Theoretical Evolutionary Biology of Sex and Disease

by

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A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy
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University of Toronto

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Abstract

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2016

Theoretical approaches have the potential to improve our conceptual understanding of evolutionary biology. Using mathematical modeling and computer simulations we can test verbal hypotheses about biological processes and make qualitative predictions about how biological factors interact to produce the patterns we observe in nature. My thesis is a series of theoretical chapters, each focused on a different aspect of evolutionary biology. In Chapter 2, I explore the accumulation of deleterious mutations by Muller’s ratchet in asexual populations experiencing temporal fluctuations in selection. My finding that temporal autocorrelation in selection increases the rate of fitness decline contributes to our understanding of the role of environmental heterogeneity and drift in the extinction of asexual lineages. In Chapter 3, I investigate virulence evolution of parasites infecting host populations that have multiple host types differing in their contact patterns and their susceptibility and resistance to disease. I found susceptibility and resistance interact with contact pattern to change evolutionarily stable virulence, highlighting the importance of considering non-random contact patterns between different host types when modeling biologically realistic host populations. In Chapter 4, I model the coevolution of virulence of a sexually transmitted disease (STD) in a host population experiencing sexual conflict over mating rate. In my model, a coevolving STD selects for higher sexually antagonistic host trait values, escalating the conflict and demonstrating that disease could be an important factor in sexually antagonistic coevolution. Overall, my chapters make advancements in their respective fields by adding some dimension of biological realism to the general model and analyzing how this addition affects the evolutionary outcome.
Dedication

To my grandparents, Tom and Grace Wardlaw
Acknowledgements

This thesis would not have been possible without the support of my supervisory committee, colleagues, family, and friends. First and foremost I would like to thank my supervisor Aneil Agrawal. Aneil has taught me more than I can probably currently appreciate. He has shaped the way I think about science and academia and exemplified the creativity and thoroughness that I admire in him.

My time in graduate school would not have been as enjoyable or productive without my friends and colleagues: Penelope Gorton, Tia Harrison, Adriana Salcedo, Nathaniel Sharp, Alethea Wang, Yuheng Huang, Eddie Ho, Andrijana Stanic, Amardeep Singh, Li Yun, Matthew Hartfield, Pepijn Luijckx, Maggie Bartowska, Megan Greischar, Thomas Platt, Philip Greenspoon, Cyrilta Guy, Tsukushi Kamiya, Michelle Afkhami, Emily Josephs, Amanda Stock, Brandon Campitelli, Corlett Wood, Susana Wadgymar, Adam Cembrowski, Jill Wheeler, Gabriel Boldt, Sarah Dowler, Young Wha Lee, Jason Laurich, Rebecca Wardlaw, Kate Garvie, and Sarah Wallace. I would especially like to thank Robert Williamson, without whom I would not have made it to the end, and David Smith, without whom this thesis would not exist as a document.

A number of U of T faculty have provided valuable support and guidance throughout my PhD, including Stephen Wright, Asher Cutter, and Peter Abrams. I would especially like to thank Helen Rodd for helping me work through the trials and tribulations of graduate school, John Stinchcombe for his office visits and advice, and Nicole Mideo for her dual role as both friend and mentor. In addition, my thesis would not have been possible without the support of EEB staff, in particular the IT department, Kitty Lam, Pam Pecoskie, Stephanie Melo, and Jennifer English.

I would also like to thank my mother and father (Margaret and David Wardlaw) for their love and generosity, my sister (Sarah Bryce) and her family for a second place to call home, and my brother (Andrew Wardlaw) for his unwavering belief that I was made for this. My extended family has also been an enormous support for me, whether that be through providing me a place to live, visit, or work.

Finally, I would like to thank NSERC for funding my stipend and research.
Contents

1 Introduction

1.0.1 When Is It Good to Use a Model? ................................. 1
1.0.2 What Makes a Good Model? .................................... 2
1.0.3 The Process of Modeling ......................................... 2
1.0.4 Value of Analytical Results ..................................... 3
1.0.5 Value of Simulation Results ..................................... 3
1.0.6 Linking Theory and Empirical Results ......................... 4
1.0.7 Evolution of Sex .................................................. 4
1.0.8 Evolution of Virulence .......................................... 5
1.0.9 Sexual Conflict .................................................. 6
1.0.10 Overview ....................................................... 7

2 Temporal variation in selection accelerates mutational decay by Muller’s ratchet 8

2.1 Abstract .............................................................. 9
2.2 Introduction .......................................................... 9
2.3 Methods ............................................................ 11
2.3.1 Overview .......................................................... 11
2.3.2 Varying Selection ............................................... 11
2.3.3 Simulation Methods ............................................. 11
2.4 Results ............................................................. 12
2.4.1 Conditional Neutrality ......................................... 12
2.4.2 Varying the Frequency of Selection ......................... 14
2.4.3 Quantitative Variation in Selection ........................... 16
2.4.4 Relaxing Genome Assumptions ............................... 19
2.5 Discussion .......................................................... 20

3 Virulence evolution of a parasite infecting male and female hosts 23

3.1 Abstract ............................................................. 24
3.2 Introduction .......................................................... 25
3.3 Model Setup .......................................................... 27
3.3.1 Homogeneous Host Population ............................... 29
3.3.2 Heterogeneous Host Population ............................. 29
3.4 Results ............................................................. 31
3.4.1 Single Differences Between Host Types ..................... 31
List of Figures

2.1 Ratchet rate as a function of selection strength. The solid curve shows a qualitative depiction of the rate of the ratchet as a function of $s$ assuming no temporal variation in selection. If selection varies temporally such that $s = s_{max}$ for a fraction $\phi$ of generations and $s = s_{min}$ for the remainder $(1 - \phi)$, overall ratchet rate might be predicted by the rate-average, $\bar{R} = \phi R_{s_{max}} + (1 - \phi) R_{s_{min}}$, or the selection-average ($R_{s}$), the rate of the ratchet if selection were held constant at $\bar{s}$, the geometric time-average of $s_{min}$ and $s_{max}$.

2.2 Effects of temporal heterogeneity on ratchet rate and fitness decline. (A-C) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE for a population of (A) 500, (B) 5 000, and (C) 50 000. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average ($R_{s}$) and rate-average ($\bar{R}$) predictions. (D-F) Mean rate of fitness decline +/- SE for the least loaded class in a population of (D) 500, (E) 5 000, and (F) 50 000. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average scenario. In most cases SE bars are too small to see.

2.3 Effect of temporal heterogeneity relative to constant selection of equivalent strength. Relative increase in (A) ratchet rate and (B) rate of fitness decline over that of populations experiencing the corresponding constant time-averaged selection coefficient. Relative increases are infinite for values of $\bar{s}$ beyond those shown because the ratchet rate is zero under constant selection. Data shown are for the high temporal autocorrelation selection regime only. For clarity, outlined regions of panels (A) and (B) are shown magnified in panels (C) and (D), respectively.

2.4 Effects of varying the frequency of selection on ratchet rate and fitness decline. (A) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE and (B) mean rate of fitness decline of the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{min} = 0$ and $s_{max}$ such that the geometric time-averaged selection coefficient $\bar{s} = 0.0513$ for all values of $\phi$. When $\phi = 1$, $s_{max} = \bar{s}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high temporal autocorrelation). In most cases SE bars are too small to see.
2.5 Effects of temporal heterogeneity with quantitative variation in selection on ratchet rate and fitness decline. (A-C) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE for a population of 50000 experiencing selection varying between $s_{\text{max}}$ and (A) $s_{\text{min}} = 0.01 * s_{\text{max}}$, (B) $s_{\text{min}} = 0.05 * s_{\text{max}}$, and (C) $s_{\text{min}} = 0.25 * s_{\text{max}}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average ($R_{\bar{s}}$) and rate average ($\bar{R}$) predictions. (D-F) Mean rate of fitness decline of the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{\text{max}}$ and (D) $s_{\text{min}} = 0.01 * s_{\text{max}}$, (E) $s_{\text{min}} = 0.05 * s_{\text{max}}$, and (F) $s_{\text{min}} = 0.25 * s_{\text{max}}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average scenario. In most cases SE bars are too small to see.

2.6 Effects of varying the fraction of the genome experiencing fluctuating selection on ratchet rate and fitness decline. (A) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE and (B) mean rate of fitness decline of the fittest individual in the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{\text{min}} = 0$ and $s_{\text{max}} = 0.1$ on a fraction, $F$, of its genome. The remainder of the genome experiences constant selection $\bar{s} = 0.0513$ such that the geometric time-averaged selection coefficient across the genome is also $\bar{s} = 0.0513$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high temporal autocorrelation) with predictions for overall ratchet rate based on $R = F*R_{\text{fluctuating}} + (1-F)*R_{\text{constant}}$ shown by the corresponding dashed line. Predictions for rate of fitness decline are calculated analogously. In most cases SE bars are too small to see.

3.1 The evolutionarily stable strategy (ESS) of a parasite expressing the same exploitation rate in both sexes changes with contact pattern when there are differences in susceptibility between the sexes. Transmission is symmetrical ($p_{ij} = p_{ji}$ and $p_{ii} = p_{jj}$) and transmission coefficients out of each sex sum to one ($p_{ij} + p_{ii} = 1$) such that as within-sex transmission increases moving from left to right across the $x$-axis, between-sex transmission decreases. A parasite that facultatively expresses different exploitation strategies in males and females has ESS exploitation rates $\epsilon_f^*$ (red) and $\epsilon_m^*$ (blue), which do not change with differential susceptibility or contact pattern. Note that $\epsilon_f^* > \epsilon_m^*$ because we have assumed females are more resistant to the disease ($\rho_f > \rho_m = 0$). The constrained ESS also does not change with contact pattern when susceptibility is equal ($\eta_f = \eta_m$, black solid line) but shifts closer to $\epsilon_f^*$ of the more susceptible sex as within sex transmission increases ($\eta_f > \eta_m$, black dashed dotted line; $\eta_f < \eta_m$, black dashed line). The source of new uninfected individuals is constant immigration, i.e. $\theta = 75$. Though the figure goes to $p_{ii} = 1$ for illustrative purposes, evolutionary branching occurs below this level (e.g. $p_{ii} > 0.94$, with the exact value depending on the parameters).
3.2 A constrained parasite has higher reproductive values in the more susceptible sex as within-sex transmission increases. The class reproductive values ($v_m$ and $v_f$) represent the contribution of each sex to future population growth of the parasite. Males and females contribute equally to parasite population growth when susceptibility is equal ($\eta_f = \eta_m$, black solid line). When there is differential susceptibility ($\eta_f > \eta_m$, black dashed dotted line; $\eta_f < \eta_m$, black dashed line), the parasite has a higher reproductive value in the less susceptible sex if there is more between-sex transmission or in the more susceptible sex if there is more within-sex transmission. The source of new uninfected individuals is constant immigration, i.e. $\theta = 75$ and the $x$-axis is the same as in figure 3.1.

3.3 (A) Asymmetrical transmission patterns lead to changes in the constrained ESS in the absence of differential susceptibility, i.e. $\eta_f = \eta_m$. Two scenarios are depicted: transmission into males from females and other males increases moving from left to right across the $x$-axis ($p_{mm} = p_{fm} = \delta; p_{mf} = p_{ff} = 1 - \delta$, dashed green line) or male to male transmission increases while transmission out of females remains random ($p_{mm} = \delta; p_{mf} = 1 - \delta; p_{ff} = p_{fm} = 0.5$, solid green line). An unconstrained parasite has ESS exploitation rates $\epsilon_f^*$ (red) and $\epsilon_m^*$ (blue), which do not change with contact pattern. Note that $\epsilon_f^* > \epsilon_m^*$ because we have assumed females are more resistant to the disease ($\rho_f > \rho_m = 0$). (B) Relative class reproductive values for a constrained parasite. The source of new uninfected individuals in both panels is constant immigration, i.e. $\theta = 75$.

3.4 The source of new uninfected individuals can affect how differential susceptibility skews the ESS towards $\epsilon_f^*$ of the more susceptible sex. Density dependent births where females are more important to reproduction (A, black lines) shift the ESS closer to $\epsilon_f^*$ compared to when both sexes are important to reproduction (B, black lines) or when there is constant immigration (both panels, grey lines). A parasite that facultatively expresses different exploitation strategies in males and females has ESS exploitation rates $\epsilon_f^*$ (red) and $\epsilon_m^*$ (blue), which do not change with differential susceptibility or contact pattern. $\eta_f = \eta_m$; solid lines; $\eta_f > \eta_m$, dashed dotted lines; $\eta_f < \eta_m$, dashed lines. The $x$-axis is the same as in figure 3.1.

3.5 For an unconstrained parasite, the exploitation rate expressed in females changes with contact pattern when there is vertical transmission. (A) The probability of vertical transmission is $\kappa = 0.5$. $\epsilon_f^*$ increases with increasing within-sex transmission (solid red line) while $\epsilon_m^*$ does not (solid blue line). The constrained parasite strategy (solid black line) is always bounded by $\epsilon_f^*$ and $\epsilon_f^*$. Only the equal susceptibility case is shown for clarity. (B) The probability of vertical transmission is $\kappa = 0.1$. $\epsilon_f^*$ changes with contact pattern to a lesser extent. Solid lines, $\eta_f = \eta_m$; dashed dotted lines $\eta_f > \eta_m$; dashed lines $\eta_f < \eta_m$. The $x$-axis is the same as in figure 3.1.

4.1 Two-way coevolution in individual-based simulations results gives evolutionary equilibria that qualitatively follow the same patterns as the analytical model. Shown here are (A) the difference between evolutionary equilibrium persistence, $y'$, and evolutionary equilibrium resistance, $x'$, (B) the average of $y'$ and $x'$. Parameters used were as follows: $\pi = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$. Each cell represents the average of 10 independent simulations.
4.2 Sample run from individual-based simulation where hosts evolve to their disease-absent equilibrium values before an STD is introduced. Male persistence is shown in blue, female resistance in red, and STD virulence in black. Parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$.

4.3 Three-way coevolution in individual-based simulations results in evolutionary equilibria that qualitatively follow the same patterns as the analytical model. Each simulation began with $x = 4$, $y = 6$, and $v = 0.8$. (In preliminary work, we found that the equilibrium values were not sensitive to initial values, provided extinction did not occur.) Shown here are (A) the difference between evolutionary equilibrium persistence, $y'$, and evolutionary equilibrium resistance, $x'$, in the presence of a sexually transmitted disease with evolutionary equilibrium virulence $v'$. Parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.

4.4 Fraction of simulation runs where a sexually transmitted disease (STD) was driven extinct by sexually antagonistic host coevolution. In each case the STD was introduced into a host population that had reached its equilibrium trait values in the absence of the parasite. (A) Non-evolving STD with $v = 0.8$, (B) Coevolving STD initially introduced with $v = 0.8$. Other parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. The value for each cell was based on 10 independent simulations.

4.5 Evolutionary equilibrium virulence of a sexually transmitted disease (STD) in a (A) co-evolving and (B) non-evolving host population. In the non-evolving host population the parasite was introduced at the STD-absent male persistence and female resistance host trait values with $v = 0.8$. Other parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.

4.6 Two-way coevolution between male persistence and female resistance yields evolutionary stable strategies across a range of persistence costs to males and mating costs to females. Shown here are (A) the difference between ESS persistence, $y^*$, and ESS resistance, $x^*$, (B) the average of $y^*$ and $x^*$. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$. 

4.7 Three-way coevolution between male persistence, female resistance, and STD virulence yields evolutionary stable strategies across a range of persistence costs to males and mating costs to females. Shown here are (A) the difference between ESS persistence, $y^*$, and ESS resistance, $x^*$, (B) the average of $y^*$ and $x^*$, and (C) ESS virulence of the sexually transmitted disease, $v^*$. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. 

54
4.8 Disease prevalence, calculated as the fraction of the host population infected with the sexually transmitted disease (STD), resulting from the three-way coevolution between male persistence, female resistance, and STD virulence in individual-based simulations. Parameters used were as follows: \( \alpha = 0.03, \delta = 0.0005, \mu = 0.2, b = 4, K = 1000, w = 1 \). Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.
Chapter 1

Introduction

Mathematical modeling has a long history in evolutionary biology. Since the pivotal work of Fisher, Wright, and Haldane on the modern synthesis in the 1930s and 40s, theoreticians have utilized mathematical models to try to understand biological processes. Models are particularly important in evolutionary biology because of the complexity of natural systems and the long time scales over which evolution occurs (Servedio et al., 2014). Progress in the field is made by forming verbal hypotheses from scientific observations and then testing those hypotheses with experiments, comparative studies, or theoretical models. Theoretical models can clarify our thinking about how various biological factors and processes interact. By transforming verbal arguments into mathematical models we are forced to specify assumptions, and in doing so, often identify hidden assumptions in the verbal model (Bell, 1982). Formalizing hypotheses (as mathematical models) can therefore provide us with a qualitative description of natural processes and expected outcomes that might otherwise be hard to predict, especially when empirical results are difficult to obtain.

1.0.1 When Is It Good to Use a Model?

Given that models can help clarify our thinking about complicated biological processes, there are certain cases where constructing mathematical models is particularly useful. Models have two general purposes, 1) test verbal hypotheses, and 2) generate predictions. As previously mentioned, using theoretical approaches to test verbal hypotheses helps identify hidden assumptions in verbal chains of logic. This can be especially useful when trying to explain conflicting or complicated empirical results because there are often many interacting factors contributing to the observed evolutionary outcome. It is also beneficial to use models to make qualitative or quantitative predictions about biological patterns we expect to observe. Theoretical biologists are often interested in qualitative predictions arising from simplified (and somewhat unrealistic) models because they can provide insight into complex systems and enhance our conceptual understanding of evolutionary biology. This type of prediction is beneficial when the appropriate experiments are too difficult to manipulate. When we can obtain the appropriate data, quantitative predictions arising from models more accurately representing the underlying biology are often useful for comparing how and why the data deviate from our predictions.
1.0.2 What Makes a Good Model?

“Everything should be as simple as possible, but no simpler” - Albert Einstein

Albert Einstein’s self-exemplary quote leaves room to capture a wide variety of model types depending on the goals of the model. Levins (1966) outlined three modeling strategies, each of which sacrificed one of the different aspects of an ideal model, where an ideal model maximizes generality, realism (how closely the model reflects the underlying biology), and precision (the accuracy of the predictions generated by the model). I favour models that sacrifice precision to realism and generality but also discuss below how sacrificing generality can help advance our understanding of evolutionary biology.

Theoretical formalizations of evolutionary processes necessitate what some would view as oversimplifications. However, the degree to which biological realism is overlooked in lieu of analytical tractability depends on the goal of the model. A model aimed at describing general biological patterns may ignore finer scale processes (sacrificing precision) to focus on important factors and their interactions at a broader scale. For example, a general epidemiological model of malaria might consider how transmission and virulence change over the course of an infection and track the density of infected individuals at each infection age (Alizon et al., 2009). A more detailed model might explicitly incorporate the within-host dynamics of malaria (sacrificing generality) such that average transmission and virulence emerge from the dynamics of the various parasite life stages inside the host (Mideo et al., 2008).

While narrowing down the focus of a model to include more biological realism allows us to make more specific predictions, these predictions can be limited in scope. In the example above, the qualitative patterns predicted by a model incorporating infection age are more readily extended to diseases in general than a nested model that tracks malarial life stages. Ultimately, the question of whether either model in this example is ‘good’ comes down to whether they reduce unexplained phenomena (Bell, 1982). By exploring how infection age or within-host dynamics affect pathogen evolution we extend our understanding of the evolution of virulence in general and broaden our knowledge of factors contributing to observed virulence levels.

Regardless of the type of model (general or specific), the model should precisely identify assumptions and make transparent the robustness of those assumptions (to the extent this is known). General models aimed at testing verbal hypotheses may ignore some underlying biological processes to ensure that these do not confound the results and make it difficult to tease apart what ecological and evolutionary factors are important. Models designed to make specific qualitative or quantitative predictions may try to incorporate biological details specific to the system they are modeled after to ensure the predictions are applicable.

1.0.3 The Process of Modeling

Converting a verbal hypothesis into a mathematical model requires explicit consideration of assumptions at the level of biological detail in question. (There will always be some implicit assumptions. For example, the model including infection age implicitly ignores within host dynamics. In verbal models, implicit assumptions are often hard to pinpoint. In contrast, the formal structure of mathematical models allows assumptions to be clearly identified by later investigators even if they were initially implicit.) Identifying or specifying assumptions is one of the most valuable stages of the modeling process. Servedio et al. (2014) outline three types of assumptions that go into a mathematical description of a biological
system, each serving a different role in the modeling process. These are 1) critical, 2), exploratory, and 3) logistical. Critical assumptions form the conceptual basis of the model. For example, in a simple two locus diploid model of natural selection the critical assumptions are whether or not both loci are on the same chromosome, affect fitness, and are polymorphic. The exploratory assumptions, that is assumptions that are important to vary and test but are not crucial to the set up of the model, include levels of dominance and epistasis and the rate of recombination between loci. Finally, logistical assumptions are those that reduce the complexity of the model to isolate the effects of critical and exploratory assumptions. Relaxing logistical assumptions should not qualitatively alter the results or at the very least, the effects of relaxing them should be well understood. In the two locus diploid model of natural selection logistical assumptions include such things as random mating, infinite population size, and non-overlapping generations.

After the model has been clearly defined, different approaches can be used to analyze the effects of the critical and exploratory assumptions. Analytical, numerical, and computer simulation techniques all offer the benefit that they can help untangle biological patterns by looking at natural processes in isolation and then extending the model to see how these processes interact. Each technique has its strengths and weaknesses with regards to isolating biological factors and interactions.

1.0.4 Value of Analytical Results

Some biological models are simple enough that analytical results are tractable and even elegant. That is not to say that the models themselves are so simple that they are not useful. On the contrary, we can often gain general biological insight from analytical results. For example, Day and Burns (2003) obtain mathematical expressions for the evolutionary stable clearance rate of hosts and the evolutionary stable virulence of the parasite infecting them. Without specifying parameter values, Day and Burns (2003) can understand how both evolutionarily stable strategies (ESS) change with parameters such as background mortality rate or the cost of immunological up-regulation to clear the parasite, and find explicit solutions for their co-ESS. Models whose analytical results are unwieldy and can only be determined numerically are still valuable albeit lack some generality. Even though their quantitative results may depend on the particular parameter values chosen, the qualitative trends provide insight into what parameters are important for the evolution of the system in question.

1.0.5 Value of Simulation Results

Sometimes the question being asked is too complicated to describe and analyze with a system of mathematical equations. This is often the case when random processes such as drift are part of the critical assumptions or the model incorporates many levels of biological complexity (e.g. population genetics models in an ecological context). Computer simulation models benefit from incorporating this biological realism and can test several aspects of verbal hypotheses. They still require the researcher to think carefully about the biology of the system being modeled and therefore serve the purpose of specifying assumptions that may have been overlooked in a verbal hypothesis. In specifying these assumptions, modelers carrying out computer simulations can use similar strategies to understand basic processes. For example, by setting certain parameters to extreme values (e.g. recombination goes to zero), we can get a better understanding of how the trait evolves in simplified situations before investigating more complex situations where it might otherwise be hard to untangle which parameters are most important.
Computer simulations offer another strategy to enhance our understanding of the underlying processes. With a little creativity, researchers can isolate interesting effects. For example, Soderberg and Berg (2007) isolated the effects of interference between mutations of different selective effects in the accumulation of deleterious mutations by Muller's ratchet. While computer simulations in and of themselves are a useful tool, they are also often used to test if the conclusions drawn from analytical models are robust to relaxing logistical assumptions made to make the mathematical model analytically tractable. These types of computer simulations usually incorporate many of the random processes we observe in nature.

1.0.6 Linking Theory and Empirical Results

In addition to theory testing verbal hypotheses borne out of empirical results and experiments testing general predictions made by theoretical models, theory and experiments also build on each other in other ways. If theoretical results are predicated on certain critical assumptions, empiricists can test if those assumptions are common in nature to determine if the model is biologically meaningful. Alternatively, experimental results that find different patterns than those predicted by formal analysis could draw attention to other assumptions that need to be specified in the model. It is important to note that such experiments are not tests of the model but indirect tests of its assumptions and its relevance in nature (Servedio et al., 2014). Experiments may also test secondary predictions generated by a model. In evolutionary biology, secondary predictions often include descriptions of expected ecological or epidemiological dynamics such as operational sex ratio in a sexually antagonistic coevolution model or equilibrium density of infected individuals in a susceptible infected compartmental model. As theory is informed and refined by empirical results, it should provide a lens through which we can interpret the biological complexity observed in nature.

In the following sections I review a brief history of the role of mathematical modeling in three sub-disciplines of evolutionary biology where theory has been essential to the advancement of their respective fields. I discuss key models that test verbal hypotheses and generate qualitative predictions, as well as examples of theory and empirical results building on one another.

1.0.7 Evolution of Sex

One of the best examples where models have been instrumental in advancing our understanding is in the study of the evolutionary enigma of sex. The evolution (and maintenance) of sex has puzzled scientists for decades because organisms that reproduce sexually suffer a two-fold cost compared to their asexually reproducing counterparts. Some of the earliest mathematical models of the evolution of sex tracked the dynamics of an allele that modified the rate of recombination (Kimura, 1956; Nei, 1967). These models investigated populations at equilibrium and found selection for reduced recombination (Kimura, 1956; Nei, 1967; Feldman, 1972; Feldman and Christiansen, 1980). This finding was inconsistent with the ubiquity of sex in nature, prompting theoreticians to investigate non-equilibrium dynamics such as populations experiencing mutation and directional selection. These later models found selection for recombination under directional selection if there was weak negative epistasis at the fitness locus (Charlesworth, 1993; Barton, 1995; Feldman and Christiansen, 1980; Kondrashov, 1984; Charlesworth, 1990; Otto and Feldman, 1997). While finding an evolutionary advantage for sex, the explanation would only hold if weak negative epistasis was common in nature. Empiricists set out to estimate epistasis
in laboratory and natural populations and found mixed results; epistasis could be positive, negative or zero (reviewed in Rice, 2002; de Visser, 2007). Without support for the key assumption that must hold for sex to be favoured in these modifier models, theoreticians had to refine their approach.

Recent models of the evolution of sex have incorporated more biological realism, accounting for variation in selection over time (Peters and Lively, 1999; Gandon and Otto, 2007) or space (Pylkov et al., 1998; Lenormand and Otto, 2000), variation in the rate of sex among individuals in a population (Redfield, 1988; Gessler and Xu, 2000; Hadany and Beker, 2003; Hadany and Otto, 2007), and finite population size (Otto and Barton, 1997; Roze, 2006; Otto and Barton, 2001; Barton and Otto, 2005; Iles et al., 2003; Keightley and Otto, 2006). The advantage for sex in finite populations is driven by recombination increasing the efficiency of selection in the face of mutation and drift (Hill and Robertson, 1966). The drift-based explanation for the evolution of sex has been supported by several experimental and comparative analyses (reviewed in Otto, 2009). Nevertheless, theoretical explanations for sex are constantly being refined to incorporate natural and empirical observations, aided by advancements in mathematical and computational techniques that build on previous models.

My second chapter is an extension of a model that explains why asex might be disadvantageous in finite populations. Using computer simulations I model Muller’s ratchet, a process whereby deleterious mutations accumulate in finite asexual populations through the process of genetic drift. I add a dimension of biological realism to the classic Muller’s ratchet model by assuming that the strength of selection against deleterious mutations can fluctuate over time.

1.0.8 Evolution of Virulence

Mathematical modeling has also played an important role in our understanding of the evolution of virulence. The idea that virulence could evolve was first noted by Pasteur in the 19th century who found that virulence of anthrax bacillus attenuated over serial transfers (as cited in Alizon et al., 2009). This and the fact that many infectious diseases of humans had low mortality rates (Smith, 1904) led to the hypothesis that parasites should evolve not to harm their hosts. The avirulence hypothesis was widely accepted despite evidence of highly virulent pathogens in nature (e.g. Ebola). It was not until the 1980s that Anderson and May (1982) proposed the tradeoff hypothesis (between virulence and recovery) to explain the evolution of intermediate virulence of myxomatosis infecting Australian rabbits. The tradeoff hypothesis, now most commonly modeled between virulence and transmission (instead of recovery), has led to an explosion of theoretical research on the evolution of virulence. Models that capture a range of host-parasite biology such as transmission mode (e.g. Lipsitch et al., 1996; Day, 2001; Ewald, 1983), multiple infections (e.g. Van Baalen and Sabelis, 1995; Frank, 1996; Alizon and van Baalen, 2008), host immunopathological responses (e.g. Day et al., 2007), heterogeneous host populations (e.g. Williams, 2012; Gandon, 2004) and coevolution between host and parasite (e.g. Day and Burns, 2003; Gandon et al., 2002) increased our understanding of what forces shape virulence evolution. A conceptual understanding of virulence evolution is particularly relevant because of the consequences of disease for human populations.

In the field of evolutionary epidemiology, the ability to make qualitative predictions from theoretical models can have important implications for public health and policy decisions. For example, Gandon et al. (2001) found that imperfect vaccines have the potential to select for higher virulence such that overall mortality is unaffected or increased with vaccination coverage. This prediction has recently been confirmed in chickens immunized against Marek’s disease virus with an imperfect vaccine (Read et al.,
New theoretical work suggests that imperfect vaccines could also play a role in virulence evolution of HIV/AIDS (Smith and Mideo, personal communication).

By testing the verbal hypothesis that overall transmission might be a function of virulence and susceptible host density, mathematical models explained the seemingly conflicting observations that some pathogens are highly virulent while others are relatively avirulent. Incorporating more biological realism into virulence evolution models has been especially important because of our interest in generating predictions that can inform disease management strategies. My third chapter extends previous models by investigating the evolution of virulence in heterogeneous host populations with different transmission patterns. I focus on differences in susceptibility and resistance to disease between males and females and model how virulence evolves in response to different contact rates between these host types. My model also explicitly studies the evolution of a parasite that can express different exploitation rates in each sex.

### 1.0.9 Sexual Conflict

The study of sexual conflict has also benefited greatly from mathematical models. When Parker (1979) first outlined the theory of sexual conflict he modeled a series of evolutionary ‘games’ where females suffered direct costs of both mating and resisting and males benefited from mating but suffered direct costs of persisting. The outcome of the game depended on the strength of selection against each sex and whether costs were paid for possessing sexually antagonistic traits or only exercising them, i.e. females suffered the cost of resistance only if they encountered a persistent male. These models and ideas were supported by empirical work on sexual conflict through the 1990s. Empiricists found ample evidence of males imposing mating costs on females (Partridge et al., 1986, 1987; Chapman et al., 1995; Rice, 1996).

It was not until 2001, however, that male persistence and female resistance were modeled as continuous traits in a quantitative genetics framework (Gavrilets et al., 2001). Theoretical papers that have modeled sexually antagonistic traits as quantitative have helped explain the variation of coevolutionary outcomes observed in nature (Gavrilets et al., 2001; Gavrilets and Hayashi, 2006; Rowe et al., 2005) and untangle the complicated selective forces acting on these traits. For example, Gavrilets et al. (2001) teases apart how the strength of sexual conflict relative to that of natural selection affects the evolutionary stable equilibrium.

More recently, Rankin et al. (2011) explicitly modeled the feedbacks between sexually antagonistic coevolution and population dynamics in an effort to explain the observation that female lizards in male-biased populations experienced higher mortality than those in female-biased populations (Le Galliard et al., 2005). Their finding that the evolution of male harassment can increase the ratio of males to females, which in turn increases the mortality rate of remaining females, highlights the importance of including population dynamics in models of sexual conflict in order to generate secondary predictions about population density on top of primary predictions about trait evolution.

The study of sexual conflict is an excellent example of empirical work informing theory and vice versa. Mathematical models have been key to understanding the various evolutionary forces involved in shaping sexually antagonistic traits and explaining observations about how ecology feeds back and affects evolution. My fourth chapter extends sexual conflict models by investigating the coevolution of sexually antagonistic host traits in the presence of a sexually transmitted disease. I incorporate ecological and epidemiological dynamics to fully elucidate the interaction between sexually antagonistic coevolution and virulence evolution.
1.0.10 Overview

In each of the fields reviewed (briefly) above, theoretical approaches have tested verbal hypotheses arising from scientific observation and made qualitative predictions about what factors affect evolutionary outcomes. Models within each field have increasingly incorporated more biological realism to explain a wider range of phenomena. My thesis will build on the conceptual foundations and mathematical tools developed by other theoretical evolutionary biologists in these fields. I add new dimensions of biological realism to general models in the fields of the evolution of sex (Chapter 2), the evolution of virulence (Chapter 3), and the coevolution of sexually antagonistic traits (Chapter 4).
Chapter 2

Temporal variation in selection accelerates mutational decay by Muller’s ratchet


A link to the published paper can be found at:
http://www.genetics.org/content/genetics/early/2012/04/25/genetics.112.140962.full.pdf
2.1 Abstract

Asexual species accumulate deleterious mutations through an irreversible process known as Muller’s ratchet. Attempts to quantify the rate of the ratchet have ignored the role of temporal environmental heterogeneity even though it is common in nature and has the potential to impact overall ratchet rate. Here we examine Muller’s ratchet in the context of conditional neutrality (i.e., mutations that are deleterious in some environmental conditions but neutral in others) as well as more subtle changes in the strength (but not sign) of selection. We find that temporal variation increases the rate of the ratchet (mutation accumulation) and the rate of fitness decline over that of populations experiencing constant selection of equivalent average strength. Temporal autocorrelation magnifies the effects of temporal heterogeneity and can allow the ratchet to operate at large population sizes in which it would be halted under constant selection. Classic studies of Muller’s ratchet show that the rate of fitness decline is maximized when selection is of a low but intermediate strength. This relationship changes quantitatively with all forms of temporal heterogeneity studied and changes qualitatively when there is temporal autocorrelation in selection. In particular, the rate of fitness decline can increase indefinitely with the strength of selection with some forms of temporal heterogeneity. Our finding that temporal autocorrelation in selection dramatically increases ratchet rate and rate of fitness decline may help to explain the paucity of asexual taxa.

2.2 Introduction

Asexual species are doomed to irreversibly accumulate deleterious mutations that can lead to a decline in overall fitness and eventually extinction (Gabriel et al., 1993; Lynch et al., 1993). In finite populations, the small number of individuals with the fewest deleterious mutations may fail to contribute mutation-free progeny to the next generation due to drift or mutation. The perpetual loss of the “least loaded class” by chance events, irreversible in the absence of recombination and back mutation, is a process known as Muller’s ratchet (Muller, 1964; Felsenstein, 1974). Quantifying the operation of the ratchet can help explain a variety of phenomena such as the extinction of asexual species (Loewe and Cutter, 2008; Loewe and Lamatsch, 2008), the degeneration of non-recombining DNA like that of human mitochondria (Loewe, 2006) or the Y chromosome (Gordo and Charlesworth, 2001; Engelstadter, 2008), and the evolutionary maintenance of sex (Howard and Lively, 1994; Gordo and Campos, 2008).

Haigh was the first to develop an explicit mathematical model of Muller’s ratchet (Haigh, 1978). Haigh’s model and subsequent variations aimed at estimating the rate of loss of the least loaded class make simplifying assumptions about the nature of selection acting on a population. Of particular relevance here, most studies have considered the environment to be unchanging such that the strength of selection acting on accumulating mutations does not vary with time (Haigh, 1978; Butcher, 1995; Gessler, 1995; Gordo and Charlesworth, 2000; Soderberg and Berg, 2007).

Besides being common and well documented in nature (see Siepielski et al., 2009, and references therein), the importance of considering temporal environmental variation is highlighted in a recent study on the budding yeast Saccharomyces cerevisae (Hillenmeyer et al., 2008). Previous work had suggested that approximately 60% of genes in the yeast genome had no detectable effect on growth rate under standard conditions (Winzeler et al., 1999). However, when growth rate was assayed in 1144 chemical environments, Hillenmeyer et al. (2008) found that 97% of gene deletions caused measurable growth
deficiencies in one or more environments. Though there are potential issues with respect to measurement
error, these results taken at face value suggest that deleterious mutations with little or no effect in one
environment could have stronger effects in a different environment. Environmental heterogeneity may
therefore lead to fluctuations in the strength of selection acting on deleterious mutations.

To understand the effects of temporal variation in selection, it is helpful to first consider the well-
studied case of the ratchet under constant selection. A major determinant of the ratchet rate \( R \) (defined
here as the rate of loss of the least loaded class) is the expected equilibrium size of the least loaded
class, \( n_0 = N - U/s \), where \( N \) is the population size, \( U \) is the genome-wide mutation rate, and \( s \) is the
strength of selection against deleterious mutations (Haigh 1978, but see Gessler 1995). After the loss
of the least loaded class, the next class becomes the most fit and its size approaches a value close to
\( n_0 \). The rest of the population re-establishes mutation-selection balance before the new least loaded
class is then lost (Stephan et al., 1993). For small \( n_0 \) the least loaded class is easily lost by genetic
drift and the ratchet rate is high. Thus, ratchet rate increases with mutation rate and decreases with
increasing population size and increasing selection strength (Haigh, 1978; Gordo et al., 2002; Soderberg
and Berg, 2007). Because \( n_0 \) is a function of \( s \), we expect the speed of the ratchet to vary if the strength
of selection varies over time. What will be its net rate, averaging over periods where selection is weak
and strong? Can we understand the average rate of the ratchet simply by using the average strength
of selection? In other classic population genetic contexts, the effects of temporal heterogeneity can be
captured simply by using the geometric mean fitnesses of different genotypes (Dempster, 1955; Nagylaki,
1975). Is the rate of the ratchet with temporal variation the same as that with constant selection of
equivalent strength (based on geometric mean fitness) or are other aspects of the temporal distribution
of selection important?

The effect of environmental heterogeneity on the ratchet rate may depend on the scale of temporal
variation in selection. In nature, changes in selection occur over days (e.g., Blanckenhorn et al., 1999),
seasons (e.g., Hendry et al., 2003), years (reviewed in Siepielski et al., 2009), and decades (Grant and
Grant, 2002). That is, selection may change rapidly or slowly across generations, depending on the life
span of the organism relative to the time scale of the environmental change. The scale of variation can
be captured by the degree of temporal autocorrelation in selection, which describes the dependency of
the selection coefficient in one generation on that of previous generations. Holding the total amount of
variation constant, a low degree of temporal autocorrelation represents a rapidly fluctuating environ-
ment while a high degree of temporal autocorrelation represents a slowly fluctuating one. The degree
of temporal autocorrelation is likely to be important in determining the overall ratchet rate because
mutations can accumulate rapidly if selection is weak for longer continuous time periods (i.e., a slowly
fluctuating environment).

As the ratchet “clicks” (i.e., as the least loaded class is lost), population mean fitness declines, which
can lead to mutational meltdown and ultimately the extinction of asexual populations (Gabriel et al.,
1993; Lynch et al., 1993). The rate of fitness decline depends on the rate of the ratchet and the strength
of selection. Under constant selection, the rate of fitness decline is maximized at intermediate \( s \) because
if \( s \) is very small the ratchet clicks quickly but with minimal fitness consequences, whereas if \( s \) is large
the ratchet clicks too slowly to cause substantial fitness loss (Felsenstein, 1974; Gabriel et al., 1993;
Butcher, 1995; Gordo and Campos, 2008). In fluctuating environments, the effects of the ratchet may
be more severe if mutations that rapidly accumulate during benign periods are strongly selected under
harsher environments.
Here we use simulations to investigate the effects of temporal heterogeneity in selection on the rate of the ratchet and the decline in fitness. We explore several forms of temporal heterogeneity and compare these results to those expected under constant selection of the same average strength. For the most part, especially with temporal autocorrelation, temporal variation gives different results than the constant selection case. Many of these differences can be interpreted from an understanding of the processes underlying the classic ratchet model. In many cases, we find that asexual populations and non-recombining genomes in heterogeneous environments may be speeding towards their eventual demise faster than classically predicted.

2.3 Methods

2.3.1 Overview

The model involves \( N \) asexual haploid individuals, each characterized by the number of deleterious mutations it carries. An individual’s prospective fitness is determined by the number of mutations it carries and the strength of selection acting that generation. An individual’s realized fitness is expected to be proportional to its prospective fitness but is subject to stochasticity (representing genetic drift). Below we describe how selection changes across generations and provide more details about the simulations.

2.3.2 Varying Selection

Unless otherwise stated, we assume selection within a generation is the same across all loci. To simulate temporal fluctuations in the environment we examined scenarios in which selection varied between \( s_{\text{min}} \) and \( s_{\text{max}} \) (i.e., \( s[t] \in \{s_{\text{min}}, s_{\text{max}}\} \)). Temporal autocorrelation in selection is quantified by the correlation in environmental state between consecutive generations, \( f \). Each generation, selection automatically remains the same as it was in the previous generation with probability \( f \). With probability \( 1 - f \) the selection coefficient is chosen at random, equaling \( s_{\text{max}} \) with probability \( \phi \) and \( s_{\text{min}} \) with probability \( 1 - \phi \). The value \( \phi \) therefore represents the expected average fraction of generations where selection is strong (\( s_{\text{max}} \)); we use \( \phi = 0.5 \) unless otherwise stated. Three levels of temporal autocorrelation were examined: (i) no temporal autocorrelation, \( f = 0 \), (ii) low temporal autocorrelation, \( f = 0.8 \), and (iii) high temporal autocorrelation, \( f = 0.95 \). Higher values of \( f \) result in longer runs of consecutive generations with the same selection strength. The no, low, and high temporal autocorrelation levels used here correspond to average run lengths of 2.0, 10.2, and 41.0 generations, respectively, when \( \phi = 0.5 \).

2.3.3 Simulation Methods

Simulations, written in C (available upon request), were used to model the accumulation of mutations in asexual haploid populations. Individuals were described by the number of mutations in their genome. The genome was initially assumed to be in mutation-selection balance and thus created from a Poisson distribution with mean \( \theta = U/\bar{s} \), where \( U \) is the genome-wide mutation rate and \( \bar{s} \) the expected geometric time-averaged selection coefficient. When \( s \) varies over time \( \bar{s} = 1 - (1 - s_{\text{max}})\phi(1 - s_{\text{min}})^{1-\phi} \). For each generation, an individual was randomly selected from the population and its fitness value was calculated. Fitness was assumed to be the multiplicative effect of all mutations in the genome, i.e., \( (1 - s[t])^k \), where \( s[t] \) is the selection coefficient in generation \( t \) and \( k \) is the number of mutations in the genome at that time.
The fitness value was compared with a uniform random variate and, if greater, the individual became a parent. The parent then produced a single clonal offspring with an additional $x$ new mutations added to its genome, where $x$ was a random number from a Poisson distribution with mean $U$. The process was repeated with replacement until $N$ new individuals were created. Simulations were carried out with a genome-wide mutation rate of $U = 0.5$ at three population sizes, $N = 500$, $N = 5000$, and $N = 50000$.

The simplest model we investigate is one of conditional neutrality: selection changes between $s_{\text{min}} = 0$ and $s_{\text{max}}$, with selection expected to be strong half of the time ($\phi = 0.5$). We then investigate two variations of this model. First, we consider other cases of conditional neutrality. To examine the effects of varying the frequency of selection, we vary $\phi$ between 0 and 1 but keep $\bar{s}$ fixed across the range of $\phi$ by setting $s_{\text{max}} = 1 - \left(\frac{1 - \bar{s}}{(1 - s_{\text{min}})^{1 - \phi}}\right)^{1/\phi}$. One end of this range thereby represents cases where selection is rare but strong ($\phi \to 0$) and the other end represents constant but comparatively mild selection ($\phi = 1$).

The second variation of the model we explore is quantitative variation in selection ($0 < s_{\text{min}} < s_{\text{max}}$) rather than conditional neutrality ($0 = s_{\text{min}} < s_{\text{max}}$). This could be explored in a number of ways but we chose to study the case where the strengths of selection across environments were proportional to one another, i.e., $s_{\text{min}} = a \times s_{\text{max}}$ where $0 < a < 1$.

For each simulation, the number of mutations in the least loaded class (the group of individuals with the fewest deleterious mutations) was tracked for 2000 generations. Ratchet rate for each treatment was determined from the average of 100 replicates. To measure the rate of fitness decline, cumulative geometric mean fitness (CGMF) of the least loaded class was calculated at each generation using $\log_{10}(\text{CGMF}) = \frac{1}{t} \sum_{i=1}^{t} W_i$, where $W_i$ is the fitness value of the least loaded class in generation $i$. The rate of decline was estimated as the slope of the regression of the log-transformed CGMF data for 100 replicates.

### 2.4 Results

We first outline some ‘benchmark’ predictions that are helpful in interpreting the simulation results. If the strength of selection varies temporally between two selection coefficients, $s_{\text{min}}$ and $s_{\text{max}}$ there are two alternative “null” predictions for the overall ratchet rate $R$ (Figure 2.1). The first is that the realized $\bar{R}$ is equal to the rate of the ratchet if selection were held constant at $\bar{s}$, the geometric time-average of $s_{\text{min}}$ and $s_{\text{max}}$. We refer to this as the “selection-average” prediction ($\bar{R}_{\bar{s}}$). Alternatively, the realized $R$ may simply equal the average of the ratchet rates at $s_{\text{min}}$ and $s_{\text{max}}$, i.e., the “rate-average”, $\bar{R} = \phi R_{s_{\text{max}}} + (1 - \phi) R_{s_{\text{min}}}$, where $R_s$ is the rate under constant selection pressure $s$ and $\phi$ is the fraction of generations where $s = s_{\text{max}}$. It is always the case that $R_s < \bar{R}$ because of the non-linear relationship between $s$ and $R_s$ (Figure 2.1). The rate-average and selection-average predictions represent an upper and lower bound, respectively, on overall ratchet rate for populations experiencing temporally fluctuating selection (Figure 2.1). Simulation runs were compared to the selection-average and rate-average predictions computed from simulation results of constant selection at $s_{\text{min}}$, $s_{\text{max}}$, and $\bar{s}$.

#### 2.4.1 Conditional Neutrality

We begin by considering the case of conditional neutrality ($0 = s_{\text{min}} < s_{\text{max}}$). With temporal variation in selection, the realized ratchet rate falls between the values predicted by $R_s$ and $\bar{R}$. The realized ratchet
Figure 2.1: Ratchet rate as a function of selection strength. The solid curve shows a qualitative depiction of the rate of the ratchet as a function of \( s \) assuming no temporal variation in selection. If selection varies temporally such that \( s = s_{\text{max}} \) for a fraction \( \phi \) of generations and \( s = s_{\text{min}} \) for the remainder \((1 - \phi)\), overall ratchet rate might be predicted by the rate-average, \( \bar{R} = \phi R_{s_{\text{max}}} + (1 - \phi) R_{s_{\text{min}}} \), or the selection-average \( (R_s) \), the rate of the ratchet if selection were held constant at \( \bar{s} \), the geometric time-average of \( s_{\text{min}} \) and \( s_{\text{max}} \).

The rate is close to the selection-average prediction when there is temporal variation (but no autocorrelation) in selection, and increases towards the rate-average prediction with increasing temporal autocorrelation (Figure 2.2A-C).

To understand these results, it is useful to think about the underlying distribution of mutations in the population. The shape of this distribution determines the number of individuals in the least loaded class and, thus, plays a key role in determining ratchet rate. Recall that the loss of the least loaded class is followed by the re-establishment of mutation-selection balance (Stephan et al., 1993). The population must transition between the two mutation-selection balance equilibrium distributions (that of \( s_{\text{min}} \) and \( s_{\text{max}} \)) when the strength of selection changes. (For \( s_{\text{min}} = 0 \), the distribution is not shaped by mutation-selection balance but rather mutation-drift balance. The mean of this distribution increases at the mutation rate but it maintains its characteristic shape (Fox and Wolf, 2006)). Consider the case where selection rapidly oscillates between \( s_{\text{min}} \) and \( s_{\text{max}} \). It is likely that the mutational distribution never obtains the shape predicted by either selection coefficient. Because selection changes rapidly, we can think of individual mutations experiencing the average selection so that the mutational distribution should be that expected under \( \bar{s} \) and the ratchet proceeds at the corresponding rate, \( R \approx R_{\bar{s}} \). At the other extreme, we can consider the limit of very strong temporal autocorrelation in which the population experiences one long period with \( s = s_{\text{min}} \), followed by another long period with \( s = s_{\text{max}} \). Relatively little time is spent transitioning between the distribution expected under \( s_{\text{min}} \) and that expected under \( s_{\text{max}} \). Mutations accumulate at the rate \( R_{s_{\text{min}}} \) during the first period and at \( R_{s_{\text{max}}} \) during the second period so the average rate is equal to the rate-average, \( R \approx \bar{R} \). At more moderate levels of temporal
autocorrelation, such as those considered here, it is reasonable to assume that a proportionally greater fraction of time is spent transitioning between the respective equilibrium distributions. Although it is difficult to find analytical approximations for the ratchet rate during these transition periods, the logic outlined above provides a qualitative understanding of why the realized ratchet rate falls between the boundary conditions set by $R_s$ and $\bar{R}$.

Even when there is no temporal autocorrelation, the realized ratchet rate is close to, but greater than, the selection-average prediction $R_s$. In this case, the absolute difference in rates is small such that the two values appear almost indistinguishable on the scale shown in Figure 2, but the proportional differences can be reasonably large as $R_s$ approaches zero. For example, with $N = 5000$ and $\bar{s} = 0.1168$, $R_s = 6.25 \times 10^{-4}$, whereas the rate with temporal heterogeneity with no autocorrelation is $R = 6.51 \times 10^{-3}$, meaning that the ratchet rate is 10.41 times faster in the heterogeneous case.

Within each level of autocorrelation, the ratchet rate decreases with increasing selection strength before reaching a plateau at large $\bar{s}$ (Figure 2.2A-C). Under constant selection, this plateau always occurs at a rate of zero ($R_s = 0$). With temporal variation the plateau can occur at considerably higher rates, especially when there is temporal autocorrelation in selection. The non-zero rate occurs because we are considering conditionally neutral mutations so that, during periods when selection is relaxed, mutations can accumulate at the neutral rate regardless of how strong selection is during the periods when $s = s_{max}$. The overall rate of fitness decline, however, may not level off at large $\bar{s}$, depending on the type of temporal heterogeneity (Figure 2.2D-F).

As expected from past studies (Gabriel et al., 1993; Butcher, 1995; Gordo and Campos, 2008) under constant selection, the rate of decline of fitness, measured here as log(CGMF), is greatest at intermediate values of $\bar{s}$ and is approximately zero for very strong and very weak selection (Figure 2.2D-F). Qualitatively similar results are observed for the case of temporal heterogeneity when there is no autocorrelation in selection. In contrast, under temporal autocorrelation, the rate of fitness decline continues to increase with the strength of selection (Figure 2.2D-F) even though ratchet rate plateaus (Figures 2.2A-C), as described above. Mutations are accumulating at the same rate across the plateau in Figures 2.2A-C but their effect on fitness when selection is operating increases in severity with $s_{max}$, thus resulting in an increased rate of fitness decline.

Above we have described the effects of temporal heterogeneity in absolute terms. It is also worth considering these effects as the proportional change from the traditional scenario of constant selection of equivalent average strength. Relative to the ratchet with constant selection, the effects of temporal heterogeneity on ratchet rate and the decline in fitness increased with the strength of selection (Figure 2.3), reaching infinity as the ratchet rate grinds to a halt with increased $s$ under constant selection. Importantly, these effects of temporal heterogeneity are more dramatic in large populations where the relative increase in ratchet rate and fitness decline over that of $\bar{s}$ reaches infinity at lower selection coefficients (Figure 2.3).

### 2.4.2 Varying the Frequency of Selection

For the conditionally neutral case, we varied $\phi$, the frequency of generations in which mutations were non-neutral, but adjusted $s_{max}$ accordingly to hold average selection constant at $\bar{s} = 0.0513$ (Figure 2.4). Consequently, in the context of Figure 2.4, temporal heterogeneity is maximized at low values of $\phi$ and minimized as $\phi$ approaches 1. Low values of $\phi$ correspond to situations where mutations are usually neutral but, in those generations where mutations are selected against, selection is strong (e.g.,
Figure 2.2: Effects of temporal heterogeneity on ratchet rate and fitness decline. (A-C) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE for a population of (A) 500, (B) 5 000, and (C) 50 000. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average ($R_{\bar{s}}$) and rate-average ($\bar{R}$) predictions. (D-F) Mean rate of fitness decline +/- SE for the least loaded class in a population of (D) 500, (E) 5 000, and (F) 50 000. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average scenario. In most cases SE bars are too small to see.
Chapter 2. Temporal variation and the ratchet

Figure 2.3: Effect of temporal heterogeneity relative to constant selection of equivalent strength. Relative increase in (A) ratchet rate and (B) rate of fitness decline over that of populations experiencing the corresponding constant time-averaged selection coefficient. Relative increases are infinite for values of \( \bar{s} \) beyond those shown because the ratchet rate is zero under constant selection. Data shown are for the high temporal autocorrelation selection regime only. For clarity, outlined regions of panels (A) and (B) are shown magnified in panels (C) and (D), respectively.

during extreme weather events). In contrast, high values of \( \phi \) correspond to situations where mutations are selected in most generations at a more moderate level. For \( \phi = 1 \), mutations experience constant selection with \( s = 0.0513 \) every generation. As shown in Figure 2.4, ratchet rate and the rate of fitness decline decrease with increasing \( \phi \). In other words, the effects of the ratchet decline as the degree of temporal heterogeneity declines. Autocorrelation increases the effects of the ratchet for all values of \( \phi \) but is particularly dramatic when temporal variation is high (i.e., \( \phi \) is low). This occurs because when selection is rare (low \( \phi \)), there are reasonably long periods where \( s = s_{\text{min}} = 0 \) (even without temporal autocorrelation) during which mutations can accumulate. Adding temporal autocorrelation exaggerates this effect.

2.4.3 Quantitative Variation in Selection

A less extreme form of heterogeneity than conditional neutrality occurs when there is quantitative variation in selection (\( 0 < s_{\text{min}} < s_{\text{max}} \)). Relative to the case of conditional neutrality with equivalent \( \bar{s} \), we expect quantitative variation in selection to be more like constant selection for the simple reason that there is a smaller difference in selection strength between “harsh” and “benign” environments
Figure 2.4: Effects of varying the frequency of selection on ratchet rate and fitness decline. (A) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE and (B) mean rate of fitness decline of the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{min} = 0$ and $s_{max}$ such that the geometric time-averaged selection coefficient $\bar{s} = 0.0513$ for all values of $\phi$. When $\phi = 1$, $s_{max} = \bar{s}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high temporal autocorrelation). In most cases SE bars are too small to see.

(i.e., less heterogeneity). For comparison with results shown in Figure 2.2C, we use $\phi = 0.5$ and $N = 50000$. When selection varies quantitatively, the patterns we observed for conditional neutrality (Figure 2.2C) weaken as the difference between $s_{min}$ and $s_{max}$ declines, as illustrated in Figure 2.5A-C showing $s_{min} = 0.01 * s_{max}$, $0.05 * s_{max}$, and $0.25 * s_{max}$, respectively. Nonetheless, it is clear that even for this more subtle form of heterogeneity, the effects of Muller’s ratchet are more severe than expected under constant selection of equivalent strength.

There is an important qualitative difference in the results between conditional neutrality and quantitative variation as we have modeled it. Unlike with conditional neutrality (Figure 2.2), with quantitative variation in selection the ratchet rate does not plateau above zero as $\bar{s}$ increases, but rather continues decreasing (Figure 2.5A-C). This occurs because both $s_{min}$ and $s_{max}$ increase with $\bar{s}$ in the model we have used for quantitative variation in selection (in which $s_{min}$ is proportional to $s_{max}$); consequently, mutations accumulate at a slower rate as $\bar{s}$ increases. The ratchet can be brought to a complete halt if $s_{min}$ is sufficiently large (as illustrated in Figure 2.5C). As a result of these effects on the ratchet rate, the decline in fitness may increase indefinitely with $\bar{s}$ (Figure 2.5D) or may be maximized at an intermediate $\bar{s}$ (Figure 2.5F) depending on whether $s_{min}$ becomes sufficiently large relative to $N$ and $U$ to halt the ratchet. If we had modeled quantitative variation by fixing $s_{min}$ (e.g., $s_{min} = 0.001$) then we could have obtained results for these population sizes more similar to the conditional neutrality case in which the ratchet does not halt with increasing $\bar{s}$.

With conditional neutrality, the effects of autocorrelated temporal heterogeneity are exaggerated in larger populations (Figures 2.2-2.3). This is because the effect of population size on ratchet rate is different for constant selection and conditional neutrality. With constant selection, the ratchet slows as population size increases. However, with autocorrelated temporal heterogeneity, the reduction in net ratchet rate with increased $N$ is lessened because the rate of accumulation during periods when
Figure 2.5: Effects of temporal heterogeneity with quantitative variation in selection on ratchet rate and fitness decline. (A-C) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE for a population of 50000 experiencing selection varying between $s_{\text{max}}$ and (A) $s_{\text{min}} = 0.01* s_{\text{max}}$, (B) $s_{\text{min}} = 0.05* s_{\text{max}}$, and (C) $s_{\text{min}} = 0.25* s_{\text{max}}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average ($R_{\bar{s}}$) and rate average ($\overline{R}$) predictions. (D-F) Mean rate of fitness decline of the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{\text{max}}$ and (D) $s_{\text{min}} = 0.01* s_{\text{max}}$, (E) $s_{\text{min}} = 0.05* s_{\text{max}}$, and (F) $s_{\text{min}} = 0.25* s_{\text{max}}$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high autocorrelation) as well as for the constant selection-average scenario. In most cases SE bars are too small to see.

Selection is absent ($s = s_{\text{min}} = 0$) is unaffected by population size. This is not the case with quantitative variation in selection ($s_{\text{min}} > 0$), as the ratchet rate will always decline for any non-zero $s$ as $N$ increases.
Nonetheless, we still observe considerable differences between autocorrelated temporal heterogeneity and constant selection at large population sizes provided $s_{\text{min}}$ and $s_{\text{max}}$ are not too similar (Figure 2.5).

2.4.4 Relaxing Genome Assumptions

For simplicity, we assumed that selection acts uniformly across the genome, i.e., all genes are equally affected by the changing environment. In reality, fluctuations in the environment are more likely to induce strong selection on only a fraction of the genes in the genome. Thus, we also examined a model in which a fraction, $F$, of accumulating deleterious mutations experienced selection fluctuating between $s_{\text{min}}$ and $s_{\text{max}}$, while the remaining fraction $(1 - F)$ experienced a constant selection coefficient $s = \bar{s}$ (Figure 2.6). The former category of mutations can be thought of as being under selection only in particular circumstances, e.g., years with extremely cold winters. The simulation model is similar to the one for the uniform genome except that members of the least loaded class can have differing numbers of mutations in each genome component. Consequently, not every member of the class has the same fitness value and the fittest member can change from generation to generation (regardless of whether or not there is mutation accumulation) if the strength of selection against the fluctuating genome component changes.

![Figure 2.6](image-url)

Figure 2.6: Effects of varying the fraction of the genome experiencing fluctuating selection on ratchet rate and fitness decline. (A) Average per generation rate of loss of the least loaded class (ratchet rate) +/- SE and (B) mean rate of fitness decline of the fittest individual in the least loaded class +/- SE for a population of 50000 experiencing selection varying between $s_{\text{min}} = 0$ and $s_{\text{max}} = 0.1$ on a fraction, $F$, of its genome. The remainder of the genome experiences constant selection $s = 0.0513$ such that the geometric time-averaged selection coefficient across the genome is also $\bar{s} = 0.0513$. Simulation results are shown for three types of temporal heterogeneity (no, low, and high temporal autocorrelation) with predictions for overall ratchet rate based on $R = F \times R_{\text{fluctuating}} + (1 - F) \times R_{\text{constant}}$ shown by the corresponding dashed line. Predictions for rate of fitness decline are calculated analogously. In most cases SE bars are too small to see.

Results were qualitatively similar to those where selection is uniform across the genome. Ratchet rate and fitness decline increased with the fraction of the genome under fluctuating selection (Figure 2.6). More precisely, ratchet rate can be accurately predicted ($r^2 = 0.996$) by calculating the weighted
average $R = F \times R_{fluctuating} + (1 - F) \times R_{constant}$, where $R_{fluctuating}$ is the rate if 100% of the genome experiences fluctuating selection and $R_{constant}$ is the rate if 100% of the genome experiences constant selection. Fitness decline can be predicted analogously ($r^2 = 0.994$).

We also considered situations where different components of the genome experienced temporal variation in selection independently of one another or in a negatively correlated fashion (out of phase) and found qualitatively similar results (not shown) as when selection fluctuates uniformly across the genome. In sum, there is no reason to believe that the types of effects reported here do not apply to more realistic scenarios when scaled appropriately for the amount of variation and temporal autocorrelation.

2.5 Discussion

In principle, the accumulation of mutations through Muller’s ratchet can lead to the decay of non-recombining chromosomes and the extinction of asexual species. Estimating the ratchet rate and the rate of fitness decline can provide some insight into how fast asexual populations are speeding towards their demise. The accuracy of these estimates, however, depends on simplifying assumptions that are not always realistic about the nature of mutation and selection. Largely overlooked in the Muller’s ratchet literature, temporal heterogeneity in selection is common in nature and has the potential to cause serious consequences for non-recombining genomes. Indeed, we found that temporal variation in selection, especially when there is some autocorrelation, dramatically increases the ratchet rate and fitness decline over that of populations experiencing constant selection of equivalent average strength.

Ratchet rate under temporal variation was bounded by the selection-average and rate-average predictions ($\bar{R}_s$ and $\bar{R}_r$, respectively), increasing towards the latter when temporal autocorrelation was stronger (Figure 2.2A-C, Figure 2.5A-C). We observed reasonably dramatic effects of temporal heterogeneity even without long periods of time between environmental changes; in Figures 2.2 and 2.5, “low” and “high” levels of autocorrelation correspond to average runs of consecutive generations with the same selection strength of 10.2 and 41.0 generations, respectively. Thus, with relatively little temporal autocorrelation, the corresponding increases in ratchet rate can have severe fitness consequences for asexual populations.

In the classic ratchet model, the rate of fitness decline peaks at intermediate values of $s$ and decreases as increasing selection strength slows the rate of mutation accumulation (Gabriel et al., 1993; Butcher, 1995; Gordo and Campos, 2008). While ratchet rate slows down with increasing average selection strength (Figure 2.2A-C, Figure 2.5A-C), fitness decline under temporal autocorrelation in selection does not always slow down with increasing $\bar{s}$ (Figure 2.2D-F, Figure 2.5D-E). In fact, fitness decline can increase indefinitely under conditional neutrality (Figure 2.2D-F). Conditionally neutral mutations can accumulate when selection is relaxed, regardless of their fitness effects during those periods when mutations are subject to selection. Consequently, fitness decline continues increasing with $s_{\text{max}}$ (Figure 2.2D-F).

Increases in ratchet rate and fitness decline with temporal heterogeneity are observed across a range of population sizes. Though the consequences of Muller’s ratchet are often considered to be pertinent only to small populations, temporal heterogeneity in selection, particularly when there is some autocorrelation, amplifies the effects of the ratchet in larger populations (see Figures 2.2-2.3). Most notably, under conditional neutrality, temporal autocorrelation allows the ratchet to operate at any finite size because the least loaded class is lost deterministically through mutation when selection is “off”. Thus, large populations of non-recombining genomes may be declining in fitness faster than previously thought.
Elevated rates of fitness decline can have dire consequences for asexual populations by increasing the advantage of sex or the probability of extinction. Gordo and Campos (2008) investigated the spread of a recombination modifier allele through asexual populations accumulating unconditionally deleterious mutations by Muller’s ratchet. They found that the probability of fixation of the modifier allele was maximized at intermediate values of $s$ where mean fitness decline was maximized in the corresponding asexual population. Following this logic, we might expect temporal autocorrelation in selection to increase the advantage of sex because we found that rates of fitness decline for asexuals are increased by temporal autocorrelation. However, in the case of conditional neutrality, there will be no advantage to sex during those generations when selection is “off”. We speculate that the critical issue is the average reduction in the genetic variance in fitness due to linkage disequilibrium. The reduction in variance will be zero during the neutral phases (because both the expected and realized variance in fitness will be zero) but the variance in fitness is likely to be strongly reduced during the selective phases because of negative disequilibrium that arises from the interaction of selection and drift acting on the mutations accumulated during the neutral phases. In future work, we will explicitly examine the consequences of temporal variation on modifiers of recombination.

Given the prevalence of temporal heterogeneity in the wild (see Siepielski et al., 2009, and references therein), future studies should incorporate fluctuating selection into estimates of mean extinction times. Furthermore, these estimates should also consider the mutational meltdown in asexual populations (Lynch et al., 1993). Briefly, the loss of fitness due to accumulating deleterious mutations leads to an eventual reduction in population size, which further increases the chance of mutation accumulation. This positive feedback loop accelerates asexual populations towards extinction (Lynch et al., 1993). Based on our results, temporal heterogeneity, and in particular temporal autocorrelation in selection, would reduce the time to mutational meltdown in small and large populations.

The role of varying selection in mutational meltdowns has been studied in one particular context. Specifically, Howard and Lively (1994), and others since (Howard and Lively, 1998; Park et al., 2010), investigated the competitive ability of sexual versus asexual populations of hosts in the presence of coevolving parasites and deleterious mutations. By focusing on the asexuals, we can compare their model with ours. Howard and Lively (1994) assume most of the genome experiences constant selection. However, a small number of loci (those involved in parasite resistance) experience a very strong form of temporally fluctuating selection in which alleles change from being selectively favored to disfavored in repeated cycles. Because selection on these loci fluctuates in sign and can be much stronger than on ‘regular’ genes, mutations can rapidly accumulate by Muller’s ratchet in susceptible genotypes when they are driven to low numbers by parasites. Later in the coevolutionary cycle, when those previously susceptible genotypes become resistant to common parasites, genotypes loaded with numerous unconditionally deleterious alleles of small effect may be favored over genomes with fewer deleterious alleles because of parasite-mediated selection. Thus, the strong and fluctuating selection on resistance loci can drive the accumulation of deleterious alleles in the rest of genome. In our model, when selection is weak or “off” deleterious alleles accumulate by mutation pressure rather than because they are linked to genes favored in the changed environment. Had we allowed for reversals in the sign of selection, we would expect even more dramatic effects of temporal heterogeneity.

While environmental heterogeneity is common, it remains a major empirical challenge to determine to what extent selection varies substantially in strength or direction across environments. Although changes in direction may be limited to a small subset of genes, changes in magnitude are likely to
be quite common (Kishony and Leibler, 2003; Jasnos et al., 2008; Wang et al., 2009). Environmental variation may therefore have damaging effects on asexual populations beyond those expected under constant selection.

Acknowledgements

S. Otto and M. Whitlock provided helpful discussion. This work was supported by the Natural Sciences and Engineering Research Council of Canada (Discovery Grant to AFA; CGS-M to AMW).
Chapter 3

Virulence evolution of a parasite infecting male and female hosts
3.1 Abstract

Parasites experience different tradeoffs between transmission and virulence in male and female hosts if the sexes vary in life history or disease-related traits. We determine the evolutionarily stable levels of exploitation by pathogens under two scenarios: an unconstrained pathogen that expresses different exploitation rates within each host type as well as a pathogen constrained to express the same exploitation rate in each sex. We show that an unconstrained horizontally-transmitted parasite evolves to express the same sex-specific exploitation rate within each sex as it would in a host population composed entirely of hosts with that sex’s resistance and intrinsic death rate. In contrast, the ESS exploitation rate of a constrained pathogen is affected by sex-differences in susceptibility and non-random contact patterns between host types that differ in resistance. As the amount of within-sex transmission increases, the ESS shifts closer to the optimum trait value in the more susceptible sex. Allowing for some degree of vertical transmission, the exploitation rate expressed in females (but not males) changes with contact pattern even in unconstrained pathogens. Differences in contact pattern and susceptibility play an important role in determining the ESS exploitation rate by shifting the reproductive value of each host type.
3.2 Introduction

A pathogen’s fitness is determined by its ability to transmit to new hosts. Parasites with higher proliferation rates inside a host release more propagules for transmission but consume more host resources at the expense of increased disease-induced mortality (virulence; Anderson and May, 1982; Ewald, 1983; Alizon et al., 2009). The tradeoff between host mortality and transmission success affects parasite fitness: too low of an exploitation rate limits the number of new infections, but too high and the parasite kills its host before it has the opportunity for transmission. Selection therefore favours intermediate exploitation rates in classic one-host one-parasite models (May and Anderson, 1990; Frank, 1996).

Pathogens infecting more than one type of host face additional tradeoffs. The ability of a parasite to proliferate inside a host is affected by host immunity and available host resources, which can vary with condition, age, or sex (Day et al., 1991; Gaillard and Spinedi, 1998; Rice et al., 2000; Shankar, 2000; Bhaskaram, 2002; Field et al., 2002; Felix et al., 2012; Cousineau and Alizon, 2014, Table 1). Because realized virulence and transmission rates are the result of an interaction between host and parasite traits, a multihost parasite experiences a different tradeoff between host mortality and transmission success in each host type. The exploitation rate that maximizes parasite fitness in one host type may not be optimal in other host types. A pathogen in a heterogeneous host population can therefore adopt one of three strategies: 1) a single exploitation strategy, 2) alternative exploitation strategies maintained as a polymorphism, or 3) facultative expression of different exploitation strategies (Pfennig, 2001).

There are several general multihost parasite models that describe the evolution of a single exploitation rate (Gandon, 2004; Regoes et al., 2000; Osnas and Dobson, 2011; Williams, 2012; Cousineau and Alizon, 2014). These multihost models investigate the evolution of virulence using dynamical equations to describe the change in the number of susceptible and infected individuals of each host type over time. Gandon (2004) and Williams (2012) both analyzed multihost models where transmission and virulence were considered increasing functions of parasite exploitation rate and exploitation was scaled to capture different transmission and disease-induced mortality rates in each host. The evolutionarily stable level of exploitation depended on the relative abundance of host types and the ability of each type to transmit the infection. Gandon (2004) numerically investigated differential transmission between and within host types. At high within-type transmission rates, Gandon (2004) found evolutionary branching in parasite virulence, leading to the coexistence of different exploitation rates in the population. Williams (2012) developed a novel analytical way of thinking about multihost parasite evolution that also accounted for differences in susceptibility to infection (i.e. the likelihood that a given host type contracts the disease given contact with an infected individual). His model makes it easy to understand how between host interactions affect the importance of each host type to parasite fitness. The evolutionarily stable exploitation rate is a compromise between the ideal rates within each host type such that some host types are overexploited while others are underexploited.

If host types are affected differently by the same exploitation rate, differential disease-induced mortality across hosts could indicate that a parasite is constrained to express one trait. For example, Krist et al. (2004) found higher mortality rates in resource-limited snails infected with the trematode parasite Microphallus sp. because the parasite did not adjust its development rate to optimally exploit low condition hosts. Similarly, a single exploitation strategy can have different effects in males and females because of differences in life history traits and immunocompetence (Cousineau and Alizon, 2014). Differential investment in reproduction in invertebrates can cause parasitized females to experience higher disease-induced mortality than males. For example, female damselflies infected by water mites suffered
reduced mass at emergence and consequently decreased survivorship compared to males (Braune and Rolff, 2001). We can not be certain that the observed differences in virulence between host types in both of these examples is entirely due to inflexible parasite strategies. Because males and females and low and high condition hosts can also differ in immunocompetence, the host type with the higher survivorship could actually be suppressing an elevated type-specific parasite growth rate as opposed to experiencing the same exploitation rate as an overexploited host.

There are few documented examples of parasites facultatively expressing different strategies in different host types. Jokela et al. (1999) infected snails of high and low condition with two types of parasites independently, *Microphallus* sp. and *Notocotylus gippyensis*. The authors observed higher mortality rates in parasitized snails from the no-food treatment, compared to the high food treatment, when infected with *N. gippyensis*. Food treatment did not affect disease-induced mortality when snails were infected with *Microphallus* indicating that the parasite adjusted its exploitation rate to host condition in order to ensure transmission. In another example, the *Ascoregarina culicis* parasite of mosquitoes (*Aedes aegypti*) has sex-specific strategies for releasing its infectious stages, called oocysts, to maximize overall transmission (Fellous and Koella, 2009). Even though there are more *A. culicis* oocysts in female mosquitoes than in males at the pupal stage, a higher proportion of oocysts are released during male emergence. This maximizes transmission from male mosquitoes, while transmission from female mosquitoes depends heavily on oocysts released later during female oviposition when the mosquito will spread infectious stages to her offspring. Remember that when it comes to mosquitoes, “we can’t go to bed until they’re all dead”. From these examples it is apparent that evolving different strategies in heterogeneous host types could be evolutionarily advantageous. Untangling how the presence of other host types affects the strategies expressed requires further investigation.

Facultative expression of different exploitation strategies in each host type could evolve such that the parasite optimally exploits each host type or such that the parasite still under- or overexploits some host types. The optimal exploitation strategy in a host type is governed strictly by the within host tradeoffs a parasite faces between transmission and virulence. However, the presence of other host types could feedback and affect selection on transmission such that between host interactions favour type-specific exploitation strategies that are not the same as they would be in a homogeneous host population composed entirely of one host type. For example, it may be beneficial to overexploit some host types if it increases the probability of getting into a highly transmissive host type. The circumstances under which between host dynamics might feedback and affect facultative parasite expression are unknown. Modelling the expression of type-specific exploitation strategies could help us understand when epidemiological feedbacks are important and make predictions to be tested experimentally.

Between-host disease dynamics could be particularly important in determining the evolutionarily stable strategy when there is asymmetrical pathogen transmission. Gandon (2004) and Cousineau and Alizon (2014) both accounted for nonrandom contact patterns by symmetrically varying the amount of within and between host type transmission. An example of symmetrical contact patterns could occur in a monogamous mating system where each individual interacts primarily with a member of the opposite sex more than with members of the same sex. Alternatively, asymmetrical contact patterns could arise when males that compete for females have high within type transmission (*e.g.* if they have direct contact with one another while fighting for access to females), while female-to-female transmission rates are comparatively lower. In this scenario, males can be thought of as more valuable hosts to a pathogen than females. Varying the transmission route altogether, females may be more valuable hosts if there
is vertical transmission in addition to horizontal transmission of the disease. Because asymmetrical transmission could change a pathogen’s relative fitness out of each host type, we might expect different evolutionary outcomes for a constrained parasite than observed in previous multihost models.

Our model builds on that of Williams (2012), incorporating heterogeneous virulence responses in the form of resistance, and adding nonrandom transmission between and among host types. This framework allows us to tease apart the role of resistance, susceptibility, and transmission patterns in determining the evolutionarily stable parasite strategy and understand how these disease-related traits affect each other’s relative importance. We also explicitly model facultative expression of exploitation rates by assuming two independent pathogen traits, exploitation rate in each host type.

Overall, we find that when there are differences in resistance between host types, differential susceptibility to disease can change evolutionary outcomes for a parasite constrained to express a single exploitation strategy, especially at high within-host type transmission rates. In comparison, an unconstrained parasite evolves to express the same exploitation rate in each host type as it would in a homogeneous population of that host type, regardless of differences in susceptibility or contact pattern. Treating the two host types as males and females and allowing for some vertical transmission, an unconstrained parasite will evolve an evolutionarily stable exploitation strategy in females that changes with contact pattern to take advantage of the alternative transmission route from mother to offspring. Our results show that transmission patterns and differential susceptibility can have important effects on virulence evolution in heterogeneous host populations.

### 3.3 Model Setup

We use a system of differential equations to describe a susceptible-infected compartmental model with two host types, which we will refer to as males and females throughout. Apart from the sections incorporating reproductive input and vertical transmission, the model can be applied to other kinds of two host-type systems where individuals do not transition between types. In the general model we assume new uninfected individuals enter the population at a constant immigration rate, θ, a fraction σ of which are males and the remaining (1 − σ) are females. Uninfected individuals of sex i become infected with the disease at the rate $\eta_i S_i (p_{ii} \beta_i I_i + p_{ji} \beta_j I_j)$ where $\eta_i$ is susceptibility, the sex-specific probability of contracting the disease given contact with an infected individual, and $p_{ii} \beta_i I_i + p_{ji} \beta_j I_j$ is the force of infection on sex i. The force of infection is the per capita rate at which type i hosts become infected and depends on the number of infected individuals of each sex ($I_i$ and $I_j$) and the parasite’s transmission rate out of each ($\beta$), modified by the probability of encounter (or transmission opportunity) between infected type j and uninfected type i individuals ($p_{ji}$). Finally, uninfected individuals of type i die at the natural host-mortality rate, $\mu_i$, and infected individuals suffer from additional disease-induced mortality (virulence, $\alpha_i$). Transmission rates and virulence both depend on the parasite’s intrinsic exploitation rate, $\epsilon_i$, inside its host. A host type with some level of resistance against the disease, $\rho_i$, can reduce the parasite’s effective exploitation rate, consequently reducing disease-induced mortality and transmission rates (see equation [3.2]). The disease dynamics are captured by the following set of differential equations.
Table 3.1: List of parameters and their definitions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_i )</td>
<td>natural host mortality rate of host type ( i )</td>
</tr>
<tr>
<td>( \eta_i )</td>
<td>susceptibility of host type ( i ) given contact with an infected individual</td>
</tr>
<tr>
<td>( \rho_i )</td>
<td>resistance, reduction in disease-induced mortality in host type ( i )</td>
</tr>
<tr>
<td>( \alpha_i[\epsilon_i] )</td>
<td>disease-induced mortality rate (virulence) of host type ( i )</td>
</tr>
<tr>
<td>( \beta_i[\alpha_i] )</td>
<td>transmission rate out of host type ( i )</td>
</tr>
<tr>
<td>( \hat{S}_i, \hat{I}_i )</td>
<td>equilibrium number of susceptible and infected individuals of host type ( i )</td>
</tr>
<tr>
<td>( p_{ij} )</td>
<td>probability of encounter between infected host type ( i ) and uninfected host type ( j )</td>
</tr>
<tr>
<td>( h_i[\hat{I}_i, \hat{I}_j] )</td>
<td>force of infection on host type ( i ) at equilibrium, ( h_i = p_{ii}\beta_i\hat{I}<em>i + p</em>{ji}\beta_j\hat{I}_j )</td>
</tr>
<tr>
<td>( \theta )</td>
<td>constant migration rate of uninfected individuals</td>
</tr>
<tr>
<td>( \sigma )</td>
<td>parameter determining the shape of the relationship between virulence and transmission</td>
</tr>
</tbody>
</table>

**Reproductive Input**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>( b )</td>
<td>number of offspring per female</td>
</tr>
<tr>
<td>( K )</td>
<td>carrying capacity</td>
</tr>
<tr>
<td>( \kappa )</td>
<td>probability of transmitting the disease vertically from mother to offspring</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
\frac{dS_m}{dt} & = \sigma \theta - \eta_m S_m (p_{mm}\beta_m I_m + p_{fm}\beta_f I_f) - \mu_m S_m \quad (3.1a) \\
\frac{dS_f}{dt} & = (1 - \sigma)\theta - \eta_f S_f (p_{mf}\beta_m I_m + p_{ff}\beta_f I_f) - \mu_f S_f \quad (3.1b) \\
\frac{dI_m}{dt} & = \eta_m S_m (p_{mm}\beta_m I_m + p_{fm}\beta_f I_f) - (\mu_m + \alpha_m) I_m \quad (3.1c) \\
\frac{dI_f}{dt} & = \eta_f S_f (p_{mf}\beta_m I_m + p_{ff}\beta_f I_f) - (\mu_f + \alpha_f) I_f \quad (3.1d)
\end{align*}
\]

\[
\begin{align*}
\alpha_i & = (1 - \rho_i)\epsilon_i \quad (3.2a) \\
\beta_i[\nu_i] & = \frac{(1 - \rho_i)\epsilon_i}{w + (1 - \rho_i)\epsilon_i} \quad (3.2b)
\end{align*}
\]

For a parasite with a given exploitation strategy, the population will reach a steady state where the number of individuals leaving each uninfected and infected class is equal to the number of individuals entering that class. We can write the steady state number of uninfected and infected males as:

\[
\begin{align*}
\hat{S}_m & = \frac{\sigma \theta}{\mu_m + h_i[\hat{I}_m, \hat{I}_f]\eta_m} \quad (3.3a) \\
\hat{I}_m & = \frac{h_i[\hat{I}_m, \hat{I}_f]\eta_m\hat{S}_m}{\mu_m + \alpha_m} \quad (3.3b)
\end{align*}
\]

where \( h_i[\hat{I}_i, \hat{I}_j] = p_{ii}\beta_i\hat{I}_i + p_{ji}\beta_j\hat{I}_j \) is the equilibrium force of infection on host type \( i \). \( \hat{S}_f \) and \( \hat{I}_f \) are defined analogously but \( \sigma \) is replaced with \( 1 - \sigma \).

We can model the evolution of the parasite using an adaptive dynamics approach, in which a mutant
parasite with a slightly different exploitation rate is introduced into a resident host-parasite system at equilibrium to determine if it has higher fitness and will replace the resident. The successive invasion of mutants can lead to an evolutionary endpoint which is an evolutionary stable strategy if it is uninvadable by nearby mutants (Otto and Day, 2007). To determine if a mutant will invade, we augment the model to include a mutant allele and perform a linear stability analysis. Using tildes to denote variables and parameters pertaining to the mutant, the dynamics of the mutant are given by equation (3.4).

\[
\frac{d\tilde{I}_m}{dt} = \eta_m S_m \left( p_{mm} \beta_m [\tilde{\epsilon}_m] \tilde{I}_m + p_{mf} \beta_f [\tilde{\epsilon}_f] \tilde{I}_f \right) - (\mu_m + \alpha_m [\tilde{\epsilon}_m]) \tilde{I}_m
\] (3.4a)

\[
\frac{d\tilde{I}_f}{dt} = \eta_f S_f \left( p_{mf} \beta_m [\tilde{\epsilon}_m] \tilde{I}_m + p_{ff} \beta_f [\tilde{\epsilon}_f] \tilde{I}_f \right) - (\mu_f + \alpha_f [\tilde{\epsilon}_f]) \tilde{I}_f
\] (3.4b)

We are interested in the stability of the equilibrium where the mutant allele is absent, i.e. \(\hat{S}_m, \hat{S}_f, \hat{I}_m, \hat{I}_f, \hat{I}_m = \hat{I}_f = 0\). Assuming the resident allele is stable before the introduction of the mutant, the mutant will invade if the leading eigenvalue, \(r[\epsilon, \tilde{\epsilon}]\), of the mutant transition matrix \(J_{Mut}\) is greater than zero.

\[
J_{Mut} = \begin{pmatrix}
  p_{mm} \beta_m [\tilde{\epsilon}_m] \eta_m S_m - (\mu_m + \alpha_m [\tilde{\epsilon}_m]) & p_{mf} \beta_f [\tilde{\epsilon}_f] \eta_m S_m \\
p_{mf} \beta_m [\tilde{\epsilon}_m] \eta_f S_f & p_{ff} \beta_f [\tilde{\epsilon}_f] \eta_f S_f - (\mu_f + \alpha_f [\tilde{\epsilon}_f])
\end{pmatrix}
\] (3.5)

### 3.3.1 Homogeneous Host Population

For a parasite with a single exploitation strategy \(\epsilon_m = \epsilon_f = \epsilon\), the direction of evolution (i.e. successive invasions) of the parasite trait is given by the fitness gradient, defined as \(\frac{\partial r}{\partial \epsilon_i} |_{\epsilon = \epsilon^*}\). In a homogeneous host population (i.e. males and females are phenotypically equivalent) the fitness gradient equals \(\beta_i^* / \beta_i - \alpha_i^* / (\mu_i + \alpha_i)\). Because this term arises repeatedly, it is convenient to define \(z_i[\epsilon] \equiv \beta_i^* / \beta_i - \alpha_i^* / (\mu_i + \alpha_i)\) following Williams (2012). The first term in \(z_i[\epsilon]\) represents the relative transmission benefit of an increase in exploitation rate, while the second term represents the relative virulence cost. If the fitness gradient is positive (negative), the parasite is under(over) exploiting its host and a mutant parasite with a higher (lower) exploitation rate will invade. When the fitness gradient equals zero, the pathogen is at an evolutionary endpoint, which is evolutionarily stable if it is a fitness maximum and any nearby mutants move toward that level of exploitation (convergence stability). The evolutionarily stable strategy (ESS) of a constrained parasite in a homogeneous host population composed entirely of host type \(i\) is \(\epsilon^* = \sqrt{\mu_i \nu_i / (1 - \rho_i)}\) (Otto and Day, 2007).

### 3.3.2 Heterogeneous Host Population

A parasite in a heterogeneous host population could be (1) constrained to express the same exploitation rate in both sexes, or (2) free to facultatively express different exploitation rates in males and females, \(\epsilon_m\) and \(\epsilon_f\), respectively, where \(\epsilon_m\) and \(\epsilon_f\) are modelled as two independently evolving traits.

**Unconstrained Parasite**

We determined the evolutionary endpoints for a facultative parasite by performing a multivariate invasion analysis (Otto and Day, 2007). In the unconstrained case, the evolutionarily stable strategy must...
simultaneously satisfy equations (3.6a) and (3.6b),

\[
0 = \frac{\partial r}{\partial \epsilon_m} (\epsilon_m, \epsilon_f, \epsilon_i, \epsilon_j) \bigg|_{\epsilon_m = \epsilon_f, \epsilon_i = \epsilon_j} = \left( \frac{\beta_m}{\beta_m} - \frac{\alpha_m}{\mu_m + \alpha_m} \right) = z_m[\epsilon_m]
\] (3.6a)

\[
0 = \frac{\partial r}{\partial \epsilon_f} (\epsilon_m, \epsilon_f, \epsilon_i, \epsilon_j) \bigg|_{\epsilon_m = \epsilon_f, \epsilon_i = \epsilon_j} = \left( \frac{\beta_f}{\beta_f} - \frac{\alpha_f}{\mu_f + \alpha_f} \right) = z_f[\epsilon_f]
\] (3.6b)

whose solution is \( \epsilon_m^* = \sqrt{\mu_m w/(1 - \rho_m)} \) and \( \epsilon_f^* = \sqrt{\mu_f w/(1 - \rho_f)} \).

We see that a parasite in a heterogeneous host population that can infect both sexes is selected to express the same exploitation rate in a given sex as it would if it were in a population composed entirely of hosts with that sex’s phenotype with respect to intrinsic death rate and resistance. The relative abundance of each sex and differential disease transmission between sexes does not affect the strategy a pathogen should adopt in its host. In other words, epidemiological feedbacks do not play a role in the evolutionary outcome when parasite fitness only depends on optimizing transmission out of its host (Mideo et al., 2008).

**Constrained Parasite**

Constraining \( \epsilon_m = \epsilon_f = \epsilon \), we examine the ESS exploitation rate in comparison to the unconstrained case where \( \epsilon_f^* \neq \epsilon_m^* \). When transmission rate depends only on the parasite’s exploitation rate inside its host \( i.e. \) transmission between and among the sexes is random, Williams (2012) found that the evolutionarily stable exploitation rate satisfies equation (3.7) where the \( z_i[\epsilon] \) are weighted by each host type’s relative contribution to the force of infection

\[
0 = \frac{\beta_m \hat{I}_m}{\beta_m \hat{I}_m + \beta_f \hat{I}_f} z_m[\epsilon] + \frac{\beta_f \hat{I}_f}{\beta_m \hat{I}_m + \beta_f \hat{I}_f} z_f[\epsilon]
\] (3.7)

These weightings however, assume that an infected host interacts with any type of uninfected host in the same way with regards to disease spread. We relaxed that assumption, allowing for differential transmission between and among sexes. Our result, given by equation (3.8), has a similar form but the \( z_i[\epsilon] \) are weighted by that sex’s relative contribution to the force of infection on the opposite sex.

\[
0 = \frac{p_{mf} \beta_m \hat{I}_m}{p_{mf} \beta_m \hat{I}_m + p_{ff} \beta_f \hat{I}_f} z_m[\epsilon] + \frac{p_{fm} \beta_f \hat{I}_f}{p_{mm} \beta_m \hat{I}_m + p_{fm} \beta_f \hat{I}_f} z_f[\epsilon]
\] (3.8)

The \( p_{ij} \) terms represent the probability of the disease spreading from an infected host of type \( i \) to an uninfected host of type \( j \). Even though the \( z_i[\epsilon] \) weightings do not include the relative contribution of within sex transmission to the force of infection, within sex transmission still affects the ESS determination. For example, decreasing female to female transmission increases the relative contribution of between sex transmission to the force of infection on females. \( z_m[\epsilon] \) is weighted more heavily than when there is random transmission so the ESS will shift closer to \( \epsilon_m^* \). It is easier to interpret equation (3.8) if we rewrite it in terms of the number of infected individuals of each sex and their relative contribution to the parasite’s long-term growth rate. Respectively, these factors are captured by the right and left eigenvectors, \( \bar{u} \) and \( \bar{v} \), of \( J_{mut} \) (Otto and Day, 2007). Writing the fitness gradient as shown in equation (3.9), we see how the stable class distribution (\( \bar{u} \)) and class reproductive values (\( \bar{v} \)) affect the evolution of the parasite trait.
The transmission benefit accompanying a small increase in exploitation rate depends on the rate infection ends \((\mu + \alpha)\) in a host relative to the transmission rate \((\beta)\) out of that host. In other words, the faster the infection ends, the more beneficial it is to increase transmission to new hosts but there is less to be gained when transmission out of host type \(i\) is already high. Increasing disease-induced mortality carries a direct cost. The tradeoff between transmission and virulence within each sex is affected by between host disease dynamics. The number of infected males and females and their reproductive value to the parasite \((v_m\) and \(v_f\)) determines how the pathogen balances the tradeoff it faces in each sex. The reproductive values not only depend on the intrinsic transmission rate out of each sex, \(\beta\), but also on transmission opportunity to uninfected hosts (eq. 3.10). For example, the contribution of an infected male to the population growth rate of the parasite depends on its transmission rate to uninfected males and females, \(p_{mm}\beta_m\eta_mS_m\) and \(p_{mf}\beta_m\eta_fS_f\), respectively, and the future reproductive value of the newly infected individuals of each sex, \(v_m\) and \(v_f\). The duration of infection \(1/(\mu + \alpha)\) also affects sex \(i\)'s reproductive value.

\[
v_m = \frac{p_{mm}\beta_m\eta_mS_m v_m + p_{mf}\beta_m\eta_fS_f v_f}{\mu_m + \alpha_m} \quad v_f = \frac{p_{fm}\beta_f\eta_mS_m v_m + p_{ff}\beta_f\eta_fS_f v_f}{\mu_f + \alpha_f}
\] (3.10)

### 3.4 Results

To get a better understanding of equation (3.9), we plot the constrained ESS for different contact patterns when the source of new uninfected individuals is constant immigration (fig.3.1). We focus on how host traits directly related to disease, e.g. resistance and susceptibility, affect the evolutionarily stable parasite strategy relative to values of \(\epsilon^*_f\) and \(\epsilon^*_m\). We therefore assume that the natural host mortality rate is the same in males and females \((\mu_m = \mu_f = \mu)\).

#### 3.4.1 Single Differences Between Host Types

**Susceptibility**

If susceptibility is the only difference between the sexes, then the population behaves as a homogeneous host population (Williams, 2012). In this case, \(\alpha_m[e] = \alpha_f[e] = \alpha\) and \(\beta_m[e] = \beta_f[e] = \beta\). \(((\mu + \alpha)/\beta)\beta' - \alpha'\) can be factored out of equation (3.9) and solved for the one host one parasite solution \(\epsilon^* = \sqrt{\mu_w/(1 - \rho)}\) (Otto and Day, 2007).

**Resistance**

To isolate the effects of differences in resistance between the sexes, we assume equal susceptibility \((\eta_m = \eta_f = \eta)\) and equal numbers of each sex entering the population \((\sigma = 0.5)\). When transmission is symmetrical, the analytical solution for the constrained ESS, \(\epsilon^*\), is given by \(\sqrt{\mu w/(1 - \rho_m)(1 - \rho_f)}\),
Chapter 3. Virulence evolution in male and female hosts

the geometric mean of $\epsilon^*_m$ and $\epsilon^*_f$. This solution does not depend on contact pattern. Regardless of the amount of within sex transmission the density of uninfected males and females is equal (not shown). Effectively, the parasite strategy reflects the fact that it is equally likely to be transmitted into either sex. Assuming males are less resistant than females, we plotted the unchanging ESS against increasing within sex transmission rates (black solid line, fig. 3.1) in order to facilitate comparison with the ESS when there are multiple differences between the sexes.

3.4.2 Multiple Differences Between Host Types; Symmetrical Transmission

When the sexes differ in both susceptibility and resistance, contact pattern does affect the evolutionarily stable exploitation rate. Compared to when only resistance is different between sexes, differential susceptibility ($\eta_m \neq \eta_f$) shifts the ESS closer to that of the more susceptible sex (black dashed and dotted dashed lines, fig. 3.1). The relative importance of susceptibility depends on the amount of within sex transmission (fig. 3.1). When there is only between type transmission, i.e. $p_{mf} = p_{fm} = 1$, the ESS equals that of $\eta_m = \eta_f$. The parasite has to pass through each sex sequentially and is therefore equally likely to be transmitted to uninfected males or uninfected females. As the amount of within sex transmission increases, the ESS moves closer to $\epsilon^*_i$ of the more susceptible sex. Once the parasite gets into that sex, it is much more likely to be transmitted within it so being closer to $\epsilon^*_i$ has a long term evolutionary advantage. More precisely, the parasite has a higher reproductive value in the more susceptible sex (fig. 3.2), making the transmission virulence tradeoff in that sex more important in the ESS determination.

At high within sex transmission rates we observe evolutionary branching because the host population is effectively two subpopulations with no disease transmission between them. When susceptibility is equal evolutionary branching is observed at within sex transmission rates greater than 0.94. Differences in susceptibility between the sexes increase the within sex transmission rate above which evolutionary branching occurs ($p_{ii} > 0.99$) because the parasite is specialized on the more susceptible sex. Since most of its transmission opportunities are in the more susceptible sex, a single specialized strategy is still a fitness maximum unless between sex transmission is so rare that males and females represent distinct subpopulations.

3.4.3 Asymmetrical Contact Patterns

In the previous section we assumed contact patterns were symmetrical, meaning that an increase in male to male transmission rates was accompanied by an increase in female to female transmission rates. However, in their efforts to obtain mates, males may interact with each other and with females more than females interact with one another. This would result in asymmetrical opportunity for disease transmission. Asymmetrical transmission patterns can lead to changes in the ESS with contact pattern even in the absence of differences in susceptibility between the sexes ($\eta_f = \eta_m$; fig. 3.3a). Figure 3.3a shows the constrained and unconstrained ESS as a function of increasing transmission into males. We first consider the case where transmission probability out of either sex into males is the same and total transmission probability out of each sex is constant, so that increasing transmission probability to males is accompanied by reduced transmission to females from both sexes ($p_{mm} = p_{fm} = \delta; p_{mf} = p_{ff} = 1-\delta$) As expected, the ESS is closer to $\epsilon^*_f$ when transmission is mostly into females and closer to $\epsilon^*_m$ when transmission is mostly into males (dashed green line, fig. 3.3a). Reproductive values in males and females
Chapter 3. Virulence evolution in male and female hosts

0.0 0.2 0.4 0.6 0.8 1.0
0.6 0.8 1.0 1.2 1.4 1.6 1.8
$\varepsilon_i^*$

Figure 3.1: The evolutionarily stable strategy (ESS) of a parasite expressing the same exploitation rate in both sexes changes with contact pattern when there are differences in susceptibility between the sexes. Transmission is symmetrical ($p_{ij} = p_{ji}$ and $p_{ii} = p_{jj}$) and transmission coefficients out of each sex sum to one ($p_{ij} + p_{ii} = 1$) such that as within-sex transmission increases moving from left to right across the $x$-axis, between-sex transmission decreases. A parasite that facultatively expresses different exploitation strategies in males and females has ESS exploitation rates $\varepsilon_f^*$ (red) and $\varepsilon_m^*$ (blue), which do not change with differential susceptibility or contact pattern. Note that $\varepsilon_f^* > \varepsilon_m^*$ because we have assumed females are more resistant to the disease ($\rho_f > \rho_m = 0$). The constrained ESS also does not change with contact pattern when susceptibility is equal ($\eta_f = \eta_m$, black solid line) but shifts closer to $\varepsilon_i^*$ of the more susceptible sex as within-sex transmission increases ($\eta_f > \eta_m$, black dashed dotted line; $\eta_f < \eta_m$, black dashed line). The source of new uninfected individuals is constant immigration, i.e. $\theta = 75$. Though the figure goes to $p_{ii} = 1$ for illustrative purposes, evolutionary branching occurs below this level (e.g. $p_{ii} > 0.94$, with the exact value depending on the parameters).

are similar (fig. 3.3b) but there are many infected individuals of the sex disproportionately contracting the disease, skewing the ESS towards that sex’s unconstrained optimum.

When we hold transmission out of females constant at $p_{ff} = p_{fm} = 0.5$ and consider changes in transmission probability out of males ($p_{mm} = \delta; p_{mf} = 1 - \delta$) we might still expect the ESS to be closer to $\varepsilon_m^*$ at high male to male contact rates. However, the ESS is closer to $\varepsilon_f^*$ even when transmission into males is high (solid green line, fig. 3.3a). The reproductive value in females is higher than that in males (fig.3.3b) because females can transmit the disease to either sex. Furthermore, regardless of the extent to which males transmit the disease amongst themselves (and not to females), there is always some disease transmission among females, maintaining enough infected females to be important in the ESS determination. This is not true for low input rates ($\theta < 55$) where there can be so few infected females that the ESS is closer to $\varepsilon_m^*$ even though the pathogen’s reproductive value is lower in males at high $\delta$ (not shown).

3.4.4 Source of New Uninfected Individuals

If new uninfected individuals in the population arise through density dependent births, ecological feedbacks could affect the evolution of the parasite. We consider two additional types of input: female
Chapter 3. Virulence evolution in male and female hosts

Figure 3.2: A constrained parasite has higher reproductive values in the more susceptible sex as within-sex transmission increases. The class reproductive values ($v_m$ and $v_f$) represent the contribution of each sex to future population growth of the parasite. Males and females contribute equally to parasite population growth when susceptibility is equal ($\eta_f = \eta_m$, black solid line). When there is differential susceptibility ($\eta_f > \eta_m$, black dashed dotted line; $\eta_f < \eta_m$, black dashed line), the parasite has a higher reproductive value in the less susceptible sex if there is more between-sex transmission or in the more susceptible sex if there is more within-sex transmission. The source of new uninfected individuals is constant immigration, i.e. $\theta = 75$ and the $x$-axis is the same as in figure 3.1.

Figure 3.3: (A) Asymmetrical transmission patterns lead to changes in the constrained ESS in the absence of differential susceptibility, i.e. $\eta_f = \eta_m$. Two scenarios are depicted: transmission into males from females and other males increases moving from left to right across the $x$-axis ($p_{mm} = p_{fm} = \delta$; $p_{mf} = p_{ff} = 1 - \delta$, dashed green line) or male to male transmission increases while transmission out of females remains random ($p_{mm} = \delta$; $p_{mf} = 1 - \delta$; $p_{ff} = p_{fm} = 0.5$, solid green line). An unconstrained parasite has ESS exploitation rates $\epsilon_f^*$ (red) and $\epsilon_m^*$ (blue), which do not change with contact pattern. Note that $\epsilon_f^* > \epsilon_m^*$ because we have assumed females are more resistant to the disease ($\rho_f > \rho_m = 0$). (B) Relative class reproductive values for a constrained parasite. The source of new uninfected individuals in both panels is constant immigration, i.e. $\theta = 75$. 

\[
\text{Log}[v_m/v_f]
\]
dominant density dependent reproduction (eq. 3.11a) and density dependent reproduction where both males and females are important for the production of offspring (eq. 3.11b). These input terms, which are a function of the number of uninfected and infected males and females, replace the constant migration rate $\theta$ in equation (3.1). Here, $b$ represents the number of offspring per female, following (Lindström and Kokko, 1998) and $(S_f + I_f)(S_m + I_m)/N$ is the harmonic birth function (Caswell, 1989). Density dependence is incorporated through logistic growth where $K$ is the carrying capacity of the population.

\[
\psi[S_m, S_f, I_m, I_f] \equiv b(S_f + I_f) \left(1 - \frac{S_m + S_f + I_m + I_f}{K}\right) \\
\psi[S_m, S_f, I_m, I_f] = 2b \frac{(S_f + I_f)(S_m + I_m)}{S_m + S_f + I_m + I_f} \left(1 - \frac{S_m + S_f + I_m + I_f}{K}\right)
\]

The source of new uninfected individuals into the population has an important effect on the evolutionarily stable exploitation rate when males and females are not equally susceptible to disease ($\eta_m \neq \eta_f$). For density dependent births where both sexes are important to reproduction, the constrained ESS is almost equal to that of a parasite in a population of similar size experiencing constant immigration (fig. 3.4b). When population growth is based on female dominant density dependent births, the ESS is closer to the unconstrained female optimum than when both sexes are equally important or when there is constant input of uninfected individuals (fig. 3.4a). This pattern arises because of changes in the density dependent birth rate and overall population size with contact pattern (not shown). Smaller population sizes with differential susceptibility to disease show greater divergence away from the equal susceptibility ESS than larger ones at high within sex transmission rates (not shown). Under female dominant reproduction when females are more susceptible, birth rate and population size decrease with increasing within sex transmission rates and the ESS diverges further away from the $\eta_f = \eta_m$ ESS (towards $\epsilon_f^*$, dashed dotted black line, fig. 3.4a). When males are more susceptible, females suffer less from the disease at high within sex transmission rates. Population size is larger and the ESS shifts towards the $\eta_f = \eta_m$ ESS (dashed black line, fig. 3.4a). Regardless of the input type, ecological feedbacks in the density dependent models can affect the ESS of a constrained parasite. However, the ESS of the unconstrained parasite remains at the optimum in males and females.

### 3.4.5 Horizontal versus Vertical Transmission

We incorporate vertical transmission into the female dominant density dependent model by allowing infected females to give birth to uninfected offspring with probability $1 - \kappa$ and infected offspring with probability $\kappa$, where $\kappa$ is not a function of the parasite’s exploitation rate. Allowing some vertical transmission has several effects. The ESS exploitation rate of females in the unconstrained model is now sensitive to the extent of within- versus between-sex transmission. The ESS in females changes with contact pattern if the disease is vertically transmitted because its long term transmission success depends on whether it is being transmitted to males or females. When the parasite is only horizontally transmitted, all that matters is maximizing transmission out of its current host (see eq. 3.6). With vertical transmission ($\kappa = 0.5$, fig.3.5a), females offer two modes of transmission and are more valuable hosts. If there is only between-sex transmission, a parasite is better off increasing the duration of infection in its female host than transmitting to males ($\epsilon_f^* < \epsilon_m^*$). As within-sex transmission increases, female transmission is increasingly into other females. Higher exploitation rates in females
ensure the parasite is transmitted to as many females as possible ($\epsilon_f^*$ is higher than $\epsilon_m^*$). As with a horizontally transmitted parasite, the ESS of the constrained model is bounded by the male and female ESS exploitation rates of the unconstrained model.

Vertical transmission also causes the ESS exploitation rate in females of an unconstrained pathogen to be sensitive to differences in susceptibility between the sexes. This is easiest to see at low rates of vertical transmission ($\kappa = 0.1$; compared to high rates of vertical transmission, $\kappa = 0.5$) where $\epsilon_f^*$ changes less drastically with increasing within-sex transmission rates (fig. 3.5b).

### 3.5 Discussion

We expanded the multihost parasite model developed by Williams (2012) to incorporate differential transmission between two host types. For horizontally transmitted parasites, transmission patterns did not change the evolutionary outcome when only one of resistance or susceptibility were different between the sexes. When both were different, the relative importance of susceptibility in determining the evolutionary stable exploitation strategy is greater when the probability of within-sex transmission is large relative to between-sex transmission. We also explicitly modelled an unconstrained parasite, that is, a parasite that can express different exploitation rates in each sex. We found that an unconstrained parasite evolves to express the same exploitation rate in a given sex as it would in a homogeneous population of that sex, regardless of susceptibility or contact pattern, unless there is vertical transmission of the disease. Thus, differential transmission patterns create changes in disease dynamics that feed back to the affect the constrained ESS, but do not feed back to affect the ESS in the unconstrained model unless females are intrinsically more valuable hosts than males because they are capable of vertical transmission.
Figure 3.5: For an unconstrained parasite, the exploitation rate expressed in females changes with contact pattern when there is vertical transmission. (A) The probability of vertical transmission is $\kappa = 0.5$. $\epsilon_f^*$ increases with increasing within-sex transmission (solid red line) while $\epsilon_m^*$ does not (solid blue line). The constrained parasite strategy (solid black line) is always bounded by $\epsilon_m^*$ and $\epsilon_f^*$. Only the equal susceptibility case is shown for clarity. (B) The probability of vertical transmission is $\kappa = 0.1$. $\epsilon_f^*$ changes with contact pattern to a lesser extent. Solid lines, $\eta_f = \eta_m$; dashed dotted lines $\eta_f > \eta_m$; dashed lines $\eta_f < \eta_m$. The x-axis is the same as in figure 3.1.

Even though an unconstrained parasite expresses different evolutionarily stable exploitation rates in males and females, transmission out of and virulence in each sex is the same because $\epsilon_i^* = \sqrt{\mu w/(1 - \rho_i)}$ and $\alpha_i = (1 - \rho_i)\epsilon_i$. This observation arises because we allow exploitation rate in males and females to be independent traits. It has been established that between-host disease dynamics do not affect a parasite’s strategy for maximizing transmission out of its host except under certain circumstances (Mideo et al., 2008). Alternatively, $\epsilon_m^*$ and $\epsilon_f^*$ will only differ from the homogeneous host population expectation if there is some correlation between traits (Gandon, 2004). In our model, between-host disease dynamics do not feed back - regardless of how relative host densities change with differential susceptibility and transmission patterns - to affect parasite proliferation within a host when there is only horizontal transmission.

Epidemiological feedbacks do, however, affect the ESS of a horizontally transmitted one-trait parasite. Because the parasite is constrained to express one exploitation rate in both males and females, virulence in males is not equal to virulence in females. The difference in virulence, and consequently transmission, means that changes in susceptibility or transmission patterns differentially affect the parasite’s ability to transmit from each sex. Though the changes in between-host disease dynamics are not feeding back to affect the tradeoffs within a host, they still affect the relative contribution of transmission from each sex to overall transmission success. The tradeoff between virulence and transmission faced in each sex is therefore weighted differently depending on susceptibility to disease and the amount of between- and among-sex transmission.

When only resistance is different between the sexes, $\epsilon^* = \sqrt{\mu w/(1 - \rho_m)(1 - \rho_f)}$. We can compare our results to those of Cousineau and Alizon (2014) who studied the evolution of virulence in sexually dimorphic hosts. Cousineau and Alizon (2014) investigated varying levels of sexual dimorphism in tolerance and resistance, separately, for only between-sex transmission, random transmission, and mostly within-sex transmission. Host tolerance decreased disease-induced mortality rates while host resistance
decreased disease-induced mortality and transmission rates. For maximal levels of sexual dimorphism in their model, one sex had no resistance to disease and the other sex’s resistance varied from zero to one. They found the rate of increase in the ESS with increasing resistance varied depending on the transmission pattern. In our model, the transmission pattern does not affect the ESS when susceptibility in both sexes is equal. Their model differs from ours in several ways, including how resistance is incorporated into the model. More importantly, Cousineau and Alizon (2014) assume constant population size and an equal sex ratio. If we also assume constant and equal numbers of each sex, the ESS does change with contact pattern under equal susceptibility ($\eta_m = \eta_f$), moving closer to the male optimum with increasing within-sex transmission. Because males are overexploited, there are higher transmission rates out of males and hence more male to male transmission. In our model increased transmission among males is balanced by increased male mortality rates resulting in the same ESS as with random transmission. Holding population size and sex ratio constant, high disease-induced mortality in males means dying infected males are replaced with uninfected males. The parasite has more transmission opportunities to uninfected males and the ESS shifts closer to $\epsilon^*_m$.

Contact patterns determine if a constrained parasite will be a specialist or a generalist given sex-specific susceptibility. High within-sex transmission causes the parasite to specialize on the more susceptible sex while high between-sex transmission drives generalism. Regoes et al. (2000) investigated a parasite with a free-living stage that traded off virulence in one host type against that in the other (e.g. $\epsilon_i \epsilon_j = c$). They found that specialization arose when the shape of the tradeoff curve was convex enough that the cost of switching host types was high. While we did not explicitly model a virulence tradeoff, the pathogen effectively faces a tradeoff between host types because of sexual dimorphism in resistance. When specialized on one sex because of high transmission opportunity within that sex, the pathogen will over or under exploit its new host type if it is transmitted between sexes. The cost of switching increases with within-sex transmission rates until it is so high that evolutionary branching occurs and two constrained exploitation rates are maintained in the population as a polymorphism.

Vertical transmission selects for less virulent pathogens because the parasite cannot be transmitted from mother to offspring if the mother dies of disease-related causes before reproducing (Yamamura, 1993). Our results are consistent with theory on vertical transmission in host pathogen systems (Lipsitch et al., 1995). The constrained exploitation rate and the exploitation rate expressed in females by an unconstrained parasite are both lower than predicted by a female dominant density dependent model with only horizontal transmission (fig. 3.5). The extent to which the parasite evolves lower exploitation rates depends on the amount of vertical transmission. Since the disease cannot be transmitted from father to offspring in our model, the male optimum is the same as predicted by equation (3.6a) and does not change with contact pattern. At high vertical transmission rates, an unchanging $\epsilon^*_m$ can result in a switch in which sex is over exploited and which is underexploited (fig. 3.5a). This switch could affect the epidemiological dynamics and have an important impact on predicting and managing the disease in male and female patients.

Considering resistance, susceptibility, and transmission patterns in isolation can over or underestimate evolutionary stable levels of virulence. Careful examination of host disease traits and contact patterns will lead to the best understanding of disease dynamics and evolutionary endpoints. This is particularly important because different host types will differ not only in immune responses such as resistance, but also in susceptibility to infection and the ways that different host types interact with one another to cause disease transmission.
Chapter 4

Sexual conflict and STDs: coevolution of sexually antagonistic host traits with a sexually transmitted disease
Chapter 4. Sexual conflict and STDs

4.1 Abstract

Sexual conflict over mating rate arises because male fitness increases with every additional mating while female fitness is maximized at some intermediate mating rate. In a sexual conflict system, males can evolve persistence traits to increase their mating rate while females evolve resistance traits to deter male advances. The outcome of this sexually antagonistic coevolution depends on the relative costs of mating and the strength of natural selection against sexually antagonistic traits. A sexually transmitted disease (STD), by definition transmitted during mating, could change the relative strength of these costs and affect the coevolutionary outcome. Conversely, the establishment and virulence of an STD could be affected by the sexually antagonistic host traits. Whether an STD is able to invade and establish within a host population can depend on genetic variation in both host and parasite traits in unexpected ways. When the disease is able to invade, we study the three-way coevolutionary interaction between male persistence, female resistance, and STD virulence. By increasing the cost of mating, an STD escalates conflict between the sexes. The increased host mortality resulting from heightened sexual conflict, in turn, selects for increased STD virulence. These results show that the evolution of both host and parasite traits operate differently in systems characterized by sexual conflict rather than by female mate choice.

4.2 Introduction

Sexual conflict over mating rate arises because male reproductive success increases with every additional mating while female reproductive success is maximized at some intermediate rate (Bateman, 1948; Arnqvist and Rowe, 2005). Males can evolve persistence traits to increase their mating or fertilization rate. These persistence traits often cause harm to females physically or physiologically without increasing female reproductive success. Females, in turn, can evolve resistance traits that deter males or offset the physiological harm. This conflict can give rise to sexually antagonistic coevolution between male persistence traits and female resistance traits, the outcome of which determines the mating rate. Sexually transmitted diseases (STDs) are, by definition, transmitted during mating; here, we explore the interplay between STD virulence evolution and host traits mediating the sexual conflict over mating rate.

Virulence of an STD evolves in much the same way as that of an ordinary infectious disease (OID), i.e. evolutionary stable virulence is proportional to the natural host mortality rate and depends on the shape of the tradeoff between transmission and virulence (Knell, 1999). Somewhat surprisingly, evolutionarily stable virulence (ESS virulence) does not depend on the mating rate even though its spread and infection prevalence does (Knell, 1999; Lipsitch and Nowak, 1995). At epidemiological equilibrium, increasing the mating rate increases spread of the STD such that there is a higher proportion of infected individuals in the population. While we might expect higher transmission opportunity to select for increased virulence, this is exactly counterbalanced by a smaller pool of susceptible individuals, which selects for decreased virulence. Despite the fact that evolutionarily stable STD virulence does not depend on host mating rate, we still expect the spread and prevalence of an STD to affect the cost of mating and, thus, alter the outcome of sexual conflict over mating rate.

STDs are known to affect the evolution of mating strategies, though this work has focused on conventional views of sexual selection. Traditionally, STDs are thought to select for monogamy (Immerman, 1986; Immerman and Mackey, 1997) but more recent theoretical studies have shown that STDs can maintain promiscuity, monogamous and promiscuous strategies together in a population, as well as select for
risky female choice (Boots and Knell, 2002; Kokko et al., 2002; Thrall et al., 1997). Female choosiness based on attractiveness of males is considered a risky strategy because it is the most popular males that have the highest mating rate and are most likely to be infected with an STD. These models suggest that the impact an STD has on the evolution of host mating strategies depends on the mating system itself. Over the last 25 years, it has become clear that, in many systems, sexual conflict over mating rate plays at least as large a role in shaping the evolution of male-female interactions as conventional sexual selection processes (Arnqvist and Rowe, 2005; Rice and Holland, 1997). We can expect entirely different predictions for an STD infecting a population of hosts experiencing sexually antagonistic coevolution.

The presence of an STD will affect the costs of mating to hosts and thus, we expect it to affect the evolution of host traits. By driving the evolution of sexually antagonistic host traits, the STD may end up changing the strength of selection on STD virulence. The outcome of this three-way coevolution is hard to intuit. Indeed, there are several examples in the host-parasite literature of coevolution leading to different or unexpected outcomes than when considering the evolution of either host or parasite in isolation (Best and White, 2009; Day and Burns, 2003; Gandon et al., 2002). Of particular interest is a full coevolutionary model of host choosiness with STD virulence (Ashby and Boots, 2015). An investigation of STD virulence in the absence of host coevolution showed that a parasite that reduces the mating success of its host should evolve to be less virulent. Knell (1999) suggested that hosts would subsequently lose disease-avoidance behaviours such as mate choice based on the degree of parasitism of potential mates and, therefore, that parasitism should not play a role in sexual selection (Knell, 1999). However, when the level of host choosiness based on disease-avoidance was allowed to coevolve with STD virulence, Ashby and Boots (2015) found that intermediate levels of disease-avoidance behaviour and virulence could evolve, and that coevolutionary cycling could occur between host choosiness and STD virulence. These unexpected results emphasize the importance of considering the coevolutionary feedbacks of a sexually transmitted disease with host mating system.

In the absence of a sexually transmitted disease, there are several possible outcomes of sexually antagonistic coevolution depending on the biology of the system. If male persistence and female resistance carry no inherent cost, traits will continually escalate in an evolutionary arms race (Gavrilets and Hayashi, 2006). Incorporating natural selection prevents runaway evolution (Gavrilets et al., 2001) and allowing for the evolution of female sensitivity can lead to female indifference to male traits, halting the coevolutionary process (Rowe et al., 2005). In all of these cases, only females suffer the cost of mating. Given that a sexually transmitted disease increases the cost of mating to both males and females it is unclear how an STD will affect sexually antagonistic host interactions.

It is conceivable that an STD could escalate or de-escalate the sexual conflict, depending on host coevolution in the absence of an STD. For example, if there is runaway selection to infinite trait values in the hosts, a sexually transmitted disease might cause further escalation by increasing the selection pressure for female resistance to match or exceed male persistence, thereby decreasing their chance of contracting an STD. Males with higher persistence will have higher mating rates and consequently higher reproductive success. Increasing male persistence will further select for increased female resistance, accelerating the rate of runaway evolution. Alternatively, the STD could de-escalate the sexual conflict. For example, if male persistence and female resistance reach equilibrium trait values where males are ‘winning’, a sexually transmitted disease might create selection against males with higher persistence because these males have a higher probability of contracting the STD and not surviving to the next generation. Indeed, there are several theoretical examples of sexually transmitted disease reducing
mating skews (Kokko et al., 2002; Thrall et al., 2000), which could decrease the average mating rate and average host trait values in a sexual conflict system.

We model coevolution of a sexually transmitted disease in a host system with sexual conflict over mating rate. Using an analytical model and individual-based simulations, we allow the STD to coevolve with male persistence and female resistance (host traits). We show that the presence of an STD can affect the outcome of sexually antagonistic coevolution in its host. Host traits escalate because they are selected to reduce transmission of the STD and the cost of mating associated with contracting the disease. Coevolution of STD virulence in response to increased host mortality feeds back and affects the evolutionary equilibrium host trait values. Our results suggest that the observed levels of sexual conflict in natural systems could be affected by disease and that coevolutionary feedbacks should be taken into consideration when estimating the strength of sexually antagonistic selection in nature.

4.3 Model Setup

4.3.1 Analytical Model

We use a system of differential equations to describe sexually antagonistic coevolution in a population of haploid hosts (parameter definitions summarized in Table 1). Male mating effort is determined by male persistence, \( y \), while females actively try to avoid or deter mating with resistance trait \( x \). The mating rate depends on the difference between male persistence and female resistance and is given by \( \phi[y, x] = 1/(1 + e^{-(y-x)}) \). The mating rate plays several important roles in the model. Firstly, it affects female fecundity. Females have a maximum birth rate \( b \) that can be decreased by density-dependence and unfertilized eggs. Her probability of not mating with any of the males she encounters is given by \( \gamma[M] = (1 - \phi[y, x])^{\alpha M} \), where \( \alpha \) is the encounter rate and \( M \) is the density of males. The mating rate also affects female mortality. Females pay a cost of mating \( d \) due to aggressive male behaviour that depends on the number of males each female mated with, which is, on average, \( \alpha M \phi[y, x] \). Both males and females die at their baseline mortality rates, \( \mu_m \) and \( \mu_f \), respectively, and face nonlinearly increasing costs of expressing their respective sexually antagonistic traits. More specifically, there is a mortality cost a male pays for his persistence trait, which we will call the “persistence cost”, and a mortality cost a female pays for her resistance trait, which we will call the “resistance cost”. Natural selection against these constitutively expressed sexually antagonistic traits, together with the cost of mating experienced by females, results in three costs incurred by hosts (persistence costs to males and resistance and mating costs to females). The ecological dynamics are captured by the following system of equations.

\[
\frac{dM}{dt} = \frac{1}{2} Fb(1 - \frac{M + F}{K})(1 - \gamma[M]) - (c e^y + \mu_m)M \\
\frac{dF}{dt} = \frac{1}{2} Fb(1 - \frac{M + F}{K})(1 - \gamma[M]) - (d \alpha M \phi[y, x] + \delta e^x + \mu_f)F
\]

We augment the system of equations by introducing a rare mutant for the persistence trait \( y \), holding the resistance trait constant. The mutant persistence trait \( y_{Mut} \) is carried by both males and females but only expressed in males. The mutant will invade a population at ecological equilibrium if its invasion fitness \( r_m[y, y_{Mut}, x] \) is greater than zero. Similarly, we can introduce a rare mutant for the resistance trait, \( x_{Mut} \), holding the persistence trait fixed, and determine where its invasion fitness \( r_f[y, x, x_{Mut}] \) is
greater than zero. Individuals expressing a mutant trait will have a different mating rate than resident individuals, thus experiencing different reproductive success and imposing or suffering different naturally selected or sexually antagonistic costs.

A co-evolutionarily stable strategy can be found where the selection gradient for both traits equals zero,

$$
\frac{\partial r_m[y, \bar{y}, x]}{\partial \bar{y}} \bigg|_{\bar{y} = y^*, x = x^*} = 0 \quad \text{and} \quad \frac{\partial r_f[y, x, \bar{x}]}{\partial \bar{x}} \bigg|_{\bar{x} = x^*} = 0,
$$

and their second derivative is negative such that the co-ESS is a fitness maximum.

$$
\frac{\partial^2 r_m[y, \bar{y}, x]}{\partial \bar{y}^2} \bigg|_{\bar{y} = y^*, x = x^*} \leq 0 \quad \text{and} \quad \frac{\partial^2 r_f[y, x, \bar{x}]}{\partial \bar{x}^2} \bigg|_{\bar{x} = x^*} \leq 0
$$

We introduce a sexually transmitted disease into the model by dividing the host population into susceptible and infected classes. Susceptible individuals contract the disease by mating with infected individuals of the opposite sex. We model transmission of the STD as density-dependent because it is reasonable to assume that the number of matings per capita will increase with density in systems governed by sexual conflict. Additionally, to determine a female’s full cost of mating, we need to keep track of the number of males a female mated with and not just the fraction of her mates that were infected (as would be done under frequency-dependent transmission). Density-dependent sexual disease transmission has been documented in nature (for example in two-spot ladybird beetles, Adalia bipunctata, Ryder et al. 2005). STD virulence, v, results in higher mortality of disease carriers. We assume a tradeoff between transmission and virulence such that the transmission rate during mating is a saturating function of virulence $\beta[v] = v/(w + v)$, where w determines the exact shape of the function. The epidemiological dynamics are described by the following set of differential equations:

$$
\begin{align*}
\frac{dS_m}{dt} &= \frac{1}{2} \psi[S_m, S_f, I_m, I_f] - \alpha f \phi[y, x] \beta[v] S_m - \gamma S_m S_m - (ce^y + \mu_m) S_m \\
\frac{dS_f}{dt} &= \frac{1}{2} \psi[S_m, S_f, I_m, I_f] - \alpha f \phi[y, x] \beta[v] S_f - (da(S_m + I_m) \phi[y, x] + \delta e^x + \mu_f) S_f \\
\frac{dI_m}{dt} &= \alpha f \phi[y, x] \beta[v] S_m - (ce^y + \mu_m + v) I_m \\
\frac{dI_f}{dt} &= \alpha f \phi[y, x] \beta[v] S_f - (da(S_m + I_m) \phi[y, x] + \delta e^x + \mu_f + v) I_f
\end{align*}
$$

where

$$
\psi[S_m, S_f, I_m, I_f] = b(S_f + I_f) \left(1 - \frac{S_m + S_f + I_m + I_f}{K}\right)(1 - \gamma S_m I_m)
$$

Similar to equation 4.6, there will be a three-way co-evolutionarily stable strategy when

$$
\begin{align*}
\frac{\partial r_m[y, \bar{y}, x, v]}{\partial \bar{y}} \bigg|_{\bar{y} = y^*, x = x^*} = 0 & \quad \text{and} \quad \frac{\partial r_f[y, x, \bar{x}, v]}{\partial \bar{x}} \bigg|_{\bar{x} = x^*} = 0 & \quad \text{and} \quad \frac{\partial r_v[y, x, v, \bar{v}]}{\partial \bar{v}} \bigg|_{\bar{v} = v^*} = 0
\end{align*}
$$

and their second derivative is negative.
Table 4.1: List of parameters and their definitions

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Model</td>
<td></td>
</tr>
<tr>
<td>$y$</td>
<td>male persistence trait</td>
</tr>
<tr>
<td>$x$</td>
<td>female resistance trait</td>
</tr>
<tr>
<td>$c$</td>
<td>persistence to males</td>
</tr>
<tr>
<td>$d$</td>
<td>mating cost to females</td>
</tr>
<tr>
<td>$\delta$</td>
<td>resistance cost to females</td>
</tr>
<tr>
<td>$\mu$</td>
<td>natural host mortality rate</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>encounter rate (rate females encounter males)</td>
</tr>
<tr>
<td>$\phi[y, x]$</td>
<td>mating rate between a male expressing persistence trait $y$ and a female expressing resistance trait $x$</td>
</tr>
<tr>
<td>$\gamma[M]$</td>
<td>probability of a female not mating given the number of males in the population, the resident persistence trait $y$, and the encounter rate $\alpha$</td>
</tr>
<tr>
<td>$v$</td>
<td>disease-induced mortality rate (virulence) of the sexually transmitted disease</td>
</tr>
<tr>
<td>$\beta[v]$</td>
<td>transmission rate</td>
</tr>
<tr>
<td>$w$</td>
<td>parameter determining the shape of the relationship between virulence and transmission</td>
</tr>
<tr>
<td>$b$</td>
<td>intrinsic birth rate of females</td>
</tr>
<tr>
<td>$K$</td>
<td>carrying capacity of the population</td>
</tr>
</tbody>
</table>

\[
\frac{\partial^2 r_m[y, \tilde{y}, x, \tilde{x}, v]}{\partial \tilde{y}^2} \bigg|_{\tilde{y}=\tilde{y}^*, \tilde{x}=\tilde{x}^*, v=v^*} \leq 0 \quad \text{and} \quad \frac{\partial^2 r_f[y, x, \tilde{x}, v]}{\partial \tilde{x}^2} \bigg|_{\tilde{x}=\tilde{x}^*, v=v^*} \leq 0 \quad \text{and} \quad \frac{\partial^2 r_v[y, x, v]}{\partial v^2} \bigg|_{y=y^*, x=x^*, v=v^*} \leq 0
\]

4.3.2 Individual-Based Simulation

We also carried out individual-based simulations, relaxing some of the simplifying assumptions inherent to the analytical model. Most notably we allowed the hosts to be diploid instead of haploid and used discrete generation times. Variation in host and parasite traits were generated by random mutation such that many different alleles for each trait could be segregating in the population at a time. In comparison, the analytical model assumes a separation of ecological and evolutionary timescales (i.e., the population always reaches ecological equilibrium before a new mutant is introduced). Furthermore, the analytical model assumes sequential invasion analysis, meaning that a mutant of one trait fixes in the population before a mutant of another trait is introduced. This avoids the complications that arise when genetic correlations must be taken into consideration but does not allow us to look at how assortative mating (males with the most persistence will more often mate with females with the least resistance) might change the evolutionary outcome. Note that in the individual-based simulation model, we change the assumption of density-dependent sexual disease transmission. We model a form of frequency-dependent transmission that assumes females encounter a certain number of males, drawn from a Poisson distribution with a mean that is independent of density, and mate with each encountered male with a probability that depends on the difference in their trait values, $u = y - x$. The probability of mating with an infected individual therefore depends on the fraction of infected males amongst all males. Individual-based simulations were carried out in Python for 50,000 generations, well after the trait values appeared to reach evolutionary equilibrium. Values from the last 1000 generations were averaged and reported in figures.
1, 3, and 5. A detailed description of the simulation model is provided in the Appendix.

4.4 Results

4.4.1 Evolution of Host Traits without STD

To understand how a coevolving sexually transmitted disease affects the outcome of sexually antagonistic coevolution we first consider how the host evolves in the absence of an STD. In the main text we focus on the results of the individual-based simulations (numerical solutions to the analytical model, provided in the Supplementary Material, show similar patterns). To help us understand how the mating rate changes with various costs we plot the difference between male persistence and female resistance, $u = y - x$, in figure 4.1A. The average of the two trait values, $(y + x)/2$, is an indicator of the magnitude of the traits (thereby, the degree of escalation in the conflict) and is plotted in figure 4.1B. Higher values (shown in yellow) therefore correspond to higher mating rates (fig. 4.1A) or a higher degree of conflict escalation (fig. 4.1B) while lower values are shown in red.

For the range of parameters shown in figure 4.1, male persistence $y$ always exceeds female resistance $x$, so the difference $u$ is positive and mating rates are not too low. As the cost a male pays for his persistence trait (persistence cost) increases, the difference between male and female traits ($u$) decreases (fig. 4.1A). Increasing the cost a female pays for mating (mating cost) selects for higher female resistance, decreasing this difference $u$ and consequently lowering mating rate (fig. 4.1A). As the cost of the females resistant trait (resistance cost) increases, $u$ increases as females with lower resistance better balance the tradeoff between sexually antagonistic selection and natural selection (data not shown). We observe negative differences between male persistence and female resistance ($u < 0$) when resistance costs are very small or zero; this results in very low mating rates. We do not explore this area of parameter space in depth because an STD cannot spread at low mating rates. We are primarily interested in comparing the outcome of sexual conflict in the presence and absence of an STD.

The extent of conflict escalation, as reflected by average trait values, increases substantially as the female mating cost increases (fig. 4.1B). This is driven by the female trait increasing to reduce the mating rate, while the male trait increases slightly in response. Males with higher persistence have more mating success but must pay the nonlinearly increasing cost of natural selection against persistence. Average trait values do not change drastically with increasing persistence costs.

4.4.2 Evolution of Host Traits with Coevolving STD

We first consider evolution of the host traits in the presence of a coevolving sexually transmitted disease and then later discuss virulence of the STD. Introducing a coevolving STD escalates the conflict between the sexes. This increase is driven by females. If only the females are allowed to evolve (not shown), female resistance will evolve to be higher than male persistence to reduce the additional cost of mating, i.e. increased rate of contracting the STD and the consequent disease-induced mortality associated with infection. Due to the absence of coevolution between males and females, female resistance evolves to be higher than male persistence such that $u = y - x$ is negative and the mating rate drops below 0.5. The STD cannot persist at low mating mates. If only the males are allowed to evolve, male persistence increases from its STD-absent equilibrium, presumably because males are selected to more quickly obtain additional mates in the face of higher mortality rates (due to infection). Opportunities
Figure 4.1: Two-way coevolution in individual-based simulations results gives evolutionary equilibria that qualitatively follow the same patterns as the analytical model. Shown here are (A) the difference between evolutionary equilibrium persistence, $y'$, and evolutionary equilibrium resistance, $x'$, (B) the average of $y'$ and $x'$. Parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$. Each cell represents the average of 10 independent simulations.

for STD transmission are high enough at large $u$ that the disease does not go extinct.

When females and males coevolve, male persistence increases further, tracking the increase in female resistance to ensure mating. These co-evolutionary feedbacks drive both traits upwards from their STD-absent equilibrium values but can decrease the difference in trait values when males do not increase their trait as much as females do (fig. 4.2). As such, we observe increased average trait values and decreased differences between traits (in some areas of parameter space) compared to when the STD is absent, in both the simulation (fig. 4.1 vs. fig. 4.3) and analytical (fig. 4.6 vs. fig 4.7) models. It is worth emphasizing that the evolution of male persistence in response to the escalation in female resistance allows the STD to remain in the system. If a lack of genetic variation in the male trait prevented its coevolution, the STD would go extinct after female resistance increased and caused a decrease in mating rates.

Compared to the disease-absent model, we observe similar trends in average trait values and differences between traits with changing costs to males and females (figs. 4.3 and 4.7). However, the difference between male persistence and female resistance ($u$) is less sensitive to the cost of mating to females in the presence of a coevolving STD. This observation is probably driven by the fact that $u$ is on average lower than in the absence of the STD. Females are mating less and the cost per mating is not affecting female resistance evolution so much as trying to reduce the costs associated with acquiring a sexually transmitted infection. Additionally, the degree of conflict escalation (as shown by the average trait values, fig. ??B) is more sensitive to changes in persistence costs than in the absence of the STD because of coevolutionary feedbacks between STD virulence and sexually antagonistic host traits.

### 4.4.3 Establishment and Virulence of the Sexually Transmitted Disease

In the section above, we focused on cases where both hosts and parasites can evolve and the disease establishes itself within the host population. (We use the term disease “establishment” rather than the
Chapter 4. Sexual conflict and STDs

Figure 4.2: Sample run from individual-based simulation where hosts evolve to their disease-absent equilibrium values before an STD is introduced. Male persistence is shown in blue, female resistance in red, and STD virulence in black. Parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$.

Figure 4.3: Three-way coevolution in individual-based simulations results in evolutionary equilibria that qualitatively follow the same patterns as the analytical model. Each simulation began with $x = 4$, $y = 6$, and $v = 0.8$. (In preliminary work, we found that equilibrium values were not sensitive to initial values, provided extinction did not occur.) Shown here are (A) the difference between evolutionary equilibrium persistence, $y'$, and evolutionary equilibrium resistance, $x'$, (B) the average of $y'$ and $x'$, in the presence of a sexually transmitted disease with evolutionary equilibrium virulence $v'$. Parameters used were as follows: $\bar{\sigma} = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.

more typical term “persistence” to avoid confusion with the host male’s “persistence” trait.) We now focus on understanding how a lack of genetic variation that prevents evolution of either host or parasite traits affects both the establishment and virulence of the STD. We discussed one important case above in which a lack of genetic variation in the male trait but not the female trait prevents the establishment
of a coevolving STD. Here we focus on contrasts between hosts and parasites in their evolvability (rather than on differences in evolvability between male and female host traits).

No Evolution of Either Hosts or Parasites

When hosts cannot evolve, the sexually transmitted disease spreads as it would in a basic susceptible-infected compartmental model. A sexually transmitted parasite near its equilibrium virulence will always persist when introduced into host populations at equilibrium for the parameter values considered here (except for rare stochastic extinctions). In comparison, a relatively avirulent STD will almost always go extinct and a highly virulent STD will only persist when the difference between host traits is large (and positive) enough that there is sufficient transmission opportunity via mating.

Evolution of Hosts But Not Parasites

In the presence of a sexually transmitted disease, females are selected to increase resistance, driving an increase in average trait values and a decrease in the difference between male persistence and female resistance (fig. 4.2). The accompanying decrease in mating rate can drive a highly virulent, non-evolving STD extinct if the difference between host trait values is small enough (i.e. at high persistence costs to males and high mating costs to females). The fraction of runs in which the parasite went extinct is shown in figure 4.4A. Extinction rates are higher over a wider range of parameter values when female resistance costs are low ($\delta = 0.001$, data not shown).

Figure 4.4: Fraction of simulation runs where a sexually transmitted disease (STD) was driven extinct by sexually antagonistic host coevolution. In each case the STD was introduced into a host population that had reached its equilibrium trait values in the absence of the parasite. (A) Non-evolving STD with $v = 0.8$, (B) Coevolving STD initially introduced with $v = 0.8$. Other parameters used were as follows: $\bar{\mu} = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. The value for each cell was based on 10 independent simulations.
Evolution of Parasites But Not Hosts

In the absence of host coevolution, a virulent evolving parasite never goes extinct (except rare stochastic extinctions) for the parameters considered here. The evolutionary equilibrium virulence level, \( v' \), is typically lower than if hosts were coevolving (fig. 5B) because average host trait values are lower in the absence of the STD (compare figure 1B to figure 3B).

Evolution of Hosts and Parasites

At negative (\( y < x \)) or small positive (\( y \sim x \)) differences between male persistence and female resistance, the mating rate is low enough that the STD goes extinct due to lack of transmission opportunity. Thus, when hosts and parasites coevolve, STD extinction occurs most often when the resistance cost to females is low (not shown) and the cost of mating is high. At higher resistance costs (e.g. \( \delta = 0.0005 \)) extinction occurs over a narrower range of parameter values (fig. 4.4B). We show the fraction of runs where a highly virulent parasite goes extinct when introduced into a coevolving population of hosts initially at their STD-absent equilibrium trait values (fig. 4.4B). At very high costs of mating, sexually antagonistic selection drives the female trait upwards and natural selection is not strong enough to keep female resistance far enough below male persistence to maintain sufficient STD transmission.

We now consider the STD’s equilibrium virulence in cases where the disease establishes. The three-way coevolution of the sexually transmitted disease with male persistence and female resistance (discussed above) gives rise to quantitatively different results than if the STD was introduced into a non-evolving host population (fig. 4.5). In general, the STD becomes more virulent if hosts coevolve than if they do not. This is because the addition of the STD to the system causes evolutionary increases in female resistance and, consequently, male persistence, increasing the host mortality rate; optimal STD virulence is expected to increase with host mortality rate (Knell, 1999). The equilibrium virulence of the STD increases as the average host trait values increase and does not depend on the difference in trait values (i.e., figs. 4.5A and B mirror figs. 4.3B and 4.1B, respectively). The difference in trait values only affects the spread and prevalence of the STD and not its evolutionary equilibrium virulence.

4.4.4 Stability of Equilibria

The evolutionary equilibrium trait values presented in figures 4.1, 4.3, and 4.5 are stable to different initial values with the exception of very low initial virulence of the STD (which goes extinct due to lack of transmission). Similarly, the co-evolutionary stable strategies (figs. 4.6 and 4.7) are convergence stable.

4.5 Discussion

Overall we found that sexually transmitted disease affected the outcome of sexual conflict. A sexual conflict system that results in equilibrium trait values in the absence of an STD will decrease its mating rate in the presence of an STD. Females increase resistance to reduce the additional cost of mating imposed by disease-induced mortality. As male persistence tries to stay above female resistance levels, average host trait values increase. A co-evolving STD will increase its virulence level in response. The three traits reach a co-ESS where the STD persists at a stable level of virulence that depends on overall host mortality.
Figure 4.5: Evolutionary equilibrium virulence of a sexually transmitted disease (STD) in a (A) coevolving and (B) non-evolving host population. In the non-evolving host population the parasite was introduced at the STD-absent male persistence and female resistance host trait values with $v = 0.8$. Other parameters used were as follows: $\alpha = 10$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.

Stabilizing selection maintains the coevolutionary equilibrium. Male persistence increases male reproductive success at the expense of increased mortality due to costs associated with expressing the persistence trait such as increased predation risk (Rowe, 1994) or reduced foraging time (Robinson and Doyle, 1985). Females suffer costs of mating but must balance these with the direct cost of expressing the resistance trait and the risk of remaining unfertilized if resistance is too high. The presence of a sexually transmitted disease changes the strength of the costs relative to the benefits; males experience stronger selection to increase reproductive success in the face of higher total mortality and females experience stronger selection to reduce the additional cost of mating associated with a prevalent STD.

One of the costs we do not explore in depth is the risk of females remaining unfertilized. In the analytical model we assumed that a female’s fecundity was reduced by her probability of not mating, $(1 - \phi)^{\alpha M}$. In the simulation model, a female that mated with at least one male could maximize her reproductive success. Female reproductive success only factored strongly into the outcome when the probability of mating was very low (in other words, when female resistance was higher than male persistence). At very high levels of female resistance, the host population cannot maintain itself. At moderately high levels of female resistance, the mating rate is so low that an STD cannot invade the host population. Beyond this, we did not investigate this area of parameter space because we were interested in the coevolution of host and STD when the STD had the potential to persist. However, if the fertilization rate was not the same as the mating rate (e.g. we included a probability of fertilization given that a sexual encounter has occurred), the risk of having reduced reproductive success might affect the evolution of female resistance. Thrall et al. (1997) constructed a model investigating how male and female mating behaviour affected reproductive success in the presence of a sexually transmitted disease. At high disease prevalence, they found that females could achieve the same reproductive success by being monogamous and reducing the probability of contracting the STD or by being promiscuous.
and maximizing the probability of fertilization but increasing the likelihood of becoming infected. It is possible that if there were higher probabilities of females being unfertilized in our model, there would be some females in the population who evolve high resistance to reduce mating rate and likelihood of infection but others who evolve low resistance to ensure fertilization.

We investigate the full three-way coevolutionary interaction over a range of mating costs to females. However, many empirical investigations of sexual conflict in natural systems have reported females suffer a cost of harassment instead of, or in addition to, the cost of mating (Watson et al., 1998; Rowe, 1994; Jormalainen, 1998; Alcock et al., 1977; Stone, 1995). Furthermore, many studies have reported increased harassment levels as the density of males increased (Gay et al., 2008; Lauer et al., 1996; Rowe, 1992). At high male densities or male-biased sex ratios, the cost of rejecting males can become so great that females are selected to decrease resistance, increasing overall mating activity in these systems (Rowe, 1992; Rowe et al., 1994; Lauer et al., 1996). If we were to incorporate a cost of harassment, we would expect selection for reduced female resistance when the cost of mating is less severe than the cost of resisting pursuing males. However, ecological feedbacks affecting male density might change these predictions when harassment costs increase as males become more common relative to females. For example, in a theoretical model, Rankin et al. (2011) found that male harassment harmed females to the extent that the population became male-biased, which further increased harassment levels and led to a positive feedback loop that eventually resulted in population extinction. Introducing a sexually transmitted disease could alter these types of ecological feedbacks between sexual conflict and male density in non-intuitive ways.

The majority of models that have investigated the evolution of host mating strategies in the presence of a sexually transmitted disease have assumed there is sexual selection, but no sexual conflict. Although closely related, the distinction between male attractiveness and female preference versus male persistence and female resistance has important consequences for the coevolution of a sexually transmitted disease. Choosiness helps females gain indirect benefits from mating with a preferred male. Resistance on the other hand helps females avoid direct costs of mating (Gavrilets et al., 2001). Females can still benefit from promiscuity or mate choice in a host population infected with an STD if the indirect benefits are good enough (Boots and Knell, 2002; Thrall et al., 1997). There is some selection for non-choosy females because the most popular males have high infection prevalence (Thrall et al., 2000). In a system with sexual conflict, those males with the highest persistence traits would be more likely than average males to be infected, adding to the cost of mating for females. In this case, females would be selected to increase resistance to reduce mating rates with “popular” males, selecting for what might be thought of as increased “choosiness”, opposite to what is observed in sexual selection models.

The STD itself could also change the coevolutionary outcome if it affects mating behaviour. One of the most well-studied ways that the presence of an STD can change host mating strategies is by transmission-avoidance (Graves and Duvall, 1995; Knell, 1999; Ashby and Boots, 2015). In a study of virulence evolution, Knell (1999) suggested that a conspicuous sexually transmitted disease that reduced its host’s ability to acquire mates would be selected for reduced virulence. Ashby and Boots (2015) did a full coevolutionary analysis of the evolution of host choosiness (based on transmission-avoidance) and STD virulence and found that the outcome, runaway selection, coevolutionary stable strategies, or coevolutionary cycling, depended on the exact parameters of the model. Coevolutionary cycling, for example, arose for low to moderate costs of transmission-avoidance strategies when the tradeoff between transmission and virulence was not too strong. Under these conditions, when virulence is high,
there is strong selection for host choosiness to avoid infected individuals. Parasites are then selected to become inconspicuous (i.e. show fewer signs of disease) by decreasing virulence, which in turn selects for less choosy behaviour. When hosts exhibit less choosiness, virulent parasites can spread again and the cycle repeats. These coevolutionary cycles are maintained by delayed negative frequency dependent selection. Because our sexual conflict system is characterized by stabilizing selection, we do not expect coevolutionary cycling if hosts could detect the degree of parasitism of a potential mate. Males with high persistence have high mating rates and therefore are more likely to contract an STD than males with lower persistence. If females were able to avoid infected males, this would decrease the advantage to males expressing higher persistence and decrease the strength of selection on females to increase resistance (and reduce the mating rate) because they can avoid the additional cost of mating associated with the STD. Therefore, we might expect less escalation of host trait values when an STD is introduced into a population of hosts with transmission avoidance experiencing sexually antagonistic selection.

Sexually transmitted diseases can also manipulate host behaviour that directly affects the sexual conflict. For example, parasitized males could be less competitive (Siva Jothy and Plaistow, 1999; Thomas et al., 1999), decreasing the risks of mating for females in a population with a highly prevalent STD. Alternatively, in the milkweed leaf beetle, males infected with a sexually transmitted disease were more aggressive than their uninfected counterparts, which could increase the number of matings and therefore the costs to females (Abbot and Dill, 2001). The STD could also manipulate host behaviour in such a way that its interests are aligned with one sex or another. It has been suggested that an STD that reduced female remating rate would actually be beneficial for males (Knell and Webberley, 2004) because a male that infects his mate would reduce her remating rate and ensure his own paternity. If the benefits of reducing sperm competition outweigh the mortality costs of the STD, males may be selected to increase persistence and consequently their likelihood of acquiring a sexually transmitted disease. Additionally, there is some evidence that infected females of the fall army worm moth have higher oviposition rates than uninfected females, meaning that males could benefit from acquiring and transmitting a sexually transmitted infection (Simmons and Rogers, 1994). There are numerous ways males and females could evolve in response to these changes in host mating behaviour. However, all of these examples suggest that a change in the cost structure in the presence of an STD could affect the outcome of sexual conflict, either increasing the difference between male persistence and female resistance such that males ‘win’, or further reducing the difference between traits.

There are many well-known examples of STDs and sexual conflict but we are aware of no systems where both are well studied. Evidence of sexual conflict and sexually transmitted diseases has been reported in ungulates (conflict, Bro-Jørgensen 2010; STD, Lockhart et al. 1996), Drosophila (conflict, e.g., Rice et al. 2006; STD, Knell and Webberley 2004), and the two-spot ladybird Adalia bipunctata (conflict, Haddrill et al. 2013; STD, Webberley et al. 2002; Ryder et al. 2005). Studies of sexually antagonistic traits in populations infected with an STD should look for escalated trait values compared to populations where the STD is absent. Research on sexually transmitted diseases should compare different populations or closely related host species that experience different costs of persistence to males and costs of resistance and mating to females. Variation in the costs of sexually antagonistic host traits could arise between populations if, for example, the persistence or resistance trait made the bearer more vulnerable to predation in an open versus closed habitat (see Fricke et al., 2009, for a discussion of the dependence of sexually antagonistic selection on environmental conditions). Higher mortality rates in one habitat should select for higher virulence in an endemic STD. Additionally, we expect lower
disease prevalence (fig. 4.8a) in populations where persistence is strongly selected against and there are high costs of mating for females.

It is natural to think that the outcome of sexual conflict over mating rate would affect the evolution of a disease transmitted via mating (i.e. an STD). However, STD virulence evolution is not affected by mating rate but depends on host mortality much like an ordinary infectious disease (OID). Furthermore, STD virulence in our model causes disease-induced mortality. Given that both STD and OID virulence affect mortality and are shaped by the same parameters, we might expect similar co-evolutionary outcomes if we model an ordinary infectious disease infecting hosts with sexual conflict over mating rate. An OID, however, is not transmitted sexually and therefore will not exert direct selection on females to reduce the mating rate. We might expect qualitatively similar patterns but quantitatively weaker ones because females will not increase resistance and drive average host trait values to increase. Indeed, a version of the model that incorporates an OID instead of an STD shows that this is the case.

We have shown that a sexually transmitted disease has the potential to influence the outcome of sexually antagonistic coevolution. Because STDs are ubiquitous in nature (Lockhart et al., 1996), they should co-occur with sexual conflict often enough that it is worth considering how STDs change sexually antagonistic selection. Furthermore, considering the full coevolutionary interaction has important implications for the conditions under which the sexually transmitted disease persists and interacts with the mating system.

4.6 Appendix

Below we describe the procedure for carrying out the individual-based simulations in Python (code available upon request).

**Sexual Conflict:** To initiate the population, diploid hosts are assigned trait values at the resistance and persistence loci by drawing random values from a normal distribution with mean $\bar{x}$ and $\bar{y}$, respectively, and variance 0.5. Each generation, females encounter a certain number of males, randomly drawn from a Poisson distribution with mean $\alpha$, and mate with each encountered male with a probability that depends on the difference in their trait values, $u = y - x$. Resistance ($x$) and persistence ($y$) levels expressed by a host are calculated as the average of the trait values from each chromosome (e.g., $x = (x_1 + x_2)/2$ where $x_1$ is the resistance allele on chromosome one and $x_2$ is the resistance allele on chromosome two). Gametes are formed with free recombination between loci and alleles experience mutation with probability $U_{host}$. The number of offspring born to a mated female is drawn from a Poisson distribution with mean $b*(1 - (M + F)/K)$. If a female has mated with multiple males (let $m$ be the number of males she mated with), a given male sires an average of $1/m$ of her offspring. After mating (but before giving birth), adult females die with probability $(1 - e^{-(\mu_f + \delta e^x + d*m)})$ and adult males die with probability $(1 - e^{-(\mu_m + \delta e^y)})$. The surviving adults and newborn offspring make up the next generation, whose mean and variance in host trait values are recorded before undergoing another round of mutation, mating, and selection.

**STD:** In host populations infected with a sexually transmitted disease (STD), the STD is introduced into 5% of hosts with the virulence of each infection drawn from a normal distribution with mean $\bar{v}$ and variance 0.1. Given that mating has occurred, the STD is transmitted from an infected host to a susceptible host with probability $\beta[v]$. A newly infected host suffers additional mortality $v$ but cannot infect other hosts unless it survives to the next generation (thus, the STD has a latent period before disease carriers are infectious). During this latent period the STD undergoes mutation with probability.
$U_{\text{STD}}$. At the start of each generation, the population mean and variance in virulence are recorded.

### 4.7 Supplementary Material

![Diagram showing two-way coevolution between male persistence and female resistance](image)

Figure 4.6: Two-way coevolution between male persistence and female resistance yields evolutionary stable strategies across a range of persistence costs to males and mating costs to females. Shown here are (A) the difference between ESS persistence, $y^*$, and ESS resistance, $x^*$, (B) the average of $y^*$ and $x^*$. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$. 


Figure 4.7: Three-way coevolution between male persistence, female resistance, and STD virulence yields evolutionary stable strategies across a range of persistence costs to males and mating costs to females. Shown here are (A) the difference between ESS persistence, $y^*$, and ESS resistance, $x^*$, (B) the average of $y^*$ and $x^*$, and (C) ESS virulence of the sexually transmitted disease, $v^*$. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. 
### Table 4.8: Disease prevalence, calculated as the fraction of the host population infected with the sexually transmitted disease (STD), resulting from the three-way coevolution between male persistence, female resistance, and STD virulence in individual-based simulations. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.

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</tbody>
</table>

Figure 4.8: Disease prevalence, calculated as the fraction of the host population infected with the sexually transmitted disease (STD), resulting from the three-way coevolution between male persistence, female resistance, and STD virulence in individual-based simulations. Parameters used were as follows: $\alpha = 0.03$, $\delta = 0.0005$, $\mu = 0.2$, $b = 4$, $K = 1000$, $w = 1$. Each cell represents the average of 10 independent simulations. A small number of simulations in which the disease went extinct are excluded from calculating the average.
Chapter 5

Conclusion

My thesis is comprised of three unrelated chapters. What links them all together is the common goal of trying to predict biological patterns using theoretical approaches. Each chapter is an extension of a more general theory (or theories as is the case in chapter 4) that incorporates an additional dimension of biological realism. I explore how this addition changes the evolutionary outcome compared to results based on classic assumptions and try to elucidate what drives any difference between results. My goal is to understand the various factors and processes that shape the evolutionary outcome.

In my second chapter I investigated the rate of accumulation of deleterious mutations by Muller’s ratchet in temporally fluctuating environments. I extended previous theory by modeling temporally autocorrelated fluctuations in selection. I proposed and tested the verbal hypothesis that conditionally neutral mutations should speed up the rate of mutation accumulation and fitness decline in asexual populations. I found that the ratchet ‘clicks’ rapidly when mutations are neutral, increasing the rate of fitness decline because accumulated mutations are strongly selected against when selection is ‘on’. Varying some of my exploratory assumptions, I found that changes in the strength of selection (rather than conditional neutrality) and changes in the fraction of the genome experiencing temporal fluctuations in selection (rather than the entire genome) quantitatively, but not qualitatively, changed the rate of mutation accumulation and fitness decline. My results make a general prediction about how temporal heterogeneity in selection should affect finite asexual populations and increase our understanding of the forces contributing to fitness decline in asexual species.

My third chapter is an exploration of the evolution of virulence in heterogeneous host populations. Again, I extended the theory to add biological realism. In this case I built on previous models of the evolution of virulence in multigroup hosts by incorporating differences in susceptibility and resistance between host types and most importantly, non-random contact patterns. I make interesting qualitative predictions about how differences in susceptibility and resistance to disease interact with contact pattern to shift the evolutionarily stable exploitation rate closer to the more susceptible host type. In addition, I had initially suggested that the evolution of an unconstrained parasite able to recognize and express different exploitation rates in each host type might be affected by the presence of interacting hosts. However, I showed that my verbal hypothesis about the evolution of an unconstrained parasite did not account for epidemiological feedbacks that selected for the pathogen to express the same exploitation rate in each host type as it would in a homogeneous population composed entirely of that host type. The exception to this was if the parasite could be vertically transmitted (from mother to offspring), in
which case the optimal exploitation rate in females depended on the amount of horizontal versus vertical transmission. Overall, I extend understanding of the types of differences between hosts that should be important for virulence evolution in heterogeneous host populations.

My fourth and final research chapter also investigated the evolution of virulence but this time of a sexually transmitted disease in a host population experiencing sexually antagonistic coevolution. I combined two previously disparate fields of theoretical biology in an attempt to understand how a parasite that is transmitted during mating affects sexual conflict over mating rate. I found that an STD selects for increased sexually antagonistic host traits because of its effects on host mortality. Males increase persistence levels in an effort to mate before dying at higher overall mortality rates. Females increase resistance levels to reduce the additional cost of mating associated with contracting the STD. Virulence of a coevolving STD increases in response to the higher baseline mortality rate of the hosts (which arises from natural selection against increased sexually antagonistic trait values). This three-way coevolution leads to stable host and parasite strategies. The patterns I observed across a range of parameters were robust to relaxing logistical assumptions (in the computer simulation model) such as haploidy and separation of ecological and evolutionary time scales. My results suggest the evolution of sexual conflict in natural systems could be escalated by the presence of disease, past or present, and that STDs should be factored into estimations of the strength of natural and sexually antagonistic selection.

Each chapter makes progress in its respective area of evolutionary biology by proposing a novel extension of previous theory. Above, I have tried to highlight how my research chapters model different aspects of theoretical biology. In particular, I have touched on how my chapters test verbal hypotheses and explore the factors affecting the evolutionary outcome by varying assumptions and parameters. Using analytical and computer simulation results I make qualitative predictions about how systems should evolve and improve our conceptual understanding of evolutionary biology.
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