

Mikael Mökkönen

Evolutionary Conflicts
in a Small Mammal:

Behavioural, Physiological and Genetic
Differences Between the Sexes



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To my parents, Leena and Pekka

ABSTRACT

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Diss.

The evolutionary interests between males and females rarely coincide, given differences in gametes, mating/parental care systems, and in the multitude of fitness-related traits. A difference in reproductive interests between the sexes is termed sexual conflict, when the fitness benefits to one sex are coupled to fitness costs in the other. Much of the previous research has focused on invertebrates, while experimental validation in vertebrates, particularly mammals, has been lacking. This dissertation aimed to investigate the factors underlying conflicts of interest between the sexes in the bank vole (*Myodes glareolus*), a small mammal commonly found in Fennoscandia. Specifically, I sought to understand the role of the hormone testosterone (T) in these conflicts, the prevalence and maintenance of antagonism both in the laboratory and field, as well as the quantitative genetics of antagonism on key life history characters. My results provide conclusive experimental evidence of sexual conflicts, and their maintenance, in the bank vole. In the first study, I found that the sexually antagonistic (SA) selection of T mediates a behavioural conflict that could maintain bank vole mating strategies. In the second study, I continued to focus on T and found that the T-profiles of paternal grandmothers affected their grandson birth mass, which could provide grandsons with a fitness advantage later in life, thereby potentially recovering costs of sexual antagonism. Having experimentally established the presence of sexual antagonism in the laboratory, the third study focused on the maintenance of SA alleles in the field. The results indicate that SA alleles can be maintained under the negative frequency dependent selection of males – a type of selection in which rare forms are favoured. The results of quantitative genetic modeling in the fourth study provided clear evidence of genomic conflict over reproductive success: individuals can pass on ‘good genes’ for a reproductive advantage to either sons or daughters, but not both. Continuing under the quantitative genetic framework, the final study found that fertility in females was under concordant selection when young, but SA selection when older. I conclude that sexual conflicts are likely to be widely prevalent in bank voles, and that future research should carefully consider the sexes as more separate entities in evolution.

Keywords: Bank vole; life history evolution; mammalian reproductive strategies; *Myodes* [*Clethrionomys*] *glareolus*; sexual antagonism; testosterone.

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LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following articles, which are denoted in the text by Roman numerals I-V. I am the first author of papers I, II, III and V, and I carried out a substantial portion of the planning, data collection, statistical analyses and writing for each paper.

- I. Mokkonen M., Koskela E., Mappes T. & Mills S.C. Sexual antagonism for testosterone maintains multiple mating behaviour. In review.
- II. Mokkonen M., Koskela E., Mappes T. & Mills S.C. An indirect grandparental effect on mammalian grandsons. Submitted manuscript.
- III. Mokkonen M., Kokko H., Koskela E., Lehtonen J., Mappes T., Martiskainen H. & Mills S.C. Negative frequency dependent selection of sexually antagonistic alleles. In review.
- IV. Koskela E., Mappes T., Mills S.C., Mokkonen M., Oksanen T.A. & Schroderus E. When trade-offs trade-off: intralocus sexual conflicts in size and number of offspring in a small mammal. In review.
- V. Mokkonen M., Koskela E., Mappes T. & Schroderus E. Age can wither her: sexual conflict over fertility increases with female age. Submitted manuscript.

1 INTRODUCTION

1.1 Why evolutionary conflicts?

The study of evolutionary conflicts of interest between males and females is a topic that has emerged relatively recently in biology. It has important implications not just across the biological sciences, but across related disciplines, due to the fundamental truth that male and female interests do not always coincide. It is an easy concept to comprehend at a superficial level, however the detailed investigation (and acceptance) of it requires long-held views in evolutionary thinking to shift.

This thesis seeks to fill important gaps in our understanding of this emerging phenomenon by comprehensively assessing conflicts of interest between males and females over various traits that are important for fitness. To achieve this, I have used laboratory and field experiments, mathematical and quantitative genetic modeling, as well as genetic analyses. By considering the sexes as more separate units in these studies, I have attempted to shed light on important differences between males and females that have not received much attention in selection theory thus far.

1.2 Evolution by selection

1.2.1 How selection operates

The genetic evolution of organic beings proceeds through either random genetic drift, whereby the gene frequencies in a population randomly change without external selective influence (Kimura 1968), or through selection, whereby the gene frequencies in a population change according to their relation with fitness (Fisher 1930). Adaptive selection allows organisms to respond to environmental changes over generations and it also allows different species to colonize new habitats that may not be completely ideal to their current composition of traits,

their phenotype. Selection acts on the phenotype, which is determined by environmental effects and mostly by an individual's collection of genes, the genotype. Over time, the genotypes of individuals best suited to a particular environment are favoured through the differential selection of heritable characteristics (Darwin 1859, Darwin 1871, Fisher 1930).

Some units, be they genes, individuals or groups, are chosen due to some characteristic that makes them favoured over others. This thesis is not concerned with exhaustively surveying all the various types of selection. What follows are the main types of selection that are the focus of this work.

1.2.2 Natural selection

Natural selection acts on genes that are heritable across generations of a species. Individuals (either male or female) are selected predominantly based on one or more characteristic such as size, colour or ornament. For selection to lead to evolution, the characteristic, or trait, has to be genetically preserved between generations, so that the offspring of those individuals selected in mating will also benefit from these traits when it is their turn to reproduce (Fisher 1930). Also, there must be variation in the trait for selection to operate. As Darwin noted: "...from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved" (Darwin 1859).

The variation in a trait allows for an optimal value to be favoured in a given environment. Different environments enact different pressures on individuals, so what is optimal in one environment may not be favoured in another. This can cause genotype-by-environment (GxE) interactions, whereby the ability of individuals to survive and/or reproduce is dependent on their environment. The Galapagos finches provide a classic example of the importance of the environment in the evolution of fitness-related traits (Grant 1986). Their beaks have evolved to suit the different food niches found on the various islands. While variation in form is important, it is not the only variation that is required.

For selection to operate, certain individuals must survive longer, and/or reproduce more than others (Darwin 1859, Darwin 1871). This is the ultimate measure of evolutionary success: how many copies of an individual's genes are passed on to future generations. A particular genotype has a high fitness if it has a high expected number of offspring. Fitness is classified as either relative or absolute. Relative fitness is typically measured as the success (e.g. number of surviving offspring) of a particular genotype compared to another genotype after one generation, while absolute fitness is the ratio of individuals of a particular genotype after selection to before selection (Falconer and MacKay 1996, Orr 2009). Commonly, measurements of reproductive success are used as a proxy for fitness, which is essentially a tally of an individual's offspring (Grafen 1988). Hence, we can test hypotheses in selection experiments by measuring how effectively and successfully certain individuals reproduce. Sexual selection can operate on heritable traits that provide an advantage in reproduction.

1.2.3 Sexual selection

Sexual selection was a seed of an idea that Charles Darwin discussed in his book *On the Origin of Species* (Darwin 1859), which germinated and then was properly defined in *The Descent of Man* (Darwin 1871). It was his answer to the questions raised by some natural observations that seemed out of place in his formalization of natural selection. Certain traits that appeared costly (in terms of survival), such as brightly coloured feathers or other conspicuous features, could be explained through the advantage they bestowed in mating (Andersson 1994). According to Darwin, “this form of selection depends, not on a struggle for existence in relation to other organic beings or to external conditions, but on a struggle between the individuals of one sex, generally the males, for the possession of the other sex. The result is not death to the unsuccessful competitor, but few or no offspring” (Darwin 1859).

The definition of sexual selection has developed into a robust theoretical framework that is still the basis for this field of theory, over 140 years later (Clutton-Brock 2007). It has been conclusively demonstrated both experimentally and observationally in the laboratory and field environments (e.g. Moller 1988, Andersson 1994 and references therein, Andersson and Simmons 2006, Clutton-Brock 2007, Rodriguez-Munoz *et al.* 2010), in addition to the strong theoretical support it has received (e.g. Lande 1980, Lande 1981, Kokko *et al.* 2003, Albert and Otto 2005, Kokko *et al.* 2006, van Doorn *et al.* 2009). Essentially, this form of selection acts on traits that are important in the competition for mates (Andersson 1994). Darwin supposed that “the sexual struggle is of two kinds: in the one it is between the individuals of the same sex, generally the males, in order to drive away or kill their rivals, the females remaining passive; while in the other, the struggle is likewise between the individuals of the same sex, in order to excite or charm those of the opposite sex, generally the females, which no longer remain passive, but select the more agreeable partner” (Darwin 1871). Interestingly, Darwin characterized sexual selection as a ‘sexual struggle’. It does not evoke a harmonious view of evolution. Furthermore, he defined the intersexual selection, or female choice, by stating that the female selects “the more agreeable partner”, which could be interpreted to mean that the female seeks to reduce her evolutionary costs just as much as it could mean to maximize her benefits. We know now that the evolutionary interests between males and females rarely coincide (Parker 1979).

During the era of the modern evolutionary synthesis, work by Bateman (Bateman 1948) further engaged evolutionary biology to consider the reproductive differences between males and females. By working with *Drosophila*, he derived three main conclusions that came to be known as Bateman’s principles: (1) there is greater variance in male vs. female reproductive success; (2) male reproductive success is more dependent on the number of mates than female reproductive success; and (3) differences between the sexes for the variance in number of mates indicates sexual selection (Bateman 1948). In the years since, Bateman (1948) has come under criticism for

the methods of the study and interpretation of results (Snyder and Gowaty 2007 and references therein). Snyder and Gowaty (2007) have claimed this study suffers from methodological problems such as sampling biases, the use of mutants, elimination of genetic variance, as well as interpretational problems such as statistical pseudo-replication and miscalculation of results. However, Wade and Shuster (2010) have defended this work and concluded that the results are to be trusted and definitively show the main cause of sexual selection. While studies on sex-role-reversed species have provided exceptions to these principles (e.g. Jones *et al.* 2000), the principles by Bateman (1948) are still generally applied today. They have provided the impetus for a commonly used statistical tool, the Bateman gradient, which measures the function of the number of mates (or mating rate) in relation to an individual's reproductive success (Jones 2009). The work by Bateman (1948) was one of the earliest studies that argued for different evolutionary interests between males and females.

1.2.4 Sexually antagonistic selection

Sexually antagonistic (SA) selection occurs when there is a difference in the optimum value of a trait between the sexes, and both sexes select for their optimum (Parker 1979, Rice 1992, Arnqvist and Rowe 2005, Cox and Calsbeek 2009). This type of selection often results in a 'compromise' between males and females for a given trait, such as with the human hip (Rice and Chippindale 2001). For example, it has been hypothesized that the selective pressures on ancient humans were different depending on their sex: for females, a wider hip structure facilitated child-birth, whereas for males, narrower hips were beneficial for activities such as running (which could be important for hunting or warfare). Hence, the evolutionary tug of war has been for wider hips in females and narrower hips in males, but the genes controlling the shape of the hip structure are the same in both sexes (Rice and Chippindale 2001).

This may, at first glance, appear to be a trivial matter. After all, a 'compromise' seems to render both sexes at a similar disadvantage. However, the expression of those genes often differs depending on the sex, causing the trait to be sexually dimorphic (Rice 1984, Cox and Calsbeek 2009). If this dimorphism is due to sex-limited gene expression, so that only one sex expresses that gene product, then it may possibly solve the conflict between the sexes (though this has recently been questioned, e.g. Connallon *et al.* 2010). The spread of genes that have sex-specific fitness effects is facilitated by sex-biased transmission (Pizzari and Birkhead 2002, and references therein), which has been further confirmed by studies on *Drosophila melanogaster* that show the X-chromosome is rife with SA genetic variation (Gibson *et al.* 2002, Innocenti and Morrow 2010b). If sexual dimorphism is simply a difference in the value of the trait expressed by both sexes (with corresponding sex-specific fitness optima), then it can be said that there is a divergence in the evolutionary interests between the sexes for that trait (Parker 1979). This is the definition of a sexual conflict, and, the underlying theme of this thesis.

1.2.5 Frequency dependent selection

Frequency dependent selection was first outlined by Poulton (1884) as it pertained to predation. It selects either for the more common (positive) or rare (negative) genotype/morph in a population. This type of selection differs from the other types of selection thus far discussed in one key respect: the value to fitness of the selected trait is dependent on its frequency in the population (Ayala and Campbell 1974). It has been popularized in the classic example of the 'rock-paper-scissor' game first applied to the side-blotched lizards, *Uta stansburiana* (Sinervo and Lively 1996, Sinervo *et al.* 2000a). In this system, males have either blue, orange or yellow throat colours that are associated with different fitness-related traits, and their relative success depends on how rare they are in the population.

In the absence of GxE interactions in a fluctuating environment, natural-, sexual- and sexually antagonistic selection (if unbalanced) are all generally expected to erode genetic variance in a population over time. However, negative frequency dependent selection can actually maintain the genetic variation in a population since the rare individuals are the ones favoured by selection. Over time, the selected rare forms increase their frequency in the population until another form becomes rarer, and then selection switches to favor this other, rarer form. In this way, negative frequency dependent selection is a transient process that is determined by the type of conspecifics (competitors or mates) in the population, the social environment. The direction of evolutionary change cannot generally be predicted without taking interactions between conspecifics into account (Kokko and López-Sepulcre 2007, Bijma 2010). Often, these conspecifics may be related, which can introduce a host of conflicts to the family members.

1.3 Evolutionary conflicts

1.3.1 Sexual conflict

Sexual conflict is a divergence in the evolutionary interests between males and females (Parker 1979, Parker 2006). It results from sexually antagonistic selection (see section 1.2.4, Chapman *et al.* 2003, Arnqvist and Rowe 2005, Cox and Calsbeek 2009, van Doorn 2009). This kind of selection creates the potential for sexual conflict. Only when the fitness of one sex is negatively affected by the fitness gains of the other sex is the conflict realized. A gender load exists when the sex-specific values of a fitness-related trait are not at their optimal fitness values (Bedhomme and Chippindale 2007).

The current theoretical framework classifies sexual conflicts as either intralocus conflict, where the conflict occurs over the genes at the same locus in males and females, or as interlocus conflict, where the conflict occurs between different sets of genes located at different loci (Parker and Partridge 1998). It is

most straightforward to consider the phenotypic representations when discerning between these two types. The previously mentioned example of the human hip serves to illustrate intralocus conflict: the genes for the hip have different optimum expression values depending on the sex they are in, even though they are the same genes (Rice and Chippindale 2001). With interlocus conflict, different traits important for fitness interact between males and females, such as the coevolution between the specialized feet of the male and longer spines of the female water strider that are important in mating (Arnqvist and Rowe 2002). This latter example is considered to be a coevolutionary arms race between males and females, and has been argued to be important for the evolution of traits that are persistent (usually in males) or resistant (usually in females) for the purposes of reproduction (Arnqvist and Rowe 2005).

Researchers have hypothesized that the disparity between males and females in their evolutionary interests stems from anisogamy, which is the difference in structure between sperm and egg cells (Bateman 1948, Trivers 1972, Arnqvist and Rowe 2005). Sperm are generally inexpensive to produce for males, while eggs are considered more resource-intensive for females to produce. Coupled with the tendency for females to bear the costs of gestation and parental care, it follows that females are choosier when it comes to mate selection (Trivers 1972). The reproductive success of males is primarily limited by the number of mates and the reproductive success of females is mostly limited by the resources available (and physiological capacity) for producing the offspring (Bateman 1948). This is considered one of the main reasons that sexual selection is thought to operate most strongly on males, but it also serves to demonstrate that the reproductive interests of males and females are often different (Bateman 1948). Only with monogamy are the evolutionary interests expected to be similar between mates: the only offspring produced by the male or female are jointly shared (Holland and Rice 1999, Hosken *et al.* 2001). However, in the animal kingdom, true, life-long genetic monogamy is thought to be extremely rare (e.g. among mammals and birds respectively: Kleiman 1977, Griffith *et al.* 2002). Hence, there can be conflicts between the reproductive interests of males and females for a variety of physiological and behavioural characteristics.

Much of the previous work on sexual conflict theory has been conducted on invertebrate species, presumably due to their well-known genetics and/or logistical ease of experimentation. However, it is important to study this evolutionary phenomenon in a variety of species, both vertebrate and invertebrate, to establish the prevalence and mechanisms of its operation. Research into vertebrates can provide new insights that invertebrate study systems are often limited to test (e.g. manipulated field experiments in (semi)natural conditions). Observational studies have demonstrated that sexual conflicts are prevalent in the field (e.g. Alatalo *et al.* 1981, Davies 1985, Robinson *et al.* 2006, Bode and Marshall 2007, Bro-Jørgensen 2007, Brommer *et al.* 2007, Foerster *et al.* 2007, Mainguy *et al.* 2009), though manipulated field experiments that test this are still rare (but see e.g. Maklakov *et al.* 2005, Løvlie and Pizzari

2007). It is not yet clear to what extent laboratory studies are confounded by artefacts: is the observed conflict natural? In this regard, manipulated experiments, especially in mammals, are critically needed.

Sexual conflicts have implications for many areas of the biological sciences and related disciplines. The conflicts arise due to different genetic interests between the sexes, which can then also be reflected in the expression of those genes in various behavioural, physiological, and morphological traits. For example, this perspective has recently been applied to understanding mental disorders in humans (Badcock and Crespi 2008), density dependence in population ecology (Kokko and Rankin 2006) and speciation (Parker and Partridge 1998). Far from being a narrow topic, the study of sexual conflicts encompasses different levels of organization, from genes to individuals to populations. Yet ultimately, it is grounded within the interactions that occur within a biological family.

1.3.2 Parent-offspring and sibling conflicts

Parent-offspring conflict stems from the classic works of Trivers on parental investment (Trivers 1972, Trivers 1974). Put simply, this type of conflict has to do with the respective interests of the parent – usually the mother – and the offspring. From the mother's perspective, the investment placed in the current litter (or brood, etc.) should be balanced against her future reproductive interests (Trivers 1972). As the evolutionary success of an individual is largely determined by the number of offspring produced, individuals are predicted to maximize their lifetime reproductive success through the balance of current vs. future reproductive effort (Trivers 1972).

The interests of offspring are quite different from those of the mother (Trivers 1974). It has been suggested that it is in the interests of the offspring to obtain the maximum amount of resources possible (e.g. food, protection from predators or heat loss), though recent work suggests that this type of conflict drives coadaptation between parent and offspring traits (Hinde *et al.* 2010). Interestingly, the parental conflict hypothesis in mammals (also referred to as the kinship theory of genomic imprinting, Haig 2004) pits the genes acquired from the mother against the genes acquired from the father within the offspring: the father provides genes that are predicted to maximize offspring growth (and hence, survival), whereas the mother confers genes that limit growth. This hypothesis is supported in mammals through research into *IGF2*, *KCNQ1OT1* and *Air* growth enhancers that are paternally expressed, as well as the *IGF2R*, *CDKN1C* and *Grb10* growth inhibitors that are maternally expressed (Haig 2004). Hence, the growth enhancers provided by fathers may affect mother-offspring conflict. This type of conflict can also be viewed as 'sexual conflict plus one generation', and demonstrates that distinguishing between these intra-familial conflicts is often not clear-cut. Nonetheless, the main interest of the offspring is to ensure a maximum probability of survival, which can be achieved through either the interaction with the parent(s) providing care, or the

interaction with siblings. Thus, the various intra-familial conflicts can render decisions about resource allocation particularly important.

Under a resource-limited scenario, it is generally in an individual's interests to have fewer siblings due to the increase in sibling conflict that arises. Previous work has shown that the presence of sibling competition can also reduce the fitness of parents (Godfray and Parker 1992). This type of conflict can generate interesting dynamics between siblings given the uncertain relatedness of individuals to each other. In mating systems where the mother (dam) or father (sire) mate with multiple partners, it is possible to have 'half-sibs', where only one of the parents is shared between offspring, compared to 'full-sibs', where both parents are common to the offspring. Hence, it is appropriate to discuss relatedness in terms of the probability that the genes between relatives are identical by descent.

The coefficient of relatedness (r) is a probability of the genes being identical by descent. In Table 1, we assume the species is a diploid organism that mates in a polygynandrous mating system (males and females mate with multiple partners), and the dam provides the parental care to the offspring.

TABLE 1 Example of parent-offspring relatedness in a polygynandrous mating system with uniparental care. Coefficient of relatedness (r) is expressed as a value between 0-1, which denotes the probability that the alleles between relatives are identical by descent.

Family member	Relatedness (r)	Conflicting interests with
Dam	0.5 to all offspring she produces	Sire, offspring
Sire	0 or 0.5 to mate's offspring Uncertain paternity	Dam
Offspring	0.5 to dam 0 or 0.5 to dam's mate 0.5 to full siblings 0.25 to half siblings	Dam, siblings

From this example, two key elements are worth noting. The first is that the coefficient of sibling relatedness can range from 0.25 to 0.5 on average. There is a lower degree of relatedness between siblings than between the dam and her offspring (ignoring the possibility of sneaky tactics such as brood parasitism). The second key element from Table 1 worth noting, which pertains more to the discussion of sexual conflict above (1.3.1), is the difference between parents in their coefficient of relatedness to the offspring. While the dam is assured relatedness, ensuring paternity requires a careful balancing act: finding opportunities to reproduce while also fending off other males that might usurp paternity. This 'mate defense' can be achieved by various means such as time-consuming mate guarding or sperm competition (Arnqvist and Rowe 2005 and

references therein). It is clear from this example that relatedness asymmetries are an important consideration in understanding the conflicts between family members.

1.3.3 Relatedness asymmetries

While we understand now that an individual's mating decisions can impact the quality of its offspring for better or worse through various genetic and non-genetic effects (e.g. maternal effects, Mousseau and Fox 1998), we have less understanding of how more distant ancestors can also impact individuals. A complication, or rather interesting feature of mammalian (and other XY species) chromosomes is their sex-biased inheritance to offspring (Fig. 1). While both sons and daughters receive one set of the autosomal chromosomes from both the mother and father, only daughters receive the X chromosome from both the mother and father; sons receive the X- from the mother and Y chromosome from the father. In this way, the Y chromosome is passed patrilineally through males, and the paternal grandmother does not ever pass her X chromosome to her grandson. Going one step further, the X chromosome passed down from the mother to offspring can be the copy passed down from either the maternal grandmother or grandfather; the X chromosome passed down to the daughter through the father is the copy inherited from the paternal grandmother. Hence, on average, females are slightly more related to their female ancestors than male ancestors, and the inheritance of sex chromosomes is more certain from the paternal- compared to maternal - grandparents (Fig. 1). The implications of this feature have only recently been gaining attention (Michalski and Shackelford 2005, Chrastil *et al.* 2006, Rice *et al.* 2010), but are still relatively under-explored.

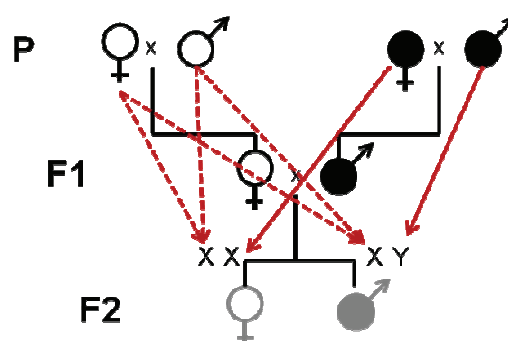


Figure 1 The contribution of sex chromosomes (X/Y) to grandchildren. Solid lines indicate that sex chromosomal relatedness is assured, while broken lines indicate that the probability of sex chromosomal relatedness is only approximately 50%.

The burgeoning field of epigenetics has overwhelmingly provided evidence that cross-generational (non-Mendelian) transmission of biological information is

possible, but the fitness consequences remain unknown. Epigenetic processes, including genomic imprinting, alter the expression and not sequence of DNA (Gregg *et al.* 2010a, Gregg *et al.* 2010b). Among vertebrates, only mammals have been shown to possess imprinted genes (Barton *et al.* 1984), whereby certain genes are expressed in a parent-of-origin specific manner, while the copy from the other parent is silenced (e.g. IGF2R from mothers, Barlow *et al.* 1991, IGF2 from fathers, DeChiara *et al.* 1991). The silencing of alleles is primarily achieved through DNA methylation or histone protein changes. While not altering the structure of DNA, selfish genetic elements (reviewed in Burt and Trivers 2006) can bias the inheritance of certain alleles that would otherwise be stochastically derived from meiosis and recombination (e.g. the t-complex in mice, Silver 1993). Further complicating the inheritance of biological information are maternal (and paternal) effects (Mousseau and Fox 1998). These effects can impose attributes of the maternal environment (e.g. availability of food resources) on the offspring without direct genetic control.

A recent hypothesis by Rice *et al.* (2010) called sexually antagonistic zygotic drive, proposed an evolutionary explanation for the interests of grandparents in humans, a species with direct grandparental care. Taking into account the relatedness asymmetry of the sex chromosomes between male and female descendants, they proposed that grandmothers should evolve grandson-harming (or granddaughter-helping) phenotypes because of their closer expected relatedness to granddaughters. Thus, there is potential for evolutionary conflicts to exist across the different life stages of an individual.

1.3.4 Ontogenetic conflict

Previous work has found that the different life stages can introduce different selection pressures, which have been shown to result in evolutionary conflicts between these life stages. Working with *Drosophila*, Rice and Chippindale (2001) demonstrated how the different life history stages can proceed from a positive fitness correlation between the sexes in the juvenile stage (where egg-to-adult viability was measured) to a negative correlation in the adult stage (where reproductive success was measured). This ontogenetic conflict arises due to reproduction because it is only after sexual maturity that the evolutionary interests diverge between males and females.

Senescence, which is the biological deterioration of an organism associated with age, is a process that affects the evolution of fitness related traits. Interestingly, it has been suggested that the costs of ageing should begin to accumulate around sexual maturity as well, as the 'usefulness' of the reproducing individual begins to decline in proportion to their reproductive success (Williams 1957). Williams (1957) proposed antagonistic pleiotropy to explain the evolution of senescence, whereby genes that confer a benefit earlier in life provide a fitness cost later in life. However, despite currently being the favoured hypothesis to explain the evolution of ageing, it has so far received weak support at best (Williams *et al.* 2006). If reproductive benefits trade-off with ageing costs, then it is important to consider evolutionary factors that

influence reproduction to better understand ageing. Additionally, discovering the effects and consequences of divergent reproductive interests between the sexes in relation to senescence is a worthwhile challenge for future research to explore, as it may provide further insights into the proximate causes of sexual conflicts.

1.4 Proximate causes of conflict

Richard Dawkins (2009) compared evolutionary biologists to detectives that arrive at the scene of a crime. These 'investigators' arrive after the act has occurred, study the evidence on display, and then make careful conclusions about what is observed. Few study systems allow us to view evolution over many generations, least of all, the more complex vertebrate species. Hence, researchers are often confined to studying changes in phenotypic traits over a few generations. This can be a challenge for research into traits under sexually antagonistic selection, since the 'tug-of-war' this kind of selection imposes on trait values between males and females could make the detection of this selection more difficult. The benefit of selection experiments lies in our ability to artificially select individuals so that we can effectively test evolutionary hypotheses, and quite importantly, prove causality of the phenomena under study. As evolutionary detectives, we can attempt to answer *what* was responsible, and *why* (Dawkins 2009).

Evolutionary conflicts are studied through the proximate mechanisms that we can reliably measure and document in various species. This thesis focuses on the various traits involved in these conflicts, as well as the quantifiable behavioural aspects that tend to diverge between males and females.

1.5 Aims of the thesis

The general focus of this thesis is to explore the behavioural, physiological and genetic differences between male and female bank voles (*Myodes glareolus*). As a study system, bank voles are an ideal mammalian species to utilize in research due to the relative ease of measuring traits, their agreeable disposition to both laboratory and field environments, and the interesting characteristics of the various life history strategies they employ. My central aims were to test whether sexually antagonistic selection acts on small mammals, the nature and strength of the sexual conflicts, as well as the evolutionary outcomes of these processes. Ultimately, the insight gained from this thesis would help us to better understand the complex process(es) by which genetic variation is maintained in a population.

With this in mind, the first aim of this thesis (paper I) was to establish that male and female bank voles have divergent reproductive interests by exploring

the mechanistic underpinning of the evolutionary conflict over the hormone testosterone (T). This hormone has previously been shown to be under strong selection in bank voles (Mills *et al.* 2007a, Mills *et al.* 2009). It is sexually dimorphic (expressed in greater quantity in plasma of male mammals, Adkins-Regan 2005), and has remarkable effects on physiology and behaviour. It also has a pleiotropic trade-off with immune function, such that producing too much T can reduce an individual's ability to battle infections from pathogens in the environment (Mills *et al.* 2010, Schroderus *et al.* 2010).

A second aim of this thesis (paper II) was to better understand the relatedness asymmetries by exploring the cross-generational impact of T selection, and how it relates to sons and daughters, as well as their offspring. Research conducted on humans has shown how grandparents may have differential interests in their grandchildren due to relatedness asymmetries. Given these relatedness asymmetries, I was interested in testing the fitness effect of grandparents in a species that did not exhibit direct grandparental care.

Since the first two papers of this thesis indicated that male and female evolutionary interests did not coincide in the laboratory environment, the third aim of this thesis (paper III) was to experimentally assess how bank voles experienced sexual antagonism in (semi-) natural conditions outdoors. SA selection is not expected to be perfectly balanced, given the variety of sex-specific selection pressures in the field. Therefore, this study assessed whether negative frequency dependent selection could maintain SA alleles in field populations of bank voles. Evidence is accumulating in a variety of species that genotype by environment interactions occur, such that an individual's performance or function may be dependent on the environment. This raises the possibility that laboratory observations might not actually be relevant to nature, if the phenomena are found to be artefacts of the laboratory environment. Hence, it was important to relate the previous findings to nature.

A fourth aim of this thesis (paper IV) was to provide empirical evidence that there is a genetic conflict between the reproductive interests of the sexes by studying the quantitative genetics of central life history characters: offspring number and size. Using a large, pedigreed laboratory population, I tested for intersexual genetic correlations between breeding values for offspring number, size and condition. Following from this analysis, my final aim of this thesis (paper V) was to explore how the genetic correlation for fertility between the sexes is affected by age. Senescence is known to widely affect reproductive success (in addition to the probability of survival) in a variety of species, though the evolutionary factors that influence this near-universal phenomenon are not yet well-understood.

2 METHODS

2.1 Characteristics of the study system

The bank vole (*Myodes glareolus*) is one of the most common mammalian species in Europe, broadly distributed throughout most of the continent (Bujalska and Hansson 2000). In northern Europe, it is found primarily in forest habitats as well as fields (Hansson 1979, Stenseth 1985). This species is generally not sensitive to disturbance and has a high trappability in the field, which makes it an ideal study species for both field and laboratory experiments (e.g. Oksanen *et al.* 2007, Mappes *et al.* 2008). In northern Fennoscandia, bank vole populations experience multi-year density cycles that impact predator-prey dynamics as well as disease transmission (Korpimäki *et al.* 2005, Kallio *et al.* 2009). Immunocompetence is important for voles in the field (Huitu *et al.* 2007). The bank vole is a reservoir host of the Puumala hantavirus, and once individuals are infected, their winter survival decreases (Kallio *et al.* 2007). Previous studies have shown that the hormone testosterone trades-off against immune function in this species, so that individuals can excel at reproduction or survival against pathogens, but not both (Mills *et al.* 2009, Mills *et al.* 2010, Schroderus *et al.* 2010).

The quality of the natural environment, as with most species, plays an important role in the evolution of the bank vole's life history. When environmental conditions are favourable (i.e. abundant food resources), mothers can successfully produce bigger litters (Koskela *et al.* 1998). Mothers bias their allocation of resources to daughters because a larger size seems to be more important for female reproductive success (Koskela *et al.* 2009). Despite this, sons are generally still more costly to produce, which can result in tradeoffs between current and future investment in offspring (Rutkowska *et al.* 2011). The density of the population, food availability, maternal effort, and frequency of voles are all factors that can affect reproduction in the field (Koskela *et al.* 1998, Koskela *et al.* 1999, Oksanen *et al.* 1999, Prévot-Julliard *et al.* 1999, Jonsson *et al.* 2002, Mappes *et al.* 2008).

This thesis focuses exclusively on the form of reproduction that concerns the majority of mammals: placental development followed by live birth. The bank voles studied here contain 56 chromosomes and propagate with an XY system of sex chromosomes (Gamperl 1982). Upon mating, the male's sperm fertilizes the female's ova, gestation lasts approximately 20 days, and on average approximately 5 pups are produced (Koivula *et al.* 2003).

Bank voles operate in a non-resource based mating system, where males do not provide any parental care for their offspring or resources for their mates. Breeding females are territorial, while the home ranges of males overlap several of these territories, hence there are frequent opportunities for multiple mating by both sexes in this polygynandrous mating system (Bondrup-Nielsen and Karlsson 1985, Koskela *et al.* 1997, Mills *et al.* 2007a, Klemme *et al.* 2008). Due to these frequent encounters, infanticide remains a risk, though synchronous breeding by females can be undertaken as a counterstrategy (Poikonen *et al.* 2008). The sexually dimorphic hormone testosterone has been found to be an important trait for reproduction: males with higher plasma testosterone levels sire more offspring (Mills *et al.* 2009).

2.2 Traits

2.2.1 Why are traits important?

The traits are the features of a species that selection (or drift) can shape during evolution. They are the manifestation of the environment and the genes that control them, and hence, are what selection 'sees'. Most traits, or characters, fall within a spectrum of possible values – they are continuously distributed, such as length and mass. This spectrum of values, or variation in the trait, is important for the process of evolution because certain forms of the trait are evolutionarily favoured over others. The variation, if it is heritable and selected, leads to a new generation of individuals whose (evolutionary) success is greatly determined by how close their selected traits are to the fitness optimum. By studying these traits, we learn about the evolution of a species.

Life history theory describes the relationships between traits which often trade-off with each other to attain an optimal living strategy (Roff 1992). Every organism has a limit to their energy budget, and the partitioning of this energy to different life processes provides near-limitless possibilities for study. Life history traits include those concerned with reproduction, growth and survival – the main life processes (Roff 1992). These areas of function are important for evolution because they affect how successful an individual will be in evolutionary units.

Physiological and behavioural traits provide a tangible, concrete measure of evolution due in part to the near-universally continuous nature of these types of traits – variation is almost always apparent. Additionally, it is these traits that form the majority of an individual's phenotype, which is what selective

forces primarily act upon in evolution. Even though there is still a lot of work to be done on the genetic architecture of these traits and their pleiotropic interactions, we do understand that there are trade-offs in their function (e.g. Schroderus *et al.* 2010).

In the following subsections, I briefly summarize the traits that have been the focus of this thesis.

2.2.2 Life history traits

The size at birth, as measured by body mass, is an informative measure that is involved in life history trade-offs in the bank vole species (Mappes and Koskela 2004). In general, this measure is sensitive to parental effects (e.g. maternal effects, Mousseau and Fox 1998, genomic imprinting, Swaney 2011), and can be greatly influenced by factors that affect allocation of resources between males and females (reviewed in West 2009). Once born, the females nurse their pups approximately 20 more days – the point at which they are independent enough to survive without the dam’s milk.



Figure 2 Newborn bank voles in the laboratory, less than 24 hours post partum.

The growth of bank voles is largely dependent on their environment. Whether it is the maternal environment of nursing pups, or the fluctuating natural environment, the growth and maintenance of individuals depends on the amount of nutrients and resources they obtain (Koskela *et al.* 2009). Food limitations create trade-offs between various life functions, which often do not allow certain traits to function at their optima. For example, limitations in food

resources likely decrease testosterone production and/or immune function also in male bank voles (Huitu *et al.* 2007), since cholesterol has important effects for these functions (e.g. production of T, regulation of immune function by estradiols, Adkins-Regan 2005). This may have deleterious effects for either reproduction, if testosterone is not produced enough, or survival, if immune function is dramatically compromised. This is evidenced by a negative genetic trade-off between T and immunocompetence (Mills *et al.* 2010, Schroderus *et al.* 2010). Hence, to be evolutionarily successful, an individual must be able to maintain their soma and growth to a degree that does not significantly harm future reproductive success or survival.

Most species are prey to some predators, which can affect the probability of survival at the different life stages. Furthermore, the intensity of competition (e.g. in battles) between members of the same species can result in elevated mortality, hence it is difficult to generalize about survival patterns among mammals, let alone vertebrates. Nonetheless, bank voles survive on average between one and two breeding seasons in the field (Bobeck 1969, Ivanter and Osipova 2000). This can make investment decisions particularly important during their first breeding season.

While most mammals invest more in their young than other vertebrate families, the number of offspring and the relative investment in them can still vary dramatically among mammals (Clutton-Brock 1991), though these differences decrease somewhat when the total lifetime reproductive success is taken into account. Species of the great apes such as common chimpanzees (*Pan troglodytes*) or western gorillas (*Gorilla gorilla*) can take up to 5 years before the 1 or 2 offspring of a single reproductive bout are reasonably developed to live independently of their mothers (Napier and Napier 1986), whereas various species of rodents, such as the bank vole can produce litters that average 5 pups and are independent and successfully reproducing within a month of birth (Koivula *et al.* 2003). Among mammals, the length of investment in offspring is associated with the evolution of mating systems in nature: species with longer parental care tend to be more monogamous, while species that have shorter periods of parental care tend to range in the degree of promiscuity (Clutton-Brock 1991). Parents can greatly affect the probability that their offspring will survive and reproduce by the amount of care they provide the offspring (Clutton-Brock 1991). Consequently, birth mass is a good predictor of an individual's future reproductive success and probability of survival in bank voles (Oksanen *et al.* 2007).

2.2.3 Testosterone

Testosterone belongs to the androgen group of steroid hormones, and is found in a wide range of different vertebrate species. It is a sexually dimorphic sex hormone found in greater concentrations in males than females, and is derived from the cholesterol molecule (Adkins-Regan 2005). The production of testosterone occurs primarily in the Leydig cells of the male testes and thecal cells of the female ovaries, but also in adrenal glands. It is regulated by the

hypothalamic-pituitary-androgen (HPA) axis, whereby gonadotropin releasing hormone (GnRH) is secreted by the hypothalamus and causes the pituitary gland to produce follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH in turn, act on the Leydig cells in the testes to produce testosterone. However, the production of T has been found to be costly for other physiological processes in mammals (e.g. immunocompetence, Folstad and Karter 1992, Mills *et al.* 2010, Schroderus *et al.* 2010), hence, there is a negative feedback loop that operates to reduce T production when the endogenous level of T increases. In this loop, T feeds back on the pituitary gland to reduce LH and FSH production, as well as the hypothalamus to reduce GnRH production. T can act through two different routes of action: it can bind with the androgen receptors found in cells, or it can be converted to estradiol.

The physiological and behavioural effects of testosterone are numerous, which contributes to the appeal of studying this hormone. Being an anabolic steroid, it is responsible for stimulating somatic tissue growth (including muscle mass, bone density and strength) as well as secondary sex characteristics (e.g. Alatalo *et al.* 1996, but see Pizzari *et al.* 2004). It is important in spermatogenesis, where it interacts with testicular Sertoli cells in the maturation of spermatogonia to spermatozoa (McLachlan *et al.* 1996, Zirkin 1998). Testosterone is involved with the process of masculinizing the male brain, as well as the female phenotype for species that have multiple offspring in one litter due to the T *in utero* secreted by brothers and the mother (Hernández-Tristán *et al.* 1999, Kerin *et al.* 2003, Lummaa *et al.* 2007). These prenatal effects can have life-long consequences on the behaviour and/or physiology of the individuals (Ruuskanen and Laaksonen 2010).

In bank voles, males with higher plasma testosterone are more dominant in male-male competition for mates and as a result, sire more offspring (Mills *et al.* 2009). The dimorphic expression of this hormone helps explain why males are typically under stronger sexual selection than females in this species (Mills *et al.* 2007a). However, the fitness consequences of testosterone selection for females remain unclear.

2.2.4 Dominance (in competition for mates)

Behavioural dominance, as it relates to male-male competition in bank voles, is an important factor that influences the selection of fitness-related traits. Male bank voles, lacking weapons or colourful displays, compete with one another in physical altercations to swiftly establish dominance, which rarely result in serious physical harm. However, lacking weapons or ornaments is not common to all species that display dominant behaviour. For example, mountain sheep have large horns that are used as weapons in social interactions, which also act as reliable predictors of their dominance (Geist 1966).

Many of the traits associated with, or contributing to dominance are influenced by testosterone. In bank voles, the dominance in male-male competition has strong associations with T: higher T individuals have greater mating and reproductive success (Mills *et al.* 2009). In other vertebrates, T has

been suggested or shown to affect dominance through its affect on basal metabolic rate (house sparrows, Buchanan *et al.* 2001), immune function (black grouse, Alatalo *et al.* 1996), endurance and activity (side-blotched lizards, Sinervo *et al.* 2000b), or aggression (various species, Hau 2007).

The most dominant male is not always preferred by females due to the lack of clear direct and indirect benefits associated with this kind of mating (Qvarnström and Forsgren 1998) and references therein). The fitness costs of sexual antagonism are potentially a further reason why females may not prefer the dominant male, if the genes associated with dominance in males are linked to sexually antagonistic fitness variation (e.g. dominant males may produce daughters of low reproductive quality).

2.3 Experimental setups

2.3.1 Conflict in the mating system (I)

I used a laboratory population of bank voles selected for the hormone testosterone in a multiple mating behavioural experiment that examined the evolutionary costs and benefits of this mating strategy from the male and female perspectives. The evolutionary benefit(s) of polyandry for females has remained one of the more puzzling questions in evolutionary biology.

2.3.2 The indirect effect of grandparents (II)

I used three generations of a laboratory colony of bank voles to study if the selection of testosterone can indirectly impact the birth mass of grandchildren. My interest was to extend the SA zygotic drive hypothesis to a species with minimal overlap between generations, and importantly, where there was no grandparental care. The logic for the evolution of SA zygotic drive should still be theoretically possible for this kind of mammalian species due to the evolution of the previously mentioned mechanisms of epigenetics, selfish genetic elements or maternal effects.

2.3.3 The maintenance of SA fitness variation (III)

Building on previous work in bank voles that showed negative frequency dependence of female reproductive effort in the field, as well as SA selection in the laboratory, I used sexually antagonistic selection in the laboratory to select males of high behavioural dominance with sisters of low fecundity, and vice versa. Having established conflict in this species, I sought to test the importance of negative frequency dependent selection in the maintenance of SA alleles in field populations housed in large outdoor field enclosures. Parameter estimates were then derived from the data to test in a mathematical model that incorporates frequency dependence into diploid genetics. In general, the factors

and mechanisms contributing to the maintenance of SA alleles remain unresolved.

2.3.4 Quantitative genetics of sexual antagonism (IV)

I used a multi-generational pedigree of bank voles to quantify the sexual antagonism over basic life history traits, offspring size and number. The relationship between these two traits is one of the central life history tradeoffs in many species; understanding the selection pressures on these traits is critical since sexual antagonism usually manifests itself in the number of offspring. The animal modeling technique was used to estimate the quantitative genetic parameters of sexual antagonism in this laboratory colony.

2.3.5 Effect of age on male and female reproductive interests (V)

I again used the animal modeling technique from quantitative genetics to explore the effect of age on fertility by using a large, multi-generational pedigree based on a laboratory population of bank voles. Fertility has been shown to decrease with age in many species, but it is not known how ageing/senescence affects the relative reproductive interests of males and females.

2.4 Laboratory environment

2.4.1 Animal husbandry

The colonies of bank voles were maintained in the facilities of the Experimental Animal Unit of the University of Jyväskylä. The voles were housed in rooms at 22 °C on a 16:8 light/dark photoperiod and provided food and water *ad libitum*. They were individually kept in cages measuring 43 x 26 x 15 cm with wood chips and hay.

When mating the voles, an unrelated male and female were placed together in one cage for a duration of 14 days, after which time they were separated and pregnancy was visually assessed by the size of the abdomen. Bank voles mate within the first week of pairing, therefore pregnancies are quite detectable 2 weeks after initial pairing. If the female showed no signs of being pregnant, then it was re-paired with a new male from the group for another 14 days.

Gravid (ie. pregnant) females were individually housed in a new cage with fresh bedding and observed once every 24 hours for births. Upon detection of a new litter (approximately 20-22 days after mating), the characteristics of the pups (e.g. body mass, head width, sex deduced by visual cues and ano-genital distance) and mother (e.g. body mass, head width, litter size, sex ratio of litter) were measured. DNA samples were obtained from the pups by clipping a

terminal portion of their tails and storing the samples at -70 °C. For adults, the terminal portions of the ears were clipped and the samples were stored in the same manner. The DNA samples were used in assessing paternity based on the procedure outlined below (section 2.4.4).

The housing, husbandry and procedures involving these animals adhered to ethical guidelines for animal research in Finland.

2.4.2 Artificial selection

The bank voles of papers I and II were obtained from selection groups for the hormone testosterone. Family-based, two-way artificial selection was utilized by measuring the T level of the males in a family, and then selecting them based on the average midson value to low ($< 4 \text{ ngml}^{-1}$) or high ($> 7 \text{ ngml}^{-1}$) T groups (Mills *et al.* 2009). Using offspring of wild-caught individuals, 104 families were used to create the selection groups. Thus, the first, second and third generations of laboratory-born individuals were utilized in these studies.

The bank voles of paper III were obtained from selection groups in which males were selected to be behaviourally dominant (Mf) or subordinate (mF), while the fertility of females was concurrently selected to be low (Mf) or high (mF). To assess these characteristics, dominance trials (see below, section 2.4.3) assessed the competitive ability of males to obtain a mate, while females were mated in the laboratory to assess fertility. Individuals used in this study were obtained from the fifth (summer 2008) and sixth (summer 2009) generations of a laboratory colony obtained from wild-caught individuals.

The bank voles of papers IV and V were obtained from two-way artificial selection lines divergent for litter size. The animal model of quantitative genetics took into account relationships and breeding design in the analysis of reproductive success of individuals. The 7 generation pedigree included 3734 individuals in paper IV, and 2141 individuals in paper V.

2.4.3 Experimental apparatus

In the experiments described in this thesis, various protocols were used to measure behavioural traits as well as to ascertain paternity of offspring by DNA analysis. A large cage measuring 60 x 38 x 20 cm was used in dominance trials (papers I, III). In these trials, two males were placed in the cage with a female that was in estrus. Female willingness to mate was checked before the trials by checking whether she showed lordosis posture for a random 'stud' male from another colony. The males would battle to establish dominance, and then the dominant male would typically attempt to court the female into mating. The lordosis and dominance trials were terminated after approximately 60 minutes if the females were not receptive to mating.

2.4.4 Genetic paternity analyses and hormone assay

For the experiments in which offspring of unknown paternity were produced, paternity of the pups could only be deduced by comparing the DNA of the pups to the potential sires. The DNA samples of the pup, dam and sire were extracted for analysis. Genotyping was assigned using 7 microsatellites according to the procedures outlined (Mills *et al.* 2007a; paper I). Likelihood-based analysis of paternity was conducted with Cervus 3.0.3 software (Kalinowski *et al.* 2007). I used the following parameters: 10 000 cycles, 100% of candidate parents sampled, 100% of loci typed, and a genotyping error rate of 1%. The 'one parent known' option was used to assign paternity. For each group of potential sires, the candidate father with the highest LOD score (95% CI) was accepted as the sire.

Plasma testosterone concentration was determined using the radioimmunoassay (RIA) technique (see methods in Mills *et al.* 2007a). Briefly, 75µl intra-orbital blood samples were taken from adult males using heparinized tubes, and then centrifuged at 10000 RPM for 5 minutes (see Oksanen *et al.* 2003 for blood sampling protocol). Males were evaluated as low (< 4 ngml⁻¹ plasma) and high (> 7 ngml⁻¹ plasma) for plasma T. The repeatability of T measures in bank voles was previously assessed by measuring T twice at a 2-week interval, which found this hormone measure to be consistent over time (repeatability = 0.637, N = 56 individuals, F ratio = 4.504, Schroderus *et al.* 2010).

2.4.5 Quantitative genetics

The restricted maximum likelihood (ReML) animal model approach utilized the measured litter characteristics (e.g. litter size for females, number of offspring sired for males) of a multi-generational pedigree of a laboratory population of bank voles (papers IV and V). This procedure of quantitative genetics partitions the phenotypic variance (V_P) into the different variance components (additive genetic variance, V_A ; non-genetic variance, V_{NG} ; environmental variance, V_E) and allows for heritabilities and genetic correlations to be estimated that take these effects, as well as the breeding design, into account (Kruuk 2004, Wilson *et al.* 2010). I used longitudinal analysis with random regression (based on Legendre polynomials) to explore the effect of age on the intersexual correlation for fertility (paper V).

2.5 Field environment

For paper III, I used 11 large, outdoor field enclosures that measured 40 x 50 m each, located near Konnevesi research station in central Finland (Fig. 3). The 0.2 hectare size of each enclosure was larger than an average home range of an individual bank vole, despite the limitations for dispersal (Bondrup-Nielsen

and Karlsson 1985). The vegetation was allowed to grow freely and was not managed, except for immediately adjacent to the enclosure walls (Fig. 4). These walls reached approximately 0.75-1.0 m above ground, which was high enough to prevent the escape of bank voles, but still low enough to allow access to potential predators (e.g. least weasel, various avian predators). Natural resources during the breeding season sustained the study individuals (Fig. 4). These semi-natural conditions allowed the voles to be exposed to the abiotic (e.g. temperature, wind, rain, sunlight) and biotic (e.g. predators, conspecifics, other animals) effects commonly faced by individuals in nature.

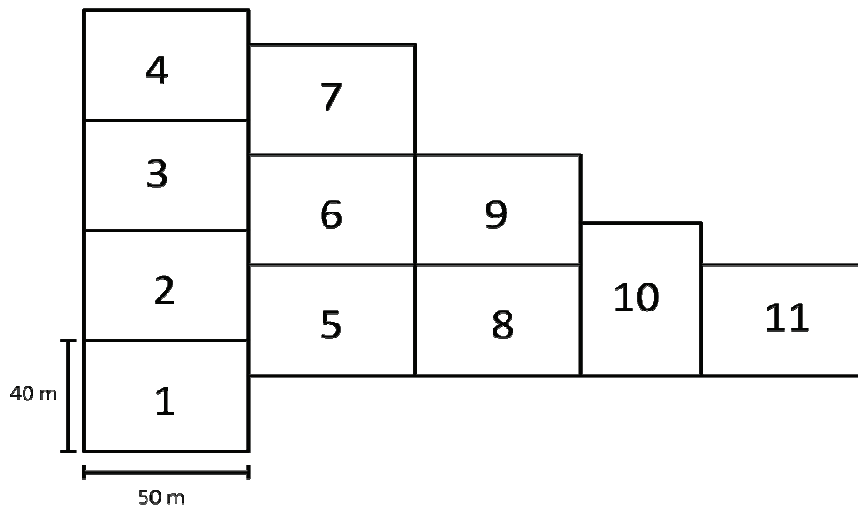


Figure 3 The layout of the 11 Peltokangas enclosures in Konnevesi, Finland. Each enclosure measures approximately 40 x 50 m, and is surrounded by a sheet metal fence that extends approximately 0.75-1.0 m above the ground.



Figure 4 Midsummer 2008 conditions at the Peltokangas field enclosures in Konnevesi, Finland.

During trapping sessions, I employed sheet-metal chimneys over the Ugglan (Grahnb, Sweden) live-traps to protect trapped voles from weather extremes. The live traps were placed in 4 x 5 grids, 10 m apart in each enclosure, and baited with seeds and potatoes. Trapping sessions were conducted approximately every 6-8 hours, depending on the temperature. I trapped an enclosure until no new individuals could be found on 3 consecutive sessions. Trapped individuals were taken back to the laboratory facilities in Konnevesi Research Station where measures (e.g. body mass, head width, gravidity) were taken.

More specific details of the field experiment protocol are found in the Methods section of paper III.

3 RESULTS AND DISCUSSION

3.1 Conflict in the mating system (I)

...her benefits are mightily misplaced...
-As You Like It

3.1.1 Conflict over benefits

Previous work has shown that testosterone is under strong sexual selection in male bank voles, and it is an important determinant of their reproductive success (Mills *et al.* 2009). In this current experiment, I found that T affected male and female mating behaviour differently. Selection for higher T translated into a higher mating success for males, but lower mating success for females. For mammals, the evidence is rather weak for a reproductive benefit associated with female mating success, however I found that a female's litter size increased with her number of mates. For this reason, there can be a significant cost for females when T is selected.

Interestingly, the experiment also revealed a significant first-male advantage in siring offspring, when a female mates with multiple males, although the advantage was not complete: nearly 37 % of the litters had multiple sires. This did not depend on the T profiles of the males or females involved.

This study revealed that there was a benefit to both males and females to mate with multiple partners, as it increased the number of their offspring. However, with the selection of T, there were sexually antagonistic effects: selection for T increased male mating rate but decreased female mating rate. Hence, the SA selection of T (higher in males, lower in females) can actually improve the mating-, and therefore, reproductive success of both sexes.

3.1.2 Implications

The widespread prevalence of multiple mating can possibly be explained through the benefits it provides the sexes. Despite the predicted conflict associated with polygamous mating systems, the benefits afforded both sexes appears to outweigh the relative costs. In this way, a seemingly costly behaviour can evolve. These results also caution that a fitness-related trait (mating rate) can be mediated by another trait (T) under SA selection. The role of hormones in sexual antagonism need to be further understood.

Evolutionarily, females face an interesting decision in mate choice: whether to mate with a male that can provide her with better quality sons at the expense of daughters, or vice versa. This decision can be rather transient, as the female's own features/traits or the environment may influence it. Hence, what is the optimal choice of partner for one individual may not be the optimal choice for another. If the choice for trait optimum is not consistent across all individuals that chose the partner, then this will erode the strength of directional sexual selection for that given trait. In addition to possibly obtaining more compatible genes (Puurttinen *et al.* 2009), an added benefit of multiple mating for females is that genetic variation in the offspring is greater. If a female cannot accurately gauge the genetic benefits of the potential mate, multiple mating can be used as a 'bet-hedging' strategy by females (due to greater genetic compatibility), whereas if the female can gauge benefits, it can be used as a 'trade-up' strategy for a better sire (reviewed in Jennions and Petrie 2000). Nonetheless, these results support recent work on bank voles that has shown fitness benefits associated with polyandry in the field (Klemme *et al.* 2008).

The first-male sperm precedent witnessed in this study may allow males to avoid the costs associated with mate guarding or care by assuring that they will sire the greatest proportion of that litter anyway, should the female mate with additional males. However, the sizeable portion of multiple-sired litters indicates that there is likely a post-copulatory selection process such as sperm competition or cryptic female choice (reviewed in Parker and Pizzari 2010). On the other hand, given that females can increase their fecundity by mating multiply, polyandry may additionally benefit males that can obtain a strong first-male advantage (see Alonzo and Pizzari 2010).

Building on recent results in a 'real world' sense, the negative genetic correlation of immunocompetence with T suggests that pathogens may potentially play a role in the evolution of the bank vole mating system (Schroderus *et al.* 2010), as pathogen resistance has been shown to suppress T production and mating rate (Mills *et al.* 2010). Thus, our results have implications for disease biology as well. Additionally, if high T males sire the most offspring, and low T females give birth to the most offspring, then this could maintain the genetic variation of T in bank voles, in addition to maintaining the gender load.

3.2 The indirect effect of grandparents (II)

A little more than kin, and less than kind.
-Hamlet

3.2.1 Inter-generational consequences of testosterone

In line with the SA zygotic drive hypothesis (section 1.3.3), I found a significant, indirect impact of the paternal grandmother on the birth mass of their grandsons, such that the grandmothers indirectly selected for high testosterone had grandsons with a higher body mass at birth (Fig. 5). There was no association between any of the grandparent testosterone profiles with granddaughter birth mass. In other mammalian species, the effects of the hormone testosterone *in utero* are known to impact the development of the offspring, which can have lifelong consequences for them (Hernández-Tristán *et al.* 1999, Manikkam *et al.* 2004, Lummaa *et al.* 2007).

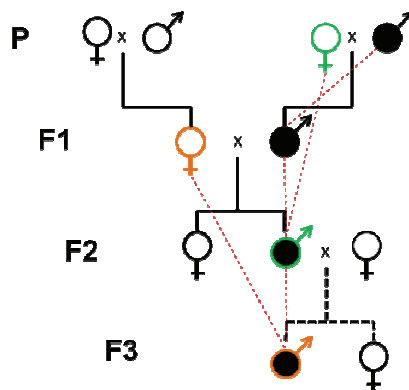


Figure 5 The influence of male and female testosterone profiles on the birth body mass of descendants. The father affects the plasma T-level of sons and paternal grandmother affects grandson birth mass in generation F2. Broken red lines indicate an effect on descendants, orange or green symbols indicate cross-generational association between like-coloured individuals. The broken black line extends the hypothesis one generation beyond this study to demonstrate how the influence of T switches between males and females across generations.

3.2.2 Implications

The indirect grandparental effect on fitness-related traits, as seen in this study, indicates that ancestors more distant than parents can influence an individual's phenotype. More generally, understanding how epigenetic processes (or other

non-Mendelian inheritance mechanisms) interact with genetic inheritance of fitness-related traits is an important question that will help clarify how fitness is influenced through the generations. Though, some caution is urged when applying these findings to non-mammalian species, as for example, evidence in birds indicates that sexual conflict does not play a significant role in yolk androgen allocation: environmental quality may be a greater determinant of hormonal manipulation of offspring growth before birth (Laaksonen *et al.* 2011).

Figure 5 highlights the combined influence of both males and females in the body mass of descendant males. However, it should be stated that females can only extend this influence to their grandsons through their reproductively successful sons. Hence, if females suffer fitness costs through sexual antagonism, they may be able to balance or offset these costs in their immediate offspring through more successful grandsons.

These results raise interesting questions to be pondered in future research. If the fitness costs of sexual antagonism are offset by the benefits afforded future generations of descendants, how rigorously do the costs and benefits need to be examined to properly ascertain a sexual conflict? How do these results impact professional breeding programs that often involve other mammalian species? Does testosterone have the potential to somehow modify the Y-bearing (male-producing) cells in the germ line of a developing fetus?

3.3 The maintenance of SA fitness variation (III)

...can one desire too much of a good thing?
-As You Like It

3.3.1 When data meets theory

Years in the making, this study was an exhaustive combination of laboratory, field and theoretical work. I artificially selected bank voles in the lab to create males of high behavioural dominance with sisters of low fertility in one group, and males of low behavioural dominance with sisters of high fertility in the other group. The males, when competing with each other, showed a strong difference in their dominance between these groups in the laboratory. However, the situation changed when these individuals were taken to the field, into outdoor field enclosures. When introduced to rare vs. common frequency treatments (see methods in III), I found that the high-dominance males had the highest reproductive success (number of offspring sired) only when they were rare in a population. Overall, there was negative frequency dependence in males, whereas the success of females was not dependent on their frequency, just their fertility. By imposing semi-natural conditions as well as frequency, I found an effect that would have otherwise not been observed under carefully controlled laboratory conditions. The data indicates that dominant males, when they become too common, are selected against in the population, however

females were always selected to maximize their fertility. There is conflict between males and females when the dominant males are selected (since related females are selected against), but the conflict is minimized/eliminated when selection changes and subordinate males are favoured (since related females are selected too).

Parameter estimates were extracted from the field data on bank voles for use in a mathematical model that theoretically expanded the study of diploid genetics and frequency to sexual antagonism. In essence, the aim was to explore the population-level evolutionary consequences of the sexually antagonistic alleles in the bank vole population's field environment. We found that over the range of most of the genetic dominance combinations, negative frequency dependent selection of males was required to maintain the gene frequencies in stable equilibria; in the absence of frequency dependence, the alleles would proceed to fixation/elimination. While this model was used explicitly with parameters derived from bank voles, it is very robust and applicable to other species as well.

3.3.2 Implications

The majority of studies on sexual selection/conflict have been conducted in the laboratory environment. While it is advantageous to carefully control possible confounding factors that may influence the results, it also raises questions about how accurately this kind of study can reflect natural processes. Nature is complex. The growing body of literature that has documented genotype \times environment interactions is a worthwhile concern to researchers that are interested in understanding important biological processes, and forces us to also ask if something observed in the laboratory also occurs in the field. The presence or absence of predators/conspecifics, fluctuations in temperature and weather phenomena, availability of food: these are all critical factors that can impact the survival and reproductive success of individuals, and are usually very controlled in the laboratory. On the other hand, the benefits of conducting experiments in the field are partially offset by the loss of control (Calisi and Bentley 2009). For example, in this study of bank voles in outdoor field enclosures, when individuals died or disappeared, I did not know if they were killed by predators, weather conditions or something else. The importance of the environment *for a study* depends very much on the question being asked and the study system being used. Certain studies are amenable to the laboratory environment (and sometimes are logistically impossible *except* in the laboratory). Researchers must carefully weigh the costs and benefits of how they conduct an experiment, taking these considerations into account.

Moving beyond merely documenting the presence of SA selection leading to conflicts, this study probed the conditions for its maintenance under more natural conditions. The picture that emerged is one of increasing complexity: the negative frequency dependence of males in this study indicates that frequency dependent selection can combine with sexually antagonistic selection to maintain the genetic variation associated with fitness in the field. SA

selection by itself is not enough to maintain the variation, as the model indicated that the alleles will soon go to fixation/elimination in the absence of frequency dependent selection. This study also provided clear evidence for the feedback between ecology and evolution, known as eco-evolutionary dynamics (Schoener 2011). The interplay between these two areas of biology will likely see a continued emphasis in research in coming years.

3.4 Quantitative genetics of sexual antagonism (IV)

A plague on both your houses!
-*Romeo and Juliet*

3.4.1 The conflict over the interests of males and females is genetic

Thus far, we have operated under the assumption that the sexual conflicts studied in this thesis are genetic. But what if they are not? The phenotype is shaped by both genes and the environment, so how can we be certain that the fitness costs associated with sexual antagonism that we observe are not due to developmental effects or other non-genetic influences? One approach is to use genetic tools in the laboratory, as has been done with *Drosophila melanogaster* (e.g. Rice 1992, Gibson *et al.* 2002, Rice *et al.* 2006, Morrow *et al.* 2008, Innocenti and Morrow 2010b). Another approach is to use quantitative genetic methods to assess the evolutionary consequences of sexual antagonism between males and females (e.g. Moore and Pizzari 2005, Brommer *et al.* 2007, Snook *et al.* 2010).

I found that there was a significant negative genetic correlation between female and male fertility (as measured by the number of offspring). This indicated that the genes associated with fertility had antagonistic fitness consequences, depending on the sex they belonged to. Genes contributing to better fertility in females are under sexually antagonistic selection to decrease fertility in males (and vice versa). This validates our understanding of the divergent evolutionary interests between male and female bank voles, despite the expectation that both sexes should maximize their number of offspring produced. These results are likely due to fertility being determined by different traits in males (e.g. sperm characteristics) and females (e.g. ovulation). Conversely, the genetic correlation for offspring size was positive between the sexes, indicating that it was in the interests of both sexes to have larger offspring.

Genomic conflict between females and males is such an interesting phenomenon to study because of the similarity of their genomes, but dissimilarity of their respective biological interests. Ultimately, evolutionary success is determined by the relative number of offspring an individual produces (that also go on to reproduce), however the strategies for achieving this success are often different between the sexes. Females are almost always responsible for prenatal care, and usually for post-natal care of offspring too

(Trivers 1972, Clutton-Brock 1991). Relative to females, males do not have to invest as much of their resources to offspring.

In bank voles, competition between males is the predominant form of sexual selection (Mills *et al.* 2007a). It results in directional selection for the trait(s) that are responsible for the mating advantage. However, as we have seen in paper I, what is optimal for males (e.g. higher T) is not always optimal for females (e.g. lower T).

3.4.2 Implications

It can be concluded that there is a conflict over fertility between male and female bank voles. Future work will be required to tease apart the various factors and traits that contribute to this conflict, as the genes that influence fertility, spanning physiological and behavioural traits, are expected to be numerous. These results show that there is conflict over offspring number, but not offspring size, thus, these results are of importance for other researchers of life history evolution.

More generally, the genetic determinism of the fitness-related traits under conflict is a topic that will yield greater insight into the genetics of conflicts. With mammals, such as the bank vole, males and females can share the autosomal chromosomes, but differ in one of the two sex chromosomes (X/Y). Pinpointing the locations of genes and transcription factors associated with traits will help both empirical and theoretical studies on antagonism. Previous studies have indicated the X-chromosome is a hotspot for sexually antagonistic fitness variation, which will have different fitness consequences compared to autosomal-linked fitness variation (Gibson *et al.* 2002, Andres and Morrow 2003, Innocenti and Morrow 2010b).

The asymmetries in both time and energy budgets between males and females provide interesting possibilities for future studies as well. While these topics are already much studied in biology, the incorporation of genomic tools will yield greater insight into the genetic underpinnings of the eco-evolutionary factors affecting fitness.

3.5 Effect of age on male and female reproductive interests (V)

Age cannot wither her, nor custom stale her infinite variety...
-Antony and Cleopatra

3.5.1 The changing genetic correlation

This study found evidence that fertility changed in females with age, which corresponded also with changes in the additive genetic variance for female fertility (and thus, heritability). Interestingly, the heritability of fertility diverged between the sexes with the age of females, indicating that a major

assumption of selection theory had not been fulfilled. Furthermore, we found that the reproductive interests of males and females diverged with female age, such that the intersexual correlation for fertility shifted from a positive to negative correlation with age.

Individuals change over the course of their lifetimes, and often the different life stages introduce unique selection pressures. Juveniles, before achieving reproductive maturity, do not have to contend with as many costly processes associated with reproduction that mature adults face (e.g. male-male combat, risky behaviours associated with finding mates, and time spent caring for a mate or offspring). Due to this, the evolutionary interests of juvenile females and males are often similar until they reach maturity. The change in the intersexual genetic correlation for fertility with female age indicates that there is concordant selection between the sexes when the females are young, but then the selection becomes sexually antagonistic when the females grow older.

If fertility-related genes are selected in older females, the intersexual genetic correlation is negative (i.e. selection on those genes will be sexually antagonistic). However, if these genes are selected in young adult females, the intersexual genetic correlation is positive (i.e. selection on those genes will be sexually concordant). Could this be due to antagonistic pleiotropy, where reproductive benefits to young females are balanced by fitness costs later in life caused by senescence? This result at least suggests that the age-dependent gene expression associated with fertility can have reproductive costs later in life, though it should be noted that fitness benefits can also be conferred by older, non-reproducing females in social species (Lahdenperä *et al.* 2004).

The increase in the additive genetic variance of fertility with age indicates that past selection has been strongest in younger females, and gradually weakened with age. This confirms one of the central ideas contained in the evolutionary theories of senescence that argues that selection is weaker in old age, thus allowing mutations to accumulate that are responsible for ageing (Williams 1957).

An assumption of quantitative genetic theory has been the stability of the genetic correlation between traits. It was previously accepted that the genetic correlation could be altered gradually with time, over many generations. Then, evidence began to accumulate that the time period required to alter the genetic correlation was on the scale of tens and not hundreds or thousands of generations, and that the environment, physiology and development could also alter it rapidly (Stearns *et al.* 1991). Our results confirm that the genetic correlation is a plastic feature of an individual's genetic architecture, which can shift within that individual's own lifetime in a constant environment. This is evidenced by the change in the sign of the intersexual genetic correlation for fertility from positive to negative: selection for fertility in young females was beneficial to the fitness of both partners, while selection for fertility in older females resulted in a fitness tradeoff between male and female offspring. This indicates that the age of females is important for the presence and degree of antagonism between the sexes. Given the changes in gene expression and

physiology that individuals experience in their lifetimes, it makes intuitive sense that the genetic correlation may change.

3.5.2 Implications

This study suggests that the process of ageing may itself be considered an adaptive process, if it reduces or eliminates the gender load through the mortality of sexually antagonistic individuals. These results show a fitness benefit for young females that reproduce, but a fitness cost when older females reproduce. This fits into the hypothesis of antagonistic pleiotropy initially developed by Williams (1957), though these results also call for the sexes to be considered separately due to the difference in heritability of fertility between them.

While the applicability of laboratory quantitative genetics studies to nature has been debated for years, I take the position in this study that the ecological constraints acting on natural populations have been removed. These ecological constraints are not always constant, and may be highly specific to a given population. Hence, to peel back these constraints allows us to glimpse the underlying genetic architecture of the trait - in this case fertility- that we are interested in. By demonstrating that there is genetic potential to exacerbate sexual antagonism with age, our results provide evidence of fitness benefits of young vs. old reproduction, despite the negative effects of senescence. It will be important for future studies to examine whether the benefits associated with reproducing earlier outweigh costs of reproduction on the mother or future siblings (Helle *et al.* 2002, Rickard *et al.* 2007). Whereas the results between studies IV and V agree that genetic conflict occurs between the sexes, they seem to disagree over the age this conflict occurs. This disagreement is mostly due to the differences in the pedigrees used in the two studies (e.g. only females that reproduced more than once were used in study V; only first parturitions were used in study IV), and thus, slightly different analyses were conducted (e.g. an individual's permanent effect was not included in the model of study IV, given the use of first parturitions only). However, the message here is that a negative genetic correlation exists between the sexes for fertility, and it grows more severe with age.

One of the most critical results to emerge from this study was the changing nature of the intersexual genetic correlation with age. Essentially, this tells us that future research will have to carefully consider the age of individuals when they are mated. It also tells us that the genetic correlation is plastic, thus allowing new ideas to be tested in life history evolution and related disciplines (Steppan *et al.* 2002, McGuigan 2006). The very idea of trade-offs may need to be developed further to incorporate age-related changes: genetic correlations may only be a 'snapshot' at that particular point in time.

The second critical result mentioned previously was the difference in heritabilities between the sexes for fertility. The majority of evolutionary studies have considered the heritability of traits the same between the sexes, while only a handful of studies have reported them separately (e.g. Foerster *et al.* 2007,

Schroderus *et al.* 2010). Resolving the prevalence of heritability differences between males and females should be of immediate importance in evolutionary biology. In this study, fertility can be viewed as an aggregate of other traits, and thus, may be quite different between the sexes. However, it is one of the main components of fitness, and therefore, these results have a wide applicability.

4 CONCLUSIONS

4.1 The phenotype-genotype link

The growth of sexual conflict theory has led to a framework whereby these conflicts are typically classified according to the similarity (intralocus) or dissimilarity (interlocus) of the conflicting genes between the sexes (Parker and Partridge 1998, Parker 2006). Depending on the type of conflict, research proceeds to test if sexually antagonistic selection operates on these genes in a 'tug-of-war' fashion, or through antagonistic coevolution between different male- and female-specific fitness related traits. In the rush to test new systems and traits, we may be overlooking several critical assumptions.

In Gould and Lewontin's (1979) much-debated critique of the adaptationist programme, they succinctly raised the question of what is a trait. While the validity of adaptation isn't under question in the current day, the conjecture over traits certainly maintains its applicability to evolutionary biology. Considerable research has been conducted over many decades that show how a variety of physiological and behavioural traits evolve. However, with respect to research into sexual conflicts, the need to resolve the trait(s) directly in conflict is absolutely necessary, given correlated selection and trade-offs that can indirectly affect traits. As Gould and Lewontin (1979) stated, individuals are a collection of many traits. Hence, we could expect these indirect processes to be quite ubiquitous when considering the whole organism. Paper I showed the underlying effect of T selection on mating behaviour between the sexes, such that selection for higher T increased the mating rate in males, but decreased it in females (and vice versa). However, through the SA selection of lower T in females and higher T in males, both sexes could increase their respective mating rates. Appreciating not just the genetic, but physiological explanations for evolutionarily important traits will help develop the understanding of trait interactions.

Although we are currently on the cusp of the genomics revolution, little is still known about how an individual's genetic architecture translates to the final

product, the phenotype. Yet, this association is a critical assumption made by most evolutionary biologists when probing sexual conflicts. With the exception of perhaps a few species (e.g. *Drosophila melanogaster*), we do not understand the genes that control the traits under selection. This is not a problem if we see a sustained selection response over generations, as we can be assured the process is genetic through the analyses of quantitative genetics (e.g. paper IV). However, until we study the genes further, it is difficult to ascertain what genes, and how many, control certain traits. Resolving the link from gene to trait to fitness effect remains an important goal for future studies (e.g. Innocenti and Morrow 2010b).

4.2 Pleiotropy: A hormone's perspective

The issue with classifying conflicts becomes apparent when examining hormones and pleiotropy. For example, testosterone is an important sex steroid used by a variety of vertebrates. It can influence physiological processes such as the production of mature sperm in males, or the expression of ornaments important for sexual selection. Testosterone can also influence a variety of behaviours through its effect on the brain, which can have consequences in the social interactions between individuals. Furthermore, in some species such as certain birds and mammals, testosterone is in a trade-off with immune function (immunocompetence handicap hypothesis, Folstad and Karter 1992). For species in the wild that need to cope with parasites and disease, this trade-off can be important for survival and factor into the costs associated with reproduction. Hence, this hormone can affect reproduction, and the traits associated with reproduction, through several channels.

Pleiotropic genes can influence multiple traits in an organism, and the nature of these genes is still relatively unknown (Williams 1957, Fitzpatrick 2004, McGuigan *et al.* 2011). This fact alone should give most evolutionary biologists pause when attempting to characterize relationships between traits. With antagonistic pleiotropy (as applied with the evolution of ageing), the same gene(s) can control one trait beneficially, while another trait to the detriment of the individual (Williams 1957). If these pleiotropic genes are found to act antagonistically across the sexes, then what may appear to be an interlocus conflict involving different traits (e.g. immune function and T production) can actually be an intralocus conflict (Schroderus *et al.* 2010). This caveat may become even more problematic, if age is not taken into account between mating pairs (paper V). The cascade effects of hormones, both upstream and downstream need to be further studied to better understand their role in pleiotropic interactions.

4.3 A step back to the genome

The temptation to classify sexual conflicts into intralocus and interlocus types is appealing, given how well sexual conflict theory fits with sexual selection theory. However, it is much more straightforward to differentiate between competition for mates (intrasexual selection) and mate choice (intersexual selection) than it is between conflict over the same gene complex (intralocus conflict) and conflict between gene complexes (interlocus conflict). Currently, microarray approaches offer promise for understanding this distinction, and next generation (454) sequencing technology will soon allow us to understand the genome in far greater detail than before.

Fedorka and Mousseau (2004) made the point that reproductive success is usually an aggregate of multiple traits. In light of this, it may be worthwhile to consider a more conservative approach to studying sexual conflict that does not always involve classifying the conflict to be intralocus or interlocus. Genomic conflict encompasses both types of conflict and does not trap us mistakenly into misidentifying it. Furthermore, we are not constrained by the (often blind) assumption of a direct link between the phenotype and genotype. While this may at first appear trivial, it may benefit research by not leading new thinking down erroneous routes and improperly concluding that certain traits are genetically linked. In this way, the body of theory can move forward cohesively until we attain a better understanding of the genetics involved with the underlying conflict.

4.4 The ubiquity of competing interests in evolution

It is likely that evolution by means of selection will inevitably harbour conflicts of interest between individuals. The very nature of selection translates to some individuals being more successful than others, which is rarely agreeable to all. One of the big challenges in selection theory is to detect and quantify the presence of evolutionary conflicts. Recently, this has come under increasing scrutiny, and there now exists measures to quantify the strength of sexually antagonistic selection (Cox and Calsbeek 2009, Innocenti and Morrow 2010a) and sexual conflict (paper I). These tools will help us to uncover conflicts more efficiently, as their calculation with these measures is not dependent on net fitness values. Symmetrical sexually antagonistic selection, if surveyed for an entire population, is expected to result in a net fitness effect of 0, as the costs and benefits are predicted to cancel each other out in the absence of other selective forces. However, in reality, balanced opposing selection between the sexes cannot be the norm, given the variety of sex-specific selection pressures individuals face in nature (paper III). Calculating sex-specific selection gradients for traits can help discern antagonistic evolutionary forces by

separating the competing interests and demonstrating the relative costs and benefits to each sex.

5 FUTURE DIRECTIONS

The interactions between molecules, genes, traits, individuals, populations and species are still too numerous and complex to fully grasp at once. Even looking at the evolution of a species such as the bank vole, there are several selective (and non-selective) forces acting in concert to propagate the species. It can be reasonably inferred that in the wild, bank voles experience at least natural, sexual, density dependent, frequency dependent, and sexually antagonistic selection of their fitness-related traits (Koskela *et al.* 1999, Oksanen *et al.* 1999, Mappes *et al.* 2008, Mills *et al.* 2009, Boratyński and Koteja 2010). The direction and intensity may change over time, which adds to the complexity, and let us not forget the genotype by environment interactions which may render the effect of these selection pressures different depending on the environment (e.g. Mills *et al.* 2007b).

As biologists, we often reduce phenomena or the systems we are studying to better understand their function. Yet, as Gould and Lewontin (1979) noted, we are collections of traits that interact with one another. Of course, some questions lend themselves to this reductionist approach- that proving some aspect of biology in a controlled manner can lead to important insights. It allows us to prove causality very effectively. However, it would be beneficial to consider interactions between traits as well as selective forces more centrally in the evolution of a species. There is little doubt that the future will provide us the tools to make this more possible. For example, the advances in sequencing technology have brought us to the verge of using whole genomes of individuals in our experiments, and should help clarify the link between the genotype and phenotype. We have only been scratching the surface of what is really going on, and the years ahead will bring great, new insights in evolutionary biology. It's an exciting time to be a scientist, at the dawn of a new era in the biological sciences.

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This chapter of life is now complete.

YHTEENVETO

Sukupuolten välinen konflikti: käyttäytymiseen, fysiologiaan ja genetiikkaan liittyvistä ristiriidoista pikkunisäkkäillä

Lähes kaikilla eliöryhmillä koiraat ja naaraat eroavat selkeästi toisistaan usean lisääntymismenestykseen liittyvän ominaisuuden suhteen. Nämä ominaisuudet voivat olla mm. morfologiaa, fysiologiaa tai käyttäytymispiirteitä, ja vastoin luonnonvalintateorian ennusteita niissä havaitaan usein paljon geneettistä muuntelua. Ilmiön taustalla voi olla niin sanottu sukupuolten välinen konflikti: ero naaraiden ja koiraiden mahdollisuuksissa kasvattaa lisääntymismenestystään. Jos seksuaalisesti antagonististen alleelien vaikutus kelpoisuuteen on vastakkaisuuntainen eri sukupuolilla, eli valinta suosii saman geenin eri alleeleja koiraisissa ja naaraisissa, voi muuntelun säilyminen selittyä. Esimerkkinä tästä voi toimia yksilön aggressiivisuustaso: aggressiivisuuden ollessa koiraille hyödyllinen piirre niiden kamppaillessa keskenään naaraista, niin naarailta sama ominaisuus voikin heikentää niiden suosiota pariutumiskumppanina ja/tai vähentää niiden jälkeläishoitotaitoja. Tällaisessa tilanteessa aggressiivisen käyttäytymisen optimitaso eri sukupuolilla on erilainen, ja luonnonvalinnan tulisi suosia erilaista käyttäytymismallia aikaansaavia alleeleita koirailta ja naarailta. Koska sekä koiras- että naaraspoikaset perivät kuitenkin vanhemmiltaan samat tiettyä käyttäytymispiirrettä koodaavat geenit, voi sukupuolesta riippuvan optimin saavuttaminen olla mahdotonta.

Valtaosa sukupuolten välistä konfliktia käsittelevästä tutkimuksesta on tehty selkärangattomilla eläimillä, erityisesti *Drosophila*-suvun kärpäksillä, ja koekellinen tutkimus aiheesta on nisäkkäillä puuttunut kokonaan. Tässä väitöskirjassa tutkin sukupuolten välistä konfliktia määrittäviä tekijöitä käyttämällä tutkimuslajina metsämyyrää (*Myodes glareolus*). Tutkin ensinnäkin lisääntymisjärjestelmien evoluutiota, joka on klassinen esimerkki sukupuolten välisen konfliktin ilmenemisestä lisääntymisen eri vaiheissa. Toisessa osatutkimuksessa tarkastelin isovanhempien mahdollisia epäsuoria vaikutuksia lastenlasten syntymäkokoontoon. Kolmannessa osatutkimuksessa pyrin selvittämään voiko frekvenssistä riippuva valinta, tietyn genotyypin kelpoisuuden riippuminen erilaisien genotyyppien esiintymistiheyksistä populaatiossa, ylläpitää seksuaalisesti antagonistista muuntelua luonnossa. Kahdessa viimeisessä osatutkimuksessa tutkin seksuaalisesti vastakkaisen valinnan merkitystä yksilöiden lisääntymispiirteissä määrittämällä geneettisiä korrelaatioita tuotettujen poikasten koolle ja lukumäärälle koiraiden ja naaraiden välillä. Väitöstutkimukseni menetelminä käytin pääasiassa empiirisiä laboratorio- ja kenttäkokeita mutta myös matemaattista mallinnusta. Kvantitatiivisen genetiikan menetelmiin perustuvissa osatutkimuksissa tärkeässä roolissa oli tuhansien metsämyyräyksilöiden suuruinen laboratoripopulaatio, jossa yksilöiden sukulaisuussuhteet olivat tarkoin tiedossa.

Väitöskirjani tulokset osoittavat, että testosteronihormonilla on vastakkainen vaikutus metsämyyränaaraiden ja -koiraiden lisääntymismenestyksessä: testosteronin nostaessa koiraiden dominanssiasemaa ja tuotettujen poikasten lukumäärää aiheuttaa se naarailta pariutumismenestyksen laskua. Löysin myös viitteitä siitä, että testosteronin vaikutukset ulottuisivat sukupolven yli isovanhemmilta lapsenlapsille vaikuttaen näiden syntymäkokoon. Kolmannessa tutkimuksessani koiraiden kelpoisuus oli ulkotarhoissa negatiivisesti frekvenssistä riippuvaa, suosien aina populaatiossa harvinaisempaa esiintyvää lisääntymistaktiikkaa riippumatta siitä, edustiko se dominanssiasemaltaan matalamman vai korkeamman genotyypin yksilöitä. Naaraiden kelpoisuus ei riippunut niistä ympäröivän populaation yksilöiden ominaisuuksista vaan ainoastaan laboratoriossa määritetystä lisääntymistaktiikasta. Tulosten perusteella voidaan päätellä, että negatiivinen frekvenssistä riippuva valinta on tärkeä mekanismi joka säilyttää muuntelua metsämyyrien lisääntymispiirteissä. Tätä tulkintaa tuki myös teoreettinen analyysi siitä todennäköisyydestä, millä frekvenssistä riippuva valinta ylläpitää geneettistä muuntelua metsämyyräpopulaatioissa. Neljäs osatutkimukseni antoi tukea aiemmille tutkimustuloksille siitä, että poikasten lukumäärää määrittäviin ominaisuuksiin kohdistuu seksuaalisesti vastakkaista valintaa: geneettinen korrelaatio koiraiden ja naaraiden tuottamien poikasten määrän välillä oli negatiivinen osoittaen, että alleelit, jotka kasvattavat koiraiden (naaraiden) hedelmällisyyttä, alentavat vastaavasti naaraiden (koiraiden) poikuekokoja. Poikasten syntymäkokoon kohdistuva valinta osoittautui kuitenkin sukupuolten välillä samansuuntaiseksi osoittaen, että poikasten kasvua koodaavat geenit ilmenevät samalla tavalla sekä koiras- että naaraspoikasissa. Viides osatutkimukseni osoitti edelleen, että poikuekoon periytymisaste, heritabiliteetti, kasvoi naarailta iän myötä kun taas koirailta vastaavaa muutosta ei havaittu. Tämä ero sukupuolten välillä johti osaltaan siihen, että edellisessä osatutkimuksessa havaittu negatiivinen geneettinen korrelaatio koiraiden ja naaraiden tuottamien poikasten määrän välillä voimistui naaraiden ikääntyessä.

Väitöstutkimukseni lisää metsämyyrän niiden lajien listaan, joilla on havaittu seksuaalisesti vastakkaista valintaa kelpoisuuteen keskeisesti vaikuttavien ominaisuuksien välillä. Toisin kuin on aikaisemmin arveltu, sukupuolten välinen konflikti lisääntymismenestykseen keskeisesti vaikuttavissa ominaisuuksissa näyttäisi siis olevan merkittävä myös muilla nisäkkäillä kuin ainoastaan vahvasti sukupuolidimorfisilla hirvieläimillä. Testosteronihormonin osoittautuminen tärkeäksi selittäväksi mekanismiksi yksilön geenien ja kelpoisuuden välillä korostaa hormonien tärkeää merkitystä yksilön ilmiänsä määrittävänä tekijänä.

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