedly superior characters of the long-lived mutant, methuselah, are tested.

Overall, I aim to achieve an overview of how genes and environments affect life histories by experimentally altering either one or both of them. The focal point is on the effects different controlled environments have on animals with a particular genetic background. The gene-by-environment interactions of these tests yield insight in the mechanisms underlying the traits. We focus on starvation resistance and longevity and whether these traits are largely determined by the same mechanism or not. Inferring about the correlation between these traits learns about the evolution of both traits, because starvation resistance can be actively selected for, whereas longevity always will be a side-product of selection (Hoekstra 1993; Partridge and Gems 2002). I will present data on organisms with different levels of relatedness, manipulating the environment, physiology and genes to infer knowledge about the relatedness, mechanisms and sensitivities of life history traits.