Invariant manifolds of models from Population Genetics

Belgin Seymenoğlu

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
of
University College London.

Department of Mathematics
University College London

January 22, 2019

I, Belgin Seymenoğlu, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the work.

Abstract

Many models in population genetics feature some form of convergence of the genetic state of the population, typically onto a globally attracting invariant manifold. This allows one to effectively reduce the dynamical system to a problem with fewer dimensions, making it easier to investigate the stability of the steady states in the model, as well as to predict the long-term evolution of the population. Moreover, along this manifold, there is a balance between multiple processes, such as selection and recombination.

For some models, restrictive assumptions such as small selection coefficients or additivity of fertilities and mortalities has helped show global contraction of dynamics onto a manifold which is close to the well-known Hardy-Weinberg manifold, and on this ‘quasiequilibrium’ manifold the dynamics can be written in terms of allele frequencies (which is of more practical interest to geneticists than the genotype frequencies).

This thesis focuses on proving the existence of an invariant manifold for two continuous-time models in population genetics: one is proposed by Nagylaki and Crow and features fertilities and mortalities (death rates), while the other is the selection-recombination model. Common themes in both proofs include a change of coordinates such that the dynamical system is monotone with respect to a certain cone. As a result, it is possible to construct an equicontinuous sequence of functions which has a convergent subsequence. We show this limiting function is indeed invariant. In fact, for the latter model, we show the manifold is globally attracting by proving the phase volume is contracting. The conditions obtained from the proofs are less restrictive than the use of parameters that are small or additive, hence our work is more widely applicable.

For the former model, numerical examples are also provided in which the manifold need not be smooth, convex, unique or globally attracting.

Impact Statement

My research impacts both the Population Genetics and Invariant Manifolds communities. Many Population Genetics models, including the two investigated in this thesis, feature some sort of convergence onto a curve, surface or a similar object with fewer dimensions than the original system. Existence of these so-called invariant manifolds has been previously proven for both models, but with very restrictive assumptions such as additivity of fertilities or small selection coefficients. My new existence conditions for the Nagylaki-Crow model covers a broader range of the parameters, hence is more widely applicable. Meanwhile, for the Selection-Recombination model, I derive easily testable conditions for the existence of the quasi-linkage equilibrium (QLE) manifold.

My work will also be of interest to those studying Monotone Systems Theory or applying it in models from biology, chemical reactions, economics, etc. My existence proof for a nonmonotone invariant manifold in the Nagylaki-Crow model does not require the system to be strongly competitive in either set of coordinates. In addition, I proved a lemma about the intimate connection between a cone being invariant under normal dynamics, and the system being competitive with respect to the dual of said cone. Although I only applied the result on the Selection-Recombination model, it should also be applicable to other dynamical systems.

Moreover I investigated the special case of the Selection-Recombination model with zero recombination. By converting the system to Lotka-Volterra dynamics and mapping its carrying simplex back, I deduced the existence of a new invariant manifold, distinct from the QLE manifold. The equations of motion for this case are identical to replicator dynamics with a symmetric fitness matrix, hence the results will be useful for evolutionary game theorists. I also predicted that similar results will hold for different-dimensional replicator systems; furthermore, the fitness matrix need not be symmetric.

One paper has been published so far, and one more is currently under review. I am now working towards one or two further publications loosely based on Chapters 6 and 7. In addition, two different talks and two conference posters were presented at various conferences.

Acknowledgements

First of all, I would like to thank both my parents for constantly supporting my goals and dreams, always being proud of me and making sure I didn't push myself when I was ill. In addition, Mum helped me to practice my presentations and baked uncountably many cakes for me and my office mates.

I am also deeply grateful to Mr Adem, my maths teacher from secondary school, for noticing my passion in mathematics and encouraging it to bloom. Without his influence, this thesis would have almost certainly been about Physics, Biology or Computer Science instead!

Special mention goes to all my PhD colleagues from the KLB and the seventh floor, past and present - not just because you happily ate Mum's cakes every Wednesday! You offered invaluable advice for my conference talks/posters, reminded me to have frequent breaks from my research, made tea for me, offered some interesting and valuable academic comments, and gave your warm wishes. I shared plenty of lunches, tea breaks, conferences, walks and banter with many of you. We even played table tennis, Set and Dobble. Most importantly, thank you for being such wonderful friends. I will miss all of you dearly, and I hope to visit you again in the future.

In addition, I feel lucky to have been jointly funded by the Department of Mathematics and the EPSRC for my research. It has been a privilege to serve as a Half-Teaching Assistant - I had a blast with my five tutor groups, and even had a good laugh while marking homework and exam scripts. The most rewarding teaching opportunity was lecturing an undergraduate course for two consecutive years. Furthermore, rewriting the lecture notes gave me plenty of LaTeX practice before using it again to type my thesis!

Many thanks also goes to Helen H, Soheni, Harry, Sukh, Ibrahim and the rest of the support staff - without them, the department wouldn't run like clockwork! Who else would handle my expense forms, replenish the KLB supply of Yorkshire Tea or install a new printer?

It has been an honour to have Rod Halburd and Josef Hofbauer as my thesis examiners, who offered plenty of valuable comments and corrections. They also provided some witty remarks during my viva!

Most importantly, I cannot imagine a better supervisor than Dr Stephen Baigent - he was always kind, patient (especially with my "relaxed" writing style!) and never ran out of ideas or jokes. Steve also held a small Journal Club, which inspired me to run a Mathematical Biology Journal Club of my own, and then the Dynamical Systems Reading Group. Moreover, he let me be the first and corresponding author of a paper! I am indebted to Steve for proofreading my work and providing helpful feedback. This thesis would not have been possible without Steve's support and advice.

In memory of my father - the original Dr Seymenoğlu.

Contents

List of Figures

List of Tables

Notation

Vectors will be denoted using bold font, e.g. $\mathbf{x}$, as done in [2]. In addition, the following notation is used throughout this thesis:

$\mathbf{x} \geq \mathbf{y}$	$x_i \geq y_i$ for $i = 1, 2, \ldots n$
$\mathbf{x} > \mathbf{y}$	$\mathbf{x} \geq \mathbf{y}$ and $\mathbf{x} \neq \mathbf{y}$
$\mathbf{x} \gg \mathbf{y}$	$x_i > y_i$ for $i = 1, 2, \ldots n$
$\mathbf{x} \geq_K \mathbf{y}$	$\mathbf{x} - \mathbf{y} \in K$; K being a proper cone
$\mathbb{R}^+$	$[0, \infty)$
$\mathbb{R}^n$	n-dimensional real space
$\mathbb{R}^n_+$	Nonnegative orthant
$\mathbb{R}^{n \times n}$	All $n \times n$-dimensional real matrices
∂S	Boundary of the set S
$\operatorname{int} S$	Interior of the set S
$\bar{S}$	Closure of S

Chapter 1

Summary

Many models in population genetics feature some form of convergence of the genetic state of the population, typically a steady state, limit cycle, invariant manifold, etc. This allows geneticists to effectively reduce the dynamical system to a problem with fewer dimensions, making it easier to investigate the stability of steady states in the model, as well as to predict the long-term evolution of the population.

In some models, the existence of an invariant manifold has only been proven in the presence of some very restrictive assumptions. For example, the existence of a manifold for the Selection-Recombination model in Chapter 6 can be proven if weak selection is assumed. None of the existence proofs in this thesis make use of small or additive parameters. Moreover, we explore the connection between the new results and whether the model is competitive with respect to some cone. A common trick used in the thesis is changing coordinates to make the analysis simpler. The new existence conditions obtained for one of the models, the Nagylaki-Crow model in Chapter 5, are more widely applicable. A gallery of numerical examples is also provided showing that the invariant manifold need not be smooth, decreasing, convex or unique.

Although the object of interest in each model is an invariant manifold, another branch of dynamical systems is used throughout this thesis: monotone systems theory. A mixture of techniques from analysis, geometry and topology is also applied.

This thesis is written with the general mathematician in mind. No prior knowledge of genetics or dynamical systems is assumed, although a background in func-

tional analysis is helpful; a good reference can be found in [3]. The required background for population genetics, invariant manifolds and monotone systems is given in Chapters 2, 3 and 4. However, those who are already familiar with all the content can start reading from Chapter 5.

Also, the equations for the continuous-time selection model are identical to replicator dynamics, which in turns out to be topologically equivalent to the Lotka-Volterra system. Any readers with a penchant for game theory or ecology are welcome to turn to Chapter 7 first (if they already know the background).

Chapter 2

Background on Population Genetics

The aim of this chapter is to introduce a mathematician to the concepts of genetics required to understand the models studied in this thesis. Basic ideas from genetics are given in Section 2.1, then Mendel's pea plants are used as an example to illustrate these ideas and to introduce Mendel's Laws of inheritance in Section 2.2. Section 2.3 goes into the Hardy-Weinberg Law. Finally, genetic recombination is discussed in Section 2.4. Much of the content in this chapter can also be found in [4, 2, 5].

2.1 Basic genetics

We have come a long way since Gregor Mendel discovered genes in 1886 [6]. By tracking the inheritance pattern in pea plants, he found that traits are inherited in discrete units called *genes*, and they come in different variants, or *alleles*. In everyday language, people might talk of someone "having a gene", such as a gene for brown eyes, a curly hair gene, or even a memory gene! What they are actually referring to is someone having the specific allele for that trait.

Genetic material is stored as DNA coiled up in long, threadlike structures called *chromosomes*. The location of a particular gene on a chromosome is called its *locus*. In 1902 Sutton and Boveri correctly predicted that genes are arranged linearly on chromosomes [7, 8, 9]. Different species have different numbers of chromosomes. For example, humans have 46 chromosomes; as these are arranged in pairs, we say that humans are a *diploid* species. The last pair of chromosomes, the *sex chromosomes*, determine the sex of the individual (XX for female, XY for male). Meanwhile, the other 22 pairs of chromosomes are called *autosomes*. Two chromosomes that belong to the same pair are said to be *homologous*. Other mammals, birds and reptiles and Mendel's pea plants are diploid too, but some fish, amphibia and many plants have more than two sets of chromosomes. The Uganda clawed frog has one of the highest numbers of sets of chromosomes in the animal kingdom [10]: twelve! In this thesis, we will only consider diploid organisms.

Reproduction of an organism can be *sexual* or *asexual*. An organism that reproduces asexually basically clones itself - the offspring are genetically identical to their single parent (except for rare mutations). Meanwhile, for sexual reproduction in diploids, there is a type of cell division called *meiosis* in which the chromosomes of a diploid cell duplicate before the cell splits into four *haploid* daughter cells, i.e. each with only one set of chromosomes (Figure 2.1). The haploid cells are called *gametes*; these are sperm and eggs in animals, or pollen and ova in plants. During mating, *fertilisation* occurs in which a sperm and an egg fuse together into a *zygote*, restoring the full number of chromosomes. A new individual develops from the zygote.

Suppose we consider just one locus with n alleles $A_1, A_2, \ldots A_n$. Then the *genotype* for a diploid organism is determined by the pair of alleles A_i/A_j it possesses at that locus. The convention of listing the paternal allele first is taken from [2]. Meanwhile, the *phenotype* of the organism is the observable expression of his or her genotype. If both alleles at that locus are identical, i.e. has genotype A_i/A_i for some i, we say the individual is *homozygous*; otherwise the alleles are different, so the individual is *heterozygous* instead and the genotype can be expressed as A_i/A_j with $i \neq j$. Note that the heterozygotes A_i/A_j and A_j/A_i are treated as the same genotype, since the order of the alleles has no effect on the individual.

Geneticists are interested in tracking the frequencies of genotypes and alleles; we will let freq(A_i/A_j) and freq(A_i) represent the frequencies of the genotype A_i/A_j and the allele A_i respectively. The genetic state of the population can be represented using a vector $\mathbf{x}$ whose i^{th} component is $x_i = \text{freq}(A_i)$. As allelic frequencies should

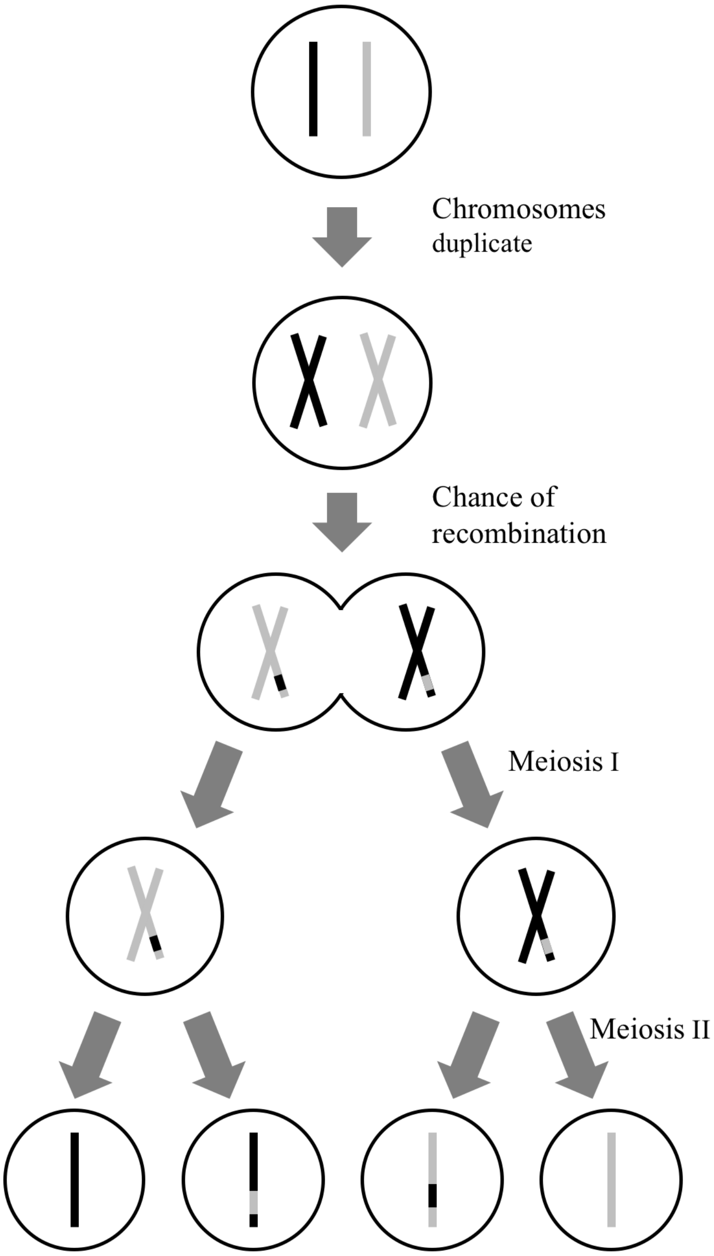


Figure 2.1: The process of meiosis, which involves two divisions, thus creating a total of four daughter cells (gametes). For simplicity, only one pair of homologous chromosomes is shown. There is a chance of the duplicated chromosomes crossing over and exchanging material before the first division; this is called *recombination* which will be discussed in Section 2.4.

be non-negative and sum up to one, the state vector $\mathbf{x}$ will belong to the following set

$$\Delta_n = \left\{ \mathbf{x} \in \mathbb{R}^n : x_i \geq 0, \sum_{i=1}^{n} x_i = 1 \right\}$$

which is called the *n-simplex* [2]. Similarly, genotype or gamete frequencies are also represented by state vectors in simplices.

One difficulty is that the number of genotypes in a population is much larger than the number of alleles and quickly becomes gigantic [4]. A diploid population consisting of 100 loci, even with only two alleles per locus would have 3^{100} distinct genotypes, which is a bigger number than any realistic population size! Even the two-locus two-allele models in this thesis have nine distinct genotypes, which is already a lot of dynamical variables to track - often it is much simpler to focus on the gametic frequencies only.

All the models discussed in this thesis are continuous-time, hence they share some common assumptions. First, the population of sexually reproducing diploids is taken to be infinite. Also, generations are not discrete and overlap, the allele frequencies are assumed to be the same in each sex, and there is no mutation or migration. In the selection-recombination and continuous-time selection models, mating is assumed to occur without regard to ancestry or genotype, hence is said to be *random* [5]. A randomly mating population is sometimes called *panmictic* instead.

2.2 Mendel's Laws

In his experiments, Mendel tracked the inheritance patterns for seven different characteristics in pea plants: seed shape, seed colour, pod shape, pod colour, flower colour, flower position and height [6]. For simplicity, let us consider flower colour only, which is governed by a single locus. There are two phenotypes: red and white; we will denote the respective alleles by R and r respectively. Then the genotype for an individual plant consists of the pair of alleles at that locus, e.g. R/R.

First, Mendel established "pure" lines of plants, which produced offspring with the same trait when self-fertilised. He bred one line for red flowers and another for white; their genotypes were R/R and r/r respectively. Next, Mendel crossed the red line plant with the white one. All the offspring in the new generation, labelled as $F1$, have the same genotype R/r and bore red flowers - the white allele r did not express itself at all. However, when he self-pollinated the $F1$ plants to produce the next generation ($F2$), the ratio of plants with red to white flowers was 3 : 1.

At the time, biologists believed in a "blending" theory of inheritance, i.e. an individual would inherit an average of its parents' traits. However, Mendel's results defied the blending theory: had it been correct, all $F1$ plants would bear pink flowers instead, which would subsequently produce more pink flower plants for generation $F2$ (Figure 2.2).

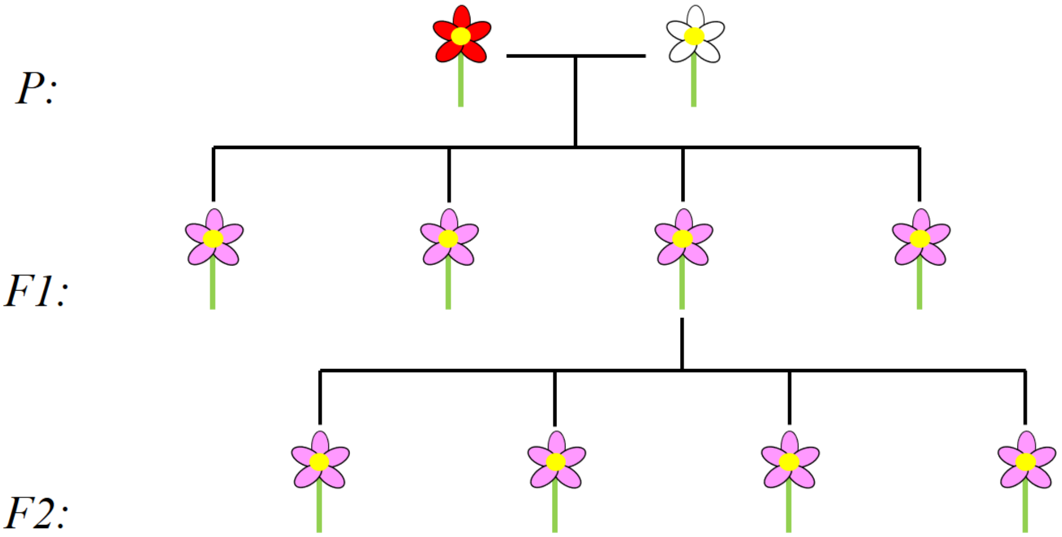


Figure 2.2: The inheritance of flower colours had the blending theory been correct. Variation is already lost by generation $F1$.

Rather, Mendel's reasoning was as follows: when self-fertilised, each homozygote R/R and r/r always gives R/R and r/r offspring respectively, hence these must be the genotypes for the red and white pure-bred lines respectively. Meanwhile, the pairing $R/R \times r/r$ always leads to R/r offspring (which corresponds to cross-fertilising the pure-bred lines to produce generation $F1$). Because all $F1$ plants had red flowers, he deduced that the red allele R was masking the effect of the white allele r, so R is said to be a *dominant* allele, while r is the *recessive* one. As shown in Table 2.1, the four (equally likely) outcomes for the pairing $R/r \times R/r$ are R/R, R/r, r/R, r/r. With R being dominant, only plants with genotype r/r will possess white flowers. The other three outcomes all lead to red flowers, hence the 3 : 1 ratio in the $F2$ generation. A summary of all this is given in Figure 2.3.

	R	r
R	R/R	R/r
r	r/R	r/r

Table 2.1: The *Punnett square* showing all the possible outcomes for the $R/r \times R/r$ pairing. Each outcome is assumed to be equally likely to occur, i.e. with probability $\frac{1}{4}$. Note that R/r and r/R are treated as the same (unordered) genotype.

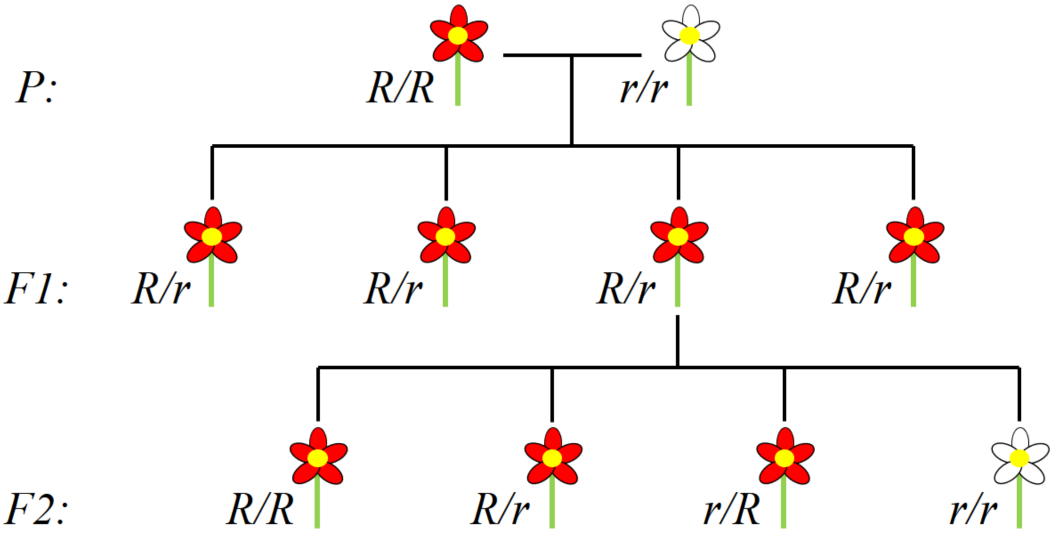


Figure 2.3: Mendelian inheritance of flower colour in pea plants.

In addition, Mendel deduced the following laws, which apply for diploid organisms:

Law of segregation: During meiosis, the two alleles at the given locus will segregate into gametes. The segregated alleles are reunited when gametes fuse together at *fertilisation*

Law of Independent Assortment: Alleles for different (non-interacting) loci are distributed to offspring independently.

Law of dominance: Some alleles are dominant, while others are recessive. If at least one dominant allele is present in the genotype, then the trait displayed will match the dominant allele.

2.3 The Hardy-Weinberg Law

To explain this principle, we present perhaps the simplest (discrete-time) model in population genetics:

Take an (infinitely) large population of diploid organisms that reproduce sexually, and consider just one locus α on an autosome with n alleles $A_1, A_2, \ldots A_n$. There are no evolutionary forces acting on the population, e.g. selection, recombination, mutation, migration. Furthermore, suppose that generations are discrete and non-overlapping, as is the case for annual plants and many insects. We also assume the genotype frequencies are the same in each sex, although it is demonstrated in [5] that the same results are reached even if the frequencies initially differ between the sexes, delayed by only one generation.

Let P_{ij} denote the frequency of genotype A_i/A_j. Then by Mendel's Law of Segregation [2]

$$p_i = \frac{1}{2}\sum_j \left(P_{ij} + P_{ji}\right),$$

is the frequency of allele A_i in the gamete pool of the population. If mating occurs randomly, i.e. without regard to the genotype at α, random union of gametes gives the genotype frequencies

$$P'_{ij} = p_i p_j \tag{2.3.1}$$

for the next generation. Hence the allelic frequencies remain unchanged,

$$p'_i = \frac{1}{2}\sum_j \left(P'_{ij} + P'_{ji}\right) = \cancel{2}\frac{1}{\cancel{2}}\sum_j p_i p_j = p_i,$$

which implies *Hardy-Weinberg proportions,*

$$P'_{ij} = p'_i p'_j \tag{2.3.2}$$

is obtained in only one generation. All this implies the *Hardy-Weinberg Law*, which states that the allelic frequencies stay constant from generation to generation, and from the second generation onwards, the proportion of homozygous genotypes A_i/A_i is given by p_i^2, while those for (unordered) heterozygous genotypes A_i/A_j $(i \neq j)$ are $2p_i p_j$.

The principle was first reported for the two-allele case ($n = 2$) with $p_1 = p_2 = 0.5$ in [11, 12], and for other values in [13]. Then Weinberg obtained the result for general p_1, p_2 assuming absence of heterozygotes in the first generation [14], while Hardy independently analysed the most general situation for two alleles [15]. Later, Weinberg extended the principle to multiple alleles [16]. The set

$$\Sigma_H = \{(P_{11}, P_{12}, P_{21}, P_{22}) \in \Delta_4 : P_{ij} = p_i p_j,\ P_{ij} = P_{ji}\}$$

is called the *Hardy-Weinberg manifold.*

2.3.1 Linkage between loci

Now take two loci α and β, each with two alleles: A, a for the locus α and B, b for the locus β.

Then there are four possible gametes ab, Ab, aB and AB; these haploid genotypes will be denoted by G_1, G_2, G_3, G_4, whose frequencies at the zygote stage (i.e. immediately after fertilisation) are freq(ab) = x_1, freq(Ab) = x_2, freq(aB) = x_3 and freq(AB) = x_4 respectively [2].

The linkage of disequilibrium coefficient $D = x_1x_4 - x_2x_3$ is a measure of the statistical dependence between the two loci. Let freq(a) denotes the frequency of allele a in the gamete pool, freq(ab) be the frequency of genotype ab, and so on. Then [2]

$$D = \text{freq}(ab) - \text{freq}(a)\text{freq}(b),$$

hence $D = 0$ if and only if

$$\text{freq}(ab) = \text{freq}(a)\text{freq}(b),$$

with similar results also holding for each of Ab, aB and AB. In this scenario, the population is said to be in *linkage equilibrium*, and the biological interpretation is that the frequency of gamete genotypes is simply the product of the frequencies of the alleles contributing to that genotype. The set corresponding to $D = 0$, i.e.

$$\Sigma_W = \{\mathbf{x} \in \Delta_4 : x_1x_4 = x_2x_3\},$$

is known as the *Wright Manifold*.

At first it is easy to confuse the Wright manifold with the $n = 2$ case of Hardy-Weinberg proportions, because both are described by genotype proportions being given as products of their component alleles. However, linkage equilibrium focuses on gamete genotypes for two or more loci. As each allele in the gamete belongs to a different locus, there are no symmetries imposed on gamete genotypes. Meanwhile, for the Hardy-Weinberg proportions described in 2.3, we concentrate on the full diploid genotype at a single locus. Moreover, there is a symmetry constraint on the full genotypes because A_1/A_2 and A_2/A_1 are treated as identical.

2.4 Genetic recombination

Towards the end of the nineteenth century Rückert predicted exchanges of genetic material between the (duplicated) maternal and paternal chromosomes during meiosis [17]. Boveri drew the same conclusion in 1904 after his experiments with sea urchins [9], before Janssens discovered that the exchanges happen when the maternal and paternal chromosomes cross over [18], see Figure 2.4.

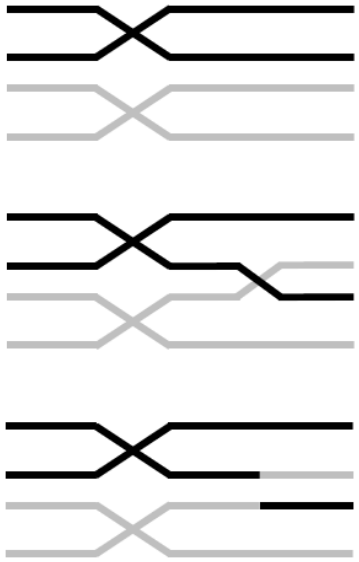


Figure 2.4: The paternal chromosome (black) crosses over with the maternal (grey) one during recombination, leading to genetic material being swapped.

This phenomenon is called recombination, and it leads to genetic variation among the resulting offspring [2, 18]. In this thesis we assume recombination does not create new genes, but produces new combinations of genes [2]. The maximum rate of crossovers with recombination, r, is a half, which occurs when the two loci belong to two different chromosomes. On the other hand, if the two loci are on the same chromosome, then $r \in (0, \frac{1}{2})$. This rate increases with physical distance between loci; Haldane's reasoning for this range of values of r is given in [19].

There has been much discussion on the evolutionary benefits of recombination, and many hypotheses were put forward [4, 20]. Two main ideas are the Fisher-Muller theory [21, 22] and the notion that recombination allows the population to adapt more readily to an ever-changing environment.

Fisher and Muller considered a population with new mutants bearing beneficial alleles at multiple different loci. Their theory is that if recombination does occur within the population, favourable alleles that occur in different individuals can ultimately combine into a single lineage, preventing future competition between multiple beneficial alleles. Such competition would slow the spread of, or even eliminate, some of the advantageous alleles [23]. Equivalently, recombination prevents the build-up of deleterious alleles in an individual. Other population geneticists investigated the theory; those whose models consisted of a finite population size saw advantages of recombination [24], while those assuming an infinite population found no benefit [25, 26, 27, 28, 29, 30, 31, 32].

The effect of selection is to continually produces linkage disequilibrium. The average effect of these disequilibria is to retard the response to selection. Recombination speeds the response to selection by breaking down this linkage disequilibrium [24]. In fact, in the absence of selection, recombination causes the linkage disequilibrium to approach zero in the long-run.

Chapter 3

Background on invariant manifolds

Invariant manifold theory is fundamental to the study of dynamical systems. The overall goal in the theory is to look for (sub)manifolds of the phase space that are invariant under the flow, i.e. orbits that start on the manifold stay in it for all time. The advantage is that restriction to the invariant manifold reduces the original system to a lower-dimensional problem or even a steady state; for a population geneticist it becomes much easier to predict the long-term evolution of the genetic state of the population.

The first rigorous results for invariant manifolds emerged at the beginning of the twentieth century [33, 34, 35, 36]. Hadamard's existence proof for stable and unstable manifolds of dynamical systems in 1901 took a different method from that of Cotton, Lyapunov and Perron. The latter technique is now known as the Lyapunov-Perron method, although Cotton's proof emerged in 1911, before Perron expanded on Cotton's ideas by 1929 to cover cases with complex eigenvalues.

We start by introducing the reader to basic ideas in dynamical systems theory in Section 3.1. Some fundamental concepts from topology and the notion of topological equivalence are also provided in Section 3.2. The stable, unstable and centre subspaces of a steady state in the system are introduced in Section 3.3, which are related to some of the types of invariant manifold reviewed in Section 3.4. Finally, four different methods of proving existence of an invariant manifold are discussed in Section 3.5. Most of the material in this chapter is based on [37, 38, 39].

3.1 Introducing dynamical systems

We begin by defining a dynamical system as given in [37, 40]:

Definition 3.1.1. *A* dynamical system *on a set E is a* C^1*-map*

$$\Phi : \mathbb{R} \times E \to E,$$

where E is an open subset of $\mathbb{R}^n$ *and if* $\Phi_t(\mathbf{x}) = \Phi(t, \mathbf{x})$*, then* Φ_t *satisfies*

(i) $\Phi_0(\mathbf{x}) = \mathbf{x} \qquad \forall \mathbf{x} \in E.$

(ii) $\Phi_t \circ \Phi_s(\mathbf{x}) = \Phi_{t+s}(\mathbf{x}) \qquad \forall s, t \in \mathbb{R} \quad \textit{and} \quad \forall \mathbf{x} \in E.$

Then the family of transformations Φ_t makes a semi-group under composition, and is called the *semi-flow* of the system. If

$$\Phi_{-t}(\Phi_t(\mathbf{x})) = \Phi_t(\Phi_{-t}(\mathbf{x})) = \mathbf{x} \qquad \forall t \in \mathbb{R} \qquad \forall \mathbf{x} \in E$$

also holds, the transformations become a group, and Φ_t is called the *flow* instead.

The *trajectory* of a point $\mathbf{x}$ is the map $\Phi(\cdot, \mathbf{x}) : \mathbb{R} \to E$, $t \to \Phi_t(\mathbf{x})$; its image

$$O(\mathbf{x}) = \{\Phi_t(\mathbf{x}) : t \geq 0\}$$

is called the *semi-orbit* of the point x. When $O(\mathbf{x}) = \mathbf{x}$, the point $\mathbf{x}$ is a *steady state* [41].

A straightforward example has $\Phi(t, \mathbf{x}) = \exp(At)\mathbf{x}$, where A is an $n \times n$ matrix. The flow defines a dynamical system on $\mathbb{R}^n$ and for each $\mathbf{x_0} \in \mathbb{R}^n$, $\Phi(t, \mathbf{x_0})$ is the solution of the initial value problem

$$\dot{\mathbf{x}} = A\mathbf{x}, \qquad \mathbf{x}(0) = \mathbf{x_0}. \tag{3.1.1}$$

A set $S \subseteq E$ is said to be *positively invariant* if $\Phi_t S \subset S$ for all $t \geq 0$. A set $S \subseteq E$ is said to be *invariant* if $\Phi_t S = S$ for all $t \geq 0$.

An orbit $O(\mathbf{x})$ is said to be a T-periodic orbit for some $T > 0$ if $\Phi_T(\mathbf{x}) = \mathbf{x}$; the smallest such T is called the *period* of $\mathbf{x}$. In that case, $\Phi_{t+T}(\mathbf{x}) = \Phi_t(\mathbf{x})$ for all $t \geq 0$, so $O(\mathbf{x}) = \{\Phi_t(\mathbf{x}) : 0 \leq t \leq T\}$. A periodic orbit is *nontrivial* if it is not an steady state.

The following definition is taken from [41]:

Definition 3.1.2. *A set $A \subset \mathbb{R}^n$ is said to* attract *a set S if for every neighbourhood U of A there exists $t_0 \geq 0$ such that*

$$t > t_0 \qquad \Rightarrow \qquad \Phi_t(S) \subset U.$$

When $S = \{\mathbf{x}\}$, we say that A attracts $\mathbf{x}$. An *attractor* A is a nonempty invariant set that attracts a neighbourhood of itself. The *basin of attraction* of A is the union of all such neighbourhoods. If the basin of an attractor A is all of E then A is called a *global attractor*.

The *omega limit set*, $\omega(\mathbf{x})$, of $\mathbf{x} \in E$ is defined by [40]:

$$\omega(\mathbf{x}) = \cap_{t \geq 0} \overline{\cup_{s \geq t} \Phi_s(\mathbf{x})}.$$

If $\overline{O(\mathbf{x})}$ is compact then $\omega(\mathbf{x})$ is nonempty, compact, connected, invariant and *attracts* $\Phi_t(\mathbf{x})$, i.e. $d(\omega(\mathbf{x}), \Phi_t(\mathbf{x})) \to 0$ as $t \to \infty$ [40]. Here we define $d(\mathbf{x}, A) = \inf_{\mathbf{y} \in A}(d(\mathbf{x}, \mathbf{y}))$

In this thesis, we will concentrate on the autonomous system of ODEs

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}), \quad \mathbf{x}(0) \in E, \tag{3.1.2}$$

where $\mathbf{f} : E \to \mathbb{R}^n$ is a C^1 function. We will assume Φ_t exists for all $t \in \mathbb{R}$. As shown in [37], we can rescale time in any C^1-system (3.1.2) so that for any $\mathbf{x} \in E$, Φ_t exists for all $t \in \mathbb{R}$. Hence we will assume, without loss of generality, that Φ_t exists for all $t \in \mathbb{R}$.

If $\mathbf{f}(\mathbf{x}^*) = \mathbf{0}$, then $\mathbf{x}^*$ is a *steady state* for the system (3.1.2), whose linearised system about $\mathbf{x}^* \in E$ is

$$\dot{\mathbf{x}} = D\mathbf{f}(\mathbf{x}^*)\mathbf{x}. \tag{3.1.3}$$

3.2 Topological equivalence of systems

3.2.1 Introducing topology

Dynamical systems theory is closely connected with almost all other branches of mathematics [42]. In particular, the author would like to highlight the overlap with topology - this arises from the emphasis on studying the long-term, qualitative behaviour of a dynamical system, rather than computing exact individual solutions. Also, it is useful to set up a mathematical framework for determining which dynamical systems have qualitatively similar behaviour. Moreover, a rigorous definition of a manifold is required before we can even start studying invariant ones.

We begin by defining the most fundamental type of mapping in topology [37]:

Definition 3.2.1. *Let* (X,d) *be a metric space and let* $A,B \subset X$*. A* homeomorphism *of* A *onto* B *is a continuous, one-to-one map of* A *onto* B*,* $\mathbf{h} : A \to B$*, such that its inverse* $\mathbf{h}^{-1} : B \to A$ *is continuous. Then the sets* A *and* B *are said to be* homeomorphic *or* topologically equivalent *if there exists a homeomorphism of* A *onto* B*.*

Saying two spaces are homeomorphic is saying that they look the same topologically - a topologist will treat them as identical [43]. Figure 3.1 depicts two homeomorphic spaces: a mug and a doughnut [39]. There are some special examples of homeomorphisms: for *diffeomorphisms*, we require $\mathbf{h}$ and $\mathbf{h}^{-1}$ to be differentiable instead [37]. Moreover, there are two more types of homeomorphisms based on the following classes of functions [37, 44, 45]:

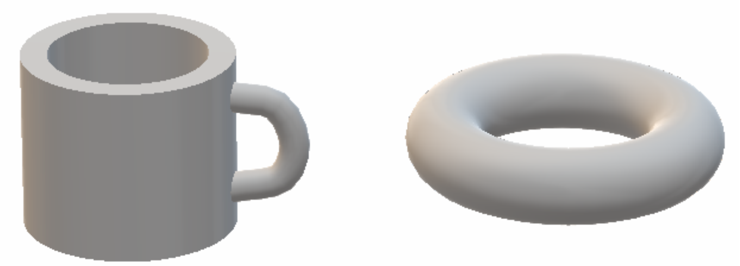


Figure 3.1: A mug (left) and a doughnut (right) are topologically equivalent. There is an old joke saying that topologists cannot tell the difference between the two.

Definition 3.2.2. *Let (X,d) be a metric space and take $A,B \subset X$. Then a function $\mathbf{f}: A \to B$ is said to be* Lipschitz continuous *(or simply* Lipschitz*) if there exists $\gamma > 0$ such that*

$$d(\mathbf{f}(\mathbf{x}),\mathbf{f}(\mathbf{y})) \leq \gamma d(\mathbf{x},\mathbf{y}) \qquad \forall \mathbf{x},\mathbf{y} \in A,$$

and γ is said to be a Lipschitz constant *of* $\mathbf{f}$. *If every $\mathbf{x} \in A$ has a neighbourhood U such that the restriction of* $\mathbf{f}$ *to U is Lipschitz continuous with some* Lipschitz constant γ*, we say that* $\mathbf{f}$ *is* locally Lipschitz.

A graphical example of a Lipschitz continuous function is depicted in Figure 3.2. In this thesis, (X,d) is taken to be $\mathbb{R}^n$ equipped with the standard Euclidean norm. Let $C_\gamma(\mathbb{R}^n)$ denote the space of functions that are Lipschitz on $\mathbb{R}^n$ with Lipschitz constant γ, as done in [42]. Similarly we will define $C_\gamma(A)$ to denote the space of Lipschitz functions on A. If a homeomorphism $\mathbf{h}$ and its inverse $\mathbf{h}^{-1}$ are both Lipschitz, then $\mathbf{h}$ is said to be *bi-Lipschitz*. On the other hand, if $\mathbf{h}$ and $\mathbf{h}^{-1}$ are locally Lipschitz instead, then the homeomorphism $\mathbf{h}$ is called a *Lipschtizeomorphism* [45].

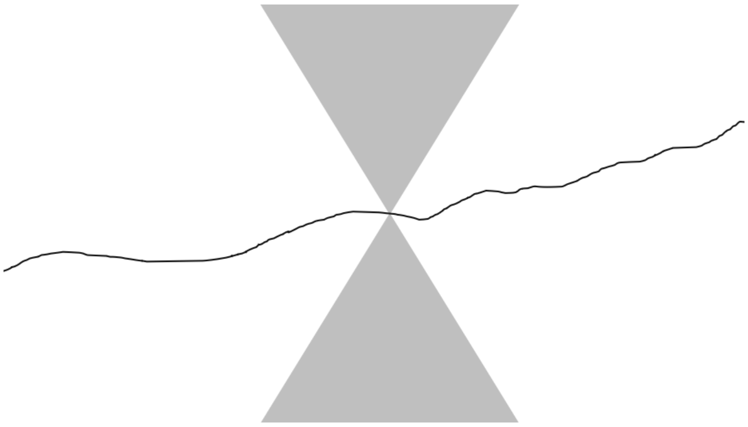


Figure 3.2: A sketch of a Lipschitz function. Informally speaking, you could translate the vertical double-cone to another point on the graph, and the double-cone will still only intersect the function at the new chosen point. The Lipschitz constant γ determines the steepness of the cones.

Also, we provide a definition of a (differentiable) manifold [37, 42]:

Definition 3.2.3. *An* n-dimensional differentiable manifold*, M is a connected metric space with an open covering $\{U_i\}$, i.e. $M = \cup_i U_i$, such that* *(i) For all i,* U_i *is homeomorphic to the open unit ball* $B = \{\mathbf{x} \in \mathbb{R}^n : |\mathbf{x}| < 1\}$*. A pair* $\{(U_i, \mathbf{h_i})\}$ *of such an open set and homeomorphism* $\mathbf{h_i} : U_i \to B$ *is called a* chart.

(ii) If $U_i \cap U_j \neq \emptyset$ *and* $\mathbf{h_i} : U_i \to B$*,* $\mathbf{h_j} : U_j \to B$ *are homeomorphisms, then* $\mathbf{h_i}(U_i \cap U_j)$ *and* $\mathbf{h_j}(U_i \cap U_j)$ *are subsets of* $\mathbb{R}^n$ *and the map*

$$\mathbf{h} = \mathbf{h_i} \circ \mathbf{h_j^{-1}} : \mathbf{h_j}(U_i \cap U_j) \to \mathbf{h_i}(U_i \cap U_j)$$

is differentiable and for all $\mathbf{x} \in \mathbf{h_j}(U_i \cap U_j)$*, the Jacobian determinant* $\det D\mathbf{h}(\mathbf{x}) \neq 0$.

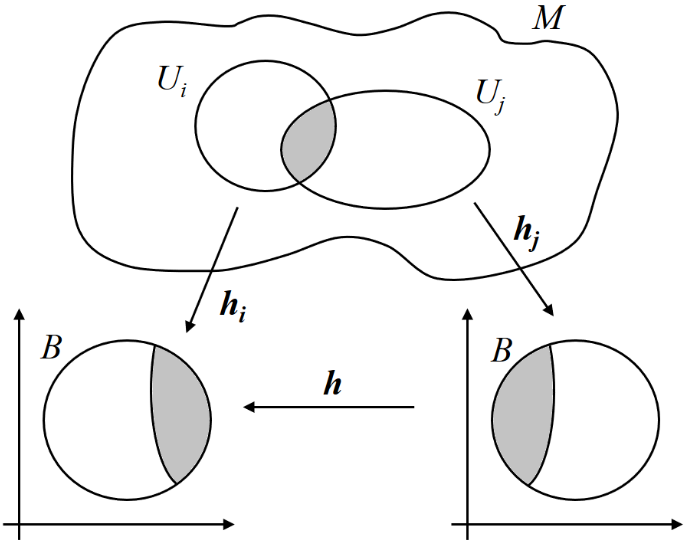


Figure 3.3: A homeomorphism $\mathbf{h_i}$ maps U_i onto the open ball $B \subset \mathbb{R}^n$ providing coordinates to a point in U_i. If $U_i \cap U_j \neq \emptyset$, the transition from one coordinate system to another, $\mathbf{h}$, is smooth.

Here, differentiable is taken to mean C^k or analytic. If instead of differentiable, $\mathbf{h}$ is required to be a Lipschitzeomorphism, M is said to be a *Lipschitz manifold* [45]. A manifold M which is invariant under the flow of the system is called an *invariant manifold*. The simplest examples of invariant manifolds include steady states and semi-orbits; other types are discussed in Section 3.4.

Let M be an m-dimensional manifold with $M \subset \mathbb{R}^{m+k}$. A *smooth curve* through a point $\mathbf{p} \in M$ is a C^1-map $\mathbf{c} : (-a, a) \to M$ for some $a > 0$ with $\mathbf{c}(0) = \mathbf{p}$. Then the velocity vector $\mathbf{v}$ tangent to $\mathbf{c}$ at the point $\mathbf{p} = \mathbf{c}(0) \in M$ is

$$\mathbf{v} = D\mathbf{c}(0),$$

At each point $\mathbf{p} \in M$, the set of all velocity vectors tangent to smooth curves passing through $\mathbf{p}$ forms an m-dimensional vector space known as the *tangent space* to M at $\mathbf{p}$ and denoted by $T_{\mathbf{p}}M$. Furthermore, we can take the union of tangent spaces for all points on M:

$$TM = \bigcup_{\mathbf{p}\in M} T_{\mathbf{p}}M,$$

which defines the *tangent bundle* of M. Similarly, differential geometers also define a *normal space* to M at $\mathbf{p}$ and denoted by $N_{\mathbf{p}}M$ [46].

$$N_{\mathbf{p}}M = \{\mathbf{n} \in \mathbb{R}^{m+k} : \mathbf{n}\cdot\mathbf{v} = 0 \qquad \forall \mathbf{v} \in T_{\mathbf{p}}M\},$$

from which we construct the *normal bundle* of M by taking the union of tangent spaces for all points on M:

$$NM = \bigcup_{\mathbf{p}\in M} N_{\mathbf{p}}M,$$

Let M be an m-dimensional manifold and let N be an n-dimensional submanifold contained in M. Then the *codimension* of N is defined to be $m-n$ [39]. Informally speaking, the codimension of an invariant (sub)manifold is the number of dimensions a mathematical model is reduced by.

3.2.2 Classifying dynamical systems

The following definitions formalise the notion of two dynamical systems having the same qualitative structure near their corresponding steady states:

Definition 3.2.4. *Suppose* $\mathbf{f} \in C^1(E_1,\mathbb{R}^n)$ *and* $\mathbf{g} \in C^1(E_2,\mathbb{R}^n)$ *where* E_1 *and* E_2 *are open subsets of* $\mathbb{R}^n$. *Then the two autonomous systems of differential equations (3.1.2) and*

$$\dot{\mathbf{x}} = \mathbf{g}(\mathbf{x}). \tag{3.2.1}$$

are said to be topologically equivalent *if there exists a homeomorphism* $\mathbf{h} : E_1 \to E_2$

which maps trajectories of (3.1.2) to (3.2.1) and preserves their time orientation, i.e. there is a continuously differentiable function $t(\mathbf{x},\tau)$ *defined for all* $\tau \in \mathbb{R}$ *such that* $\frac{\partial t}{\partial \tau} > 0$ *and*

$$\mathbf{h} \circ \Phi_{t(\mathbf{x},\tau)}(\mathbf{x}) = \Psi_\tau \circ \mathbf{h}(\mathbf{x}) \quad \forall \mathbf{x} \in E_1 \quad \forall \tau \in \mathbb{R},$$

where Φ_t *and* Ψ_t *are the flows. In this case the vector fields* $\mathbf{f}$ *and* $\mathbf{g}$ *are said to be topologically equivalent. If* $E = E_1 = E_2$*, then the systems (3.1.2) and (3.2.1) are said to be* topologically equivalent on *E and the vector fields* $\mathbf{f}$ *and* $\mathbf{g}$ *are said to be topologically equivalent on E.*

The required relationship between $\mathbf{h}$ and the flows Φ_t and Ψ_t can be represented using the following commutative diagram:

$$\begin{tikzcd}
E_1 \arrow[r, "\Phi_{t(\mathbf{x},\tau)}"] \arrow[d, "\mathbf{h}"] & E_1 \arrow[d, "\mathbf{h}"] \\
E_2 \arrow[r, "\Psi_\tau"] & E_2
\end{tikzcd}$$

Note that although $\mathbf{h}$ is required to preserve their time orientation, it need not preserve the parametrisation by time along trajectories. The special case where time parametrisation is indeed preserved, i.e. $t(\mathbf{x},\tau) = \tau$, is addressed in the following definition:

Definition 3.2.5. *Suppose* $\mathbf{f} \in C^1(E_1,\mathbb{R}^n)$ *and* $\mathbf{g} \in C^1(E_2,\mathbb{R}^n)$ *where* E_1 *and* E_2 *are open subsets of* $\mathbb{R}^n$*. Then the two autonomous systems of differential equations (3.1.2) and (3.2.1) are said to be* topologically conjugate *if there exists a homeomorphism* $\mathbf{h} : E_1 \to E_2$ *which maps trajectories of (3.1.2) to (3.2.1) and preserves their time parametrisation, i.e. if* Φ_t *and* Ψ_t *are the flows then*

$$\mathbf{h} \circ \Phi_t(\mathbf{x}) = \Psi_t \circ \mathbf{h}(\mathbf{x}) \quad \forall \mathbf{x} \in E_1 \quad \forall t \in \mathbb{R}.$$

Then the vector fields $\mathbf{f}$ *and* $\mathbf{g}$ *are said to be topologically conjugate. If* $E = E_1 = E_2$*, then the systems (3.1.2) and (3.2.1) are said to be* topologically conjugate on *E and* *the vector fields* **f** *and* **g** *are said to be topologically conjugate on E.*

There are two particular cases of topological equivalence between (3.1.2) and (3.2.1) which have a simple analytical relation between **f** and **g**. The first case is given in the following definition [38]:

Definition 3.2.6. *Suppose systems (3.1.2) and (3.2.1) satisfy*

$$\mathbf{f}(\mathbf{x}) = (D\mathbf{h}(\mathbf{x}))^{-1}\mathbf{g}(\mathbf{h}(\mathbf{x})),$$

for some diffeomorphism $\mathbf{h} : E_1 \to E_2$*, where* $D\mathbf{h}(\mathbf{x})$ *is the Jacobian matrix of* $\mathbf{h}(\mathbf{x})$ *evaluated at the point* $\mathbf{x}$*. Then the two systems are called* smoothly equivalent *(or* diffeomorphic*).*

Remark. *If* $\mathbf{h}$ *and* $\mathbf{h}^{-1}$ *are* C^k*-smooth, then (3.1.2) and (3.2.1) are said to be* C^k*-diffeomorphic.*

Diffeomorphic systems are treated as equivalent and can be interpreted as the same system written in new coordinates; for example, the eigenvalues of the respective steady states are identical. Moreover, diffeomorphic limit cycles have the same multiplicity and time period.

The latter property calls for a thorough analysis of different *time parametrizations*, motivating the other form of topological equivalence considers two systems that have identical-looking orbits, which are followed at differing velocities.

Definition 3.2.7. *Two systems (3.1.2) and (3.2.1) satisfying*

$$\mathbf{f}(\mathbf{x}) = \mu(\mathbf{x})\mathbf{g}(\mathbf{x})$$

for a smooth scalar positive function $\mu : E \to \mathbb{R}$ *are said to be* orbitally equivalent*.*

Here the homeomorphism $\mathbf{h}$ is the identity map $\mathbf{h}(\mathbf{x}) = \mathbf{x}$. Furthermore $E_1 = E_2 = E$. Two orbitally equivalent systems need not be diffeomorphic, e.g. orbitally equivalent systems containing identically shaped periodic orbits with different time periods are not diffeomorphic [38].

The next definition can be viewed as a combination of smooth and orbital equivalence:

Definition 3.2.8. *Two systems (3.1.2) and (3.2.1) are called* smoothly orbitally equivalent *if (3.2.1) is smoothly equivalent to a system that is orbitally equivalent to (3.1.2).*

By this definition, two systems are equivalent in $\mathbb{R}^n$ or an open subset if we can transform one of them into the other by a (C^1-)smooth invertible change of coordinates and then a multiplication by a positive smooth function of the coordinates. Two smoothly orbitally equivalent systems are topologically equivalent, but the converse is not true [38].

The next theorem, known as the Hartman-Grobman Theorem, is relevant for the following type of steady state:

Definition 3.2.9. *A steady state* $\mathbf{x}^*$ *of (3.1.2) is said to be* hyperbolic *if none of the eigenvalues of* $D\mathbf{f}(\mathbf{x}^*)$ *have zero real part.*

If a steady state has pure imaginary eigenvalues, it is said to be *nonhyperbolic*.

The Hartman-Grobman Theorem gives a rigorous justification to perform linear stability analysis near a (hyperbolic) steady state [37].

Theorem 3.2.10. *Let E be an open subset of* $\mathbb{R}^n$ *containing* $\mathbf{x}^*$*, let* $\mathbf{f} \in C^1(E)$ *and let* Φ_t *be the flow of the nonlinear system (3.1.2). Suppose that* $\mathbf{f}(\mathbf{x}^*) = \mathbf{0}$ *and the matrix* $A = D\mathbf{f}(\mathbf{x}^*)$ *has no eigenvalues with zero real part. Then there exists a homeomorphism* $\mathbf{h}$ *of an open set U containing* $\mathbf{x}^*$ *onto an open set V containing the origin such that for all* $\mathbf{x_0} \in U$*, there is an open interval* $I_0 \subset \mathbb{R}$ *containing* 0 *such that*

$$\forall \mathbf{x_0} \in U,\ t \in I_0, \quad \mathbf{h} \circ \Phi_t(\mathbf{x_0}) = \exp(At)\mathbf{h}(\mathbf{x_0}), \tag{3.2.2}$$

i.e. $\mathbf{h}$ *maps trajectories of (3.1.2) near* $\mathbf{x}^*$ *onto trajectories of (3.1.3) near the origin and preserves the time parametrisation.*

Statement (3.2.2) is represented using the following commutative diagram:

$$\begin{tikzcd}
U \arrow[r, "\Phi_t"] \arrow[d, "\mathbf{h}"] & U \arrow[d, "\mathbf{h}"] \\
V \arrow[r, "\exp(At)"] & V
\end{tikzcd}$$

3.3 Stable, unstable and centre subspaces

Consider a linear system

$$\dot{\mathbf{x}} = A\mathbf{x}, \tag{3.3.1}$$

where $\mathbf{x} \in \mathbb{R}^n$ and A is a real-valued $n \times n$ matrix.

The following definition applies for repeated eigenvalues of a given matrix [37]. If an eigenvalue λ of matrix A is repeated m times, we call m the *multiplicity* of λ.

Definition 3.3.1. *Let λ be an eigenvalue of the $n \times n$ matrix A of multiplicity $m \leq n$. Then for $k = 1, 2, \ldots, m$, any non-zero solution $\mathbf{v}$ of*

$$(A - \lambda I)^k \mathbf{v} = 0,$$

where I denotes the identity matrix, is called a generalised *eigenvector of A.*

Now we are in a position to define the stable, unstable and centre subspaces of the linearised system (3.3.1).

Definition 3.3.2. *Let $\mathbf{w_j} = \mathbf{u_j} + i\mathbf{v_j}$ be a (generalised) eigenvector of the real matrix A with corresponding eigenvalue $\lambda_j = a_j + ib_j$. Note that if $b_j = 0$ for some j, then $\mathbf{v_j} = \mathbf{0}$. Also, let*

$$B = \{\mathbf{u_1}, \mathbf{u_2}, \ldots, \mathbf{u_k}, \mathbf{u_{k+1}}, \mathbf{v_{k+1}}, \mathbf{u_{k+2}}, \mathbf{v_{k+2}}, \ldots, \mathbf{u_m}, \mathbf{v_m}\}$$

be a basis of $\mathbb{R}^n$ (with $n = 2m - k$).

Then the stable, centre and unstable subspaces *of the system are defined as*

$$E^s = \mathrm{Span}\left\{\mathbf{u_j}, \mathbf{v_j} : a_j < 0\right\},$$
$$E^c = \mathrm{Span}\left\{\mathbf{u_j}, \mathbf{v_j} : a_j = 0\right\},$$
$$E^u = \mathrm{Span}\left\{\mathbf{u_j}, \mathbf{v_j} : a_j > 0\right\},$$

respectively.

The following theorem states that $\mathbb{R}^n$ can be decomposed into the stable, unstable and centre subspaces, each of which is invariant with respect to the flow of the linear system

Theorem 3.3.3. *Let A be a real $n \times n$ matrix. Then*

$$\mathbb{R}^n = E^s \oplus E^u \oplus E^c,$$

where E^s, E^u and E^c denote the stable, unstable and centre subspaces respectively. Furthermore, E^s, E^u and E^c are all invariant with respect to the flow $\exp(At)$ *of (3.3.1) respectively.*

3.4 Invariant manifold theorems

We start with one of the most important results in the local qualitative theory of ODEs, the Stable Manifold Theorem [37]:

Theorem 3.4.1. *Let E be an open subset of $\mathbb{R}^n$ containing a hyperbolic steady state $\mathbf{x}^*$, let $f \in C^1(E)$, and let Φ_t be the flow of the nonlinear system (3.1.2). Suppose $D\mathbf{f}(\mathbf{x}^*)$ has k eigenvalues with negative real part and $n-k$ eigenvalues with positive real part. Then there exists a k dimensional differentiable manifold $W^s_{loc}(\mathbf{x}^*)$ tangent to the stable subspace E^s of (3.1.3) at $\mathbf{x}^*$ such that for all $t \geq 0$, $\Phi_t(W^s_{loc}(\mathbf{x}^*)) \subset W^s_{loc}(\mathbf{x}^*)$ and*

$$\forall \mathbf{x_0} \in W^s_{loc}(\mathbf{x}^*) \quad \lim_{t\to\infty} \Phi_t(\mathbf{x_0}) = \mathbf{x}^*;$$

and there exists an $n-k$ dimensional differentiable manifold $W^u_{loc}(\mathbf{x}^*)$ tangent to the unstable subspace E^u of (3.1.3) at x^* such that for all $t \leq 0$, $\Phi_t(W^u_{loc}(\mathbf{x}^*)) \subset W^u_{loc}(\mathbf{x}^*)$

and

$$\forall \mathbf{x_0} \in W^u_{loc}(\mathbf{x}^*) \quad \lim_{t \to -\infty} \Phi_t(\mathbf{x_0}) = \mathbf{x}^*.$$

We call $W^s_{loc}(\mathbf{x}^*)$ and $W^u_{loc}(\mathbf{x}^*)$ the *local stable and unstable manifolds at* $\mathbf{x}^*$ respectively; these are only defined within a neighbourhood of the steady state. These can be extended to *global* stable and unstable manifolds respectively by tracing points in $W^s_{loc}(\mathbf{x}^*)$ backwards in time and those in $W^u_{loc}(\mathbf{x}^*)$ forwards in time, as done in the following definition:

Definition 3.4.2. *Let Φ_t be the flow of the (nonlinear) system (3.1.2). Then the* global stable *and* unstable manifolds *at* $\mathbf{x}^*$ *are defined by*

$$W^s(\mathbf{x}^*) = \cup_{t \leq 0} \Phi_t(W^s_{loc}(\mathbf{x}^*))$$

and

$$W^u(\mathbf{x}^*) = \cup_{t \geq 0} \Phi_t(W^u_{loc}(\mathbf{x}^*))$$

A nonhyperbolic steady state also has a centre subspace E^c, from which emanates yet another kind of invariant manifold: the *(global) centre manifold.* This leads to the Centre Manifold Theorem [37]:

Theorem 3.4.3. *Let $\mathbf{f} \in C^r(E)$, where E is an open subset of $\mathbb{R}^n$ containing $\mathbf{x}^*$, and $r \geq 1$. Suppose $\mathbf{f}(\mathbf{x}^*) = 0$ and $D\mathbf{f}(\mathbf{x}^*)$ has*

- *k eigenvalues with negative real part,*
- *j eigenvalues with positive real part, and*
- *$m = n - k - j$ eigenvalues with zero real part.*

Then there exists:

- *a k-dimensional stable manifold $W^s(\mathbf{x}^*)$ of class C^r tangent to the stable subspace E^s of (3.1.3) at $\mathbf{x}^*$.*
- *a j-dimensional unstable manifold $W^u(\mathbf{x}^*)$ of class C^r tangent to the unstable subspace E^u of (3.1.3) at $\mathbf{x}^*$, and*

- *an m-dimensional centre manifold* $W^c(\mathbf{x}^*)$ *of class* C^r *tangent to the centre subspace* E^c *of (3.1.3) at* $\mathbf{x}^*$.

Furthermore $W^s(\mathbf{x}^*)$, $W^u(\mathbf{x}^*)$ *and* $W^c(\mathbf{x}^*)$ *are invariant under the flow* Φ_t *of (3.1.2).*

Note that stable, unstable and centre manifolds are defined relative to a steady state. In addition, a stable manifold can be an unstable manifold, too! For example, consider the following type of orbit:

Definition 3.4.4. *An orbit* $O(\mathbf{x})$ *starting at a point* $\mathbf{x} \in \mathbb{R}^n$ *is called* heteroclinic *to the steady states* $\mathbf{x}_1^*$ *and* $\mathbf{x}_2^*$ *of the system (3.1.2) if*

$$\Phi_t(\mathbf{x}) \to \mathbf{x}_1^* \quad as \quad t \to \infty$$

and

$$\Phi_t(\mathbf{x}) \to \mathbf{x}_2^* \quad as \quad t \to -\infty.$$

Figure 3.4 shows that a heteroclinic orbit to the steady states $\mathbf{x}_1^*$ and $\mathbf{x}_2^*$ is a subset of $W^s(\mathbf{x}_1^*) \cap W^u(\mathbf{x}_2^*)$. Hence is a subset of both the stable and unstable manifold, albeit for distinct fixed points [38]. There are similar definitions for stable, unstable and centre manifolds relative to periodic orbits, but are irrelevant for this thesis where we restrict to hyperbolic steady states, hence are omitted.

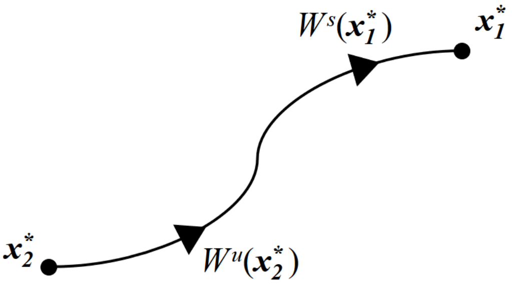


Figure 3.4: An example of a heteroclinic orbit to the steady states $\mathbf{x}_1^*$ and $\mathbf{x}_2^*$

Rather, we move on to discuss another type of invariant manifold related to centre manifolds which was first considered in [47]. Known as a normally hyperbolic invariant manifold, it is also regarded as a generalisation of hyperbolic steady states:

Definition 3.4.5. *Let M be a compact smooth manifold, $\Phi_t : M \to M$ be the flow generated by the vector field f and $D\Phi_t : TM \to TM$ be the differential of Φ_t. An invariant (sub)manifold Λ of M is said to be a* normally hyperbolic invariant manifold *if the restriction to Λ of the tangent bundle of M admits a splitting into a sum of three invariant subbundles:*

$$T_\Lambda M = T\Lambda \oplus E^s \oplus E^u,$$

with respect to some Riemannian metric on M, there exists constants $\lambda < 0 < \mu$, $c > 0$ such that $\mu < |\lambda|$ and

$$\begin{aligned} ||D\Phi_{-t}(\mathbf{v})|| &\leq ce^{\lambda t}||\mathbf{v}|| \quad \forall \mathbf{v} \in E^u,\ \forall t \geq 0 \\ ||D\Phi_t(\mathbf{v})|| &\leq ce^{\lambda t}||\mathbf{v}|| \quad \forall \mathbf{v} \in E^s,\ \forall t \geq 0 \\ ||D\Phi_t(\mathbf{v})|| &\leq ce^{\mu|t|}||\mathbf{v}|| \quad \forall \mathbf{v} \in T\Lambda,\ \forall t \in \mathbb{R} \end{aligned}$$

So the component of the flow normal to Λ of $D\mathbf{f}$ is hyperbolic and dominates the tangent behaviour [48].

One type of invariant manifold which frequently occurs in biological models is the inertial manifold [49, 50]:

Definition 3.4.6. *A finite-dimensional Lipschitz manifold Σ is called an* inertial manifold *if*

- *Σ is positively invariant under the flow Φ_t:*

  $$\forall \mathbf{x} \in \Sigma, \quad \forall t \geq 0, \quad \Phi_t(\mathbf{x}) \in \Sigma.$$

- *For each point $\mathbf{x}$ not on the manifold, the distance between Σ and the flow starting at $\mathbf{x}$ decreases exponentially:*

  $$\forall \mathbf{x} \notin \Sigma, \quad \exists C > 0, \quad \exists \alpha > 0 \quad \text{s.t.} \quad \forall t \geq 0 \quad d(\Phi_t(\mathbf{x}), \Sigma) < Ce^{-\alpha t},$$

  where α is a constant independent of $\mathbf{x}$ and C is a constant depending on $||\mathbf{x}||$.

3.5 Four main means of proving existence

There are four main methods that can be used to prove an invariant manifold exists in a dynamical system:

- Hadamard's graph transform method, which our proofs are based on.
- Cauchy's geometric method.
- The elliptic method.
- Lyapunov-Perron method.

Hadamard and Cauchy's methods take on a more geometric approach, whereas the others are more analytical. Both Hadamard and Lyapunov-Perron methods rely on constructing an operator acting on a (Banach) space of Lipschitz functions, which is a contraction mapping. As a consequence we can look for a (unique) fixed point of the operator, which will be the desired invariant manifold.

These are not the only methods available. An example of a non-standard but equally valid approach is taken in [51].

3.5.1 Hadamard (graph transform) method

The idea of using a graph transform traces back to [33]. The main idea of this method is to start with an initial guess for the manifold $M_0 = \mathrm{graph}(\phi_0(\cdot))$ for some Lipschitz function ϕ_0, and track its evolution according to the flow Φ_t of the dynamical system. Hence we can construct a sequence of manifolds $\{M_t\}$ where $M_t = \Phi_t(M_0)$ and $t \geq 0$. The aim is to show that the sequence converges uniformly to a unique invariant surface Σ, usually by proving that $M_t = \mathrm{graph}(\phi_t(\cdot))$ is (uniformly) Lipschitz for all $t > 0$. A sketch of this method is given in Figure 3.5 Suppose (3.1.2) can be decomposed into the following form

$$\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x}, \mathbf{y}) \tag{3.5.1}$$

$$\dot{\mathbf{y}} = \mathbf{g}(\mathbf{x}, \mathbf{y}). \tag{3.5.2}$$

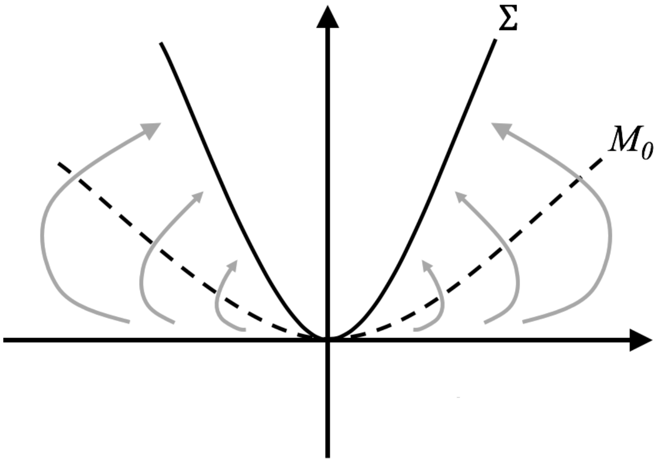


Figure 3.5: At time $t = 0$ we take M_0 (black, dashed) as the initial guess for Σ (black, solid), and start the clock. As t increases, the dashed line will deform into M_t according to the flow of the system (grey arrows), which should converge to Σ.

where $\mathbf{x} \in \mathbb{R}^{n-k}$, $\mathbf{y} \in \mathbb{R}^k$ and $\mathbf{f} : \mathbb{R}^n \to \mathbb{R}^{n-k}$, $\mathbf{g} : \mathbb{R}^n \to \mathbb{R}^k$ are vector fields. Often this is done for computing centre manifolds, as done in [37], for which $\mathbf{x} \in E^c$, while $\mathbf{y} \in E^s \oplus E^u$. Next, assume each $M_t = \text{graph}(\phi_t(\mathbf{x}))$, i.e. $\mathbf{y}(t) = \phi_t(\mathbf{x}(t))$. If we write $\phi_t(\cdot) = \phi(\cdot, t)$ and differentiate with respect to t, the Chain Rule gives

$$\dot{\mathbf{y}}(t) = D\phi(\mathbf{x}(t), t)\dot{\mathbf{x}}(t) + \frac{\partial \phi}{\partial t}(\mathbf{x}(t), t)$$

where $D\phi(\mathbf{x}(t), t)$ is the Jacobian of ϕ with respect to $\mathbf{x}$. Substituting in (3.5.1) and (3.5.2) gives

$$\mathbf{g}(\mathbf{x}(t), \phi(\mathbf{x}(t), t)) = D\phi(\mathbf{x}(t), t)\mathbf{f}(\mathbf{x}(t), \phi(\mathbf{x}(t), t)) + \frac{\partial \phi}{\partial t}(\mathbf{x}(t), t), \tag{3.5.3}$$

which is the PDE governing the time evolution of M_t. Then suppose that $\phi(\mathbf{x}(t), t)$ converges uniformly to $\phi^*(\mathbf{x})$ as $t \to \infty$, and that Σ can be represented by the graph $y = \phi^*(\mathbf{x})$, which has no time dependence. Hence substitution into (3.5.3) leads to the *tangency condition* [38, 39]:

$$\mathbf{g}(\mathbf{x}, \phi^*(\mathbf{x})) = D\phi^*(\mathbf{x})\mathbf{f}(\mathbf{x}, \phi^*(\mathbf{x})), \tag{3.5.4}$$

The graph-transform method is used in [42] for their proof of the Stable Manifold Theorem.

3.5.2 Cauchy (geometric) method

This method is commonly used when seeking inertial manifolds from ODEs of the form [52]

$$\dot{\mathbf{u}} + A\mathbf{u} = \mathbf{f}(\mathbf{u}),$$

where $\dot{u} \in H$ for some Hilbert space H that can be divided into two orthogonal subspaces $\mathcal{P}$ and $\mathcal{Q}$, where $\mathcal{P}$ is finite-dimensional, with the same dimension as the inertial manifold being sought. We will denote the denote the projection of H onto $\mathcal{P}$ by P_N. Start by defining a ball of radius ρ, say Σ_ρ, and truncating $\mathbf{f}$ such that it equals zero outside the ball. Then take the boundary of the projection of Σ_ρ, $\Gamma = \partial P_N \Sigma_\rho$, and let

$$\Sigma = \overline{\cup_{t\geq 0}\Phi_t(\Gamma)}.$$

By definition, Σ is positively invariant. We still need to show Σ is Lipschitz using a cone condition. We then define the manifold

$$M = \Sigma \cup \{\mathbf{u} : \mathbf{u} \in P_N, |\mathbf{u}| \geq \rho\}.$$

which is also invariant. Moreover, Σ is Lipschitz, therefore M is Lipschitz also. Those who are seeking an inertial manifold would go on to show that M is exponentially attracting.

3.5.3 Elliptic regularisation method

Introduced by [53], the elliptic regularisation starts with exactly the same PDE as in the graph transform method, i.e. (3.5.4), which is then modified by introducing another term on the right hand side:

$$\mathbf{g}(\mathbf{x}, \phi_\varepsilon(\mathbf{x})) = D\phi_\varepsilon(\mathbf{x})\mathbf{f}(\mathbf{x}, \phi_\varepsilon(\mathbf{x})) - \varepsilon\Delta\phi_\varepsilon, \tag{3.5.5}$$

where $\varepsilon > 0$ and Δ denotes the Laplacian operator. Then ϕ^* is constructed by taking the limit of ϕ_ε as $\varepsilon \to 0^+$. There are theorems on the differentiability of solutions of elliptic equations which ensure that (3.5.5) has a unique, sufficiently regular solution.

3.5.4 Lyapunov-Perron method

For simplicity, we will illustrate this method in the context of the stable manifold of a hyperbolic steady state as done in [37], but the method is similar for centre and inertial manifolds.

Suppose we can decompose (3.1.2) into,

$$\begin{aligned}\dot{\mathbf{x}} &= P\mathbf{x} + \mathbf{F}(\mathbf{x},\mathbf{y})\\ \dot{\mathbf{y}} &= Q\mathbf{y} + \mathbf{G}(\mathbf{x},\mathbf{y}).\end{aligned}$$

where the matrices P and Q contain all the eigenvalues of the Jacobian $D\mathbf{f}(\mathbf{x}^*)$ that have negative and positive real part respectively, while F and G are nonlinear, Lipschitz functions. Then the growth/decay of $\exp(Pt)$ and $\exp(Qt)$ are bounded by suitable constants; the bound applies for all $t \geq 0$ for the stable subspace, and for all $t \leq 0$ for the unstable subspace. Define

$$U(t) = \begin{pmatrix} \exp(Pt) & 0 \\ 0 & 0 \end{pmatrix}, \quad V(t) = \begin{pmatrix} 0 & 0 \\ 0 & \exp(Qt) \end{pmatrix}$$

where each 0 denotes a zero matrix and define an integral operator

$$\begin{aligned}\mathcal{T}(\phi(t,\mathbf{x_0})) = U(t)\mathbf{x_0} &+ \int_0^t \Big(\exp(P(t-s))F(\mathbf{x_0},\phi(s,\mathbf{x_0})) \Big) \mathrm{d}s \\ &- \int_t^\infty \begin{pmatrix} 0 \\ \exp(Q(t-s))G(\mathbf{x_0},\phi(s,\mathbf{x_0})) \end{pmatrix} \mathrm{d}s\end{aligned} \tag{3.5.6}$$

then the invariant manifold is a fixed point ϕ^* of $\mathcal{T}$, i.e. $\mathcal{T}(\phi^*) = \phi^*$. To find the fixed point, we construct a sequence of functions $\{\phi_j\}_{j=0}^{\infty}$ with $\phi_0(t,\mathbf{x_0}) = 0$ and $\phi_{j+1}(t,\mathbf{x_0}) = \mathcal{T}\phi_j(t,\mathbf{x_0})$, which is a Cauchy sequence of functions in the (Banach) space of uniformly bounded Lipschitz functions, hence $\{\phi_j\}_{j=0}^{\infty}$ converges to a limit.

A more general version of this method for centre manifolds in a Banach space is given in the preprint [54].

Chapter 4

Background on monotone systems

In this chapter we survey a useful class of dynamical systems, known as monotone systems, also called order-preserving or increasing. We will introduce some useful definitions from cone theory and the concept of a partially ordered space first before defining a monotone system. Then we consider the quasimonotone condition, which turns out to be an alternative characterisation of the usual monotonicity. We also discuss cooperative and competitive systems, and address a special class of systems (Kolmogorov) which is known to bear invariant manifold(s) under conditions similar to those for competitiveness.

The earliest results for monotone systems date back to 1926 [55, 56]. Much of the theory was developed by Hirsch [57, 58, 59, 60, 61] and Smith in the context of ordinary differential equations [62, 63]. In this thesis the focus is on finite dimensional systems; a large portion of this chapter is based on their handbook chapter [41] and Smith's monograph [40].

Monotonicity is a very powerful property. Much is known about the long-term evolution of monotone systems; some typical conclusions are given in the introduction of [41]. Moreover, monotone systems appear in various biological, chemical, physical and economic models.

4.1 Some basic concepts

4.1.1 Cone theory

Monotone systems theory relies heavily on cone theory, hence has an overlap with geometry and linear algebra. The following concepts from cone theory are based on [64]:

A set $K \subseteq \mathbb{R}^n$ is called a *cone* if $\mu K \subseteq K$ for all $\mu > 0$. A cone is said to be *proper* if it is closed, convex (or equivalently $K + K \subset K$ [65]), has a non-empty interior and is *pointed* ($K \cap (-K) = \{0\}$). A closed cone is *polyhedral* provided that it is the intersection of finitely many closed half spaces; one example is the orthant. Another common choice for a cone is the ice cream cone $K_{ice} = \{\mathbf{x} \in \mathbb{R}^n : |x_n| \geq \sqrt{\sum_{i=1}^{n-1} x_i^2}\}$.

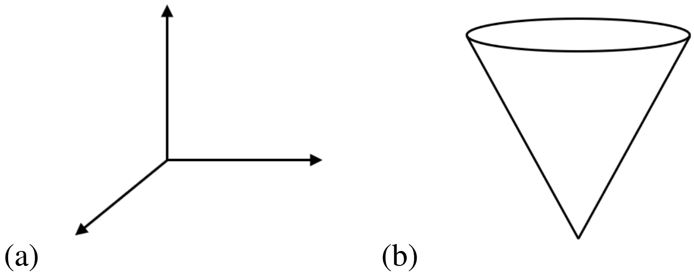

(a) (b)

Figure 4.1: (a) The standard orthant $\mathbb{R}^n_+$. (b) An ice cream cone.

The *dual of* K, denoted by K^*, is the convex cone [64]

$$K^* = \{\boldsymbol{\ell} \in (\mathbb{R}^n)^* : \mathbf{x} \cdot \boldsymbol{\ell} \geq 0 \quad \forall \mathbf{x} \in K\}.$$

If K and $F \subseteq K$ are pointed closed cones, we call F a *face* of K if [64]

$$\forall \mathbf{x} \in F \quad 0 \leq_K \mathbf{y} \leq_K \mathbf{x} \quad \Rightarrow \quad \mathbf{y} \in F.$$

The face F is *non-trivial* if $F \neq \{\mathbf{0}\}$ and $F \neq K$.

4.1.2 Assigning order in spaces

We would like to be able to assign a (partial) order to distinct points in the state space. The following definition gives the mathematical framework for doing so:

Definition 4.1.1. *A* partially ordered space *is some metric space X and a* partial order relation $\mathrm{R} \subset X \times X$. *We write* $\mathbf{x} \leq \mathbf{y}$ *to mean* $(\mathbf{x},\mathbf{y}) \in \mathrm{R}$, *and the order relation is:* $\forall \mathbf{x},\mathbf{y},\mathbf{z} \in X$,

(i) $\mathbf{x} \leq \mathbf{x}$

(ii) $\mathbf{x} \leq \mathbf{y} \quad \text{and} \quad \mathbf{y} \leq \mathbf{z} \quad \Rightarrow \quad \mathbf{x} \leq \mathbf{z}$,

(iii) $\mathbf{x} \leq \mathbf{y} \quad \text{and} \quad \mathbf{y} \leq \mathbf{x} \quad \Rightarrow \quad \mathbf{x} = \mathbf{y}$.

In addition, [41] also imposes that if $\lim_{n\to\infty} \mathbf{x_n} = \mathbf{x}$, $\lim_{n\to\infty} \mathbf{y_n} = \mathbf{y}$ *and* $\mathbf{x_n} \leq \mathbf{y_n}$ *for all n, then* $\mathbf{x} \leq \mathbf{y}$. *In other words,* R *is a closed subset of* $X \times X$.

We call X an *ordered subspace* of an ordered space X' if $X \subset X'$ and the order and topology on X identical to that on X'.

For simplicity, concepts will be presented in Euclidean space $X = \mathbb{R}^n$ for the rest of this chapter, although most of what is discussed can be realised in a general Banach space (see, for example, [65, 41]). Given a convex, pointed cone K, we can define a partial order relation $\leq_K$ via $\mathbf{x} \leq_K \mathbf{y}$ if and only if $\mathbf{y} - \mathbf{x} \in K$. Similarly we say $\mathbf{x} <_K \mathbf{y}$ if and only if $\mathbf{x} \leq_K \mathbf{y}$ and $\mathbf{x} \neq \mathbf{y}$ and also $\mathbf{x} \ll \mathbf{y}$ if and only if $\mathbf{y} - \mathbf{x} \in \mathrm{int}K$, where $\mathrm{int}K$ is the interior of K. We write $\mathbf{x} \geq_K \mathbf{y}$ to mean $\mathbf{y} \leq_K \mathbf{x}$, and similarly for $\mathbf{x} >_K \mathbf{y}$, $\mathbf{x} \gg_K \mathbf{y}$. Two points $\mathbf{x},\mathbf{y} \in \mathbb{R}^n$ are *order related* if $\mathbf{x} <_K \mathbf{y}$ or $\mathbf{y} <_K \mathbf{x}$, otherwise they are said to be *unrelated* [41].

Now we are in a position to define a monotone system:

Definition 4.1.2. *A (semi-)flow* Φ *in a (partially) ordered metric space that preserves the weak order relation*

$$\mathbf{x} \leq_K \mathbf{y} \quad \Rightarrow \quad \Phi_t(\mathbf{x}) \leq_K \Phi_t(\mathbf{y}) \quad \forall t > 0.$$

is called monotone.

Figure 4.2 shows a visual example of a monotone system

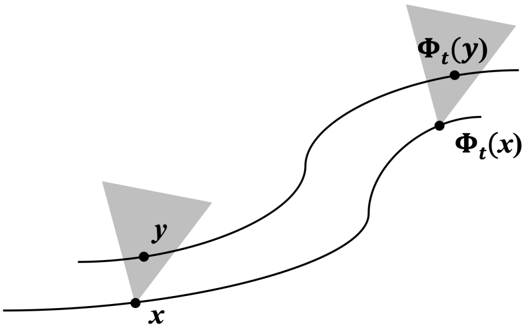


Figure 4.2: A monotone system visualised.

4.2 Quasimonontone, cooperative and competitive systems

As done in Chapter 3, we restrict our attention to the autonomous C^1-system of ODEs (3.1.2). Then we introduce the *quasimonotone condition:*

Definition 4.2.1. *The vector field* $\mathbf{f}$ *is said to be* quasimonotone *if for all* $\mathbf{x}, \mathbf{y} \in E$ *and* $\phi \in K^*$ *we have*

$$\mathbf{x} \leq_K \mathbf{y} \quad \text{and} \quad \phi(\mathbf{x}) = \phi(\mathbf{y}) \quad \Rightarrow \quad \phi(\mathbf{f}(\mathbf{x})) \leq_K \phi(\mathbf{f}(\mathbf{y})) \tag{4.2.1}$$

It turns out that quasimonotone systems are equivalent to normal monotonicity for certain domains [41, 40]:

Theorem 4.2.2. *Assume f is quasimonotone on an open set E and* $\mathbf{x_0}, \mathbf{y_0} \in E$. *Let* $\prec$ *denote any one of the relations* $<_K$, $\leq_K$, $\ll_K$. *If* $\mathbf{x_0} \prec \mathbf{y_0}$, $t > 0$ *and* $\Phi_t(\mathbf{x_0})$ *and* $\Phi_t(\mathbf{y_0})$ *are both defined, then* $\Phi_t(\mathbf{x_0}) \prec \Phi_t(\mathbf{y_0})$, *thus the system of differential equations (3.1.2) generates a monotone flow. Conversely, if (3.1.2) generates a monotone flow, then it is also quasimonotone.*

The theorem also holds if E is a closed set; a justification is given in [40].

4.2.1 K-cooperative and K-competitive systems

A necessary and sufficient condition for the cone K being an invariant set of (3.1.2) which is based on Proposition 3.3 in [41] is given here:

Proposition 4.2.3. *The cone K is positively invariant under (3.1.2) if and only if $K \subset E$ and*

$$\boldsymbol{\ell} \in K^*,\ \mathbf{x} \in \partial K,\ \mathbf{x}\cdot\boldsymbol{\ell} = 0 \quad \Rightarrow \quad \mathbf{f}(\mathbf{x})\cdot\boldsymbol{\ell} \geq 0 \tag{4.2.2}$$

where $\langle\cdot,\cdot\rangle : K^* \times K \to \mathbb{R}$ denotes the inner product.

It will be convenient to refer to (4.2.2) when applying on systems other than (3.1.2) by saying that it holds for $\mathbf{f} : E \to \mathbb{R}^n$ where $K \subset E$.

For a general cone K, (3.1.2) is said to be *K-cooperative* if K is invariant under the forward flow of the linear system

$$\dot{\mathbf{x}} = D\mathbf{f}(\mathbf{y})\mathbf{x}. \tag{4.2.3}$$

Applying Proposition 4.2.3 reveals that K-cooperativeness is equivalent to checking that (4.2.3) satisfies (4.2.2) for all $x^* \in E$, i.e.

$$\forall\boldsymbol{\ell} \in K^*,\ \mathbf{x} \in \partial K \text{ such that } \quad \mathbf{x}\cdot\boldsymbol{\ell} = 0,\ (D\mathbf{f}(\mathbf{y})\mathbf{x})\cdot\boldsymbol{\ell} \geq 0, \tag{4.2.4}$$

which also implies that $D\mathbf{f}(\mathbf{y})K \subseteq K$ for all $\mathbf{x} \in E$.

Similarly we say that (3.1.2) is K-competitive if $\dot{\mathbf{x}} = -\mathbf{f}(\mathbf{x})$ is $K-$cooperative with flow Φ_{-t}. Results in this section can also be applied for K-competitive dynamical systems through time-reversal.

The next theorem from [41] shows that under certain conditions, a system (3.1.2) being K-cooperative and quasimonotone are the same. Before declaring it, we define a set $E \subset \mathbb{R}^n$ to be *p-convex* if whenever $\mathbf{x}, \mathbf{y} \in E$ and $\mathbf{x} <_K \mathbf{y}$ then $[\mathbf{x}, \mathbf{y}] := \{\mathbf{z} \in \mathbb{R}^n : \mathbf{x} \leq_K \mathbf{z} \leq_K \mathbf{y}\} \subseteq E$.

Theorem 4.2.4. *Let $D\mathbf{f}(\mathbf{x})$ be continuous on E. If $\mathbf{f}$ satisfies the quasimonotone condition, then it is also K-cooperative. Conversely, if E is p-convex and $\mathbf{f}$ is K-cooperative, then the quasimonotone condition holds.*

Additionally, the same conditions are sufficient for a K-cooperative system being monotone as well [41]:

Theorem 4.2.5. *Let* $\mathbf{f}$ *be a K-cooperative vector field in an open set* $E \subset \mathbb{R}^n$*, generating a local (semi-)flow* Φ*. Then* Φ *is locally monotone. Moreover if E is p-convex,* Φ *is also monotone.*

(A map is *locally monotone* if each point in its domain E has a neighbourhood on which the map is monotone.)

Theorem 4.2.5 states that when (3.1.2) is $K-$cooperative and E is p-convex, (4.1.2) holds. Therefore the time-reversed flow of a K-competitive system (3.1.2), when it exists, is monotone, i.e.

$$\mathbf{x} \leq_K \mathbf{y} \quad \Rightarrow \quad \Phi_t(\mathbf{x}) \leq_K \Phi_t(\mathbf{y}) \quad \forall t < 0.$$

In fact, if $\mathbf{x}, \mathbf{y}$ are unrelated, then $\Phi_t(\mathbf{x}), \Phi(\mathbf{y})$ are unrelated for all $t > 0$ (because $\Phi_t(\mathbf{x})$ and $\Phi_t(\mathbf{y})$ being related would imply $\mathbf{x}, \mathbf{y}$ are related; this can be seen through applying Φ_{-t}).

We now provide results about the limit sets of K-cooperative or K-competitive systems, starting with Theorem 3.2 from [40].

Theorem 4.2.6. *A compact limit set of a K-cooperative or K-competitive system cannot contain two points related by* $\ll_K$*.*

Theorem 3.4 from [40] states that a compact limit set of a K-cooperative or K-competitive system is no more complicated than an invariant set for a general system in one less dimension.

Theorem 4.2.7. *The flow on a compact limit set of a K-cooperative or K-competitive system in* $\mathbb{R}^n$ *is topologically equivalent to a flow on a compact invariant set of a Lipschitz system of differential equations in* $\mathbb{R}^{n-1}$*.*

4.2.2 Standard competitive and cooperative systems

For the special case $K = \mathbb{R}^n_+$, the standard orthant, we can identify K^* with K using the standard inner product. Moreover, taking $\phi(\mathbf{x}) = \mathbf{e_i} \cdot \mathbf{x}$, where $\mathbf{e_i}$ corresponds to the unit vector in the x_i-direction, leads to the *Kamke-Müller condition* [55, 56]:

$$\mathbf{x} \leq \mathbf{y} \quad \text{and} \quad \exists i \ s.t. \ x_i = y_i \quad \Rightarrow \quad f_i(x) \leq f_i(y).$$

For differentiable $\mathbf{f}$, this condition reduces to

$$\frac{\partial f_i}{\partial x_j}(\mathbf{x}) \geq 0, \quad \forall \mathbf{x} \in E,\ i \neq j. \tag{4.2.5}$$

If E is p-convex, then (4.2.5) implies the Kamke-Müller condition; furthermore, the system (3.1.2) is said to be cooperative.

If instead the partial derivatives satisfy

$$\frac{\partial f_i}{\partial x_j}(\mathbf{x}) \leq 0, \quad \forall \mathbf{x} \in E,\ i \neq j. \tag{4.2.6}$$

then (3.1.2) is competitive on a p-convex domain E.

4.3 A special class of competitive systems

In [66], Smale considered *Kolmogorov* systems which have the form

$$\dot{x}_i = x_i N_i(\mathbf{x}), \qquad i = 1, 2, \ldots, n \tag{4.3.1}$$

where $\mathbf{N} : \mathbb{R}^n_+ \to \mathbb{R}^n$ is a C^1-smooth function. The system is called *strongly competitive* if [67]

$$\frac{\partial N_i}{\partial x_j}(\mathbf{x}) < 0, \qquad \forall \mathbf{x} \in \mathbb{R}^n_+, \qquad \forall i, j = 1, 2, \ldots, n, \qquad i \neq j,$$

in which case the system (4.3.1) also satisfies (4.2.6), thus is competitive in the standard sense as well. If a strongly competitive Kolmogorov system also satisfies $\frac{\partial N_i}{\partial x_i}(\mathbf{x}) < 0$ for all $i = 1, 2, \ldots, n$, then it is said to be *totally competitive* [68].

Smale proved that an arbitrary smooth flow in the simplex Δ_n can be embedded as an attracting invariant manifold in a Kolmogorov system [66]. His intention behind this was to warn population biologists that systems designed to model competition could have complicated dynamics.

However, Hirsch showed that strongly competitive systems possess a countably infinite or finite sequence of nonmonotone manifolds that divide the phase space into regions, and that these manifolds are attracting [59]. Each manifold played the role of Smale's attracting simplex Δ_n, suggesting that Smale's construction was not as special as it seemed. A set S is said to be *balanced* if any two points $\mathbf{x}, \mathbf{y}$ on S are unrelated with respect to $\gg$, and is *nonmonotone* or *strongly balanced* if $\mathbf{x}, \mathbf{y}$ are unrelated with respect to $>$. A steady state $\mathbf{x}^*$ called a *weak source* if $|\Phi_{-t}(\mathbf{x}) - \mathbf{x}^*|$ converges uniformly to 0 as $t \to \infty$ for all $\mathbf{x} \in U$ for some non-empty set U.

Hirsch's theory is captured in the following theorem:

Theorem 4.3.1 (Adapted from Theorem 1.1 in [59])**.** *Let* Phi_t *denote the flow in* $\mathbb{R}^n_+$ *of a strongly competitive Kolmogorov system (4.3.1). Then there is a countable disjoint family* $\mathcal{F} = \{M_i\}$ *of invariant Lipschitz manifolds in* $\mathbb{R}^n_+$ *having the following properties:*

(a) Suppose the trajectory of $\mathbf{x}$ *is non-convergent and* $\omega(\mathbf{x}) \subset M_i \cap \mathrm{int}(\mathbb{R}^n_+)$*. Then if* $\mathbf{x} \notin M_i$*, there exists* $\mathbf{y} \in M_i$ *such that*

$$|\Phi_t(\mathbf{x}) - \Phi_t(\mathbf{y})| \to 0 \quad \text{as} \quad t \to \infty.$$

In other words, the trajectory of $\mathbf{x}$ *is asymptotic to a trajectory in* M_i*.*

(b) Homeomorphic to $\mathbb{R}^{n-1}$*.*

(c) Each M_i *is balanced, while* $M_i \cap \mathrm{int}(\mathbb{R}^n_+)$ *is strongly balanced*

(d) The cardinality of $\mathcal{F}$ *is at most one plus the number of weak sources in* $\mathrm{int}(\mathbb{R}^n_+)$*.*

Furthermore, Hirsch obtained a set of conditions for totally competitive system possessing a unique invariant manifold called the *carrying simplex* [59, 68]:

Theorem 4.3.2. *In a Kolmogorov system (4.3.1) with, for all* $i, j = 1, 2, \ldots, n$*,*

$$N_i(\mathbf{0}) > 0 \quad and \quad \frac{\partial N_i}{\partial x_j}(\mathbf{x}) < 0$$

there is a unique Lipschitz invariant manifold Σ *that attracts* $\mathbb{R}^n_+ \setminus \{\mathbf{0}\}$ *and every trajectory in* $\mathbb{R}^n_+ \setminus \{\mathbf{0}\}$ *is asymptotic to one in* Σ*. The submanifold* Σ *is homeomorphic* *to* Δ_n *under radial projection. Moreover,* Σ *is balanced, while its interior,* $\mathrm{int}\,\Sigma$ *is strongly balanced.*

The geometry, smoothness and dynamics of carrying simplices have been studied in [69, 70, 67, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80]. However, to the best of the author's knowledge the smoothness of a carrying simplex on its interior remains an open problem. Meanwhile, an alternative method of proving existence of the carrying simplex for the cases $n = 2, 3$ is to apply the Hadamard transform on the simplex Δ_n, as done in [81, 68].

Chapter 5

The Nagylaki-Crow Model

This chapter, based on the paper [82], focuses on a continuous-time model proposed in [83] called the Nagylaki-Crow model. Many models in population genetics, including those discussed later in this thesis, assume random mating (or a random union of gametes) resulting in Hardy-Weinberg proportions at the zygote stage. The other common assumption is selection by means of viability differences in the genotypes.

In reality though, natural selection is more complicated. Random mating does not occur in nature (for example, tall women prefer tall men). Furthermore some pairings may be more fertile than others. The Nagylaki-Crow model takes nonrandom mating into account by assuming different fertilities for mating pairs, as well as different death rates of genotypes, which is why it is sometimes referred to as the fertility-mortality model [2].

By fertility, we mean the average number of offspring produced per unit time by parents with specified genotypes. Meanwhile, mortality refers to the death rate for a given (parental) genotype. These are all assumed to be constant in time.

5.1 What is already known about the model?

One of the earliest attempts at considering different fertilities for mating pairs was made by Penrose in [84]. He showed that his basic discrete-time model with additive fertilities gave essentially the same results as the usual discrete selection model. For the next few decades, most investigations into differential fertility were only made for the discrete model [85].

Then in 1961 Rucknagel and Neel produced experimental evidence of fertility differences among mating pairs for the locus corresponding to sickle cell anaemia [86], a single-locus genetic disorder affecting humans. This revived interest in differential fertility models.

Over a decade later, Nagylaki and Crow provided a derivation for a continuous-time model [83, 5], now known as the Nagylaki-Crow model. However, they restricted their attention to the case of additive fertilities when analysing the model. Another special case of this model is analysed in [87, 88] with symmetric fertilities and no deaths. Hadeler and Glas showed that all orbits for the Nagylaki-Crow model with no deaths converge to some steady state [89]. They also proposed a change of variables, which was later used in [90] to demonstrate that the model can have periodic orbits. In 1988, Hofbauer and Sigmund proved the existence of an invariant manifold connecting the two homozygotic fixation states in a two allele fertility-selection model where the fertilities were additive in Section 26.5 of [91]. They also showed that with the assumption of additivity of mortalities this invariant manifold coincided with the Hardy-Weinberg manifold where the genotypic frequencies are the product of allele frequencies, and that the Hardy-Weinberg manifold is invariant; this was also shown in [92]. Then Szucs and Akin commented on conditions on the relative sizes of fertilities and differences in mortalities required for attractiveness of the Hardy-Weinberg manifold [93].

Our aim here is to extend this work by showing that the Nagylaki-Crow model possesses at least one nonmonotone invariant manifold *without assuming additivity of fertilities or mortalities*, which will make our result more widely applicable than Akin and Szucs. In the context of our planar model, a nonmonotone manifold is a manifold which is the graph of a decreasing continuous function. We also find conditions that ensures that the invariant manifold is the graph of a convex function, as is the case for the Hardy-Weinberg manifold.

Section 5.2 introduces the $n-$allele model, while Section 5.5 discusses the two-allele case of the model and shows how to rewrite the Nagylaki-Crow model as a competitive system using a change of coordinates, although later we will drop one of the two inequalities that render the model competitive, so that we obtain results for not-necessarily competitive models. It turns out that the model always has steady states on two corners of the triangular phase plane (axial steady states), and our numerical evidence suggests the existence of at least one nonmonotone invariant manifold Σ connecting the two steady states in the phase plot. We analyse both axial steady states in Section 5.6, and investigate their relationship with the condition for the system being competitive in the new coordinates. Finally, for Section 5.7, we prove that a nonmonotone invariant manifold Σ does indeed exist for a certain case of the Nagylaki-Crow model, and that it is the graph of a convex function.

5.2 The model

A derivation of the panmictic Nagylaki-Crow model for diploid populations can be found in [83], where the authors consider a single locus with n alleles $A_1, \dots A_n$, and the dynamical variables of their system are the frequencies P_{ij} for the ordered genotype A_i/A_j.

The Nagylaki-Crow model also features the fertilities $a_{ik,lj}$ that are defined as the product of the average number of matings of an arbitrary individual per unit time and the average number of progeny per $A_i/A_k \times A_l/A_j$ union. With this definition in mind, we expect the fertilities to be non-negative, hence we assume

$$a_{ik,lj} \geq 0 \quad \forall i, j, k, l.$$

Moreover, it will be assumed that these fertilities are also time-independent for all i, j, k, l.

In addition, the model contains the mortalities d_{ij}, the death rate for genotype A_i/A_j. These are also taken to be non-negative and constant for all time.

The governing equations for the genotype frequencies P_{ij}

$$\dot{P_{ij}} = \left(\sum_{kl} a_{ik,lj} P_{ik} P_{lj} - d_{ij} P_{ij} \right) - P_{ij} \sum_{uv} \left(\sum_{kl} a_{uk,lv} P_{uk} P_{lv} - d_{uv} P_{uv} \right), \tag{5.2.1}$$

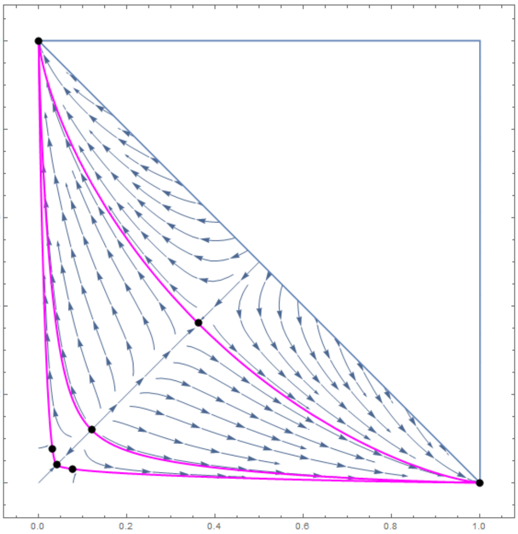


Figure 5.1: A case of the Nagylaki-Crow model with five interior steady states, three of which occur on the line $y = x$ with $y = 0.04, 0.12$ and 0.36 respectively. There are three different nonmonotone invariant manifolds, one of which passes through three interior steady states. Here, the fertilities are $F_{11} = 6$, $F_{12} = 1/2$, $F_{13} = 1$, $F_{22} = 1/14$, $F_{23} = 1/2$, $F_{33} = 6$, while the mortalities are $D_1 = 2$, $D_2 = 1$, $D_3 = 2$, making this system competitive in (w, t) coordinates. The notation for the fertilities and mortalities are as given in (5.3.2) and (5.3.3)

form a system of n^2 nonlinear first order ordinary differential equations (see [83] or [5]). Note that if $P_{ij}(0) \geq 0$ then $P_{ij}(t) \geq 0$ for all $t \geq 0$. Moreover $\sum_{i,j=1}^{n} P_{ij}(t) = 1$ for all $t \geq 0$. The marginal $\sum_{j=1}^{n} P_{ij}(t) = \sum_{j=1}^{n} P_{ji}(t) = p_i(t)$ is the frequency of allele A_i at time $t \geq 0$.

Figure 5.1 shows an example of the phase portrait for the Nagylaki-Crow model. In this example, there are five interior steady states, which is the maximum number that the two-allele model can possess (Exercise 21.2.6 in [2]). In the figure there are three different nonmonotone invariant manifolds, one of which passes through three interior steady states.

Even for this simple model it is not possible to obtain self-contained evolution equations for the allele frequencies, which often are the variables of most interest to the geneticist. First, note that the genotypes A_i/A_j and A_j/A_i are effectively the same, hence we have

$$P_{ij} = P_{ji}.$$

With this symmetry law in mind, let

$$P_{11} = x, \quad P_{12} = P_{21} = z/2, \quad P_{22} = y. \tag{5.2.2}$$

hence the allellic frequencies satisfy

$$\begin{aligned} p_1 &= P_{11} + P_{12} = x + \frac{1}{2}z \\ p_2 &= P_{21} + P_{22} = \frac{1}{2}z + y. \end{aligned}$$

Eliminating for z yields

$$p_1 = x + \frac{1}{2}(1 - x - y) = \frac{1}{2}(1 + x - y) \tag{5.2.3}$$

$$p_2 = y + \frac{1}{2}(1 - x - y) + P_{22} = \frac{1}{2}(1 - x + y), \tag{5.2.4}$$

which is not invertible. However, the presence of an attracting manifold means that differential equations can be obtained for the allele frequencies when restricted to that manifold. Suppose the invariant manifold Σ can be expressed as the graph $y = \varphi(x)$, and substitute into (5.2.3). We obtain

$$p_1 = \frac{1}{2}(1 + x - \varphi(x)) \tag{5.2.5}$$

Moreover, we can claim $x = X(p_1)$ for some function X, because x is the frequency of the homozygote A_1A_1, which contains the allele A_1 only. So we can rearrange (5.2.5) as follows:

$$\begin{aligned} p_1 &= \frac{1}{2}(1 + X(p_1) - \varphi(X(p_1))) \\ \Rightarrow \quad \varphi(X(p_1)) &= 1 + X(p_1) - 2p_1, \end{aligned}$$

i.e. φ can be expressed completely in terms of p_1 (or alternatively $p_2 = 1 - p_1$.)

If an initial point is attracted to the manifold rapidly then after a short transient the equations for the allele frequencies on the manifold will be a good approximation of the true allele frequencies. Note that if there is at least one attracting manifold, which manifold is approached will depend upon the initial conditions.

The special case where the fertilities and mortalities are additive means that $a_{ik,lj} = \alpha_{ik} + \beta_{lj}$ and $d_{ij} = \mu_i + \kappa_j$, where $\alpha_{ik}, \beta_{lj}, \mu_i, \kappa_j \geq 0$. In this special case all trajectories converge to the Hardy-Weinberg manifold connecting the axial steady states [93], which is obtained by solving the simultaneous equations

$$\begin{aligned} (P_{11} =)x &= p_1^2 \\ (P_{22} =)\varphi_{HW}(x) &= p_2^2 \\ p_2 &= 1 - p_1 \end{aligned}$$

giving the graph of the strictly convex function $\varphi_{HW} : [0,1] \to [0,1]$ defined by

$$\varphi_{HW}(x) = 1 + x - 2\sqrt{x}. \tag{5.2.6}$$

For comparison, the Hardy-Weinberg manifold is shown in Figure 5.2. Our results

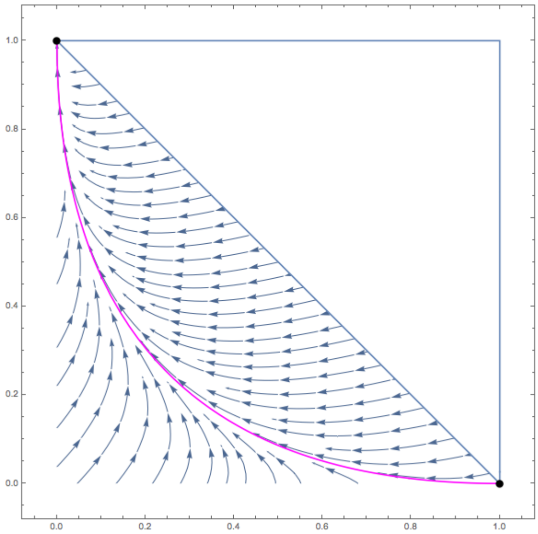


Figure 5.2: An example where the fertilities are additive, leading to the Hardy-Weinberg manifold which is the graph of the function φ_{HW} in Equation (5.2.6). Here, the fertilities are $F_{11} = 0.6$, $F_{12} = 0.9$, $F_{13} = 1.3$, $F_{22} = 1.2$, $F_{23} = 1.6$, $F_{33} = 1.3$, while the mortalities are $D_1 = 0.3$, $D_2 = 0.25$, $D_3 = 0.2$, making this system competitive in (w,t) coordinates. Again, the notation for the fertilities and mortalities are as given in (5.3.2) and (5.3.3).

show that under mild conditions, when the condition of additivity of fertilities and mortalities is relaxed, there is at least one such nonmonotone manifold, and we give conditions that ensure that any such nonmonotone manifold is the graph of a convex function. A detailed analysis of concerning uniqueness or nonuniqueness of this manifold has not yet been done.

5.3 Some relabelling required

Even for $n = 2$ the Nagylaki-Crow is not a straightforward model to analyse and to the best of the author's knowledge there is currently no understanding of this model for three or more alleles [2]. In the sequel we will always assume $n = 2$ and ignore the order of the genotypes, i.e. treat A_i/A_j and A_j/A_i as identical.

Many of the original parameter names are cumbersome, so we will start by relabelling them in the notation of [90]. The first step is to assume, as is done in [5], that the fertilities $a_{ik,lj}$ possess the symmetries

$$a_{ij,kl} = a_{kl,ij}, \quad a_{ij,kl} = a_{ji,kl}. \tag{5.3.1}$$

The first equation in (5.3.1) means that swapping the genotypes of the parents does not affect the fertility of the pairing. The order of the genotype has no effect, too, hence the second symmetry rule in (5.3.1) holds. These bring the number of (independent) fertility parameters down to six. Using the notation of [90] these are relabelled as follows:

$$\begin{aligned} F_{11} &= a_{11,11}, & F_{33} &= a_{22,22}, \\ F_{12} &= a_{11,12}, & F_{23} &= a_{12,22}, \\ F_{22} &= a_{12,12}, & F_{13} &= a_{22,11}. \end{aligned} \tag{5.3.2}$$

Meanwhile, as $d_{12} = d_{21}$, there are only three independent mortality parameters. They are rewritten as

$$D_1 = d_{11}, \quad D_2 = d_{12}, \quad D_3 = d_{22}. \tag{5.3.3}$$

Thus the Nagylaki-Crow model (5.2.1) reduces to [90]

$$\dot{x} = F_{11}x^2 + F_{12}xz + \frac{1}{4}F_{22}z^2 - D_1x - x\bar{m}, \tag{5.3.4}$$

$$\dot{z} = F_{12}xz + 2F_{13}xy + F_{23}yz + \frac{1}{2}F_{22}z^2 - D_2z - z\bar{m}, \tag{5.3.5}$$

$$\dot{y} = F_{33}y^2 + F_{23}yz + \frac{1}{4}F_{22}z^2 - D_3y - y\bar{m}, \tag{5.3.6}$$

with mean fitness

$$\begin{aligned}\bar{m} &= \sum_{uv}\left(\sum_{kl} a_{uk,lv}P_{uk}P_{lv} - d_{uv}P_{uv}\right)\\ &= F_{11}x^2 + 2F_{12}xz + F_{22}z^2 + 2F_{23}yz + 2F_{13}xy + F_{33}y^2\\ &- D_1x - D_2z - D_3y.\end{aligned}$$

However, we also have the condition

$$\sum_{ij} P_{ij} = 1 \qquad \text{or} \qquad x + y + z = 1, \qquad x, y, z \geq 0 \tag{5.3.7}$$

thus, by eliminating $z = 1 - x - y$, the two-allele Nagylaki-Crow model can be expressed using just two ordinary differential equations of the form

$$\dot{x} = f(x, y), \qquad \dot{y} = g(x, y), \tag{5.3.8}$$

on the phase space given by the triangle

$$T = \{(x, y) \in \mathbb{R}^2_+ : x + y \leq 1\}. \tag{5.3.9}$$

The full equations for x, y are (A.0.1) and (A.0.2).

5.4 An early attempt at rewriting the model

The explicit equations for the Nagylaki-Crow model are still complicated to analyse: they are cubic and many of the coefficients consist of (lengthy!) combinations of the fertilities and mortalities. Hence it would be helpful to rewrite the already relabelled model in a simpler form; an early attempt at doing so is outlined in this section. The approach taken here is to propose a new set of parameters, all expressed in terms of the fertilities and death rates. Although it ultimately does not help with proving Σ exists in the model, constructing a numerical example containing three interior steady states along the line $y = x$ becomes simpler. In Equations (A.0.1) and (A.0.2), the mortalities always appear in multiples of $(D_1 - D_2)$, $(D_3 - D_2)$ and $(D_1 - D_3) = (D_1 - D_2) - (D_3 - D_1)$, suggesting that we rename the death rates as follows:

$$D_{11} = D_1 - D_2, \quad D_{22} = D_3 - D_2, \tag{5.4.1}$$

Then define the following parameters

$$\begin{aligned} \alpha &= 2F_{23} - F_{33} - F_{22}, & \beta &= F_{12} + F_{23} - F_{22} - F_{13}, \\ \gamma &= 2F_{12} - F_{11} - F_{22}, & \delta &= F_{23} - \frac{3}{2}F_{22} - D_{22}, \\ \theta &= F_{12} - \frac{3}{2}F_{22} - D_{11}, & E &= \frac{1}{4}F_{22}. \\ & & F &= F_{13}, \end{aligned} \tag{5.4.2}$$

and substitute into (A.0.1) and (A.0.2) to obtain

$$\begin{aligned} \dot{x} &= E(y-1)^2 + x\left[-(\beta+\delta+F)y + \alpha y^2 + \theta\right] \\ &\quad + x^2\left[2y\beta - (\gamma+\theta+E)\right] + \gamma x^3, \\ \dot{y} &= E(x-1)^2 + y\left[-(\beta+\theta+F)x + \gamma x^2 + \delta\right] \\ &\quad + y^2\left[2x\beta - (\alpha+\delta+E)\right] + \alpha y^3, \end{aligned}$$

which can be rearranged as follows

$$\begin{aligned} \dot{x} &= \alpha xy^2 + \beta xy(2x-1) + \gamma x^2(x-1) - \delta xy + \theta x(1-x) \\ &\quad + E\left[(y-1)^2 - x^2\right] - Fxy, \end{aligned} \tag{5.4.3}$$

$$\begin{aligned} \dot{y} &= \alpha y^2(y-1) + \beta xy(2y-1) + \gamma x^2 y + \delta y(1-y) - \theta xy \\ &\quad + E\left[(x-1)^2 - y^2\right] - Fxy. \end{aligned} \tag{5.4.4}$$

The last two equations appear to have a duality between them. More precisely, swapping x with y, α with γ, δ with θ and doing the vice versa of each everywhere in (5.4.3) gives (5.4.4). Conversely, repeating the procedure on (5.4.4) yields (5.4.3) again. In light of this, suppose $\alpha = \gamma$ and $\delta = \theta$, which is equivalent to

$$F_{11} - F_{33} = 2(F_{12} - F_{23}) = 2(D_1 - D_3). \tag{5.4.5}$$

In this case, Equations (5.4.3) and (5.4.4) become

$$\begin{aligned}\dot{x} &= \alpha x\left[x(x-1)+y^2\right]+\beta xy(2x-1)+\delta x(1-x-y)\\ &\quad +E\left[(y-1)^2-x^2\right]-Fxy,\\ \dot{y} &= \alpha y\left[y(y-1)+x^2\right]+\beta xy(2y-1)+\delta y(1-x-y)\\ &\quad +E\left[(x-1)^2-y^2\right]-Fxy.\end{aligned}$$

We now consider the behaviour of the Nagylaki-Crow model when the proportions of the two homozygotes A_1A_1 and A_2A_2 are equal, i.e. when $x = y$. In that case,

$$\dot{x} = \dot{y} = E + y(\delta - 2E) - y^2(F + \alpha + \beta + 2\delta) + 2y^3(\alpha + \beta) \tag{5.4.6}$$

As this is a cubic polynomial, a maximum of three steady states can be found on the line $y = x$, an example attaining this maximum is portrayed in Figure 5.3.

5.5 Rewriting the Nagylaki-Crow model

As an alternative, we use the following coordinate change introduced in [89, 90]

$$(x,y) \mapsto (w,t) = \Phi(x,y) := \left(\frac{2x}{1-x-y}, \frac{2y}{1-x-y}\right). \tag{5.5.1}$$

The map Φ is a diffeomorphism from $\mathrm{int}(T)$ to $\mathrm{int}(\mathbb{R}^2_+)$ with inverse

$$\Phi^{-1}(w,t) = \left(\frac{w}{2+w+t}, \frac{t}{2+w+t}\right) \tag{5.5.2}$$

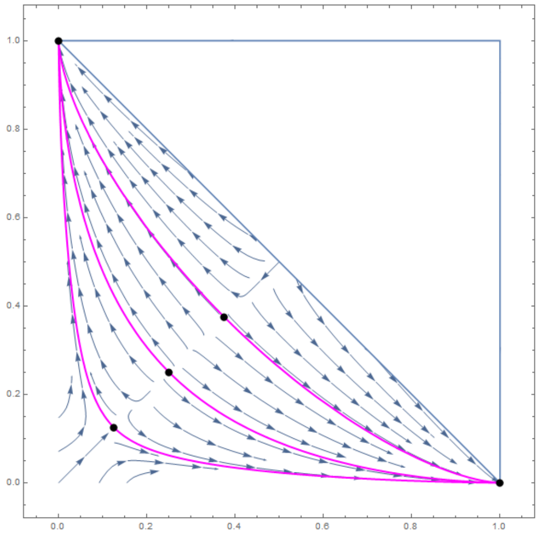


Figure 5.3: A case of the Nagylaki-Crow model with three interior steady states, all of which occur on the $y = x$ line. In this example, the three points occur on $y = 1/8$, $1/4$, and $3/8$.
Here, the fertilities are

$$\begin{array}{ll} F_{11} = \dfrac{249}{160}, & F_{33} = \dfrac{4}{5}, \\ F_{12} = \dfrac{63}{160}, & F_{23} = \dfrac{1}{64}, \\ F_{22} = \dfrac{3}{64}, & F_{13} = \dfrac{3}{64}, \end{array}$$

while the mortalities are

$$D_1 = \frac{151}{320}, \quad D_2 = 0 \quad D_3 = \frac{3}{32},$$

making this system competitive in (w,t) coordinates.

and the Jacobian J of Φ on the interior of T is given by

$$J = \begin{pmatrix} -\frac{2(y-1)}{(x+y-1)^2} & \frac{2x}{(x+y-1)^2} \\ \frac{2y}{(x+y-1)^2} & -\frac{2(x-1)}{(x+y-1)^2} \end{pmatrix}, \quad \det J = \frac{4}{(1-x-y)^3}. \tag{5.5.3}$$

In the new coordinates, the system (5.3.8) reduces to

$$\dot{w} = p(w,t), \qquad \dot{t} = q(w,t), \tag{5.5.4}$$

where

$$\begin{aligned} p(w,t) &= (F_{11} - F_{12} + D_2 - D_1)w^2 + (2(F_{12} + D_2 - D_1) - F_{22})w \\ &\quad + F_{22} - wt(F_{23} - D_2 + D_1 + F_{13}w), \qquad (5.5.5) \\ q(w,t) &= (F_{33} - F_{23} + D_2 - D_3)t^2 + (2(F_{23} + D_2 - D_3) - F_{22})t \\ &\quad + F_{22} - wt(F_{12} - D_2 + D_3 + F_{13}t). \qquad (5.5.6) \end{aligned}$$

Here by $\dot{w}, \dot{t}$ we mean differentiation with respect to time; the time variable will be denoted by s in the rest of this chapter.

In this set of coordinates, the phase space is the whole (non-compact) first quadrant $w \geq 0, t \geq 0$. For the boundary $w = 0$, we have $\dot{w} = F_{22} \geq 0$, which shows that $w < 0$ can never occur. Likewise, we have $\dot{t} = F_{22} \geq 0$ for the boundary at $t = 0$, therefore it is impossible to attain $t < 0$. As a result, the phase space $\mathbb{R}^2_+$ is forward invariant.

Necessary and sufficient condition for Equations (5.5.4) being competitive on $\mathbb{R}^2_+ = \{(w,t) \in \mathbb{R}^2 : w \geq 0, t \geq 0\}$ are derived in [90]. By (4.2.6), this is equivalent to the all off-diagonal entries of the Jacobian

$$J' = \begin{pmatrix} p_w & p_t \\ q_w & q_t \end{pmatrix},$$

being nonnegative for all $w, t \geq 0$, i.e. $p_t, q_w \leq 0$ [90, 89]. This simplifies to checking that

$$\begin{aligned} p_t &= (-F_{23} + D_2 - D_1)w - F_{13}w^2 \\ q_w &= (-F_{12} + D_2 - D_3)t - F_{13}t^2, \end{aligned}$$

are both non-positive, which occurs if and only if

$$D_2 \leq \min(D_1 + F_{23}, D_3 + F_{12}). \qquad (5.5.7)$$

Hence (5.5.7) is a necessary and sufficient condition for Equations (5.5.4) to be competitive on $\mathbb{R}^2$. It is known that an orbit of a planar competitive system is either unbounded or converges to a steady state in increasing time [2, 89]. For this system, if an orbit Γ in (w,t) is unbounded, then $z \to 0$, i.e. $(x+y) \to 1$. This shows that the corresponding ω-limit set for Γ in (x,y) coordinates is a subset of the bounding line $x+y=1$.

Examples of nonmonotone manifolds in the model are the three solid curves in Figure 5.1. Although our model is competitive, it does not satisfy the setting of Hirsch's Theorem 4.3.1 since $\partial\mathbb{R}^2_+$ is not invariant. However, we found numerical evidence of similar sequences of nonmonotone manifolds. For example, Figure 5.1 shows three nonmonotone manifolds (solid curves) that all connect the axial steady states. These are the only *nonmonotone* invariant manifolds in the figure. A monotone invariant manifold passes through 3 interior steady states along the line $x=y$. Two of the nonmonotone manifolds pass through a single interior steady state, and the third passes through 3 interior steady states. A detailed analysis of the stability of each nonmonotone manifold in our model has not been done yet. The focus in this thesis is to prove the existence of at least one nonmonotone invariant manifold and to establish conditions that the manifold is the graph of a convex function. It turns out that to do this it is much easier to carry out some calculations in the (w,t) coordinates where the phase space is not compact, mapping back results to the system in (x,y) coordinates, and some calculations in (x,y) coordinates where the phase space is compact, but there is no obvious ordering in (x,y) coordinates for which the system is monotone or competitive. Our key observation is that manifolds that are nonmonotone and graphs of convex functions in (w,t) coordinates are also nonmonotone and graphs of convex functions in (x,y) coordinates.

The first step is to prove the following lemma:

Lemma 5.5.1. *Suppose $\Gamma \subset \mathbb{R}^2_+$ is the graph of a twice-continuously differentiable function $\psi : (a,b) \subset \mathbb{R}_+ \to \mathbb{R}_+$ $(0 < a < b)$ such that*

$$\psi'(w) < 0, \quad \psi''(w) > 0, \ \forall w \in (a,b).$$

Then $\Gamma' = \Phi^{-1} \circ \Gamma$ *is the graph of a twice-continuously differentiable convex and decreasing function* $\phi : (A,B) \to \mathbb{R}_+$ *where* $A = \frac{a}{2+a+\psi(a)}, B = \frac{b}{2+b+\psi(b)}$, *and* $\psi = \phi \circ \Phi$*:*

$$\phi'(x) < 0, \quad \phi''(x) > 0, \ \forall x \in (A,B).$$

Proof. This is a simple calculation using that $(w,\psi(w)) = \Phi(x,\phi(x))$

$$\phi'(x) = \frac{(2+w)\psi'(w) - \psi(w)}{(2+\psi(w)) - w\psi'(w)}.$$

However, recall that $w, t = \psi(w) > 0$, therefore

$$\psi'(w) < 0 \quad \Rightarrow \quad \phi'(x) < 0. \tag{5.5.8}$$

Furthermore,

$$\phi''(x) = \frac{2(2+w+\psi(w))^3}{(2+\psi(w) - w\psi'(w))^3}\psi''(w). \tag{5.5.9}$$

Again, using $w, t = \psi(w) > 0$ we deduce

$$\psi'(w) < 0, \quad \psi''(w) > 0 \quad \Rightarrow \quad \phi''(x) > 0. \tag{5.5.10}$$

□

Remark. *It is known that linear-fractional transformations such as* Φ *map convex sets to convex sets (see, for example, [94]). Hence graphs of convex functions in* (w,t) *coordinates map to graphs of convex functions in* (x,y) *coordinates.*

Regarding interior steady states,

Lemma 5.5.2. *A steady state in the interior of* T *in* (x,y) *coordinates corresponds to a steady state in the interior of* $\mathbb{R}^2_+$ *in* (w,t) *coordinates.*

Proof. Since $(w,t) = \Phi(x,y)$ we have $(\dot{w},\dot{t}) = J(\dot{x},\dot{y})$, where J is given by (5.5.3). As J is invertible when $0 < x+y < 1$, and Φ maps the interior of T to the interior of $\mathbb{R}^2_+$, steady states in $0 < x+y < 1$ correspond to interior steady states in $\mathbb{R}^2_+$. □

5.6 Steady states and stability

The two points $(1,0)$ and $(0,1)$ in T represent the cases where all members of the population are homozygotes A_1A_1 and A_2A_2 respectively, both of these are homozygotic fixation. They are always steady states for the model (5.3.8) regardless of the parameter values, and their local invariant manifolds are investigated via spectral analysis of the Jacobian

$$J = \begin{pmatrix} f_x & f_y \\ g_x & g_y \end{pmatrix}$$

for both points.

Evaluating the Jacobian at $(0,1)$ gives

$$J^{(0,1)} = \begin{pmatrix} D_3 - D_1 - F_{33} & 0 \\ D_1 - D_2 - 2F_{13} + F_{23} & D_3 - D_2 + F_{23} - F_{33} \end{pmatrix},$$

with eigenvalues $\lambda_1^{(0,1)} = D_3 - D_1 - F_{33}$, $\lambda_2^{(0,1)} = D_3 - D_2 + F_{23} - F_{33}$.

For simplicity, we only consider the generic case where $(0,1)$ is a hyperbolic steady state and $\lambda_1^{(0,1)} \neq \lambda_2^{(0,1)}$.

If $D_1 - D_2 - 2F_{13} + F_{23} \neq 0$, suitable respective eigenvectors for $\lambda_1^{(0,1)}, \lambda_2^{(0,1)}$ are

$$\mathbf{v_1^{(0,1)}} = \left(-\frac{D_1 - D_2 + F_{23}}{D_1 - D_2 - 2F_{13} + F_{23}}, 1\right)^T, \quad \mathbf{v_2^{(0,1)}} = (0,1)^T, \tag{5.6.1}$$

which indicates that the tangent space for one of the local invariant manifolds at $(0,1)$ is then vertical. The positioning relative to T of the local invariant manifold tangent to $\mathbf{v_1^{(0,1)}}$ is not immediately obvious. On closer inspection, it turns out that the local invariant manifold will lie locally in the triangular region T if and only if the gradient of its tangent line, spanned by, $\mathbf{v_1^{(0,1)}}$, is strictly less than -1, which occurs when $F_{23} < D_2 - D_1$. Notice that this condition is satisfied if and only if $\lambda_2^{(0,1)} < \lambda_1^{(0,1)}$. In the case that $D_1 - D_2 + F_{23} - 2F_{13} = 0$, so that $J^{(0,1)}$ is diagonal, and since we are assuming that $\lambda_1^{(0,1)} \neq \lambda_2^{(0,1)}$, not a multiple of the identity, then $(1,0)$ and $(0,1)$ are suitable respective eigenvectors, and only $(0,1)$ lies in T. Note that for general F_{ij} and D_k the signs of the eigenvalues remain unspecified, hence it is unclear whether each local manifold is stable, unstable or centre.

Meanwhile, the Jacobian at $(1,0)$ is

$$J^{(1,0)} = \begin{pmatrix} D_1 - D_2 + F_{12} - F_{11} & D_3 - D_2 + F_{12} - 2F_{13} \\ 0 & D_1 - D_3 - F_{11} \end{pmatrix},$$

which has eigenvalues

$$\lambda_1^{(1,0)} = D_1 - D_3 - F_{11}, \quad \lambda_2^{(1,0)} = D_1 - D_2 + F_{12} - F_{11}, \tag{5.6.2}$$

Similarly to above we assume that $(1,0)$ is hyperbolic and $\lambda_1^{(1,0)} \neq \lambda_2^{(1,0)}$.

When $D_3 - D_2 + F_{12} - 2F_{13} \neq 0$, $J^{(1,0)}$ has suitable respective eigenvectors for $\lambda_1^{(0,1)}, \lambda_2^{(0,1)}$ given by

$$\mathbf{v_1^{(1,0)}} = \left(-\frac{D_3 - D_2 + F_{12} - 2F_{13}}{D_3 - D_2 + F_{12}}, 1\right)^T, \quad \mathbf{v_2^{(1,0)}} = (1,0)^T.$$

Hence the tangent space for one local manifold at the point is guaranteed to be horizontal at $(1,0)$. A necessary condition for the respective tangent space of the other local invariant manifold being inside the triangle T is that the gradient of $\mathbf{v_1^{(1,0)}}$ should be strictly bounded by the values -1 and 0, or equivalently,

$$\frac{F_{13}}{D_3 - D_2 + F_{12}} < 0.$$

This is satisfied if $F_{12} < (D_2 - D_3)$, which is equivalent to $\lambda_2^{(1,0)} < \lambda_1^{(1,0)}$. Again, the two eigenvalues can be generally either positive, negative or zero, hence the respective tangent spaces corresponding with the local invariant manifolds could be stable, unstable or centre manifolds.

Note that since all fertilities and death rates are taken to be real numbers, the triangular Jacobian for both steady states must always have real eigenvalues. Therefore, when hyperbolic, these steady states cannot have spirals or centres in their vicinity.

The system is strongly competitive in (w,t) coordinates if and only if strict inequality in (5.5.7) holds, which is equivalent to the following inequalities combined

$$\begin{aligned} F_{23} > (D_2 - D_1) \quad &\Leftrightarrow \quad \lambda_2^{(0,1)} > \lambda_1^{(0,1)}, \\ F_{12} > (D_2 - D_3) \quad &\Leftrightarrow \quad \lambda_2^{(1,0)} > \lambda_1^{(1,0)}. \end{aligned}$$

As noted above, however, this means that the tangent spaces of the local manifolds corresponding to the eigenvector $\mathbf{v_1}$ for both $(0,1)$ and $(1,0)$ lie outside the (x,y) phase space T. Thus strong competitiveness in the (w,t) phase space is equivalent to the local invariant manifolds at $(0,1)$ being always vertical at that steady state, and similarly, any local manifolds at $(1,0)$ are always horizontal at that point.

All this is summarised by the following result:

Proposition 5.6.1. *The following are equivalent:*

1. *Both* $\lambda_2^{(0,1)} > \lambda_1^{(0,1)}$ *and* $\lambda_2^{(1,0)} > \lambda_1^{(1,0)}$ *hold.*
2. *The Nagylaki-Crow model is strongly competitive in* (w,t) *coordinates.*
3. *The tangent spaces of the local manifolds corresponding to* $\mathbf{v_1^{(0,1)}}$ *and* $\mathbf{v_1^{(1,0)}}$ *lie outside the* (x,y) *phase space* T.

5.7 Existence of a nonmonotone invariant manifold

The aim of this section is to prove that at least one nonmonotone invariant manifold Σ does indeed exist when

$$F_{12} > D_2 - D_3,$$

which is also the graph of a convex function if in addition

$$F_{11} > D_1 - D_3 > -F_{33}.$$

Here the first inequality is similar to the condition (5.5.7) for competition, except that $D_2 \leq D_1 + F_{23}$ is not required and the inequalities are now strict.

We recall that the time variable is denoted by s, so as to avoid confusion with the vertical coordinate t from Section 5.5.

5.7.1 In the original (x, y) coordinates

In the style of [81], we consider the temporal evolution of a function $\varphi : [0,1] \times [0,\tau_0) \to \mathbb{R}_+$ satisfying $\varphi(x,0) = \varphi_0(x)$ and

$$\varphi(1,s) = 0, \qquad \varphi(0,s) = 1 \qquad \forall s \in [0,\tau_0). \tag{5.7.1}$$

Here $\tau_0 > 0$ is the maximal time of existence of φ as a solution of the first order partial differential equation

$$\frac{d\varphi}{ds} = \varphi_s + f\varphi_x = g, \tag{5.7.2}$$

where f and g are defined as in Equations (5.3.8), and $\varphi_s = \frac{\partial\varphi}{\partial s}$, subject to boundary and initial conditions explained below.

We let Σ_s be the graph of $\varphi(\cdot, s)$ for $s \in [0,\tau_0)$ (we will later show that $\tau_0 = +\infty$). The boundary conditions (5.7.1) force the endpoints of Σ_s to remain fixed for all time. We let

$$\varphi_0(x) = (1-x)(1-\varepsilon x), \quad \text{where} \quad 0 < \varepsilon \ll 1. \tag{5.7.3}$$

When $\epsilon = 0$, $\varphi_0(x) = 1 - x$ and the image of the graph of φ_0 under Φ is not defined. But by choosing $\epsilon > 0$ small the graph G_0 of φ_0 is close to $x + y = 1$ and is mapped by Φ to the graph of a continuous function $\psi_0 : (\frac{2}{\epsilon}, \infty) \to \mathbb{R}_+$ given by

$$\psi_0(w) = \frac{2(\epsilon w - 2 - w)}{2 - \epsilon w}. \tag{5.7.4}$$

The aim is to show that Σ_s converges (in the Hausdorff metric) to some manifold Σ as $s \to \infty$.

Using d/ds to denote the time derivative which follows trajectories in the phase plane, differentiating Equation (5.7.2) gives Lemma 2.1 from [81], which is

$$\frac{d\varphi_x}{ds} = g_x + (g_y - f_x - f_y\varphi_x)\varphi_x, \tag{5.7.5}$$

In fact, this is (3.5.3) applied to the Nagylaki-Crow model.

It is possible to investigate the right and left-sided limits of φ_x as $x \to 0, 1$ respectively, i.e. $\varphi_x(0+, s)$ and $\varphi_x(1-, s)$. These can be evaluated by substituting the expressions for f_x, f_y, g_x and g_y for $(x,y) = (0,1)$ into Equation (5.7.5) to obtain the following ordinary differential equation for $\varphi_x(0,s)$:

$$\frac{d\varphi_x}{ds}(0,s) = (\lambda_2^{(0,1)} - \lambda_1^{(0,1)})(\varphi_x(0,s)+1) - 2F_{13}. \tag{5.7.6}$$

whose initial condition is

$$\varphi_x(0,0) = -1-\varepsilon < -1.$$

Although this equation is separable, we will not calculate the explicit solution for $\varphi_x(0,s)$, although we do note that since (5.7.6) is linear $\varphi_x(0,s)$ is bounded for all finite forward and backward time. If $F_{13} > 0$ we conclude that $\varphi_x(0,s) < -1$ for all $s \geq 0$, which follows from the fact that when $\varphi_x(0,s) = -1$,

$$\frac{d\varphi_x}{ds}(0,s) < 0.$$

Meanwhile, if $F_{13} = 0$ we observe that $\varphi(\cdot, s) = -1-\varepsilon$ is the unique solution of (5.7.6) satisfying $\varphi(\cdot, 0) = -1-\varepsilon$. Thus for all $F_{13} \geq 0$ we have

$$\varphi_x(0,s) < -1, \ \forall s \geq 0. \tag{5.7.7}$$

Now we repeat the procedure for $(x,y) = (1,0)$. This time we obtain a differential equation for $\varphi_x(1,s)$:

$$\frac{d\varphi_x}{ds}(1,s) = -\varphi_x[(\lambda_2^{(1,0)} - \lambda_1^{(1,0)})(\varphi_x+1) - 2F_{13}\varphi_x], \tag{5.7.8}$$

with

$$\varphi_x(1,0) = -1+\varepsilon \in (-1,0).$$

Therefore if $F_{13} > 0$, then $\varphi_x(1,s) = -1$ leads to

$$\frac{d\varphi_x}{ds}(0,s) > 0,$$

while if $F_{13} = 0$, $\varphi_x(\cdot,s) = -1 + \varepsilon$ is the unique solution of (5.7.8) satisfying $\varphi(\cdot,0) = -1-\varepsilon$. Finally, regardless of whether F_{13} is positive or zero, there is another solution corresponding to the function constantly equal to zero. Therefore, as the solution is bounded, we can conclude that

$$-1 < \varphi_x(1,s) < 0, \; \forall s \geq 0. \tag{5.7.9}$$

Note, however, that there may be no lower bound for $\varphi_x(0,s)$.

To obtain information on $\varphi_x(x,s)$ for $x \in (0,1)$ and $s \in [0,\tau_0)$ using (5.7.5) and Lemma 2.1 in [81] is not so easy due to the complicated form of $g_x = \frac{1}{2}F_{22}(x-1) + 2y^2(F_{12}-F_{22}+F_{23}-F_{13}) + y(D_1-D_2+\frac{5}{2}F_{22}-2F_{12}-F_{23}+2xy(2F_{12}-F_{11}-F_{22})$, whose sign on T is not obvious.

Equation (5.7.5) can be differentiated to obtain an equivalent version of Lemma 3.1 in [81]. This governs the evolution of the convexity of φ through the value of φ_{xx}. However, this approach will not be pursued in this thesis, since we have found it too involved to track the sign of φ_{xx}. Since an approach in (x,y) coordinates does not easily lead to establishing that $\varphi_x < 0$, $\varphi_{xx} > 0$, we revert to (w,t) coordinates where establishing convexity is simpler via Lemma 5.5.1.

5.7.2 In the new (w,t) coordinates

5.7.2.1 The set-up

We seek to map the graph of φ in T to the graph of a new function ψ in $\mathbb{R}^2_+$. The function $\psi(\cdot,s)$ satisfies the first order quasilinear partial differential equation

$$\psi_s + p(w,\psi(w,s))\psi_w = q(w,\psi(w,s)) \tag{5.7.10}$$

for suitably defined $w \in \mathbb{R}_+$. For $s \in [0, \tau_0)$, $\psi(\cdot, s)$ is known to exist since it is obtained from $\varphi(\cdot, s) : [0,1] \to \mathbb{R}$ via

$$(w(x,s), \psi(w(x,s),s)) = \left(\frac{2x}{1-x-\varphi(x,s)}, \frac{2\varphi(x,s)}{1-x-\varphi(x,s)} \right), \; x \in (0,1), s \in [0,\tau_0). \tag{5.7.11}$$

Also needed is an initial condition $\psi(w,0) = \psi_0(w)$, where ψ_0 is a function to be determined from φ_0.

Unfortunately the straight line $y = 1-x$ does not have a well-defined counterpart in (w,t) coordinates, and so is an inappropriate choice for an initial data curve to map onto ψ_0. Instead, we construct ψ_0 by defining φ_0 as given in (5.7.3), and transforming that into (w,t) coordinates (see Figure 5.4). By substituting $y = \varphi_0(x)$ and $z = 1-x-y$ in Equations (5.5.1), we obtain

$$w = \frac{2}{(1-x)\varepsilon}, \qquad t = \frac{2(1-x\varepsilon)}{x\varepsilon}, \qquad x \in (0,1).$$

Then by eliminating x and letting $t = \psi_0(w)$, where $\psi_0 : (\frac{2}{\epsilon}, \infty) \to \mathbb{R}_+$ we obtain the hyperbola

$$\psi_0(w) = \frac{-2(2+w-w\varepsilon)}{2-w\varepsilon}.$$

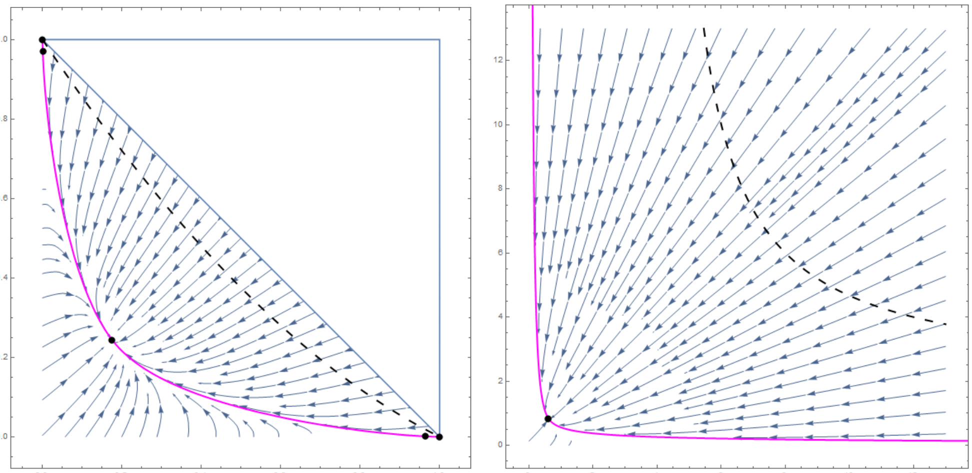
The graph of $\psi_0(w)$ lies in the open first quadrant with vertical and horizontal asymptotes $w = 2/\varepsilon$ and $t = 2(1-\varepsilon)/\varepsilon$ respectively. In addition,

$$(\psi_0)_w = \frac{-4}{(w\varepsilon-2)^2} < 0 \qquad (\psi_0)_{ww} = \frac{8\varepsilon}{(w\varepsilon-2)^3} > 0. \tag{5.7.12}$$

5.7.2.2 Equivalent boundary conditions

Boundary conditions for the partial differential equation (5.7.10) are needed, and should be equivalent to the boundary conditions in (5.7.1). It turns out that the equivalent condition is that ψ must have a horizontal and vertical asymptote at all times, even if the positions of these asymptotes vary in time. For now, these asymptotes will be said to occur at t^* and w^* respectively (both functions of s).

Let us determine the boundary condition for (5.7.10) corresponding to the



(a) A plot of the initial data curve, the graph of φ_0, in (x,y) coordinates.

(b) A plot of the initial data curve, the graph of ψ_0, in (w,t) coordinates.

Figure 5.4: The initial data curve for the two coordinate systems (dashed line), which deforms in time according to the flow, converging to the invariant manifold Σ (solid line). For these plots, we take $\varepsilon = 1/2$.

point $(0,1)$ using the transformation (5.5.1). Recall that $\varphi(\cdot, s) : [0,1] \to \mathbb{R}$ is defined and smooth for each $s \in [0, \tau_0)$. Then by l'Hôpital's rule, for all $s \in [0, \tau_0)$ we have $\lim_{x\to 0+} w(x,s) = \frac{2}{-1-\varphi_x(0,s)}$, whereas $\lim_{x\to 1-} w(x,s) = +\infty$. Similarly, $\lim_{x\to 0+} t(x,s) = +\infty$, whereas $\lim_{x\to 1-} t(x,s) = \frac{2\varphi_s(1,s)}{-1-\varphi_x(1,s)}$. The graph of $\psi(\cdot,s)$ has a vertical asymptote at $w = w^*(s) := \frac{2}{-1-m_0(s)}$ and a horizontal asymptote at $t = t^*(s) := \frac{2m_1(s)}{-1-m_1(s)}$, where $m_0(s) = \varphi_x(0,s)$ and $m_1(s) = \varphi_x(0,s)$. Since from (5.7.7) and (5.7.9) we have, $m_0 < -1$ and $-1 < m_1 < 0$, we find that $w^*(s)$, $t^*(s)$ are well-defined and positive for $s \in [0, \tau_0)$. Hence the image of each $\varphi(\cdot, s)$ under Φ is a continuous curve that is the graph of a function $\psi(\cdot, s) : (w^*(s), +\infty) \to \mathbb{R}$. This indicates that both asymptotes will lie in the interior of $\mathbb{R}^2_+$.

5.7.2.3 Investigating the gradient and convexity

Differentiating Equation (5.7.10) gives Lemma 2.1 from [81], which is

$$\frac{d\psi_w}{ds} = q_w + (q_t - p_w - p_t\psi_w)\psi_w, \quad s \in [0, \tau_0). \tag{5.7.13}$$

Furthermore, we can repeat the procedure to obtain an equivalent version of Lemma 3.1 [81], which states that for all $s \in [0, \tau_0)$

$$\frac{d\psi_{ww}}{ds} = q_{ww} + \psi_w(2q_{wt} - p_{ww}) + \psi_w^2(q_{tt} - 2p_{wt}) - p_{tt}\psi_w^3 + \psi_{ww}(q_t - 2p_w - 3p_t\psi_w). \tag{5.7.14}$$

However, as the equations of motion are already simpler in (w, t), the partial derivatives of p and q are also easier to compute. In fact, we find that

$$p_{tt} = q_{ww} = 0,$$

which simplifies Equation (5.7.14) to

$$\frac{d\psi_{ww}}{ds} = \psi_w[(2q_{wt} - p_{ww}) + \psi_w(q_{tt} - 2p_{wt})] + \psi_{ww}(q_t - 2p_w - 3p_t\psi_w). \tag{5.7.15}$$

Also,

$$\begin{aligned}
p_{ww} &= 2(D_2 - D_1 + F_{11} - F_{12} - F_{13}t), \\
q_{tt} &= 2(D_2 - D_3 + F_{33} - F_{23} - F_{13}w), \\
p_{wt} &= D_2 - D_1 - F_{23} - 2F_{13}w, \\
q_{wt} &= D_2 - D_3 - F_{12} - 2F_{13}t,
\end{aligned}$$

and so

$$\begin{aligned}
2q_{wt} - p_{ww} &= 2(D_1 - D_3 - F_{11} - F_{13}t), \\
q_{tt} - 2p_{wt} &= 2(D_1 - D_3 + F_{33} + F_{13}w),
\end{aligned}$$

which are negative and positive when $F_{11} > D_1 - D_3$ and $F_{33} > D_3 - D_1$ respectively. Combining these two conditions gives the constraint

$$F_{11} > D_1 - D_3 > -F_{33}, \tag{5.7.16}$$

which is equivalent to having both $\lambda_1^{(1,0)} < 0$ and $\lambda_1^{(0,1)} < 0$. Meanwhile, a sufficient condition for $q_w < 0$ is $t > 0$ and $D_2 < D_3 + F_{12}$ (i.e. $\lambda_2^{(1,0)} > \lambda_1^{(1,0)}$). Then, assuming (5.7.16) and $D_2 < D_3 + F_{12}$, let $\alpha = \psi_w$ and $\beta = \psi_{ww}$ and rewrite Equations (5.7.13) and (5.7.15) as two coupled ordinary differential equations:

$$\frac{d\alpha}{ds} = A\alpha^2 + B\alpha + C \tag{5.7.17}$$

$$\frac{d\beta}{ds} = \alpha(D + E\alpha) + \beta(F + G\alpha), \tag{5.7.18}$$

where

$$\begin{aligned} A &= -p_t & E &= q_{tt} - 2p_{wt} > 0 \\ B &= q_t - p_w & F &= q_t - 2p_w \\ C &= q_w < 0 & G &= -3q_t \\ D &= 2q_{wt} - p_{ww} < 0 \end{aligned}$$

are all continuous (in fact, polynomial) functions of w and ψ (which replaces t). We already found that ψ_0 is strictly decreasing and convex, with $\alpha_0 < 0$ and $\beta_0 > 0$, where $\alpha_0 = \alpha(w,0)$ and $\beta_0 = \beta(w,0)$. Now the aim is to prove

$$\alpha < 0, \qquad \beta > 0 \qquad \forall s \in [0, \tau_0), \tag{5.7.19}$$

for all values of w for which $\psi(w,s)$ is defined. In other words, if the initial data curve is both strictly decreasing and convex in (w,t) coordinates, then it will remain that way as s increases in $[0,\tau_0)$.

The following lemma is based on Corollary 2.2 of [81], whose proof makes use of the fact that $C = q_w < 0$:

Lemma 5.7.1. *If the smooth initial curve ψ_0 satisfies both $\psi_0 > 0$ and $(\psi_0)_w < 0$, then for all $s \in [0,\tau_0)$, $\psi(\cdot,s)$ is defined and smooth for all $w > w^*(s)$ (where $w^*(s)$ is the vertical asymptote of $\psi(\cdot,s)$ mentioned in the previous remark), with $\psi(\cdot,s) > 0$, $\psi_w(\cdot,s) < 0$ and $\psi_{ww}(\cdot,s) > 0$.*

Proof. We already know that $\varphi(\cdot,s):[0,1]\to\mathbb{R}$ exists for $s\in[0,\tau_0)$ for some $\tau_0>0$, and hence via the coordinate change Φ, $\psi(\cdot,s):(w^*(s),\infty)\to\mathbb{R}$ satisfying (5.7.10) exists for all $s\in[0,\tau_0)$. The function $\psi(\cdot,s):(w^*(s),\infty)\to\mathbb{R}$ also satisfies Equations (5.7.13) and (5.7.15) for $s\in[0,\tau_0)$.

As the vertical asymptote $w^*(s)$ is changing in time, it is convenient to rescale the asymptote to unity by a change of variables, taking

$$v=\frac{w}{w^*(s)}. \tag{5.7.20}$$

Note that $w^*(s)>0$ for $s\in[0,\tau_0)$ so that this transformation is defined for at least $s\in[0,\tau_0)$.

We define $\tilde{\psi}(\cdot,s):[1,\infty)\to\mathbb{R}_+$ via

$$\tilde{\psi}(v,s)=\psi(w,s)=\psi(vw^*(s),s),\quad s\in[0,\tau_0).$$

Now compute

$$\begin{pmatrix}\psi_w\\ \psi_s\end{pmatrix}=\begin{pmatrix}v_w & 0\\ v_s & 1\end{pmatrix}\begin{pmatrix}\tilde{\psi}_v\\ \tilde{\psi}_s\end{pmatrix},$$

so that via (5.7.20)

$$\begin{pmatrix}\psi_w\\ \psi_s\end{pmatrix}=\begin{pmatrix}\frac{1}{w^*(s)} & 0\\ \frac{-ww^{*\prime}(s)}{(w^*(s))^2} & 1\end{pmatrix}\begin{pmatrix}\tilde{\psi}_v\\ \tilde{\psi}_s\end{pmatrix}. \tag{5.7.21}$$

Next, using a similar argument to that used to obtain (5.7.13) and the Chain Rule, we have $\tilde{\psi}_v=w^*(s)\psi_w$ along with

$$\frac{d\tilde{\psi}_v}{ds}=w^*q_w+(q_t-p_w+(\ln w^*)'-\frac{p_t}{w^*}\tilde{\psi}_v)\tilde{\psi}_v,\quad v\geq 1, s\in[0,\tau_0), \tag{5.7.22}$$

and $(\tilde{\psi}_0)_v<0$. Note that in Equation (5.7.22) we find that

$$(\ln w^*)'(s)=-\frac{d\varphi_x(0,s)/ds}{1+\varphi_x(0,s)},$$

which by (5.7.7) is bounded for $s\in[0,\tau_0)$.

Following Corollary 2.2 in [81], but with strict inequalities, we note that in

(5.7.22) the term $w^* q_w < 0$ so that if $\tilde{\psi}_v = 0$ for some value of $v \geq 1$ and $s \in [0, \tau_0)$, then from (5.7.22) we have $\frac{d\tilde{\psi}_v}{ds} < 0$, and so we deduce that $\tilde{\psi}(v, s)$ is strictly decreasing for $v \geq 1$ and $s \in [0, \tau_0)$. In turn this implies from $\psi_w = \frac{d\tilde{\psi}_v}{ds}/w^*$ that

$$\alpha = \psi_w(w, s) < 0, \ \forall w > w^*(s), \ s \in [0, \tau_0). \tag{5.7.23}$$

Now we turn to the sign of $\beta = \psi_{ww}$. If we let $\theta = \alpha(D + E\alpha)$ and $\sigma = (F + G\alpha)$, (5.7.18) may be written as

$$\frac{d\beta}{ds} = \sigma\beta + \theta, \tag{5.7.24}$$

and $D < 0$, $E > 0$ which, combined with $\alpha < 0$, yields $\theta > 0$. But $\beta_0 > 0$, so by Lemma 4.1 from [81], $\beta > 0$ whenever $s \in [0, \tau_0)$. Thus (5.7.19) holds, which indicates that

$$\psi_{ww} > 0 \qquad \forall w > w^*(s), \forall s \in [0, \tau_0). \tag{5.7.25}$$

In particular, (5.7.25) together with (5.7.23) implies from Lemma 5.5.1 that

$$\varphi_x(x, s) < 0, \ \varphi_{xx}(x, s) > 0, \ \forall x \in (0, 1), \ s \in [0, \tau_0). \tag{5.7.26}$$

Now we show that we may take $\tau_0 = +\infty$.

Since $\varphi_{xx}(\cdot, s) > 0$, $\varphi_x(x, s)$ is increasing with $x \in (0, 1)$, and hence finite, for each $s \in [0, \tau_0)$. Let us suppose that $\varphi_x(\bar{x}, s_i)$ becomes unbounded as $i \to \infty$ for some sequence $s_i \to \tau_0$, and some $\bar{x} \in (0, 1)$. Since $\varphi_{xx}(x, s) > 0$ for $s \in [0, \tau_0)$ and $x \in (0, 1)$ we have that $\varphi_x(x, s) \leq \varphi_x(\bar{x}, s)$ for all $x \in [0, \bar{x}]$ and $s \in [0, \tau_0)$. In particular $\varphi_x(0, s) \leq \varphi_x(\bar{x}, s)$ for all $s \in [0, \tau_0)$ and so $\varphi_x(0, s_i) \leq \varphi_x(\bar{x}, s_i)$. Letting $i \to \infty$ shows that $\varphi_x(0, s_i)$ is unbounded below which contradicts that solutions to the ordinary differential equation (5.7.6) remain bounded in finite time. This contradiction shows that $\tau_0 = \infty$.

We have thus shown that $\varphi_x(0, s)$ exists and is finite for all $s \in \mathbb{R}_+$ and that $\varphi(0, s) = 1$, $\varphi(1, s) = 0$ for all $s \in [0, \tau_0)$, and hence $\varphi(\cdot, s) : [0, 1] \to \mathbb{R}$ is a strictly decreasing smooth convex function for all $s \geq 0$. □

By Lemma 2.7 from [81], the graph of each $\varphi(\cdot, s)$ is a nonmonotone Lipschitz manifold Σ_s with Lipschitz constant unity. By the Arzelà-Ascoli Theorem, the space of Lipschitz functions in a compact space is itself compact. Hence a sequence of Lipschitz manifolds, such as the one constructed from φ, will always have a convergent subsequence whose limit is in turn also a nonmonotone Lipschitz manifold which we call Σ. It is not immediate that Σ is invariant. However, as we now show, we do not need to select a subsequence as the sequence of manifolds Σ_s is actually monotone decreasing in $s \geq 0$, from which it follows that the limit Σ is invariant.

We rewrite (5.7.2) in the form

$$\varphi_s = \mathbf{N} \cdot \mathbf{f}, \tag{5.7.27}$$

where $\mathbf{f} = (f, g)$ and $\mathbf{N} = (-\varphi_x, 1)$ is the upward normal which normalises to $\mathbf{n}$.

As done in [81], we track the time evolution of $b = \mathbf{n} \cdot \mathbf{f}$, the component of the flow normal to the curve. Suppose that $\varphi_0(x) = 1 - x$. Then at $s = 0$, $\mathbf{n} = \frac{1}{\sqrt{2}}(1, 1)$ and

$$b = 2F_{13}x(x - 1),$$

which is negative for $x \in (0, 1)$, as long as $F_{13} > 0$. Moreover, if ε is sufficiently small, we still have the same sign for b at $s = 0$ for all $x \in (0, 1)$ when $\varphi_0(x) = (1 - x)(1 - \varepsilon x)$, since this initial data curve is a perturbation of $y = 1 - x$.

Next, we invoke Lemma 2.6 from [81], i.e.

$$\dot{b} = (\mathbf{n} \cdot \nabla\mathbf{f} \cdot \mathbf{n})\, b,$$

which shows that b, and in turn φ_s, stays negative for all $s > 0$. So the graphs Σ_s of $\varphi(\cdot, s)$ always move downwards with increasing s under the flow of the system for all positive time, hence the limiting manifold Σ is indeed invariant.

Hence we can summarise our results in the following theorem:

Theorem 5.7.2. *In the Nagylaki-Crow model (5.3.4) - (5.3.6) suppose that*

$$D_2 < D_3 + F_{12}, \quad F_{13} > 0. \tag{5.7.28}$$

Then the model has at least one nonmonotone invariant manifold that connects the steady states $(0,1)$ *and* $(1,0)$ *in* $T = \{(x,y) \in \mathbb{R}_+^2 : 0 \leq x+y \leq 1\}$.

If in addition

$$F_{11} > D_1 - D_3 > -F_{33} \tag{5.7.29}$$

holds, this nonmonotone manifold is the graph of a convex function.

Observe that all of (5.5.7) is not needed, so existence works for not necessarily competitive models that satisfy (5.7.28) only. A similar result applies by interchanging w and t leading to a version of Theorem 5.7.2 with (5.7.28) replaced by $D_2 < D_1 + F_{23}$ and (5.7.29).

The nonmonotone invariant manifold of Theorem 5.7.2 is a connecting orbit that connects the two axial steady states (possibly via other steady states) in T. When both inequalities in (5.5.7) hold, so that the system is competitive, it is also monotone with the order $\geq$. In this case, existence of a connecting orbit (even with additional steady states ordered by $\geq$) follows from [95]; a similar result for discrete-time systems is the subject of [96]. Jiang showed that for cooperative systems, this connecting orbit is unique if the Jacobian is irreducible at the two steady states. Even if Jiang's result on irreducibility can be modified for planar competitive systems, in our model the Jacobian at the axial steady states is reducible and so an alternative approach is needed to determine when the nonmonotone manifold is unique. In any case our existence result does not require a competitive model for existence, and so conditions for uniqueness of the manifold are not at all clear and will be dealt with elsewhere.

5.8 Discussion

We have shown the existence of a nonmonotone invariant manifold for a continuous-time differential fertility model in Population Genetics without requiring additivity of fertilities or mortalities, nor competitive dynamics. Note that the additive case generally does not satisfy the new conditions, i.e. (5.7.28) (or its alternative in (5.5.7)) and (5.7.29).

To do this, we set up an invertible mapping between an evolving curve φ in (x, y) space and an evolving (unbounded) curve ψ in (w, t) space. Through our lemmata it then suffices to check the signs of the first and second derivatives of ψ (as it then follows that the graph of φ is decreasing and convex). Then convergence is established in (x, y) space using Lipschitz and bounded sequences of the graph of φ. Thus the crucial part is setting up the map between φ and ψ by a change of dynamical variables. A similar technique is remarked on in [68] which involves applying the transformation $y_i = \log x_i$ $(i = 1, 2, 3)$ on the Lotka-Volterra equations. This coordinate change maps the invariant surface from something which is not necessarily concave to a concave surface.

There was no need to assume that the system was competitive in either coordinate system; nonetheless, the existence proof given in this thesis for a decreasing manifold only applies when the inequality (5.7.28) (or its alternative in (5.5.7)) applies. We also showed that when the Nagylaki-Crow model satisfies the inequalities (5.7.29), the invariant manifold is the graph of a convex function. In Figure 5.5 we show that when (5.7.29) is not satisfied the invariant manifold, which still exists as two heteroclinic connections of axial and interior steady states, may be non smooth and not the graph of a continuous decreasing convex function. How far the conditions for convexity can be weakened is an open problem.

Meanwhile, it is also unknown what conditions are required for the constructed invariant manifold to be smooth. Even when the model is competitive or strongly competitive, results such as in [97] are not immediately applicable as $\partial\mathbb{R}^2_+$ is not invariant for our system. Since f and g are bivariate polynomials each heteroclinic connection (orbit) along Σ is an analytic invariant manifold [37], hence only the interior steady states on Σ need to be checked for C^1-smoothness. In addition, the Stable Manifold Theorem also indicates that the stable and unstable subspaces for any saddle point in the dynamical system are both one-dimensional. Moreover Σ, which is itself one-dimensional, must be tangential to one of the aforementioned subspaces, as well as C^1-smooth, even at the saddle point. Hence all that remains is to find conditions for Σ to be also C^1-smooth at interior steady states of the model that are not saddles.

Recall that in Figure 5.1 the invariant manifold Σ is not unique. In fact, numerics suggest that the model has at most finitely countably many nonmonotone invariant manifolds; these are analogous to the family of manifolds described by Hirsch in Theorem **??**. Our model, however, is not immediately covered by Hirsch's results because the boundary of the phase space in Hirsch's system is invariant whereas in our case, the flow on the boundary points towards the interior of T. Nevertheless we believe that the difference is not problematic, as long as we have a repelling boundary for the phase space.

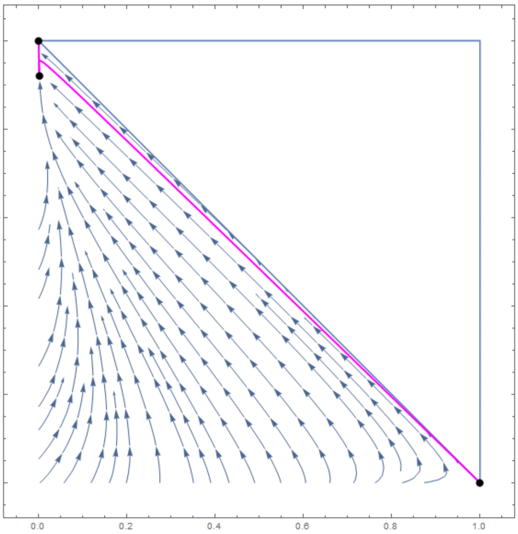


Figure 5.5: A numerical example where the invariant manifold, which consists of a union of two heteroclinic orbits, is not nonmonotone, smooth or the graph of a convex function. The values of the fertilities are $F_{11} = 2/5$, $F_{12} = 1/100$, $F_{13} = 1/81$, $F_{22} = 98/100$, $F_{23} = 11/12$, $F_{33} = 1/97$, while the mortalities are $D_1 = 93/100$, $D_2 = 9/10$, $D_3 = 1/10$, so that this example does not satisfy either of $D_2 \leq D_1 + F_{23}$ or $D_2 \leq D_3 + F_{12}$.

Chapter 6

The Selection-Recombination model

As mentioned in Chapter 2, a multi-locus model is needed in order to study genetic recombination, and the resulting dynamical system is referred to as the selection-recombination model. This chapter focuses on the simplest of these models, with only two loci and two alleles. It was first proposed by Kimura in [98]; the derivation is also given in [4]. More general versions of the model can be found in the literature - a two-locus multiallelic model is given in [2], while [99] discusses a multi-locus one.

Even just the two-locus two-allele (TLTA) model already has nine distinct diploid genotypes! It is far simpler to focus on the state of the gamete pool using just four dynamical variables, rather than keep track of all nine genotypes. Assuming random union of gametes lets us recover the frequencies of the full genotypes at the zygote stage; multiplying these by the corresponding fitness gives the proportions at the adult stage [2].

6.1 What is already known about the model?

A QLE manifold is known to exist for weak selection [99]. Currently though, it is unclear to what extent the manifold persists when selection is not weak.

Meanwhile, it is shown in [100, 101, 102] that stable limit cycles can be present in the two loci two allele model. However, these do not occur for weak selection if all the steady states in the model are hyperbolic [99]; what happens when the hyperbolicity condition is not satisfied is an open problem.

6.2 The two-locus two-allele (TLTA) model

Suppose both loci α and β come with two alleles: A, a for the locus α and B, b for the locus β. Hence there are four possible gametes ab, Ab, aB and AB; these haploid genotypes will be denoted by G_1, G_2, G_3, G_4, whose frequencies at the zygote stage (i.e. immediately after fertilisation) are freq(ab) = x_1, freq(Ab) = x_2, freq(aB) = x_3 and freq(AB) = x_4 respectively [2].

Let W_{ij} denote the probability of survival from the zygote stage to adulthood for an individual resulting from a G_i-sperm fertilising a G_j-egg. If the genotypes of the gametes from each parent are swapped, we expect the fitness to stay the same, hence $W_{ij} = W_{ji}$. Another assumption is the *absence of position effect*, i.e. $W_{14} = W_{23} = \theta$ [5], since the full diploid genotype of an individual obtained by G_1 and G_4 gametes, (ab/AB) is identical to that of an individual resulting from G_2 and G_3 gametes (Ab/aB) [2]. The fitness matrix is the following symmetric matrix:

$$W = \begin{pmatrix} W_{11} & W_{12} & W_{13} & \theta \\ W_{12} & W_{22} & \theta & W_{24} \\ W_{13} & \theta & W_{33} & W_{34} \\ \theta & W_{24} & W_{34} & W_{44} \end{pmatrix}, \tag{6.2.1}$$

Then the governing equations for the selection-recombination model are

$$\dot{x}_i = x_i(m_i - \bar{m}) + \varepsilon_i r\theta D, \qquad i = 1,2,3,4. \tag{6.2.2}$$

Here $m_i = (Wx)_i$ represents the fitness of G_i, while $\bar{m} = x^{\top}Wx$ is the mean fitness in the gamete pool of the population. Also included are the recombination rate $0 < r \leq \frac{1}{2}$ and $\varepsilon_i = -1, 1, 1, -1$.

The linkage disequilibrium coefficient $D = x_1x_4 - x_2x_3$ is a measure of the statistical dependence between the two loci. Let freq(a) denote the frequency of allele a, freq(ab) be the frequency of genotype ab, and so on. Then [2]

$$D = \text{freq}(ab) - \text{freq}(a)\text{freq}(b),$$

hence $D = 0$ if and only if

$$\text{freq}(ab) = \text{freq}(a)\text{freq}(b),$$

with similar results also holding for each of Ab, aB and AB. In this scenario, the population is said to be in linkage equilibrium. As already mentioned, the manifold corresponding to $D = 0$ is known as the Wright Manifold.

It is possible to fix $\theta = 1$ without loss of generality [4, 2, 5]. However, we will not do so because later in this chapter we will consider a special case which uses a different value of θ. A derivation of the model (6.2.2) is given in [4]. We will sometimes represent this dynamical system by $\dot{\mathbf{x}} = \mathbf{f}(\mathbf{x})$, where $\mathbf{x} = (x_1, x_2, x_3, x_4)$.

The phase space for this dynamical system is the simplex

$$\Delta_4 = \{(x_1, x_2, x_3, x_4) \in \mathbb{R}^4 : x_i \geq 0, \sum_{i=1}^{4} x_i = 1\}. \tag{6.2.3}$$

We will denote the vertices of Δ_4 by $\mathbf{e_1} = (1,0,0,0)$, $\mathbf{e_2} = (0,1,0,0)$, $\mathbf{e_3} = (0,0,1,0)$ and $\mathbf{e_4} = (0,0,0,1)$. Moreover, each edge connecting vertex $\mathbf{e_i}$ with $\mathbf{e_j}$ will be denoted by E_{ij}.

The linchpin of this paper is the QLE manifold, a connected invariant manifold of codimension one,which will be denoted as Σ_M. The QLE manifold is close to the Wright manifold and its (relative) boundary corresponds to the union of the four edges E_{12}, E_{13}, E_{42} and E_{43}. Moreover, all orbits are attracted to Σ_M, except for any steady states not in Σ_M. Our numerical evidence so far suggests that Σ_M exists for a large range of values of the fitnesses and r. However, the existence of Σ_M has not previously been shown other than for weak selection (relative to r), or additive fitnesses or strong recombination and it is unknown whether Σ_M is always Lipschitz, or whether it is of class C^1.

To begin the study of (6.2.2), it is first convenient to follow other authors and change dynamical variables via $\Phi : \Delta_4 \to \mathbb{R}^3_+$

$$\mathbf{x} \mapsto \mathbf{u} = \Phi(x) := (x_1 + x_2, x_1 + x_3, x_1 + x_4), \tag{6.2.4}$$

where $\mathbf{u} = (u, v, q)$. The mapping has inverse

$$\Phi^{-1}(\mathbf{u}) = \frac{1}{2}(u+v+q-1, u-v-q+1, -u+v-q+1, -u-v+q+1). \tag{6.2.5}$$

Φ maps Δ_4 to the tetrahedron in $\mathbb{R}^3_+$:

$$\Delta = \mathrm{Conv}\{\tilde{e}_1, \tilde{e}_2, \tilde{e}_3, \tilde{e}_4\}, \tag{6.2.6}$$

where $\tilde{\mathbf{e}}_\mathbf{i} = \Phi(\mathbf{e_i})$ with $\tilde{\mathbf{e}}_\mathbf{1} = (1,1,1)$, $\tilde{\mathbf{e}}_\mathbf{2} = (1,0,0)$, $\tilde{\mathbf{e}}_\mathbf{3} = (0,1,0)$, $\tilde{\mathbf{e}}_\mathbf{4} = (0,0,1)$ and $\mathrm{Conv\,S}$ denotes the convex hull of a set S.

Remark. *There is a biological interpretation for two of these new dynamical variables:*

$$u = \mathrm{freq}(ab) + \mathrm{freq}(Ab) = \mathrm{freq}(b), \tag{6.2.7}$$

$$v = \mathrm{freq}(ab) + \mathrm{freq}(aB) = \mathrm{freq}(a). \tag{6.2.8}$$

Both allelic frequencies have been used in [103]. It is unclear if there is any biological meaning behind q.

Φ maps the system (6.2.2) to new equations of motion for u, v and q, which have the following form:

$$\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u}) \tag{6.2.9}$$

where $\mathbf{u} = (u, v, q)$ and $\mathbf{F} = (U, V, Q)$, are cubic multivariate polynomials of u, v and q given explicitly in Appendix B.

Figure 1 shows the advantage of using the new coordinates $\mathbf{u}$. The Wright manifold is shown in (a) for simplex coordinates $\mathbf{x}$ and (b) the Wright manifold is shown in the new tetrahedral coordinates $\mathbf{u}$. Notice that in (b), the new coordinates allow the manifold to be written as the graph of a function over $[0,1]^2$. In (c), (d) we also show an example of the TLTA model with positive recombination rate. Here we see that the QLE manifold is a perturbation of the Wright manifold (see [99] for an analysis of this perturbation for a n-allele model using the method of normal

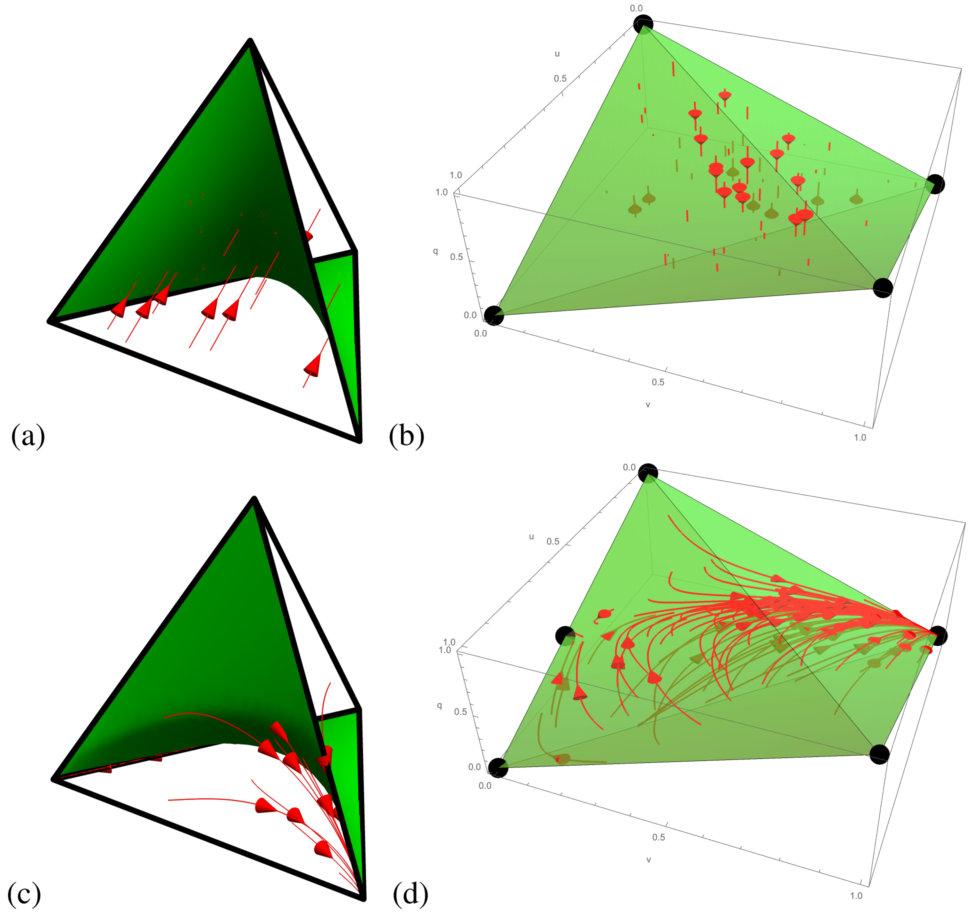


Figure 6.1: (a) The Wright manifold (neutral selection and $r = 0.3$) in $\mathbf{x}$ coordinates. (b) The Wright manifold (neutral selection and $r = 0.3$) in (u, v, q) coordinates. (c) The QLE manifold ($r > 0$) in $\mathbf{x}$ coordinates. (d) The QLE manifold ($r > 0$) in (u, v, q) coordinates. (Parameters chosen: $W_{11} = 0.1, W_{12} = 0.3, W_{13} = 0.75, W_{22} = 0.9, W_{24} = 1.7, W_{33} = 3.0, W_{34} = 2.0, W_{44} = 0.3, \theta = 1.0, r = 0.3$)

hyperbolicity). Although the Wright manifold is depicted for neutral selection with $r > 0$, it is also invariant for additive fitnesses regardless of r [104, 2].

Figure 6.2 depicts an example where the QLE manifold Σ_M could not be computed numerically - it may not even exist for this example! The author notes that some of the fitnesses are much larger than the rate of recombination, e.g. $W_{13} = 20$, while $r = \frac{1}{19}$.

6.3 Main result

Our objective is to establish explicit parameter value ranges in the TLTA model that guarantee the existence of a globally attracting QLE manifold. Here we establish:

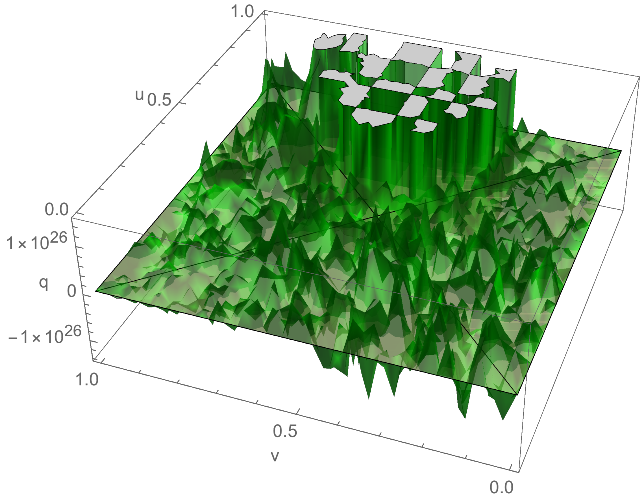


Figure 6.2: The QLE manifold Σ_M could not be computed numerically for this example. The parameters chosen are $W_{11} = 0.1, W_{12} = 0.3, W_{13} = 20.0, W_{22} = 0.9, W_{24} = 10.0, W_{33} = 1.3, W_{34} = 2.0, W_{44} = 0.5, \theta = 1.0, r = \frac{1}{19}$

Theorem 6.3.1 (Existence of a globally attracting Quasi-linkage Equilibrium manifold)**.** *Consider the TLTA model (6.2.2). If (6.4.30) and (6.6.11), then there exists a Lipschitz invariant manifold that globally attracts all initial polymorphisms.*

Our approach is to first establish conditions for the TLTA model (6.2.9) to be a competitive system. This will be achieved by showing that, when considered backwards in time, (6.2.9) is a K_M-monotone system with respect to a proper (non-simplicial) polyhedral cone K_M. In establishing this, it is particularly fortuitous that the boundary of the Wright manifold in (u, v, q) coordinates is invariant under the TLTA dynamics. The invariant boundary then provides fixed Dirichlet boundary conditions for a computation of the QLE manifold as the limit $\phi(\cdot)$ of a time-dependent solution $\phi(\cdot, t)$ of a quasilinear partial differential equation (see Equation (6.3.2) below). The global existence in time of $\phi(\cdot, t)$ and convergence to a Lipschitz limit is guaranteed by the confinement of the normal of the graph of $\phi(\cdot, t)$ to K_M. Finally global convergence to the QLE manifold is established by showing that phase space volume is strictly decreasing in time. The graph of the limit ϕ is identified as the QLE manifold Σ_M.

The space of Lipschitz continuous functions with Lipschitz constant γ is denoted by $C_\gamma(\mathbb{R}^2)$ in [42]. In a similar manner, we will use $C_\gamma([0,1]^2)$ to denote the space of Lipschitz functions on $[0,1]^2$, also with Lipschitz constant γ.

Then define the space of functions

$$B = \{\phi \in C_1([0,1]^2) : \text{graph}\,\phi \subset \Delta, \partial\text{graph}\,\phi = \tilde{\text{E}}_{12} \cup \tilde{\text{E}}_{13} \cup \tilde{\text{E}}_{42} \cup \tilde{\text{E}}_{43}\}, \tag{6.3.1}$$

where ∂S denotes the boundary of a surface S relative to the interior of S. Also, $\tilde{E}_{ij} = \Phi(E_{ij})$. All functions in B have the same Lipschitz constant one, and hence B is an uniformly equicontinuous family of functions. The graph of any function in B is always contained in Δ which is a closed and bounded subset of $\mathbb{R}^3$, hence B is bounded, as well as closed. Hence by the Arzelà-Ascoli Theorem, B is also compact.

Let $\phi_t = \mathcal{L}_t\phi_0$, where $\mathcal{L}_t$ is the graph transform of ϕ_0 according to the flow of (6.2.9. Let $\phi(u,v,t) = \phi_t(u,v)$; then similar to [68], we track the time evolution of the function $\phi : [0,1]^2 \times [0,\tau_0) \to \mathbb{R}_+ = [0,\infty)$ with an initial condition $\phi(u,v,0) = \phi_0(u,v) \in B$. Here, τ_0 is the maximal time of existence of ϕ as a solution of the first order partial differential equation

$$\frac{\partial\phi}{\partial t} = Q - U\frac{\partial\phi}{\partial u} - V\frac{\partial\phi}{\partial v}, \quad (u,v) \in (0,1)^2, t > 0. \tag{6.3.2}$$

The initial condition is chosen as $\phi_0(u,v) = 1 - u - v + 2uv$ so the graph of ψ initially coincides with the Wright manifold in the new coordinate system.

Boundary conditions are also required that are consistent with the invariance of the edges $\tilde{E}_{42}$, $\tilde{E}_{12}$, $\tilde{E}_{13}$ and $\tilde{E}_{43}$; these are:

$$\phi(u,0,t) = 1 - u, \qquad \text{i.e. freq}(B) = 0, \tag{6.3.3}$$

$$\phi(1,v,t) = v, \qquad \text{i.e. freq}(a) = 0, \tag{6.3.4}$$

$$\phi(u,1,t) = u, \qquad \text{i.e. freq}(b) = 0, \tag{6.3.5}$$

$$\phi(0,v,t) = 1 - v, \qquad \text{i.e. freq}(A) = 0, \tag{6.3.6}$$

respectively. The biological interpretation is that each of the four conditions (or edges) corresponds to the scenario where one of the alleles A, a, B or b is absent in the population for all time.

Moreover, all four edges being invariant indicates that for all $t > 0$

$$\partial \mathrm{graph}\,\phi_{\mathrm{t}} = \partial \mathrm{graph}\,\phi_0 = \tilde{\mathrm{E}}_{12} \cup \tilde{\mathrm{E}}_{13} \cup \tilde{\mathrm{E}}_{42} \cup \tilde{\mathrm{E}}_{43} \tag{6.3.7}$$

But Δ is also forward invariant, hence, $\mathrm{graph}\,\phi \subset \Delta$ for all $t \geq 0$.

We now have a partial differential equation for the evolution of a surface $S_t :=$ $\mathrm{graph}(\phi(\cdot,\cdot,t))$. Since we wish to recover the QLE manifold as S_t in the limit as $t \to \infty$, we need that the solution $\phi(\cdot,\cdot,t) :\to [0,1]^2 \to \mathbb{R}$ exists globally in $t > 0$, and that it remains suitably regular, say uniformly Lipschitz. We will achieve this goal by showing that the normal bundle of S_t, denoted is contained in a proper convex cone for all $t \geq 0$. As we show in the next section, it turns out that keeping the normal bundle of S_t is contained within a proper convex cone is intimately related to monotonicity properties of the flow of (6.2.9).

6.4 Conditions for the TLTA model to be competitive

6.4.1 Competitive dynamics

Let us assume there is a proper convex cone K such that $-D\mathbf{F}K \subset K$, i.e. that the TLTA model (6.2.9) is competitive with respect to the cone K.

We will now relate the invariance of the cone K for $D\mathbf{F}$ to properties of surfaces that evolve in $[0,1]^3$ under the flow Φ_t generated by (6.2.9). Let S_0 be a compact connected surface in $[0,1]^3$, and $S_t = \Phi_t(S_0)$ be S_0 translated by the flow Φ_t. As stated in [68], the governing equation for the time evolution of a vector $\mathbf{n}$ in the direction of the outward unit normal at $\mathbf{u}$ is

$$\dot{\mathbf{n}} = -D\mathbf{F}(\mathbf{u})^{\top}\mathbf{n} + \mathrm{Tr}(\mathrm{D}\mathbf{F}(\mathbf{u}))\mathbf{n}, \tag{6.4.1}$$

where $\mathbf{F} = (U, V, Q)$. Note that $\mathbf{n}$ is not necessarily a unit vector.

The condition for the normal bundle of S_t, NS_t, to remain inside a convex cone K for all time is that $\mathbf{Y}(t,\mathbf{n}) = -D\mathbf{F}(\mathbf{u})^{\top}\mathbf{n} + \mathrm{Tr}(\mathrm{D}\mathbf{F}(\mathbf{u}))\mathbf{n}$ satisfies $\mathbf{Y}(t,\mathbf{n}) \cdot \boldsymbol{\ell} \geq 0$ for all

$\mathbf{n} \in \partial K, \boldsymbol{\ell} \in K^*, \mathbf{n} \cdot \boldsymbol{\ell} = 0$:

$$\left(-D\mathbf{F}(\mathbf{u})^\top \mathbf{n} + \mathrm{Tr}(\mathrm{D}\mathbf{F}(\mathbf{u}))\mathbf{n}\right) \cdot \boldsymbol{\ell} \geq 0 \ \forall \mathbf{n} \in \partial K, \boldsymbol{\ell} \in K^*, \mathbf{n} \cdot \boldsymbol{\ell} = 0,$$

that is

$$\begin{aligned} & \mathbf{n} \cdot (-D\mathbf{F}(\mathbf{u}))\boldsymbol{\ell} \geq 0 \ \forall \mathbf{n} \in \partial K, \boldsymbol{\ell} \in K^*, \mathbf{n} \cdot \boldsymbol{\ell} = 0 \\ \Leftrightarrow \quad & \mathbf{n} \cdot (-D\mathbf{F}(\mathbf{u}))\boldsymbol{\ell} \geq 0 \ \forall \mathbf{n} \in K, \boldsymbol{\ell} \in K^*, \mathbf{n} \cdot \boldsymbol{\ell} = 0, \\ \Leftrightarrow \quad & \mathbf{n} \cdot (-D\mathbf{F}(\mathbf{u}))\boldsymbol{\ell} \geq 0 \ \forall \mathbf{n} \in K, \boldsymbol{\ell} \in \partial K^*, \mathbf{n} \cdot \boldsymbol{\ell} = 0, \end{aligned}$$

which is the condition that $-D\mathbf{F}(\mathbf{u})\boldsymbol{\ell} \in K^*$ for all $\boldsymbol{\ell} \in K^*$, i.e. that the original dynamics with vector field $\mathbf{F}$ is K^*-competitive.

Hence we have shown

Lemma 6.4.1. *A cone K stays invariant under the flow of normal dynamics (6.4.1) if and only if the original dynamical system (6.2.9) is K^*-competitive.*

6.4.2 Application to the TLTA model

The respective normals to $S_t = \phi_t(S_0)$ at the vertices $\tilde{\mathbf{e}}_1, \tilde{\mathbf{e}}_2, \tilde{\mathbf{e}}_3, \tilde{\mathbf{e}}_4$ at $t = 0$ are

$$\mathbf{p_1} = (-1, -1, 1) \tag{6.4.2}$$

$$\mathbf{p_2} = (1, -1, 1) \tag{6.4.3}$$

$$\mathbf{p_3} = (-1, 1, 1) \tag{6.4.4}$$

$$\mathbf{p_4} = (1, 1, 1). \tag{6.4.5}$$

However, if we set $\mathbf{u} = \tilde{\mathbf{e}}_1$ and $\mathbf{n}(\mathbf{0}) = \mathbf{p_1}$, it turns out that $\mathbf{p_1}$ is an eigenvector of $-D\mathbf{F}(\mathbf{u})^\top + \mathrm{Tr}(\mathrm{D}\mathbf{F}(\mathbf{u}))\mathrm{I}$. As a result, the right hand side of Equation (6.4.1) equals a constant multiple of $\mathbf{p_1}$ for all $t \geq 0$, indicating that the direction of $\mathbf{n}$ matches that of $\mathbf{p_1}$ for all time at the vertex $\tilde{\mathbf{e}}_1$. Similarly, for $i = 2, 3, 4$ also, $\mathbf{n}$ always shares the same direction as $\mathbf{p_i}$ at $\tilde{\mathbf{e}}_\mathbf{i}$.

Thus let us generate a polyhedral cone K_M from the four linearly independent vectors $\mathbf{p_1}$, $\mathbf{p_2}$, $\mathbf{p_3}$ and $\mathbf{p_4}$:

$$K_M = \mathbb{R}_+\mathbf{p_1} + \mathbb{R}_+\mathbf{p_2} + \mathbb{R}_+\mathbf{p_3} + \mathbb{R}_+\mathbf{p_4}.$$

Using the formulae for $\mathbf{p_1}, \mathbf{p_2}, \mathbf{p_3}$ and $\mathbf{p_4}$ given by (6.4.2) to (6.4.5), we have

$$K_M^* = \mathbb{R}_+\boldsymbol{\alpha_1} + \mathbb{R}_+\boldsymbol{\alpha_2} + \mathbb{R}_+\boldsymbol{\alpha_3} + \mathbb{R}_+\boldsymbol{\alpha_4},$$

where

$$\begin{aligned}
\boldsymbol{\alpha_1} &= \mathbf{p_1} \times \mathbf{p_2} = 2(0,1,1) && (6.4.6)\\
\boldsymbol{\alpha_2} &= \mathbf{p_2} \times \mathbf{p_4} = 2(-1,0,1) && (6.4.7)\\
\boldsymbol{\alpha_3} &= \mathbf{p_4} \times \mathbf{p_3} = 2(0,-1,1) && (6.4.8)\\
\boldsymbol{\alpha_4} &= \mathbf{p_3} \times \mathbf{p_1} = 2(1,0,1), && (6.4.9)
\end{aligned}$$

although in what follows we drop the factors of 2 without loss of generality. The aim is to show that the normal bundle of graphϕ_{t} stays a subset of K_M for all time t. As shown in subsection 6.4.1 the required condition is

$$-\boldsymbol{\ell} \cdot D\mathbf{F}(\mathbf{u})^T\mathbf{n} \geq 0 \text{ whenever } \boldsymbol{\ell} \in K_M^*, \mathbf{n} \in \partial K_M, \cdot \mathbf{n} = 0. \qquad (6.4.10)$$

In fact, in (6.4.10) we may restrict to the generators $\boldsymbol{\alpha_i}$ for K_M:

$$-\boldsymbol{\alpha_i} \cdot D\mathbf{F}(\mathbf{u})^T\mathbf{n} \geq 0 \text{ whenever } \mathbf{n} \in \partial K_M, \boldsymbol{\alpha_i} \cdot \mathbf{n} = 0, \;\; i = 1,2,3,4. \qquad (6.4.11)$$

Actually, noting for example that, $\boldsymbol{\alpha_1} \cdot \mathbf{n} = 0 \Rightarrow \mathbf{n} = \lambda_1\mathbf{p_1} + \lambda_2\mathbf{p_2}$ for $\lambda_1 \geq 0, \lambda_2 \geq 0$ (and not both zero), and repeating for $\boldsymbol{\alpha_j}$, $j = 2,3,4$ we find that we require

$$-\alpha_i \cdot D\mathbf{F}(\mathbf{u})^T\mathbf{p_j} \geq 0 \; i,j = 1,2,3,4, \text{ with } i \neq j, \qquad (6.4.12)$$

which gives eight sufficient conditions for the normal bundle of ϕ_t to remain within

K_M for all $t > 0$:

$$\alpha_1 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_1} = (\mathbf{p_1} \times \mathbf{p_2}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_1} \leq 0 \tag{6.4.13}$$

$$\alpha_1 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_2} = (\mathbf{p_1} \times \mathbf{p_2}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_2} \leq 0 \tag{6.4.14}$$

$$\alpha_2 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_2} = (\mathbf{p_2} \times \mathbf{p_4}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_2} \leq 0 \tag{6.4.15}$$

$$\alpha_2 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_4} = (\mathbf{p_2} \times \mathbf{p_4}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_4} \leq 0 \tag{6.4.16}$$

$$\alpha_3 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_4} = (\mathbf{p_4} \times \mathbf{p_3}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_4} \leq 0 \tag{6.4.17}$$

$$\alpha_3 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_3} = (\mathbf{p_4} \times \mathbf{p_3}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_3} \leq 0 \tag{6.4.18}$$

$$\alpha_4 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_3} = (\mathbf{p_3} \times \mathbf{p_1}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_3} \leq 0 \tag{6.4.19}$$

$$\alpha_4 \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_1} = (\mathbf{p_3} \times \mathbf{p_1}) \cdot D\mathbf{F}(\mathbf{u})^\top \mathbf{p_1} \leq 0. \tag{6.4.20}$$

Our other key ingredient is $D\mathbf{F}(\mathbf{u})^\top$ which, in the original $\mathbf{x} = (x_1, x_2, x_3, x_4)$ coordinates, takes on the following form

$$D\mathbf{F}(\mathbf{u})^\top = r \begin{pmatrix} 0 & 0 & 2x_1 + 2x_2 - 1 \\ 0 & 0 & 2x_1 + 2x_3 - 1 \\ 0 & 0 & -1 \end{pmatrix} + \mathbf{M_S}, \tag{6.4.21}$$

where $\mathbf{M_S}$ is a matrix whose entries are quadratic polynomials of x_1, x_2, x_3 and x_4. Its explicit form is too complicated to be included. However, we can still derive sufficient conditions for (6.4.13)-(6.4.20); (6.4.13) reduces to

$$\begin{aligned} &2x_4\,[2x_2\,(W_{11} - 2W_{12} + W_{22}) + 2x_3\,(W_{11} - W_{12} - W_{13} + \theta) \\ &+ 2x_4\,(W_{11} - W_{12} - \theta + W_{24}) - 2W_{11} + 2W_{12} + \theta - W_{24}] - 2\theta r(x_3 + x_4) \leq 0. \end{aligned}$$

We divide throughout by 2 and define $\hat{r} = r\theta$, which leads to

$$\begin{aligned} &x_4\,[2x_2\,(W_{11} - 2W_{12} + W_{22}) + 2x_3\,(W_{11} - W_{12} - W_{13} + \theta) \\ &+ 2x_4\,(W_{11} - W_{12} - \theta + W_{24}) - 2W_{11} + 2W_{12} + \theta - W_{24}] - \hat{r}(x_3 + x_4) \leq 0, \end{aligned}$$

or equivalently

$$\begin{aligned}\hat{r}(x_3+x_4) \geq x_4\,[&2x_2\,(W_{11}-2W_{12}+W_{22})+2x_3\,(W_{11}-W_{12}-W_{13}+\theta)\\ &+ 2x_4\,(W_{11}-W_{12}-\theta+W_{24})-2W_{11}+2W_{12}+\theta-W_{24}]\,.\end{aligned}$$

But $\hat{r} \geq 0$, and so $\hat{r}(x_3+x_4) \geq \hat{r}x_4$, hence it suffices to consider

$$\begin{aligned}\hat{r}x_4 \geq x_4\,[&2x_2\,(W_{11}-2W_{12}+W_{22})+2x_3\,(W_{11}-W_{12}-W_{13}+\theta)\\ &+ 2x_4\,(W_{11}-W_{12}-\theta+W_{24})-2W_{11}+2W_{12}+\theta-W_{24}]\end{aligned}$$

or

$$\begin{aligned}0 \geq x_4\,[&2x_2\,(W_{11}-2W_{12}+W_{22})+2x_3\,(W_{11}-W_{12}-W_{13}+\theta)\\ &+ 2x_4\,(W_{11}-W_{12}-\theta+W_{24})-2W_{11}+2W_{12}+\theta-W_{24}-\hat{r}]\end{aligned}$$

which is obviously true for $x_4 = 0$. Meanwhile, for $x_4 > 0$ we can divide throughout by x_4, which yields

$$\begin{aligned}0 &\geq 2x_2\,(W_{11}-2W_{12}+W_{22})+2x_3\,(W_{11}-W_{12}-W_{13}+\theta)+2x_4\,(W_{11}-W_{12}-\theta+W_{24})\\ &\quad -2W_{11}+2W_{12}+\theta-W_{24}-\hat{r}\\ &= 2x_2\,(W_{11}-2W_{12}+W_{22})+2x_3\,(W_{11}-W_{12}-W_{13}+\theta)+2x_4\,(W_{11}-W_{12}-\theta+W_{24})\\ &\quad +(-2W_{11}+2W_{12}+\theta-W_{24}-\hat{r})\,(x_1+x_2+x_3+x_4),\end{aligned}$$

where the constant terms have been multiplied by $\sum_{i=1}^{4} x_i = 1$. Finally, we can rearrange the previous inequality to obtain (6.4.22)

$$\begin{aligned}&x_1\,(\hat{r}+2W_{11}-2W_{12}-\theta+W_{24})+x_2\,(\hat{r}+2W_{12}-\theta-2W_{22}+W_{24})\\ &+x_3\,(\hat{r}+2W_{13}-3\theta+W_{24})+x_4\,(\hat{r}+\theta-W_{24}) \geq 0,\end{aligned} \tag{6.4.22}$$

with $\sum_{i=1}^{4} x_i = 1$. Repeating the entire procedure on each of (6.4.14) to (6.4.20) gives also

$$\begin{aligned}
&x_1(\hat{r}-2W_{11}+2W_{12}+W_{13}-\theta)+x_2(\hat{r}-2W_{12}+W_{13}-\theta+2W_{22})\\
&+x_3(\hat{r}-W_{13}+\theta)+x_4(\hat{r}+W_{13}-3\theta+2W_{24})\geq 0 && (6.4.23)\\
&x_1(\hat{r}+2W_{12}-3\theta+W_{34})+x_2(\hat{r}-\theta+2W_{22}-2W_{24}+W_{34})\\
&+x_3(\hat{r}+\theta-W_{34})+x_4(\hat{r}-\theta+2W_{24}+W_{34}-2W_{44})\geq 0 && (6.4.24)\\
&x_1(\hat{r}-W_{12}+\theta)+x_2(\hat{r}+W_{12}-\theta-2W_{22}+2W_{24})\\
&+x_3(\hat{r}+W_{12}-3\theta+2W_{34})+x_4(\hat{r}+W_{12}-\theta-2W_{24}+2W_{44})\geq 0 && (6.4.25)\\
&x_1(\hat{r}-W_{13}+\theta)+x_2(\hat{r}+W_{13}-3\theta+2W_{24})\\
&+x_3(\hat{r}+W_{13}-\theta-2W_{33}+2W_{34})+x_4(\hat{r}+W_{13}-\theta-2W_{34}+2W_{44})\geq 0 && (6.4.26)\\
&x_1(\hat{r}+2W_{13}-3\theta+W_{24})+x_2(\hat{r}+\theta-W_{24})\\
&+x_3(\hat{r}-\theta+W_{24}+2W_{33}-2W_{34})+x_4(\hat{r}-\theta+W_{24}+2W_{34}-2W_{44})\geq 0 && (6.4.27)\\
&x_1(\hat{r}-2W_{11}+W_{12}+2W_{13}-\theta)+x_2(\hat{r}-W_{12}+\theta)\\
&+x_3(\hat{r}+W_{12}-2W_{13}-\theta+2W_{33})+x_4(\hat{r}+W_{12}-3\theta+2W_{34})\geq 0 && (6.4.28)\\
&x_1(\hat{r}+2W_{11}-2W_{13}-\theta+W_{34})+x_2(\hat{r}+2W_{12}-3\theta+W_{34})\\
&+x_3(\hat{r}+2W_{13}-\theta-2W_{33}+W_{34})+x_4(\hat{r}+\theta-W_{34})\geq 0, && (6.4.29)
\end{aligned}$$

where $\hat{r}=r\theta$.

Each of the inequalities (6.4.22) to (6.4.29) represents one row in a matrix inequality of the form

$$M\mathbf{x}\geq\mathbf{0}, \qquad (6.4.30)$$

where M is an 8×4 matrix that depends on W and r. $M\geq\mathbf{0}$ (i.e. all entries of M are nonnegative) is a necessary and sufficient condition for (6.4.30) to hold, for all $x\in\Delta_4$. Hence it suffices to have $M\geq\mathbf{0}$ to ensure

$$\mathbf{n}\in K_M \quad \forall u,v\in[0,1]\ \ \forall t\geq 0.$$

But the ice cream cone K_{ice} satisfies $K_{ice}\subset K_M$, therefore $\phi_t\in C_1([0,1]^2$. Hence $M\geq\mathbf{0}$ is sufficient to have $\phi_t\in B$. A special case of M will be considered in Section

6.7; for example, the $r = 0$ case yields conditions required for the selection matrix to preserve monotonicity.

But what about a condition for the general fitnesses W_{ij}? Each row of (6.4.30) defines a half-space, so this matrix inequality is equivalent to finding the intersection of eight half-spaces in $\mathbb{R}^4$. The following theorem from discrete geometry concerns the intersection of finitely many convex sets [105]:

Theorem 6.4.2 (Helly's theorem)**.** *Let $X_1, X_2, \ldots, X_N$ be a finite collection of convex subsets of $\mathbb{R}^d$, with $n > d$. If the intersection of every $d+1$ of these sets is non-empty, then the whole collection has a non-empty intersection, i.e.*

$$\cap_{k=1}^{n} X_k \neq \emptyset$$

If we intend to use Helly's theorem to check that the intersection of all eight half-spaces is non-empty (n=8, d=4), we would have to check the intersection of every five of these half-planes. This leads to 56 different cases to consider, which is not feasible. Moreover, even if we do find that the common intersection is indeed non-empty this way, Helly's theorem does not provide information on whether the intersection intersects the simplex Δ_4. If the values of each A_{ij} are known, the set of inequalities can be checked, but a general condition cannot be derived.

6.5 Existence of an invariant manifold Σ_M for the TLTA model

As B is a compact space, any sequence of Lipschitz manifolds constructed from ϕ_t, starting from any smooth initial manifold $\phi_0 \in B$, will have a convergent subsequence, whose limit will be denoted by ϕ^*. So far, we have assumed that $M \geq \mathbf{0}$.

We now turn to the proof of Theorem 6.3.1. The problem now is to show that (i) graph ϕ^* is invariant under (2.9) and (ii) graph ϕ^* *globally attracts* all points in Δ. In fact, in our approach (i) will follow from (ii).

6.6 Global attraction to Σ_M

We will use the limit ϕ^* from the previous section (with the graph of ϕ_0 as the Wright Manifold), and return to general fitnesses W. Take an arbitrary smooth function $\psi_0 \in B$ and, as done with ϕ_0, define $\psi_t = \mathcal{L}_t \psi_0$. Let

$$\operatorname{epi} f = \{(u,v,q) \in \mathbb{R}^3 : q \geq f(u,v)\}$$

denote the epigraph of a function f. Then define the set

$$G_t = (\operatorname{epi} \phi^*) \triangle (\operatorname{epi} \psi_{\mathrm{t}}), \tag{6.6.1}$$

where $\triangle$ denotes the symmetric difference between two sets. Informally speaking, G_t is the set of all points trapped between the graphs of ϕ^* and ψ_t.

The volume of this set is

$$\operatorname{vol}(G_t) = \int_{G_t} \mathrm{d}\lambda_3, \tag{6.6.2}$$

where λ_3 denotes Lebesgue measure in $\mathbb{R}^3$. The Liouville formula states that [2]:

$$\frac{d}{dt}[\operatorname{vol}(G_t)] = \int_{G_t} \nabla_{\mathbf{u}} \cdot \mathbf{F} \, \mathrm{d}\lambda_3, \tag{6.6.3}$$

where $\nabla_{\mathbf{u}} = \left(\frac{\partial}{\partial u}, \frac{\partial}{\partial v}, \frac{\partial}{\partial q}\right)$. Hence $\nabla_{\mathbf{u}} \cdot \mathbf{F} < 0$ would suffice to show that $\operatorname{vol}(G_t)$ is decreasing in t. As the volume is also bounded below by zero, $\operatorname{vol}(G_t)$ will converge to some limit; in fact, $\lim_{t \to 0} \operatorname{vol}(G_t) = 0$.

First, we prove a remarkable result regarding the divergence of the vector field for the model in both sets of coordinates:

Lemma 6.6.1. *Let $f_i(\mathbf{x})$ denote the right hand side of (6.2.2). Then*

$$\nabla_{\mathbf{u}} \cdot \mathbf{F} = \nabla_x \cdot \mathbf{f}, \tag{6.6.4}$$

Proof. Let us set up two more mappings; the first one being the projection

$$(x_1, x_2, x_3, x_4) = \mathbf{x} \mapsto \Pi_4(\mathbf{x}) = (x_1, x_2, x_3).$$

Let $\Pi_4|_{\Delta_4}$ be Π_4 restricted to Δ_4. Then Π_4 is a diffeomorphism with inverse

$$\Pi_4^{-1}(\mathbf{x}') = (x_1, x_2, x_3, 1 - x_1 - x_2 - x_3),$$

where $\mathbf{x}' = (x_1, x_2, x_3)$. Then define the second diffeomorphism from $\Pi_4(\Delta_4)$ to Δ as follows:

$$\mathbf{x}' \mapsto \mathbf{u} = \Xi(\mathbf{x}') = (x_1 + x_2, x_1 + x_3, 1 - x_2 - x_3),$$

which maps $\Pi_4(\Delta_4)$ to Δ and has inverse

$$\Xi^{-1}(\mathbf{u}) = \frac{1}{2}(u + v + q - 1, u - v - q + 1, -u + v - q + 1).$$

Then $\Phi = \Xi \circ \Pi_4$ (or $\Phi^{-1} = \Pi_4^{-1} \circ \Xi^{-1}$), which is depicted in the following commutative diagram:

$$\begin{tikzcd}
\Delta_4 \arrow[r, "\Phi"] \arrow[d, "\Pi"] & \Delta \\
\Pi(\Delta_4) \arrow[ur, "\Xi"] &
\end{tikzcd}$$

In (x_1, x_2, x_3) coordinates, the equations of motion become

$$\dot{x}_i = g_i(x_1, x_2, x_3) = f_i(x_1, x_2, x_3, 1 - x_1 - x_2 - x_3), \quad i = 1, 2, 3. \tag{6.6.5}$$

Thus the Chain Rule yields

$$\frac{\partial g_i}{\partial x_j} = \frac{\partial f_i}{\partial x_j} - \frac{\partial f_i}{\partial x_4}, \tag{6.6.6}$$

and so

$$\begin{aligned}\nabla_{\mathbf{x}'}\cdot\mathbf{g} &= \sum_{i=1}^{3}\frac{\partial g_i}{\partial x_i}\\ &= \sum_{i=1}^{3}\frac{\partial f_i}{\partial x_i}-\sum_{i=1}^{3}\frac{\partial f_i}{\partial x_4}\\ &= \sum_{i=1}^{4}\frac{\partial f_i}{\partial x_i}-\sum_{i=1}^{4}\frac{\partial f_i}{\partial x_4}\\ &= \nabla_x\cdot\mathbf{f}-\frac{\partial}{\partial x_4}\left(\sum_{i=1}^{4}f_i\right).\end{aligned}$$

But $\sum_{i=1}^{4} f_i = 0$, so that

$$\nabla_{\mathbf{x}'}\cdot\mathbf{g} = \nabla_{\mathbf{x}}\cdot\mathbf{f}. \tag{6.6.7}$$

Meanwhile,

$$\mathbf{g}(\mathbf{x}') = (D\Xi(\mathbf{x}'))^{-1}\mathbf{F}(\Xi(\mathbf{x}')),$$

which is the definition of the systems (6.6.5) and $\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u})$ being smoothly equivalent, with Ξ as the diffeomorphism [38]. However,

$$D\Xi(\mathbf{x}') = \begin{pmatrix}1 & 1 & 0\\ 1 & 0 & 1\\ 0 & -1 & -1\end{pmatrix} \quad\Rightarrow\quad (D\Xi(\mathbf{x}'))^{-1} = \frac{1}{2}\begin{pmatrix}1 & 1 & 1\\ 1 & -1 & -1\\ -1 & 1 & -1\end{pmatrix}$$

which are constant matrices, thus we will simply write $D\Xi$ from here on. Also,

$$D\mathbf{g}(\mathbf{x}') = (D\Xi)^{-1}D(\mathbf{F}(\Xi(\mathbf{x}'))),$$

and the Chain Rule yields

$$D\mathbf{g}(\mathbf{x}') = (D\Xi)^{-1}D\mathbf{F}(\Xi(\mathbf{x}')))D\Xi, \tag{6.6.8}$$

but

$$\nabla_{\mathbf{x}'}\cdot\mathbf{g} = \mathrm{Tr}(D\mathbf{g}(\mathbf{x}')).$$

So by taking the trace on both sides of (6.6.8), we obtain

$$\begin{aligned}\nabla_{\mathbf{x}'}\cdot\mathbf{g} &= \mathrm{Tr}((D\Xi)^{-1}D\mathbf{F}(\Xi(\mathbf{x}'))D\Xi)\\ &= \mathrm{Tr}(D\mathbf{F}(\mathbf{u}))\\ &= \nabla_{\mathbf{u}}\cdot\mathbf{F},\end{aligned}$$

so

$$\nabla_{\mathbf{u}}\cdot\mathbf{F} = \nabla_{\mathbf{x}'}\cdot\mathbf{g},$$

which, combined with (6.6.7), gives the desired result. □

We conclude that it suffices to seek conditions for the right hand side of (6.6.4) to be negative to ensure the volume of G_t is decreasing. Thus we compute

$$\begin{aligned}\nabla_{\mathbf{x}}\cdot\mathbf{f} &= \sum_{i=1}^{4}[(m_i-\bar{m})+x_i(W_{ii}-2m_i)]-r\theta\\ &= \sum_{i=1}^{4}(W_{ii}x_i+m_i)-6\bar{m}-r\theta\\ &\le \sum_{i,j=1}^{4}W_{ii}x_ix_j-\sum_{k=1}^{4}m_k-6\sum_{i,j=1}^{4}W_{ij}x_ix_j\\ &= \sum_{i,j=1}^{4}\left(W_{ii}-6W_{ij}\right)x_ix_j-\sum_{k=1}^{4}m_k\\ &= \sum_{i,j=1}^{4}\left(W_{ii}-6W_{ij}\right)x_ix_j-\sum_{j,k=1}^{4}W_{kj}x_j\\ &= \sum_{i,j=1}^{4}\left(W_{ii}-6W_{ij}\right)x_ix_j-\sum_{i,j,k=1}^{4}W_{kj}x_ix_j\\ &= \sum_{i,j=1}^{4}\left(W_{ii}-6W_{ij}-\sum_{k=1}^{4}W_{kj}\right)x_ix_j\\ &= \sum_{i,j=1}^{4}W'_{ij}x_ix_j. \qquad (6.6.9)\end{aligned}$$

So we arrive at the requirement $\mathbf{x}^\top W'\mathbf{x} < 0$ for $\mathbf{x} > 0$, where

$$W'_{ij} = W_{ii} - 6W_{ij} - \sum_{k=1}^{4} W_{kj}. \tag{6.6.10}$$

A matrix A is said to be strictly copositive if $\mathbf{x}^\top A\mathbf{x} > 0$ for $\mathbf{x} > 0$. If, for some cone K_M, this holds for all $\mathbf{x} \in K$, we say A is strictly copositive with respect to K_M. So (6.6.9) is equivalent to the matrix $-W'$ being strictly copositive with respect to $\mathbb{R}^4_+$.

Remark. *There are necessary and sufficient conditions for a* 3×3 *matrix being copositive [106], but no known counterpart for* 4×4 *matrices (which is beyond the scope of this thesis anyway). For copositivity it would have to hold for at least each* 3×3 *submatrix, but this would be a cumbersome task, and we will not pursue it here.*

Instead we will use a weaker sufficient condition: verify that all components of W' are negative, i.e.

$$W_{ii} < 6W_{ij} + \sum_{k=1}^{4} W_{kj} \quad \forall\, i,j = 1,2,3,4. \tag{6.6.11}$$

This automatically holds for $i = j$, so only the off-diagonal entries of W' need to be checked. Actually, it suffices to check only the largest off-diagonal component of W'_{ij}.

Lemma 6.6.2. *Suppose* $\lim_{t\to\infty} \mathrm{vol}(G_t) = 0$. *Then* ψ_t *converges pointwise to* ϕ^*.

Proof. Suppose, for a contradiction that ψ_t does not converge pointwise to ϕ^*. Then

$$\exists u,v \in [0,1] \;\; \exists \varepsilon > 0 \;\; \forall c \;\; \exists t > c \quad |\psi_t(u,v) - \phi^*(u,v)| \geq 2\varepsilon.$$

We can fix $c = 0$ in the above definition. Moreover, $\psi_t(u,v) = \phi^*(u,v)$ for each of $u = 0,1$ and $v = 0,1$, therefore

$$\exists u,v \in (0,1) \;\; \exists \varepsilon > 0 \;\; \exists t > 0 \quad |\psi_t(u,v) - \phi^*(u,v)| \geq 2\varepsilon. \tag{6.6.12}$$

Define $\mathbf{p_c} = (u,v,\frac{1}{2}(\psi_t(u,v)+\phi^*(u,v)))$ and $\mathbf{p}_\pm = \mathbf{p_c} \pm (0,0,l)$, where $l = \frac{1}{2}|\psi_t(u,v) - \phi^*(u,v)|$. Note that

$$\frac{1}{2}(\psi_t(u,v)+\phi^*(u,v)) \pm l = \psi_t(u,v) \quad \text{or} \quad \phi^*(u,v),$$

so in fact $\mathbf{p}_\pm = (u,v,q_\pm)$ where

$$\begin{aligned} q_+ &= \max(\psi_t(u,v),\phi^*(u,v)) \\ q_- &= \min(\psi_t(u,v),\phi^*(u,v)). \end{aligned}$$

We define

$$\begin{aligned} \mathbf{p}_- + K_{ice} &= \{\mathbf{p}_- + \mathbf{v} : \mathbf{v} \in K_{ice}\} \\ \mathbf{p}_+ - K_{ice} &= \{\mathbf{p}_+ - \mathbf{v} : \mathbf{v} \in K_{ice}\}. \end{aligned}$$

Now we seek an open ball $B(\mathbf{p_c},\rho)$ such that

$$B(\mathbf{p_c},\rho) \subset \tilde{K} \subset G_t, \tag{6.6.13}$$

where $\tilde{K} = (\mathbf{p}_- + K_{ice}) \cap (\mathbf{p}_+ - K_{ice})$ and

$$\rho = \min_{\mathbf{v}\in\partial\tilde{K}} ||\mathbf{v} - \mathbf{p_c}||_2, \tag{6.6.14}$$

or by symmetry of $\mathbf{p}_- + K_{ice}$ and $\mathbf{p}_+ - K_{ice}$,

$$\rho = \min_{\mathbf{v}\in\partial(\mathbf{p}_-+K_{ice})} ||\mathbf{v} - \mathbf{p_c}||_2, \tag{6.6.15}$$

Translating these sets by $(-\mathbf{p}_-)$ shifts $\mathbf{p}_-$ to the origin, while $\mathbf{p_c}$ and $\partial(\mathbf{p}_- + K_{ice})$ are shifted to $(0,0,l)$ and K_{ice} respectively. Then

$$\rho = \min_{\mathbf{v}\in\partial K_{ice}} ||\mathbf{v} - (0,0,l)||_2. \tag{6.6.16}$$

Put $\mathbf{v} = (\tilde{u}, \tilde{v}, \tilde{q})$. Then (6.6.16) is solved by minimising

$$\tilde{u}^2 + \tilde{v}^2 + (\tilde{q} - l)^2, \tag{6.6.17}$$

subject to the constraint $\tilde{q}^2 = \tilde{u}^2 + \tilde{v}^2$, which we use to rewrite (6.6.17) in terms of $\tilde{q}$ only:

$$\tilde{q}^2 + (\tilde{q} - l)^2,$$

whose minimum occurs where

$$\frac{d}{d\tilde{q}}\left(\tilde{q}^2 + (\tilde{q} - l)^2\right) = 0 \quad \Leftrightarrow \quad 4\tilde{q} - 2l = 0,$$

which occurs iff $\tilde{q} = \frac{l}{2}$. Hence

$$\rho = \sqrt{\left(\frac{l}{2}\right)^2 + \left(-\frac{l}{2}\right)^2} = \frac{l}{\sqrt{2}},$$

but by (6.6.12), $l \geq \varepsilon$, so choose $\rho = \frac{\varepsilon}{\sqrt{2}}$.

Hence $B(\mathbf{p_c}, \rho) \subset G_t$, and so for all $t > 0$:

$$\mathrm{vol}(G_t) \geq \mathrm{vol}(B(\mathbf{p}, r)) = \frac{4\pi}{3} r^3 = \frac{\pi\sqrt{2}}{3}\varepsilon^3 > 0,$$

hence

$$\exists \varepsilon > 0 \;\; \forall t > 0 \quad \mathrm{vol}(G_t) \geq \frac{\pi\sqrt{2}}{3}\varepsilon^3.$$

which contradicts our earlier assumption that $\mathrm{vol}(G_t)$ is decreasing and tends to 0 as $t \longrightarrow \infty$. □

Since for all $t > 0$ ψ_t is a Lipschitz function on a compact set (namely $[0, 1]^2$), pointwise convergence is sufficient to ensure uniform convergence to ϕ^*. Moreover, $\psi_0 \in B$ is arbitrary. Furthermore for any initial point $(u_0, v_0, q_0) \in \Delta$ there exists $\psi_0 \in B$ such that $(u_0, v_0, q_0) \in \operatorname{graph} \psi_0$, but then the sequence ψ_t converges uniformly to ϕ^*. Therefore any orbit will converge to $\Sigma_M = \operatorname{graph} \phi^*$, i.e. the QLE manifold is globally attracting.

To conclude, if we can find a suitable condition on r and W such that (6.6.9) holds and $M(W,r) \geq 0$, then there exists a globally attracting invariant manifold Σ_M with (relative) boundary corresponding to the union of the four edges E_{12}, E_{13}, E_{42} and E_{43}. This completes the proof of Theorem 6.3.1.

6.7 The modifier gene case of the TLTA model

The two-locus two-allele (TLTA) model has often been used to investigate the effect of a modifier gene β on a primary locus α, in the context of Fisher's theory on the evolution of dominance [107]. Fisher believed that dominance was due to selection of specific modifier genes which caused the fitness of the heterozygote to approach that of the wild type homozygote, which would protect the population from deleterious effects of mutant alleles. Fisher's theory received swift criticism in [108, 109, 110, 111]. Both Wright and Haldane argued that dominance may be a property inherent in genes thus cannot evolve and thought the effect of selective pressure would be too small to make the process effective; rather, Wright suggested a physiological origin behind dominance. Although Wright's theory gained more favour, it is still thought that Fisher's theory may still apply in some scenarios [112, 113].

The fitnesses for this case is:

$$W = \begin{pmatrix} 1-s & 1-hs & 1-s & 1-ks \\ 1-hs & 1 & 1-ks & 1 \\ 1-s & 1-ks & 1-s & 1 \\ 1-ks & 1 & 1 & 1 \end{pmatrix}. \tag{6.7.1}$$

Traditionally these fitnesses are denoted as follows: [114, 115, 116, 1, 103, 117]

	AA	Aa	aa
BB	1	1	$1-s$
Bb	1	$1-ks$	$1-s$
bb	1	$1-hs$	$1-s$,

Table 6.1: Table of fitnesses for the nine different diploid genotypes. Here $0 < s \leq 1$, $0 \leq k \leq h \leq \frac{1}{s}$ and $h \neq 0$ [1].

The parameter s is often called the "selection intensity" or "selection coefficient" [118, 103], while h and k are referred to as measures of "the influence of the dominance relations between alleles" [119]. In [118] s is interpreted as the recessive allele effect, while h (and k) is the heterozygote effect. The biological interpretation for the different values of h is given in Table 6.2. Our given range of values for h excludes the case of overdominance ($h < 0$).

$h = 0$	A dominant, a recessive
$h = 1$	a dominant, A recessive
$0 < h < 1$	Incomplete dominance
$h < 0$	Overdominance
$h > 1$	Underdominance

Table 6.2: The different cases for the heterozygote effect h and their biological meanings.

The idea of using s and h traces back to [108]; Wright's third parameter h' is used similarly to k, except the fitness of the double heterozygotes AB/ab is $1 - ks$ instead of 1.

The case with $k = 0$ is considered in [107, 120, 108, 121]. Later, Ewens assumed that modification depends on whether B occurs in a homozygote B/B or a heterozygote B/b [115], which prompted him to include the third parameter k.

For this special case the matrix problem (6.4.30) becomes

$$\begin{pmatrix} \hat{r}+2h+k-2 & \hat{r}-2h+k & \hat{r}+3k-2 & \hat{r}-k \\ \hat{r}-2h+k+1 & \hat{r}+2h+k-1 & \hat{r}-k+1 & \hat{r}+3k-1 \\ \hat{r}-2h+3k & \hat{r}+k & \hat{r}-k & \hat{r}+k \\ \hat{r}+h-k & \hat{r}-h+k & \hat{r}-h+3k & \hat{r}-h+k \\ \hat{r}-k+1 & \hat{r}+3k-1 & \hat{r}+k+1 & \hat{r}+k-1 \\ \hat{r}+3k-2 & \hat{r}-k & \hat{r}+k-2 & \hat{r}+k \\ \hat{r}-h+k & \hat{r}+h-k & \hat{r}-h+k & \hat{r}-h+3k \\ \hat{r}+k & \hat{r}-2h+3k & \hat{r}+k & \hat{r}-k \end{pmatrix} \begin{pmatrix} x_1 \\ x_2 \\ x_3 \\ x_4 \end{pmatrix} \geq \mathbf{0}. \tag{6.7.2}$$

It suffices to determine when the matrix is nonnegative, i.e. all of its components must be nonnegative, which is equivalent to

$$\hat{r} \geq \max(k, -k, 1-k, -1-k, h-k, k-h, h-3k, 2h-3k, 1-3k, 2-3k, 2-k, \quad (6.7.3)$$
$$2h-k, 2h-k-1, -2h-k+1, 2-2h-k).$$

As $k > 0$, we can obviously eliminate any non-positive entries in the right hand side of (6.7.3), leading to

$$\hat{r} \geq \max(k, 1-k, h-k, h-3k, 2h-3k, 1-3k, 2-3k, 2-k, 2h-k, 2h-k-1,$$
$$-2h-k+1, 2-2h-k),$$

and, by inspection, we can narrow down the options to

$$\begin{aligned} \hat{r} &\geq \max(k, h-k, 2-k, 2h-k, 2-2h-k) \\ &= \max(k, 2-k, 2h-k). \end{aligned}$$

Moreover, since $h \geq k$,

$$2h-k = 2(h-k)+k \geq k,$$

leaving us with

$$\hat{r} \geq \max(2-k, 2h-k),$$

which can be summarised as

$$\hat{r} \geq 2\max(1,h)-k. \quad (6.7.4)$$

Next, we use (6.6.11) to obtain the condition for decreasing phase volume. Here, the largest component of W' is $i = 2, j = 1$, which yields the condition $-9 + 2s + 7hs + ks < 0$, which rearranges to $9 > s(2+7h+k)$. Combining this with (6.7.4), we obtain the folowing result:

Theorem 6.7.1 (Existence of a globally attracting Quasilinkage Equilibrium manifold)**.** *Consider the TLTA model (6.2.2) with W given by (6.7.1). Then if* $0 \leq s \leq 1$

and $0 \leq k \leq h \leq \frac{1}{s}$, $h > 0$, $9 > s(2+7h+k)$ *and*

$$r(1-ks) \geq s\,(2\max(1,h)-k)\,, \tag{6.7.5}$$

there exists a Lipschitz invariant manifold that globally attracts all initial polymorphisms.

Hence we have sufficient conditions on r, s, h and k for existence of the invariant manifold.

6.8 Discussion

We proved the existence of a globally attracting invariant manifold Σ_M for the continuous-time selection-recombination model and obtained a sufficient condition on the parameters for a simplified case of the model. In previous attempts, it is simply declared that a value of s exists which ensures existence of the QLE manifold; however, explicit conditions were never given [2, 99, 5].

We did this by eliminating one of the four variables, then applying a further (invertible) coordinate transformation. Next, we investigated the time evolution of the normal to graph ϕ_{t}, which aided in establishing convergence using bounded Lipschitz sequences of graph ϕ_{t} and is closely related to monotonicity of the system. Finally we showed the phase volume decreases in time. Although our algorithm is a general result, we applied it to the modifier gene case, which requires just four parameters rather than ten. Other examples where monotone systems theory is applied to prove existence of an invariant manifold are found in [81, 68, 82].

Much is known for continuous or C^1 two-dimensional systems on compact sets, e.g. in [37], and these results, such as the Poincare-Bendixson Theorem, are expected to apply to dynamics on Σ_M also (which is homeomorphic to the unit square $[0,1]^2$). Thus we conclude that the only possible ω-limit sets on Σ_M are steady states or periodic orbits. Examples of periodic orbits for the model are mentioned in [100, 101, 102]. Perhaps we could seek conditions which, when satisfied, guarantee periodic orbits for the selection-recombination model. One possible route would be to use Smith's work on Poincare-Bendixson theory for three-dimensional competitive systems, see Theorem 2.3 in [122]. See also [123] for a general cone. This could give a new angle on Akin's work.

Our numerical evidence depicts Σ_M as a saddle surface, as with the example in Figure 6.1. However, it is unknown whether this is always the case or what conditions would be required. One possible approach would be to track the change in the second fundamental form of graph ϕ_t, in the style of [68].

As r decreases, our method breaks down. We believe what happens is that the polygonal cone K_M is no longer invariant for small values of r. Nevertheless, for $r = 0$ and (7.4.4), we have numerical evidence for an invariant QLE manifold Σ_M in some cases. This suggests there is an invariant solution to replicator dynamics with a symmetric fitness matrix that is the graph of a function in (u, v, q)-coordinates, which is the subject of the next chapter.

Chapter 7

The continuous-time selection model

In this chapter we consider the continuous-time selection equation. The work here is not complete, but is in progress. We start by discussing the motivation behind studying the model, then state the equations. Recall that when the fitnesses are additive in the Selection-Recombination, all orbits tend to the Wright manifold regardless for all r, including $r = 0$ [104]. Hence the QLE manifold does exist, at least for this special case. The numerical evidence suggests that the QLE manifold will not exist for all values of the fitnesses, though. The algorithm in Chapter 6 for checking existence of the QLE manifold does not work on this model. Instead we convert the model to a Lotka-Volterra one, which has an invariant manifold of its own when competitive. We translate the condition in terms of the fitnesses, then map back to the original coordinates…but does this give the QLE manifold? The answer is revealed shortly before the discussion.

7.1 Background for the continuous time selection equation

The inspiration behind studying this model was to investigate the QLE manifold Σ_M for the special case of the Selection-Recombination model (6.2.2) in the limiting case $r = 0$, which turns out to be the continuous-time selection equation. This is a classical model from population genetics, where the only evolutionary force present is selection.

The equations of motion are identical to those for replicator dynamics from evolutionary game theory [124], with symmetric fitnesses; thus the mean fitness increases [2] and all orbits converge. In evolutionary game theory, such systems are known as partnership games [2].

A derivation of the replicator model is given in [4]. However, it is claimed in [2] that its derivation us rather shaky. In particular, Crow and Kimura make the unrealistic assumption of Hardy-Weinberg proportions; as a result, some population geneticists are reluctant to use this model. An alternative derivation of this model starts with the discrete-time model and assigning the fitnesses as follows: $W_{ij} = 1 + hm_{ij}$, where h is the generation length, and obtaining the continuous-time counterpart by letting $h \to 0$.

The replicator model is topologically equivalent to the Lotka-Volterra system [2]. More precisely, the two models are smoothly orbitally equivalent. This will be exploited later in the chapter.

7.2 Replicator dynamics

The continuous-time selection equation for two loci with two alleles is as follows

$$\dot{x}_i = x_i(m_i - \bar{m}), \qquad i = 1,2,3,4. \tag{7.2.1}$$

Again, $\mathbf{x} \in \Delta_4$ represents the gametic frequencies. As we are interested from the perspective of population genetics, we will make the same assumptions on the fitnesses as those made for the selection-recombination model. However, we can still reach the same results without this assumption.

We have numerical evidence suggesting that the QLE manifold Σ_M still exists for some, but not all, values of the fitnesses. Figure 7.1 shows an example in which Σ_M could not be computed using our current numerical method. This raises the question of when Σ_M appears in the continuous-time selection model - can conditions for existence be derived?

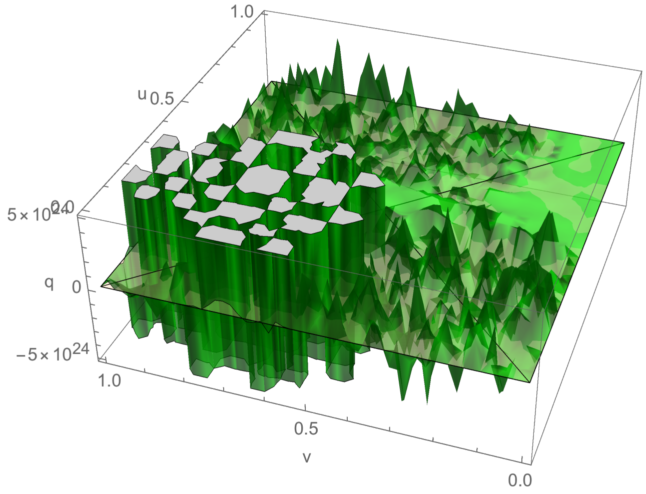


Figure 7.1: The QLE manifold Σ_M could not be computed numerically for this example. The parameters chosen are $W_{11} = 0.6, W_{12} = 5.1, W_{13} = 4.532, W_{22} = 3.1, W_{24} = 9.1, W_{33} = 0.1, W_{34} = 3.2, W_{44} = 2.9, \theta = 0.2$

7.3 Applying the cone algorithm

When we attempt to use our algorithm from Chapter 6 for this model, the only matrix W that works is

$$W = \theta \begin{pmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{pmatrix},$$

which is neutral selection. For this case, the equations of motion (7.2.1) is nothing more than $\dot{x}_i = 0$, hence there is no reason to even consider (6.6.11).

Hence we need to use a different method to find the QLE manifold.

7.4 Converting to the Lotka-Volterra model

We apply the coordinate change [2]

$$\mathbf{x} \mapsto \mathbf{y} = \Psi(\mathbf{x}) := \left(\frac{x_1}{x_4}, \frac{x_2}{x_4}, \frac{x_3}{x_4}\right), \tag{7.4.1}$$

which is a diffeomorphism from the interior of Δ_4 to the interior of $\mathbb{R}^3_+$ with inverse [2]

$$\Psi^{-1}(\mathbf{y}) = \left(\frac{y_1}{1+y_1+y_2+y_3}, \frac{y_2}{1+y_1+y_2+y_3}, \frac{y_3}{1+y_1+y_2+y_3}, \frac{1}{1+y_1+y_2+y_3}\right). \tag{7.4.2}$$

The map Ψ converts replicator dynamics to the three-species Lotka-Volterra system:

$$\dot{y_i} = y_i(b_i - \sum_{j=1}^{3} a_{ij} y_j), \qquad i = 1,2,3, \tag{7.4.3}$$

with $b_i = W_{i4} - W_{44}$ and $a_{ij} = W_{4j} - W_{ij}$ [2].

7.4.1 Another invariant manifold

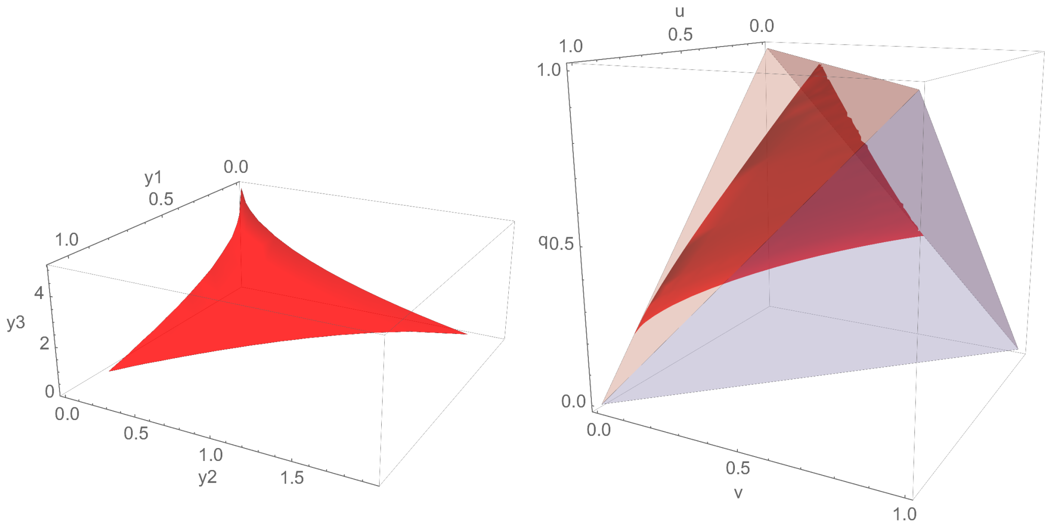
Note that the Lotka-Volterra system is totally competitive whenever $b_i > 0$ and $a_{ij} > 0$, which is equivalent to

$$W_{i4} > W_{44}, \qquad W_{ij} < W_{4j}, \qquad \forall i,j = 1,2,3. \tag{7.4.4}$$

So for each column of the fitness matrix we would like the 4th entry to be the largest, except in the last column. However, for the final column, the 4th entry needs to be the smallest instead (up to a relabelling of the indices).

Then for this case, we use Theorem 4.3.2 to conclude that the system has a carrying simplex in the y_i coordinates. When we switch back to using x_i this maps onto an invariant manifold, which will be denoted by Σ_C. Our original intention was to obtain the QLE manifold Σ_M this way... but, assuming Σ_M does exist, does it coincide with Σ_C?

Remark. *By inspection of (7.4.2), we can locate* $\hat{\mathbf{e}}_\mathbf{i} = \Psi(\mathbf{e_i})$ *for each vertex* $\mathbf{e_i}$ *(*$i = 1,2,3,4$*). For example, we would like* $\Psi^{-1}(\hat{\mathbf{e}}_\mathbf{1}) = (1,0,0,0)$*, which is established by letting* $y_1 \to \infty$*, (*y_2*,* y_3 *need not grow unbounded). Similarly, the remaining vertices* $\mathbf{e_2}$ *and* $\mathbf{e_3}$ *both correspond to the limiting cases of* $y_2 \to \infty$ *and* $y_3 \to \infty$ *respectively. Meanwhile,* $\Psi^{-1}(\hat{\mathbf{e}}_\mathbf{4}) \to (0,0,0,1)$ *and (7.4.2) imply that* $\mathbf{e_4}$*, maps to the origin* $y_i = 0$ *in the y-space.*



(a) The carrying simplex $\Psi^{-1}(\Sigma_C)$ for the Lotka-Volterra system (7.4.3).

(b) The invariant manifold Σ_C for (6.2.9).

Figure 7.2: The carrying simplex $\Psi^{-1}(\Sigma_C)$ transforms back to an invariant manifold Σ_C, which is distinct from the QLE manifold. The parameter values are $W_{11} = 0.2, W_{12} = 0.3, W_{13} = 0.75, W_{22} = 0.9, W_{33} = 1.5, W_{42} = 1.7, W_{43} = 1.8, W_{44} = 0.3, \theta = 1, r = 0$, and the system is competitive in y_i-coordinates.

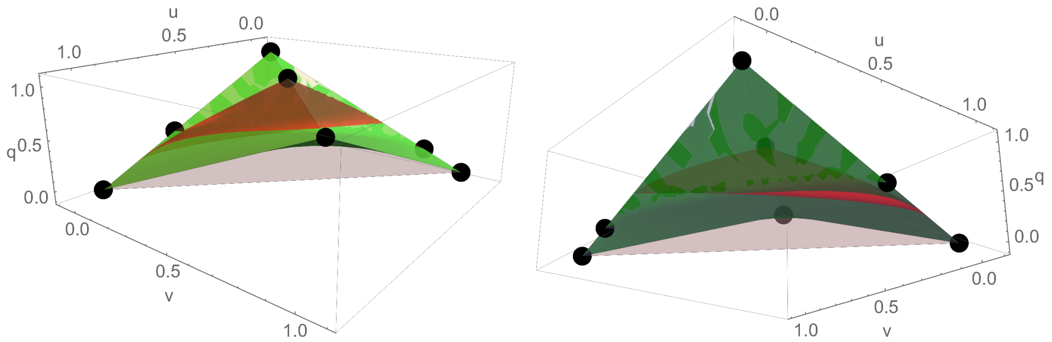


Figure 7.3: A numerical example of the continuous-time selection model with the limit of the QLE Σ_M as $r \to 0$ and Σ_C in the same system; the two manifolds are clearly distinct. The parameter values are identical to those in Figure 7.2

Now we look back at the PDE (6.3.2). As part of the boundary conditions, the manifold Σ_M is supposed to always contain all four vertices $\hat{\mathbf{e}}_\mathbf{i}$. However, the vertices $\hat{\mathbf{e}}_\mathbf{1}$, $\hat{\mathbf{e}}_\mathbf{2}$ and $\hat{\mathbf{e}}_\mathbf{3}$ are located at infinity. That can only mean one thing - when plotted in the y_i coordinates, we should expect Σ_M to be an unbounded surface in the y-space! Hence it cannot possibly correspond to the carrying simplex, which is compact; i.e. Σ_M and Σ_C are distinct invariant manifolds, as shown in 7.3. So, what does the carrying simplex look like in (u, v, q) coordinates? We know it is bounded in the Lotka-Volterra coordinates. In addition, the carrying simplex is the attractor of all orbits in $\mathbb{R}^3_+ \backslash \{0\}$, as well as homeomorphic to the closed unit simplex satisfying $y_1 + y_2 + y_3 = 1$ [68, 59]. If we attempt to translate all these facts into corresponding ones in (u, v, q) coordinates, we have the following result:

Theorem 7.4.1. *Let $r = 0$ in the selection-recombination model (6.2.2), and suppose that the fitnesses W_{ij} satisfy (7.4.4). Then there exists a two-dimensional, compact invariant manifold Σ_C which satisfies the following properties:*

1. *Its graph never intersects the face $q = u + v - 1$, which corresponds to $x_4 = 0$.*
2. *Attracts the entire phase space, excluding the steady states at $(0, 0, 1)$ and on any steady states lying within the face $q = u + v - 1$.*
3. *Homeomorphic to the plane $u + v = q$.*

Note that the edges $\tilde{E}_{42}, \tilde{E}_{12}, \tilde{E}_{13}, \tilde{E}_{43} \not\subseteq \partial\Sigma_C$, indicating that this invariant manifold is distinct from the QLE manifold Σ_M.

7.5 Discussion

As r decreases towards 0, the method from Chapter 6 breaks down. We believe what happens is that the polygonal cone is no longer invariant for small values of r. Nevertheless, for $r = 0$ and (7.4.4), we have numerical evidence for an invariant QLE manifold Σ_M in some cases, and we know it exists for additive fitnesses. This suggests there is an invariant solution to replicator dynamics with a symmetric fitness matrix that is the graph of a Lipschitz function in (u, v, q)-coordinates.

In addition, also for pure selection, the existence of another invariant manifold diffeomorphic to the carrying simplex, Σ_C, has been established for the competitive case, which is distinct from Σ_M. Although we took W to be symmetric, the assumption was not used while proving existence of Σ_C, hence it will still exist for general W. Also, Theorem 4.3.2 implies that a carrying simplex exists in a general $(n-1)$-dimensional Lotka-Volterra model ($n \geq 2$), implying that a different-dimensional analogue of Σ_C should exist in general replicator systems (when competitive).

On closer inspection of Figure 7.3, it appears that all the orbits converge towards a one-dimensional subset of Σ_M when $r = 0$ and (7.4.4) both hold. Σ_C is an attractor for the system, and our numerical examples suggest this should also be true for Σ_M, so we ask the following question (based upon numerical explorations):

Question. *Suppose the fitnesses satisfy (7.4.4) and* $r = 0$*. Is there a heteroclinic orbit connecting the steady states on the interior of the edges* $\tilde{E}_{12}$ *and* $\tilde{E}_{13}$ *that attracts almost all orbits (excluding steady states) and coincides with* $\Sigma_M \cap \Sigma_C$*?*

In other words, $\Sigma_M \cap \Sigma_C$ is an attracting invariant manifold with codimension 2.

Moreover, it appears that Σ_M is continuous but non-differentiable on $\Sigma_M \cap \Sigma_C$ only, which would have measure zero relative to Σ_M. This is consistent with a result stating that a Lipschitz manifold is differentiable almost everywhere. Often for inertial manifolds, if there is an invariant cone, we can expect the manifold to be smooth everywhere [125]. However, any general results for other invariant manifolds, including Σ_M, are unknown. For this case, we cannot interpret Σ_M as a stable or unstable manifold of a steady state, nor as the boundary of the basin of repulsion of a repelling steady state; it seems to be more complicated than a carrying simplex. A possible strategy for establishing existence of Σ_M is to split it up into two separate manifolds, on either side of $\Sigma_M \cap \Sigma_C$, then find an invariant cone for each piece. The author suspects that one piece of Σ_M will be a flat manifold contained in the convex hull of $\mathbf{e_4}$ and the two steady states on $\tilde{E}_{42}$ and $\tilde{E}_{43}$ respectively; Figure 7.4 portrays a sketch of this idea.

We expect that Σ_C can emerge in the selection-recombination model for small non-zero values of r, although this is currently an open problem. Also, we have evidence that Σ_C can exist outside of its current existence conditions, which maps to a non-competitive Lotka-Volterra system. It is already known that the carrying simplex can exist in the non-competitive case [68], although the origin still needs to be unstable (i.e. $W_{i4} > W_{44}$). However, if the parameters stray too far from a competitive system, Σ_C may disappear.

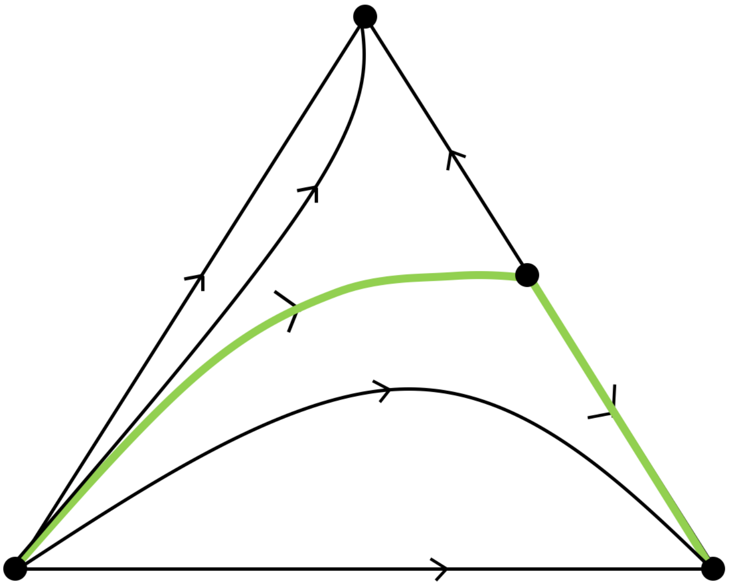


Figure 7.4: A sketch to illustrate the QLE manifold in the continuous-time selection model. Here, the invariant manifold (green) is Lipschitz, but it would be more straightforward to treat the two pieces separately.

Chapter 8

Concluding remarks

The aim of this thesis was to investigate invariant manifolds for two different continuous-time models in Population Genetics, plus a special case of the Selection-Recombination model. For each model, the manifold was previously known to exist for small or additive parameters. In particular, the requirements for the Selection-Recombination model possessing a QLE manifold, even with the assumption of small selection relative to recombination, are not explicit. With this in mind, the original intention was to simply avoid assuming small or additive parameters with the hope of gaining new, less restrictive conditions for existence of the invariant manifold.

This is indeed achieved for the Nagylaki-Crow model in Chapter 5. We choose a change of coordinates which blows up the interior of a triangular set T to the open first quadrant, sending one edge of T away to infinity. We switch between the two sets of dynamical variables as needed: we start by setting up the graph transform in the original coordinates where T is compact, then change to the new coordinates where it is far easier to derive conditions for which the evolving curve is both non-monotone and convex, and then translate the findings back into the original system. Outside of those parameter values, the manifold need not be smooth, convex, non-monotone, unique or globally attracting. To the best of the author's knowledge, this is the first attempt to prove existence of a nonmonotone invariant manifold for a system that is not strongly competitive. Also remarkable is that the new conditions do not require additivity of fertilities or mortalities, unlike previous studies.

In Chapter 6, we discover that if the dynamics of the normal to the transforming surface remains within a specific cone for all time, then the system is competitive with respect to the dual of said cone. We produce a new proof for existence of the QLE manifold in the Selection-Recombination model by combining this result with the requirement for a decreasing phase volume. Unlike previous approaches described in the literature, our method gives testable conditions on the model parameters for existence of the QLE manifold, which determine when the TLTA model is competitive for a polyhedral cone. When the model is competitive, there exists a Lipschitz invariant manifold of codimension one which is unordered by points in the polyhedral cone. We apply our conditions on the modifier gene case, which yields explicit conditions for the QLE manifold existing in the system.

Chapter 7 concerns the the continuous-time selection model, whose QLE manifold is already known to exist for additive fitnesses; numerical evidence suggests it will not exist for all parameter values. The model is essentially four-strategy replicator dynamics with a symmetric fitness matrix. Similar to the one used on the Nagylaki-Crow model, the chosen change of variables maps the interior of a 4-simplex to a 3-dimensional orthant. The new variables satisfy the Lotka-Volterra model, which already has a carrying simplex when totally competitive. When converted back to the original coordinates, the carrying simplex does not transform to the QLE manifold - rather we have a new invariant manifold.

For all the models covered in the thesis, a change of dynamical variables is utilised to make the analysis simpler. Three different diffeomorphisms are applied on the Selection-Recombination model in Chapter 6. One of them basically rotates, translates and stretches the simplex into a tetrahedron in which the QLE manifold is the limit of a sequence of surfaces which are graphs of functions over $[0, 1]^2$. One further diffeomorphism, Ψ, is used in Chapter 6 for the $r = 0$ case of the Selection-Recombination model (i.e. the continuous-time selection model). These four diffeomorphisms are summarised in the following commutative diagram:

$$\begin{tikzcd}
\mathbb{R}^3_+ & \Delta_4 \arrow[l, "\Psi"'] \arrow[r, "\Phi"] \arrow[d, "\Pi"] & \Delta \\
& \Pi(\Delta_4) \arrow[ur, "\Xi"] &
\end{tikzcd}$$

Note that although we know the invariant manifold is Lipschitz in each model, it is still unclear if and when the manifold is differentiable. A similar question was asked by Hirsch in the context of carrying simplices [59]. To the best of the author's knowledge the smoothness of a carrying simplex on its interior is currently an open problem, hence the same can be said for Σ_C from the continuous-time Selection model. One possible approach to partially answer the problem, at least for the Selection-Recombination model, might be to investigate when the manifold is actually an inertial one, and employ the theory of Chow et. al. [125].

Moreover, the methods used in this thesis do not show that the invariant manifold is asymptotically complete (i.e. in the context of the Selection-Recombination model, we have not shown that for each $(u_0, v_0, q_0) \in \Delta$ there exists an orbit in Σ_M which 'shadows' the orbit through (u_0, v_0, q_0)). If Σ_M were an inertial manifold which is also normally hyperbolic, it would be asymptotically complete [126]. In the absence of selection, the Wright manifold is an inertial manifold, and so is asymptotically complete (as can be shown using explicit solutions when $W_{ij} = 1$ for all i, j.)

There are many possible areas for future research. One such avenue would be to investigate higher-dimensional analogues for the models discussed earlier. For example, there is a multilocus version of the Selection-Recombination model, whose Wright manifold is diffeomorphic to $\Delta_{m_1} \times \Delta_{m_2} \times \ldots \times \Delta_{m_n}$, where n denotes the number of loci and each m_i is the number of alleles at the locus labelled i [99]. The multilocus model is also known to possess a QLE manifold when selection is much weaker than recombination. Unfortunately, the codimension of the QLE manifold for this scenario is typically more than one, making the normal dynamics more complicated. Instead, we would track the time evolution of the second fundamental form of graph $\phi_t(\cdot)$ and aim to show that it is bounded, which is the approach taken in [68]. Perhaps this strategy would also be useful for a three-allele Nagylaki-Crow model. Meanwhile, for the continuous-time Selection model, the author believes that the carrying simplex-like manifold will still exist in dimensions other than four.

The wonder of studying invariant manifolds in population genetics (or other models) is that it lies at the intersection of many different branches of mathematics. Tools from Geometry, Topology, Functional Analysis and Dynamical Systems Theory are applied to unearth the long-term evolution of the genetic state of the population. Notably, the results yielded includes a contribution to Monotone Systems Theory, namely Lemma 6.4.1, which concerns the intimate connection between the normal dynamics of an evolving surface and monotonicity under time-reversed flow. Perhaps the most fundamental conclusion one can draw from this thesis is that Pure and Applied Mathematics are not separate from one another; they share a symbiotic relationship with one another. Also, Pure versus Applied is not a clear-cut boundary, but a spectrum, and this project lies somewhere in the middle of that spectrum.

Appendix A

The explicit equations for the Nagylaki-Crow model

This appendix provides the governing equations for the three genotype frequencies, and demonstrates that only two of the three equations are required.

Substituting (5.2.2) into Equation (5.2.1) gives the following three equations of motion:

$$
\begin{aligned}
\dot{x} &= \frac{1}{4}z^2F_{22} + x\left[y(D_3 - 2zF_{23}) + z(F_{12} + D_2) - y^2F_{33} - z^2F_{22} - D_1\right] \\
&\quad + x^2(-2yF_{13} - 2zF_{12} + F_{11} + D_1) - x^3F_{11} \\
\dot{y} &= \frac{1}{4}z^2F_{22} + y\left[x(D_1 - 2zF_{12}) + z(F_{23} + D_2) - x^2F_{11} - z^2F_{22} - D_3\right] \\
&\quad + y^2(-2xF_{13} - 2zF_{23} + F_{33} + D_3) - y^3F_{33} \\
\dot{z} &= 2xyF_{13} + z\left[y(F_{23} + D_3 - 2xF_{13}) + x(F_{12} + D_1) - x^2F_{11} - y^2F_{33} - D_2\right] \\
&\quad + z^2\left(-2yF_{23} - 2xF_{12} + \frac{1}{2}F_{22} + D_2\right) - z^3F_{22}
\end{aligned}
$$

As $x + y + z = 1$ (and hence $\dot{x} + \dot{y} + \dot{z} = 0$), the variable z can be eliminated and the system can be rewritten as just two ODEs

$$
\begin{aligned}
\dot{x} = {} & \frac{1}{4}y^2F_{22} - \frac{1}{2}yF_{22} + \frac{1}{4}F_{22} \\
& + x\left(y\left(-F_{12} + \frac{5}{2}F_{22} - 2F_{23} - D_2 + D_3\right) + y^2(-F_{22} + 2F_{23} - F_{33}) \right. \\
& \left. + F_{12} - \frac{3}{2}F_{22} - D_1 + D_2\right) \\
& + x^2\left(y(2F_{12} - 2F_{22} + 2F_{23} - 2F_{13}) + F_{11} - 3F_{12} + \frac{9}{4}F_{22} + D_1 - D_2\right) \\
& + x^3\,(-F_{11} + 2F_{12} - F_{22})
\end{aligned}
\tag{A.0.1}
$$

$$
\begin{aligned}
\dot{y} = {} & \frac{1}{4}x^2F_{22} - \frac{1}{2}xF_{22} + \frac{1}{4}F_{22} \\
& + y\left(x\left(-2F_{12} + \frac{5}{2}F_{22} - F_{23} + D_1 - D_2\right) + x^2(-F_{11} + 2F_{12} - F_{22}) \right. \\
& \left. - \frac{3}{2}F_{22} + F_{23} + D_2 - D_3\right) \\
& + y^2\left(x(2F_{12} - 2F_{22} + 2F_{23} - 2F_{13}) + \frac{9}{4}F_{22} - 3F_{23} + F_{33} - D_2 + D_3\right) \\
& + y^3\,(-F_{22} + 2F_{23} - F_{33})
\end{aligned}
\tag{A.0.2}
$$

Appendix B

The Selection-Recombination model

The equations of motion for $\dot{u}$, $\dot{v}$, and $\dot{q}$ are:

$$\begin{aligned}
\dot{u} = \frac{1}{4}\{ & W_{11} - 2W_{12} - W_{13} + W_{22} + W_{42} \\
& + v(2q(W_{11} - 2W_{12} + W_{22}) - 2(W_{11} - 2W_{12} + W_{22} + W_{42} - \theta)) \\
& + v^2(W_{11} - 2W_{12} + W_{13} + W_{22} + W_{42} - 2\theta) - 2q(W_{11} - 2W_{12} - W_{13} + W_{22} + \theta) \\
& + q^2(W_{11} - 2W_{12} - W_{13} + W_{22} - W_{42} + 2\theta) \\
& + u\,[-3W_{11} + 2W_{12} + 4W_{13} + W_{22} - W_{33} - 2W_{42} - 2W_{43} - W_{44} + 2\theta \\
& + v(-2q(W_{11} - 2W_{12} + W_{22} - W_{33} + 2W_{43} - W_{44}) \\
& + 2(2W_{11} - 2W_{12} - W_{33} + 2W_{42} + W_{44} - 2\theta)) \\
& + q^2(-W_{11} + 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2w_{42} + 2W_{43} - W_{44} - 4\theta) \\
& + 2q(2W_{11} - 2W_{12} - 3W_{13} + W_{33} + W_{42} - W_{44} + 2\theta) \\
& + v^2(-W_{11} + 2W_{12} - 2W_{13} - W_{22} - W_{33} - 2W_{42} + 2W_{43} - W_{44} + 4\theta)\big] \\
& + u^2\,[3W_{11} + 2W_{12} - 5W_{13} - W_{22} + 2W_{33} - W_{42} + 4W_{43} + 2W_{44} - 6\theta \\
& - 2\,(W_{11} - 2W_{13} - W_{22} + W_{33} + 2W_{42} - W_{44})\,q - 2v\,(W_{11} - W_{22} - W_{33} + W_{44})] \\
& + u^3(-W_{11} - 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2W_{42} - 2W_{43} - W_{44} + 4\theta)\},
\end{aligned}$$

$$
\begin{aligned}
\dot{v} = \frac{1}{4}\{ & W_{11} - W_{12} - 2W_{13} + W_{33} + W_{43} \\
& + u(2(-W_{11} + 2W_{13} - W_{33} - W_{43} + \theta) + 2q(W_{11} - 2W_{13} + W_{33})) \\
& + u^2(W_{11} + W_{12} - 2W_{13} + W_{33} + W_{43} - 2\theta) \\
& - 2q(W_{11} - W_{12} - 2W_{13} + W_{33} + \theta) + q^2(W_{11} - W_{12} - 2W_{13} + W_{33} - W_{43} + 2\theta) \\
& + v[-3W_{11} + 4W_{12} + 2W_{13} - W_{22} + W_{33} - 2W_{42} - 2W_{43} - W_{44} + 2\theta \\
& + u(-2q(W_{11} - 2W_{13} - W_{22} + W_{33} + 2W_{42} - W_{44}) \\
& + 2(2W_{11} - 2W_{13} - W_{22} + 2W_{43} + W_{44} - 2\theta)) \\
& + q^2(-W_{11} + 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2W_{42} + 2W_{43} - W_{44} - 4\theta) \\
& + 2q(2W_{11} - 3W_{12} - 2W_{13} + W_{22} + W_{43} - W_{44} + 2\theta) \\
& + u^2(-W_{11} - 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2W_{42} - 2W_{43} - W_{44} + 4\theta)] \\
& + v^2[3W_{11} - 5W_{12} + 2W_{13} + 2W_{22} - W_{33} + 4W_{42} - W_{43} + 2W_{44} - 6\theta \\
& -2q(W_{11} - 2W_{12} + W_{22} - W_{33} + 2W_{43} - W_{44}) - 2u(W_{11} - W_{22} - W_{33} + W_{44})] \\
& + v^3(-W_{11} + 2W_{12} - 2W_{13} - W_{22} - W_{33} - 2W_{42} + 2W_{43} - W_{44} + 4\theta)\},
\end{aligned}
$$

$$
\begin{aligned}
\dot{q} = \frac{1}{4}\{ & W_{11} - W_{12} - W_{13} + W_{42} + W_{43} + W_{44} - 2\theta \\
& + u(-2(W_{11} - W_{13} + W_{43} + W_{44} - 2\theta) + 2v(W_{11} + W_{44} - 2\theta)) \\
& + u^2(W_{11} + W_{12} - W_{13} - W_{42} + W_{43} + W_{44} - 2\theta) \\
& - 2v(W_{11} - W_{12} + W_{42} + W_{44} - 2\theta) + v^2(W_{11} - W_{12} + W_{13} + W_{42} - W_{43} + W_{44} - 2\theta) \\
& + q[-3W_{11} + 4W_{12} + 4W_{13} - W_{22} - W_{33} - 2W_{42} - 2W_{43} + W_{44} \\
& + u(-2v(W_{11} - W_{22} - W_{33} + W_{44}) \\
& + 2(2W_{11} - 3W_{13} - W_{22} + W_{33} + W_{42} + 2W_{43} - 2\theta)) \\
& + u^2(-W_{11} - 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2W_{42} - 2W_{43} - W_{44} + 4\theta) \\
& + 2v(2W_{11} - 3W_{12} + W_{22} - W_{33} + 2W_{42} + W_{43} - 2\theta) \\
& + v^2(-W_{11} + 2W_{12} - 2W_{13} - W_{22} - W_{33} - 2W_{42} + 2W_{43} - W_{44} + 4\theta)\Big] \\
& + q^2[3W_{11} - 5W_{12} - 5W_{13} + 2W_{22} + 2W_{33} - W_{42} - W_{43} - W_{44} + 6\theta \\
& - 2u(W_{11} - 2W_{13} - W_{22} + W_{33} + 2W_{42} - W_{44}) \\
& - 2v(W_{11} - 2W_{12} + W_{22} - W_{33} + 2W_{43} - W_{44})] \\
& + q^3(-W_{11} + 2W_{12} + 2W_{13} - W_{22} - W_{33} + 2W_{42} + 2W_{43} - W_{44} - 4\theta)\} \\
& + r(1 - q - u - v + 2uv).
\end{aligned}
$$

Bibliography

[1] R. Bürger. Dynamics of the classical genetic model for the evolution of dominance. *Mathematical Biosciences*, 67(2):125–143, 1983.

[2] J. Hofbauer and K. Sigmund. *Evolutionary Games and Population Dynamics*. Cambridge University Press, Cambridge, 1998.

[3] E. Kreyszig. *Introductory functional analysis with applications*. Wiley, New York ; London, 1978.

[4] J. F. Crow and M. Kimura. An introduction to population genetics theory. *An introduction to population genetics theory.*, 1970.

[5] T. Nagylaki. *Introduction to Theoretical Population Genetics*. Springer-Verlag, Berlin, 1992.

[6] G. Mendel. Versuche über Pflanzenhybriden. *Verhandlungen des naturforschenden Vereines in Brünn*, 4:3–47, 1866.

[7] W. S. Sutton. On the morphology of the chromosome group in brachystola magna. *The Biological Bulletin*, 4(1):24–39, 1902.

[8] W. S. Sutton. The chromosomes in heredity. *The Biological Bulletin*, 4(5):231–250, 1903.

[9] T. Boveri. *Ergebnisse über die Konstitution der chromatischen Substanz des Zellkerns*. Verlag von Gustav Fischer in Jena, 1904.

[10] L. Du Pasquier, M. Wilson, and B. Sammut. The fate of duplicated immunity genes in the dodecaploid xenopus ruwenzoriensis. *Front Biosci*, 14:177–191, 2009.

[11] G. U. Yule. Mendel's laws and their probable relation to intra-racial heredity. *New Phytologist*, 1(10):222–238, 1902.

[12] K. Pearson. On a generalized theory of alternative inheritance, with special references to mendel's laws. *Philosophical Transactions of the Royal Society A*, 203, 1904.

[13] W. E. Castle. The laws of heredity of galton and mendel, and some laws governing race improvement by selection. *Proceedings of the American Academy of Arts and Sciences*, 39(8):223–242, 1903.

[14] W. Weinberg. Über den Nachweis der Vererbung beim Menschen. *Jahres. Wiertt. Ver. Vaterl. Natkd.*, 64:369–382, 1908.

[15] G. H. Hardy et al. Mendelian proportions in a mixed population. *Science*, 28:49–50, 1908.

[16] W. Weinberg. Über Vererbungsgesetze beim Menschen. *Zeitschrift für induktive Abstammungs-und Vererbungslehre*, 2(1):276–330, 1909.

[17] J. Rückert. Zur Entwickelungsgeschichte des Ovarialeies bei Selachiern. *Anatomischer Anzeiger*, 7:107–158, 1892.

[18] F. A. Janssens. La théorie de chiasmatype, nouvelle interprétation des cinèses de maturation. *Cellule*, 25:387–411, 1909.

[19] J. B. S. Haldane. The combination of linkage values and the calculation of distances between the loci of linked factors. *J Genet*, 8(29):299–309, 1919.

[20] J. Felsenstein. The evolutionary advantage of recombination. *Genetics*, 78(2):737–756, 1974.

[21] R. A. Fisher. *The genetical theory of natural selection*. Oxford: Clarendon Press, 1930.

[22] H. J. Muller. Some genetic aspects of sex. *The American Naturalist*, 66(703):118–138, 1932.

[23] P. J. Gerrish and R. E. Lenski. The fate of competing beneficial mutations in an asexual population. *Genetica*, 102:127, 1998.

[24] W. G. Hill and A. Robertson. The effect of linkage on limits to artificial selection. *Genetics Research*, 8(3):269–294, 1966.

[25] J. F. Crow and M. Kimura. Evolution in sexual and asexual populations. *The American Naturalist*, 99(909):439–450, 1965.

[26] J. F. Crow and M. Kimura. Evolution in sexual and asexual populations: a reply. *The American Naturalist*, 103(929):89–91, 1969.

[27] J. Maynard Smith. Evolution in sexual and asexual populations. *The American Naturalist*, 102(927):469–473, 1968.

[28] J. Maynard Smith. What use is sex? *Journal of theoretical biology*, 30(2):319–335, 1971.

[29] I. Eshel and M. W. Feldman. On the evolutionary effect of recombination. *Theoretical population biology*, 1(1):88–100, 1970.

[30] M. W. Feldman. Selection for linkage modification: I. random mating populations. *Theoretical population biology*, 3(3):324–346, 1972.

[31] S. Karlin. Sex and infinity: a mathematical analysis of the advantages and disadvantages of genetic recombination. *The mathematical theory of the dynamics of biological populations*, pages 155–194, 1973.

[32] M. Kimura and T. Ohta. The average number of generations until extinction of an individual mutant gene in a finite population. *Genetics*, 63(3):701–709, 1969.

[33] J. Hadamard. Sur l'itération et les solutions asymptotiques des équations différentielles. *Bulletin de la Société Mathématique de France*, 29:224–228, 1901.

[34] E. Cotton. Sur les solutions asymptotiques des équations différentielles. In *Annales Scientifiques de l'Ecole Normale Supérieure*, volume 28, pages 473–521. Elsevier, 1911.

[35] A. Lyapunov. Problème général de la stabilité du mouvement. In *Annales de la Faculté des sciences de Toulouse: Mathématiques*, volume 9, pages 203–474, 1907.

[36] O. Perron. Über Stabilität und asymptotisches Verhalten der Integrale von Differentialgleichungssystemen. *Mathematische Zeitschrift*, 29(1):129–160, 1929.

[37] L. Perko. *Differential Equations and Dynamical Systems*. Springer-Verlag, New York, third edition, 2001.

[38] Y. A. Kuznetsov. *Elements of applied bifurcation theory*, volume 112. Springer Science & Business Media, 2013.

[39] S. Wiggins. *Introduction to applied nonlinear dynamical systems and chaos*, volume 2. Springer Science & Business Media, 2003.

[40] H. L. Smith. Monotone dynamical systems: An introduction to the theory of competitive and cooperative systems. *Mathematical Surveys and Monographs*, 41, 1995.

[41] M. W. Hirsch and H. L. Smith. Monotone dynamical systems. In *Handbook of differential equations: ordinary differential equations*, volume 2, pages 239–357. Elsevier, 2006.

[42] A. Katok and B. Hasselblatt. *Introduction to the modern theory of dynamical systems*, volume 54. Cambridge university press, 1997.

[43] J. H. Hubbard and B. H. West. *Differential equations: a dynamical systems approach: higher-dimensional systems*, volume 18. Springer Science & Business Media, 2012.

[44] M. W. Hirsch, S. Smale, and Robert L. Devaney. *Differential equations, dynamical systems, and an introduction to chaos*. Academic Press, Waltham, MA, 3rd edition, 2013.

[45] J. Rosenberg et al. Applications of analysis on lipschitz manifolds. In *Mini-conference on Harmonic Analysis and Operator Algebras*, pages 269–283. Centre for Mathematics and its Applications, Mathematical Sciences Institute, The Australian National University, 1987.

[46] M. Nakahara. *Geometry, Topology and Physics*. Institute of Physics Publishing, Bristol, UK and Philadelphia, USA, 2^{nd} edition, 2003.

[47] N. Fenichel and J. K. Moser. Persistence and smoothness of invariant manifolds for flows. *Indiana University Mathematics Journal*, 21(3):193–226, 1971.

[48] M. W. Hirsch, C. Pugh, and M. Shub. *Invariant Manifolds*, volume 583 of *Lecture Notes in Mathematics*. Springer Berlin Heidelberg, Berlin, Heidelberg, 1977.

[49] Giuseppe Rega and Hans Troger. Dimension reduction of dynamical systems: methods, models, applications. *Nonlinear Dynamics*, 41(1-3):1–15, 2005.

[50] P. Iannelli. *Inertial manifolds in biological systems*. PhD thesis, UCL (University College London), 2009.

[51] A. Ruiz-Herrera. Exclusion and dominance in discrete population models via the carrying simplex. *Journal of Difference Equations and Applications*, 19(1):96–113, 2013.

[52] R. Temam. *Infinite-dimensional dynamical systems in mechanics and physics*. Applied mathematical sciences (Springer-Verlag New York Inc.); v. 68. Springer, New York, 2nd ed. edition, 1997.

[53] R. J. Sacker. A new approach to the perturbation theory of invariant surfaces. *Communications on Pure and Applied Mathematics*, 18(4):717–732, 1965.

[54] Y. M. Chung and E. Schaal. Center manifolds of differential equations in banach spaces. Preprint on the arXiv webpage at `https://arxiv.org/pdf/1710.07342.pdf`, number arXiv:1710.07342, 2017.

[55] M. Müller. Über das Fundamenthaltheorem in der Theorie der gewöhnlichen Differentialgleichungen. *Acta Mathematica*, 26:619–645, 1926.

[56] E. Kamke. Zur Theorie der Systeme gewöhnlicher Differentialgleichungen. II. *Acta Mathematica*, 58(1):57–85, 1932.

[57] M. W. Hirsch. Systems of differential equations which are competitive or cooperative: I. limit sets. *SIAM Journal on Mathematical Analysis*, 13(2):167–179, 1982.

[58] M. W. Hirsch. Systems of differential equations that are competitive or cooperative ii: Convergence almost everywhere. *SIAM Journal on Mathematical Analysis*, 16(3):423–439, 1985.

[59] M. W. Hirsch. Systems of differential equations which are competitive or cooperative: III. Competing species. *Nonlinearity*, 1(1):51–71, February 1988.

[60] M. W. Hirsch. Systems of differential equations that are competitive or cooperative. v. convergence in 3-dimensional systems. *Journal of differential equations*, 80(1):94–106, 1989.

[61] M. W. Hirsch. Systems of differential equations that are competitive or cooperative. iv: Structural stability in three-dimensional systems. *SIAM journal on mathematical analysis*, 21(5):1225–1234, 1990.

[62] H. L Smith. Periodic orbits of competitive and cooperative systems. *Journal of differential equations*, 65(3):361–373, 1986.

[63] H. L. Smith. Systems of ordinary differential equations which generate an order preserving flow. a survey of results. *SIAM review*, 30(1):87–113, 1988.

[64] A. Berman and R. J. Plemmons. *Nonnegative Matrices in the Mathematical Sciences*. Philadelphia: Society for Industrial and Applied Mathematics, 1994.

[65] D. Angeli and E. D. Sontag. Monotone control systems. *IEEE Transactions on automatic control*, 48(10):1684–1698, 2003.

[66] S. Smale. On the differential equations of species in competition. *Journal of Mathematical Biology*, 3(1):5–7, 1976.

[67] J. Mierczyński. The C^1 Property of Carrying Simplices for a Class of Competitive Systems of ODEs. *Journal of differential equations*, 111(2):385–409, July 1994.

[68] S. A. Baigent. Geometry of carrying simplices of 3-species competitive Lotka-Volterra systems. *Nonlinearity*, 26(4):1001–1029, April 2013.

[69] M. Benaïm. On invariant hypersurfaces of strongly monotone maps. *journal of differential equations*, 137(2):302–319, 1997.

[70] P. Brunovský. Controlling nonuniqueness of local invariant manifolds. *J. Reine Angew. Math*, 446:115–135, 1994.

[71] J. Mierczyński. A remark on m. w. hirsch's paper: "chain transitive sets for smooth strongly monotone dynamical systems". *Dynamics of Continuous, Discrete and Impulsive systems. Series A, Mathematical Analysis*, 7(3):455–461, 2000.

[72] J. Mierczyński. On peaks in carrying simplices. In *Colloq. Math*, volume 81, pages 285–292, 1999.

[73] A. Tineo. On the convexity of the carrying simplex of planar lotka–volterra competitive systems. *Applied mathematics and computation*, 123(1):93–108, 2001.

[74] Y. Wang and J. Jiang. Uniqueness and attractivity of the carrying simplex for discrete-time competitive dynamical systems. *Journal of Differential Equations*, 186(2):611–632, 2002.

[75] M. L. Zeeman and P. van den Driessche. Three-dimensional competitive lotka–volterra systems with no periodic orbits. *SIAM Journal on Applied Mathematics*, 58(1):227–234, 1998.

[76] E. C. Zeeman. Classification of quadratic carrying simplices in two-dimensional competitive lotka–volterra systems. *Nonlinearity*, 15(6):1993, 2002.

[77] M. L. Zeeman. Hopf bifurcations in competitive three-dimensional lotka–volterra systems. *Dynamics and Stability of Systems*, 8(3):189–216, 1993.

[78] E. C. Zeeman and M. L. Zeeman. On the convexity of carrying simplices in competitive lotka-volterra systems. *Lecture Notes in Pure and Applied Mathematics*, pages 353–353, 1993.

[79] E. C. Zeeman and M. L. Zeeman. An n-dimensional competitive lotka–volterra system is generically determined by the edges of its carrying simplex. *Nonlinearity*, 15(6):2019, 2002.

[80] E. C. Zeeman and M. L. Zeeman. From local to global behavior in competitive Lotka-Volterra systems. *Transactions of the American Mathematical Society*, 355(2):713–734, 2003.

[81] S. A. Baigent. Convexity-preserving flows of totally competitive planar Lotka–Volterra equations and the geometry of the carrying simplex. *Proceedings of the Edinburgh Mathematical Society*, 55:53–73, November 2012.

[82] B. Seymenoğlu and S. A Baigent. Nonmonotone invariant manifolds in the Nagylaki-Crow model. *Nonlinear Analysis: Real World Applications*, 41:570–587, 2018.

[83] T. Nagylaki and J. F. Crow. Continuous Selective Models. *Theoretical Population Biology*, 5:257–283, 1974.

[84] L. S. Penrose. The meaning of “Fitness” in human populations. *Annals of eugenics*, 14(4):301–304, 1949.

[85] W. F. Bodmer. Differential Fertility in Population Genetics Models. *Genetics*, 51(3):411–424, March 1965.

[86] D. L. Rucknagel and J. V. Neel. The hemoglobinopathies. *Progress in Medical Genetics*, pages 158–260, 1961.

[87] K. P. Hadeler and U. Liberman. Selection models with fertility differences. *Journal of Mathematical Biology*, 2(1):19–32, 1975.

[88] G. J. Butler, H. I. Freedman, and P. Waltman. Global dynamics of a selection model for the growth of a population with genotypic fertility differences. *Journal of Mathematical Biology*, 14(1):25–35, 1982.

[89] K. P. Hadeler and D. Glas. Quasimonotone systems and convergence to equilibrium in a population genetic model. *Journal of mathematical analysis and applications*, 95(2):297–303, 1983.

[90] M. Koth and F. Kemler. A one locus-two allele selection model admitting stable limit cycles. *Journal of Theoretical Biology*, 122(3):263–267, 1986.

[91] J. Hofbauer and K. Sigmund. *The theory of evolution and dynamical systems: mathematical aspects of selection*. Cambridge University Press, Cambridge, 1988.

[92] J. M. Szucs. Equilibria and dynamics of selection at a diallelic autosomal locus in the Nagylaki-Crow continuous model of a monoecious population with random mating. *Journal of Mathematical Biology*, 31(4):317–349, 1993.

[93] E. Akin and J. M. Szucs. Approaches to the Hardy-Weinberg manifold. *Journal of Mathematical Biology*, 32(7):633–643, 1994.

[94] S. Boyd and L. Vandenberghe. *Convex optimization*. Cambridge university press, 2004.

[95] J. Jiang. On the Existence and Uniqueness of Connecting Orbits for Cooperative Systems. *Acta Mathematica Sinica, New Series*, 8:184–188, 1986.

[96] E. N. Dancer and P. Hess. Stability of fixed points for order-preserving discrete-time dynamical systems. *Journal Für Die Reine Und Angewandte Mathematik*, 419:125–139, 1991.

[97] J. Mierczyński. Smoothness of unordered curves in two-dimensional strongly competitive systems. *Applicationes Mathematicae*, 25(4):449–455, 1999.

[98] M. Kimura. A model of a genetic system which leads to closer linkage by natural selection. *Evolution*, 10(3):278–287, 1956.

[99] T. Nagylaki, J. Hofbauer, and P. Brunovský. Convergence of multilocus systems under weak epistasis or weak selection. *Journal of Mathematical Biology*, 38(2):103–133, 1999.

[100] E. Akin. Cycling in simple genetic systems. *Journal of Mathematical Biology*, 13(3):305–324, 1982.

[101] E. Akin. Hopf bifurcation in the two locus genetic model. *Memoirs of the American Mathematical Society*, 1983.

[102] E. Akin. Cycling in simple genetic systems: II. The symmetric cases. In A Kurzhanski and K Sigmund, editors, *Dynamical Systems*, pages 139–153. Springer, Berlin, 1987.

[103] G. P. Wagner and R. Bürger. On the evolution of dominance modifiers II: a non-equilibrium approach to the evolution of genetic systems. *Journal of theoretical biology*, 113(3):475–500, 1985.

[104] W. J. Ewens. Mean fitness increases when fitnesses are additive. *Nature*, 221(5185):1076, 1969.

[105] Eduard Helly. Über mengen konvexer körper mit gemeinschaftlichen punkte. *Jahresbericht der Deutschen Mathematiker-Vereinigung*, 32:175–176, 1923.

[106] K. P. Hadeler. On copositive matrices. *Linear Algebra and its Applications*, 49:79–89, 1983.

[107] R. A. Fisher. The Possible Modification of the Response of the Wild Type to Recurrent Mutations. *The American Naturalist*, 62(679):115–126, 1928.

[108] S. Wright. Fisher's Theory of Dominance. *The American Naturalist*, 63(686):274–279, 1929.

[109] S. Wright. The Evolution of Dominance. *The American Naturalist*, 63(686):556–561, 1929.

[110] S. Wright. Physiological and evolutionary theories of dominance. *The American Naturalist*, 68(714):24–53, 1934.

[111] J. B. S. Haldane. A note on fisher's theory of the origin of dominance, and on a correlation between dominance and linkage. *The American Naturalist*, 64(690):87–90, 1930.

[112] D. Bourguet. The evolution of dominance. *Heredity*, 83(1):1, 1999.

[113] H. C. Bagheri. Unresolved boundaries of evolutionary theory and the question of how inheritance systems evolve: 75 years of debate on the evolution of dominance. *Journal of Experimental Zoology Part B: Molecular and Developmental Evolution*, 306(4):329–359, 2006.

[114] W. J. Ewens. Further notes on the evolution of dominance. *Heredity*, 20(3):443, 1965.

[115] W. J. Ewens. Linkage and the evolution of dominance. *Heredity*, 21:363–370, 1966.

[116] W. J. Ewens. A Note on the Mathematical Theory of the Evolution of Dominance. *The American Naturalist*, 101(917):35–40, 1967.

[117] M. W. Feldman and S. Karlin. The evolution of dominance: A direct approach through the theory of linkage and selection. *Theoretical population biology*, 2(4):482–492, 1971.

[118] J. H. Gillespie. *Population genetics: a concise guide*. Johns Hopkins University Press, 2004.

[119] R. Bürger. On the Evolution of Dominance Modifiers I. A Nonlinear Analysis. *Journal of theoretical biology*, 101(4):585–598, 1983.

[120] R. A. Fisher. The evolution of dominance: Reply to Professor Sewall Wright. *The American Naturalist*, 63(686):553–556, 1929.

[121] W. J. Ewens. A note on Fisher's theory of the evolution of dominance. *Annals of Human Genetics*, 29:85–88, 1965.

[122] M. W. Hirsch and H. L. Smith. Competitive and cooperative systems: a mini-review. In *Positive Systems: Lecture Notes in Control and Information Science*, pages 183–190. Springer, 2003.

[123] R. Ortega and L. Sánchez. Abstract competitive systems and orbital stability in $\mathbb{R}^3$. *Proceedings of the American Mathematical Society*, 128:2911–2919, 2000.

[124] P. D. Taylor and L. B. Jonker. Evolutionary stable strategies and game dynamics. *Mathematical biosciences*, 40(1-2):145–156, 1978.

[125] S. N. Chow, K. Lu, and G. R. Sell. Smoothness of inertial manifolds. *Journal of Mathematical Analysis and Applications*, 169(1):283–312, 1992.

[126] J. C. Robinson. *Infinite-dimensional dynamical systems: an introduction to dissipative parabolic PDEs and the theory of global attractors*, volume 28. Cambridge University Press, 2001.