Universidad Nacional de Asunción

Facultad Politécnica

Mathematical model and control of arbovirus vectors by *Wolbachia* infection

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Tesis presentada a la Facultad Politécnica, Universidad Nacional de Asunción, como requisito para la obtención del Grado de Doctor en Ciencias de la Computación.

San Lorenzo - Paraguay

Noviembre, 2019

Pastor E. Pérez Estigarribia.

Mathematical model and control of arbovirus vectors by *Wolbachia* infection / Pastor E. Pérez Estigarribia Orientadores: Pierre-Alexandre Bliman and Christian E. Schaerer — San Lorenzo: FPUNA, 2019.
i-xix; 174 p; il:30cm.

Incluye bibliografía (CD)

Tesis Doctoral (Doctorado en Ciencias de la Computación). – UNA. Facultad Politécnica, 2019.

1. Modeling. 2. Control theory 3. Mosquito control. 4. Population Genetics. 5. Population dynamics.

SCDD 005.8 «_____»
C174d. «_____»

Thesis Approval Sheet

Mathematical model and control of arbovirus vectors by *Wolbachia* infection.

Pastor E. Pérez Estigarribia

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Dedicado con cariño a las futuras generaciones de biólogos matemáticos y teóricos de Paraguay. Y a aquellos que han de preparar el camino para que ellos existan.

Acknowledgment

We acknowledge the support of CONACyT, Paraguay in the framework of FEEI-PROCIENCIA program (POS007, POSG17-53, PVCT15-273, PVCT17-156, PVCT18-53), acknowledge the CONACyT-PRONII program, the support of the STIC AmSud projects MOSTICAW (2016-2017) and NEMBICA (2020-2021).

A Karen Colman Neris por su continuo apoyo y acompañamiento en estos años de crecimiento, aprendizaje e investigación incesante.

A mis padres, Myrian Estigarribia y Pastor Pérez Espinoza por permitir que crezca conmigo esa curiosidad por aprender y entender la naturaleza, que me ha llevado hacia el oficio de la ciencia. A mis hermanos, Liz, Soledad, Víctor y Verónica, por enseñarme de que no hay nada más importante que tener raíces fuertes para soportar los desafíos de la vida.

A mis orientadores, Christian E. Schaerer y Pierre-Alexandre Bliman por su contribución invaluable a mi crecimiento.

Pastor E. Pérez Estigarribia.

"En aquel imperio, el arte de la cartografía logró tal perfección que el mapa de una sola provincia ocupaba toda una ciudad, y el mapa del imperio, toda una provincia. Con el tiempo, estos mapas desmesurados no satisficieron y los colegios de cartógrafos levantaron un mapa del imperio, que tenía el tamaño del imperio y coincidía puntualmente con él.

Menos adictas al estudio de la cartografía, las generaciones siguientes entendieron que ese dilatado mapa era inútil y no sin impiedad lo entregaron a las inclemencias del sol y los inviernos. En los desiertos del oeste perduran despedazadas ruinas del mapa, habitadas por animales y por mendigos; en todo el país no hay otra reliquia de las disciplinas geográficas." Jorge Luis Borges, Del Rigor en la Ciencia.

Resumen

Los mosquitos son vectores de enfermedades virales con potencial epidémico en muchas regiones. El control poblacional de mosquitos es la principal alternativa debido a las dificultades en el uso de vacunas contra estas enfermedades. En este sentido, el control químico a través de insecticidas ha sido una de las estrategias convencionales. Sin embargo, con el tiempo las poblaciones de mosquitos desarrollan resistencia a los insecticidas codificada a nivel genético. Además, los productos químicos utilizados como insecticidas pueden afectar a otros grupos de insectos y causar daños ecológicos. Por estas razones, se han propuesto nuevas alternativas de control. Uno de ellos es el control mediante la liberación de mosquitos infectados con *Wolbachia*. Esta última es una bacteria heredada de la madre a su descendencia y, dependiendo de la cepa, puede suprimir el tamaño de las poblaciones de mosquitos o inhibir su competencia vectorial. En este contexto, esta tesis aporta modelos matemáticos, análisis y simulaciones para comprender cómo la *Wolbachia* puede trabajar en la interacción con rasgos genéticos como la resistencia a los insecticidas.

Para dar cuenta de la aparición y propagación de fenómenos de resistencia por el efecto de la exposición a larvicidas y/o adulticidas, desarrollamos un modelo poblacional general de tiempo continuo con dos fases de vida, posteriormente simplificado a través de la "slow manifold theory". Los modelos derivados presentan tasas de reclutamiento y mortalidad dependientes de la densidad de una manera no convencional. Mostramos que, en ausencia de selección, evolucionan de acuerdo con el principio de Hardy-Weinberg; mientras que en presencia de selección, en los casos dominantes o codominantes, se produce la convergencia al genotipo más apto. Luego, presentamos un enfoque de modelado explícito y simulaciones numéricas que ilustran los resultados analíticos en este contexto. Además de la selección direccional para la evolución de la resistencia a los insecticidas, a fin de ilustrar la cualidad descriptiva de la clase de modelos propuestos, se simulan otros escenarios de evolución no direccional, *i.e.*, sobredominancia y subdominancia. Del mismo modo, presentamos simulaciones que ilustran cómo el nivel de dominación y la inversión da la evolución de la resistencia pueden prolongar la efectividad del control químico.

Finalmente, con base a la clase de modelos presentados anteriormente, se deriva un modelo que unifica el control químico con el control biológico para las infecciones

por *Wolbachia*. Se propone un modelo poblacional representado por la combinación de atributos de herencia autosómica para resistencia a insecticidas y herencia materna para *Wolbachia*. Se deduce una ley de control para la liberación de genotipos específicos de mosquitos infectados con *Wolbachia* para el control por remplazo. Se presentan resultados analíticos que describen el comportamiento cualitativo del sistema. Se demuestra la validez de la ley de control propuesta. Finalmente, para ilustrar los resultados analíticos, se presentan simulaciones computacionales, que evidencian la influencia que algunos factores deben tener en las campañas de liberación de mosquitos de genotipo específico infectados con *Wolbachia*.

Palabras clave: *Wolbachia*, Mosquitos vectores, Resistencia a insecticidas, Teoría de control, Genética de poblaciones, Dinámica de poblaciones.

Abstract

Mosquitoes are vectors of viral diseases with epidemic potential in many regions. Due to difficulties in the use of vaccines against these diseases, the main alternative is the control of mosquitoes population. In this regard, chemical control through insecticides has been one of the conventional strategies. Nevertheless, over time mosquito populations develop insecticide resistance encoded at the genetic level. In addition, chemicals used as insecticides can affect other groups of insects and cause ecological damage. For these reasons, new control alternatives have been proposed. One of these is control by the release of mosquitoes infected with *Wolbachia*, a bacterium inherited from the mother to offsprings that, depending on the strain, it can suppress mosquito populations size or inhibit its vector competence. In this context, this thesis contributes with mathematical models, analyzes, and simulations that aim to understand how *Wolbachia* can work while interacting with a genetic trait like insecticide resistance.

To account for the emergence and spread of such phenomenon as an effect of exposition to larvicide and/or adulticide, we developed a general time-continuous population model with two life phases, subsequently simplified through slow manifold theory. The derived models present density-dependent recruitment and mortality rates in a non-conventional way. We show that in the absence of selection, they evolved in compliance with the Hardy-Weinberg principle. While in the presence of selection, in the dominant or codominant cases, there was convergence to the fittest genotype. We present next an explicit modeling approach and numerical simulations that illustrate analytical results in this context. In addition to the directional selection for the evolution of insecticides resistance, we simulated other scenarios of non-directional evolution, i.e., overdominance and underdominance, to illustrate the descriptive quality of the class of the proposed models. In the same way, we present simulations that illustrate how the level of dominance and the reversal in the evolution of resistance can prolong the effectiveness of chemical control.

At last, based on the class of models previously presented, we derived a model that unifies the chemical control with the biological control for *Wolbachia* infections. We also proposed a population model of individuals represented by the combination of autosomal inheritance attributes for insecticide resistance and maternal inheritance

for *Wolbachia*. We have deduced a biological control law for the release of specific genotypes of mosquitoes infected with *Wolbachia* for replacement control, and present the analytical results that describe the qualitative behavior of the system. In addition, we prove the validity of the proposed control law. Finally, to illustrate the analytical results, we present computational simulations, which also illustrate the influence that some factors should have on the releasing campaigns of mosquitoes with specific genotype infected with *Wolbachia*.

Keywords: *Wolbachia*, Vector mosquitoes, Insecticide resistance, Control theory, Population genetics, Population dynamics.

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Chapter 1

General introduction

1.1 Mosquitoes and arbovirosis

The dynamics of arboviruses depend on a circulation between hematophagous arthropods and host vertebrates. These viruses need a vector for replication, propagation and subsistence. Controlling vector populations is an efficient way to mitigate arboviruses related health problems.

Nearly 700 million people get mosquito-borne diseases every year (Caraballo and King, 2014). Over 500 known arboviruses, 150 are known to cause disease in humans (Roehrig and Lanciotti, 2009). Arboviruses with severe morbidity and mortality transmitted by mosquitoes to humans belong to the families *Flaviviridae*, *Togaviridae* and *Bunyaviridae* (Blair et al., 2000). These viruses are classified according to their epidemiological characteristics in causes of hemorrhagic complications or predominance of neurological damage (Zuckerman, 2009). Except for the O'nyong-nyong virus, transmitted by mosquitoes *Anopheles*, all other viruses are transmitted by *Culicidae*, especially by *Aedes* and *Culex* (Franz et al., 2015). In particular, dengue fever, spread by *Ae. aegypti*, is the most important viral disease transmitted by mosquitoes because of its global epidemic potential (Bhatt et al., 2013; Organization et al., 2014; Shepard et al., 2016). In addition, *Ae. aegypti* is the main vector for yellow fever (Tomori, 2004), Chikungunya (Halstead, 2015) and zika (Bharucha and Breuer, 2016).

The attributes that convert some insects like *Ae. aegypti* in global epidemic risk factor are: (a) its widespread distribution in tropical and subtropical regions (Kraemer et al., 2015); (b) it is in close association with human populations (Powell and Tabachnick, 2013); and (c) has vector competence for several viruses (Nene and *et al.*, 2007).

The risk of disseminating severe insect-borne diseases was recently evidenced by the

propagation of zika, a virus that, in infections during pregnancy, causes microcephaly in those born (Gulland, 2016) As a matter of fact, in 2007, a zika outbreak was reported with only fourteen confirmed cases in humans with geographic distribution in tropical Africa and Southeast Asia (Duffy et al., 2009; Faye et al., 2014). However, in May 2015 a third outbreak of Zika was identified in Brazil, which quickly spread across South America and then to 62 countries (Kindhauser et al., 2016).

Furthermore, in the climate change scenarios, the occurrence of theses mosquito-borne diseases adds to predictions of the expansion of regions with suitable ecological conditions for vectors (Kamal et al., 2018).

This overview has motivated the recent search for advanced strategies to control mosquito populations.

1.2 Control of mosquito populations

The most efficient mitigation strategies for arbovirosis are based on vector population control (Beaty et al., 2010). For this reason, it is essential to understand the insect populations dynamics to achieve effective artificial control. In this regard, two types of mechanisms can act on the dynamics of these populations —see (Turchin, 2003): a) intrinsic (endogenous) controllers that operate through density-dependent negative feedback mechanisms, such that survival and fertility are decrease when population density increases; b) extrinsic (exogenous) controllers, which include environmental variables and human control actions that affect the population density, but are not affected by it (*e.g.* rains and breeding sites available (Yang et al., 2008), temperature (Lahondère and Lazzari, 2012; Ewing et al., 2016), insecticides use). In general, mosquito populations show strong natural intrinsic regulation depending on density (Yang et al., 2008).

In practice, the most widely used insect control strategy is based on chemical methods (Levick et al., 2017), *i.e.*, the use of larvicides and/or adulticides. However, it has been warned that the use of insecticides affects the ecosystems (Oosthoek, 2013). Besides, their prolonged use generates resistance to insecticides (Brown, 1986; Hemingway and Ranson, 2000; Schechtman and Souza, 2015) which reduces the effectiveness of chemical control campaigns and limits their useful life (Koella et al., 2009a; Gourley et al., 2011).

Due to the problems associated with insecticide use, there has been progressing in the last 15 years in developing alternative strategies ranging from biological control methods to the genetic modification of insect populations (McGraw and O'Neill,

2013). Among these are the innovations known as genetic control, which are defined as biological control methods that depend on the spread of hereditary factors that reduce the damage of plagues (Alphey, 2014). These control strategies may have the purpose of suppressing a population as insecticides do, or replacing it with mosquitoes with reduced or null vector competence (Walker et al., 2011b; Alphey, 2014). However, before the widespread application of these methods, there are theoretical and experimental questions related to the independent or simultaneous use of these strategies that must be answered —see (Hoffmann and Turelli, 2013a; Alphey, 2014; Hoffmann et al., 2015).

In this sense, mathematical modeling and computational simulation —in the context of population dynamics and population genetics on biology, and at intersection with control theory of the engineering— can help to find effective implementation strategies and anticipate inconvenience or difficulties.

1.3 Insecticide resistance and the use of *Wolbachia* as a control strategy

The problem of insecticide resistance in mosquitoes provides an illustrative biological model to understand how new adaptations evolve by natural selection —see (Daborn et al., 2004). In many cases:

- the selection agent is known, *e.g.*, a certain insecticide (Vontas et al., 2012a);
- the evolution is recent and rapid, a few years after the use an insecticide (Koella et al., 2009a);
- biological and genetic mechanisms for resistance are often known (Labbé et al., 2011).

In this regard, due to the cost, risk and logistical difficulties of prospective experimental field studies of the evolution of resistance, mathematical models and computer simulations can help improve the management of insecticides and their joint application with other advanced strategies of control. All this has particular relevance because the range of possibilities for mosquito control strategies has increased significantly in the last decade (Kean et al., 2015). Therefore, understand and anticipate the limitations and potential of the simultaneous use of some of these strategies represents a recent challenge.

An example of this would be the joint use of insecticide applications and the release of mosquitoes infected by *Wolbachia*. A recent modeling study predicts that

the success of *Wolbachia* use is influenced by chemical control in a local mosquito-resistant population (Hoffmann and Turelli, 2013a). Indeed, the scope of use *Wolbachia* and its interaction with other genetic traits such as resistance to insecticides without the use of mathematical models representing inheritance cannot be covered —see *e.g.* (Echaubard et al., 2010). Consequently, are necessary mathematical models that integrate widespread fundamentals of population dynamics and population genetics in a context of control theory are necessary.

1.4 State of knowledge

1.4.1 On models for insecticide resistance

We cannot talk about insecticide resistance or genetic control strategies without considering evolutionary biology. The literature on models of evolution by selection, as well as models of the evolution of resistance in diploid populations is quite extensive. It is not our intention to provide an extensive inventory here. Rather, in this section we want to position the contribution of the thesis with respect to the state of knowledge in the temporal context of its elaboration.

For an overview of the state of knowledge on evolution by selection in biology, we refer the reader to the following texts: (Hofbauer and Sigmund, 1998; Ewens, 2011; Schuster, 2011b; Bürger, 2011). In this kind of texts, continuous time Fisher's selection equation occupies a central part (Schuster, 2011a), generally framed in evolutionary game theory as an replicator equation (Schuster and Sigmund, 1983), which use a *simplex* for describes the evolution in allelic or genotypic frequencies. This formulation leaves it in the same class of differential equations that Generalized Lotk-Volterra equation, hypercycle equation and game dynamics equation (Sigmund, 2011).

In particular, for the evolution of insecticide resistance in diploid populations, the approach and assumptions often made are guidelines used to construct population genetics models —see (Levick et al., 2017) and classic texts, *e.g.*, (Freeman and Herron, 2007).

Below are some comments on the classic population genetics models assumption.

In population genetics models, to omit the effect of genetic drift, in a probabilistic framework, it is common to appeal to the law of large numbers and assume an infinite population size. Then, it is possible to focus the mathematical analysis on a *simplex* that represents allelic or genotypic frequencies, just as in evolutionary game theory. Certainly, reproduction and selection are known to have inherent stochastic effects,

the incorporation of these effects produces models that are formulated in terms of stochastic processes, generally Markovians, and add considerable mathematical complexity (Bürger, 2011). However, the effect inherent to these phenomena are not of interest in this thesis.

Regarding population size, in contrast to the aforementioned, in the suppression strategies by chemical control and when the resistance evolution is maintained, one wishes to study, in addition to the changes in allelic or genotypic frequencies, the efficiency in the suppression of population size—even if an extinction can be caused, or a desired population size threshold. In this sense, the study of suppression a population of mosquitoes is not compatible with the theoretical assumption of a population with infinite size.

Another fundamental aspect of population genetics is the concept of fitness (Orr, 2009; Wu et al., 2013), a measure related to the reproductive rate that depends on the relative viability and/or decreased fertility. For simplicity, it is common in population geneticsto not always specify the mechanisms by which fitness reduce (Wilson and Bossert, 1971; Barbosa and Hastings, 2012; Levick et al., 2017).

In this sense, in the context of theoretical evolutionary genetics (Felsenstein, 2005) and evolutionary games theory, there are models with non-negligible degrees of complication for diploid populations with selection by fertility and mortality. In this regard, the application of an insecticide must affect the mortality of individuals in the population Therefore, the consideration of models of selection by mortality models may be enough to capture the phenomenon.

However, given the complexity of mosquito life history —the occupation of an aquatic ecological niche in the larvae phase and a different one in the adult phase— and the principles of inheritance for sexual reproduction, some realistic scenarios may require a more general treatment for the mechanisms affecting fitness. For example, the use of larvicides and/or adulticides for mosquito control differently affects viability in the pre-reproductive and reproductive phases, respectively. Besides, viability may decrease in a growing population in a given life phase due to the limitation of some resources by competition, and may depend on density.

Langemann *et al.* present an unconventional approach to resistance models (Langemann et al., 2013). These authors propose a deterministic model that combines logistic growth in a population with the rearrangement of alleles in the genotypes given by Mendelian inheritance. In addition, they show how this model can be applied for multiple loci cases, extend it to polyploids and multiple alleles.

1.4.2 On models for *Wolbachia* Control strategies

On the other hand, regarding *Wolbachia*, several mathematical models have been proposed for mosquitoes —see (Keeling et al., 2003; Farkas and Hinow, 2010; Zheng et al., 2014; Yakob et al., 2017; Xue et al., 2017; Campo-Duarte et al., 2017, 2018; Bliman et al., 2018a; Almeida et al., 2019) and (Hughes and Britton, 2013; Koiller et al., 2014a; Ndii et al., 2015) in the context of dengue epidemic). To mention some examples, Turelli (Turelli, 2010) describes a simple model with a single differential equation, sufficient to reveal the bistable nature of the dynamics of *Wolbachia*. Koiller *et al.* (Koiller et al., 2014b) describe a model that accurately estimates some biological parameters when fitting it with field and laboratory data. More recently, Bliman *et al.* (Bliman et al., 2018a; Bliman, 2019) presented simplified version of the previous model, with four dimensions of state variables (pre-adult and adult, infected and uninfected), focusing their main effort on the control problem from a Control Theory point of view —see (Bliman, 2019).

Hoffmann and Turelli published a research close to the main purpose of this thesis (Hoffmann and Turelli, 2013a). These authors propose a model for the simultaneous use of insecticide resistance and infection by *Wolbachia*. The proposed assumes discrete generations and focuses on the study of the frequencies of the population's biotypes. This approach was similar to that of classical population genetics.

1.5 Problem formulation and objectives

A fundamental issue regarding the release of *Wolbachia* infected mosquitoes into wild populations is how to guarantee success even in a population with local adaptations such as resistance to insecticides. In this sense, we want to answer the following question in this thesis:

How to introduce *Wolbachia* into a population of uninfected insecticide-resistant wild mosquitoes using laboratory mosquitoes infected with *Wolbachia* and susceptible to insecticides?

To answer this question, we use mathematical modeling and computational simulations are used. In this way, the objectives of this thesis are disclosed below.

General objective

Establish a biological control strategy for insecticide resistant mosquitoes using *Wolbachia*.

Specific objectives

1. Model a Mendelian inheritance system for insecticide resistance in mosquitoes.
2. Analyze the proposed Mendelian inheritance model for insecticide resistance in mosquitoes.
3. Illustrate scenarios related to the evolution of insecticide resistance by computational simulations.
4. Propose a unified model of maternal and autosomal inheritance for the analysis of a control strategy with *Wolbachia* for insecticide-resistant mosquitoes.
5. Simulate control scenarios with the proposed Resistance-Wolbachia unified model.

To full fill objectives 1 and 2, Chapter 2 presents a class of population model with an inheritance that covers aspects of mosquito life history and a Mendelian inheritance mechanism. In Chapter 2, we provide analytical results on the qualitative behavior of population dynamics in conditions of the use of insecticides and the evolution of resistance, namely, directional selection. We also demonstrate that the class of models proposed capture fundamental theoretical aspects of population genetics —*e.g.*, the Hardy-Weinberg principle.

In Chapter 3, simulations of evolutionary scenarios are presented based on modeling presented in Chapter 2 to illustrate the analytical results, and to illustrate the power of the class of models proposed to represent genetic evolutionary phenomena. In Chapter 4, according to the specific objective 3, we present simulations for the class of models proposed are presented in the context of insecticide resistance. The impact of the levels of genetic dominance of resistance on population dynamics and population genetics is illustrated, and how this affects of the resistance reversal.

In Chapter 5, according to the specific objectives 4 and 5, —in the same direction of the class models introduced, analyzed and simulated in previous chapters—, we provide a model for control by replacement, based on the release of specific mosquitoes genotype infected by *Wolbachia* in a population with evolution of insecticide resistance. In the same chapter, we provide simulations that the analytical results, besides, factors that would influence control campaigns with *Wolbachia* (*e.g.* genotype released, level of resistance dominance, use of larvicides or adulticides , increase in scramble

competition due to elimination of breeding sites, complete or incomplete cytoplasmic incompatibility induced by *Wolbachia*).

Chapter 2

A class of fast-slow models for adaptive resistance evolution

2.1 Introduction

2.1.1 Insect pests and insecticide use

A tiny insect is one of the deadliest animals for human: the mosquitoes. Nearly 700 million people contract diseases transmitted by mosquito every year (Caraballo and King, 2014). Just for the transmission of malaria, almost a million people die every year (Qureshi, 2018), and 3.4 billion people are at risk worldwide (Organization et al., 2014). Amongst the 150 arboviruses that cause diseases in humans, about 20 that are transmitted by mosquitoes are of primary medical importance (Roehrig and Lanciotti, 2009). In particular dengue, transmitted by the primary vector *Aedes aegypti* with its human and economic costs, ranks as the most important mosquito-borne viral disease with epidemic potential in the world (Bhatt et al., 2013; Shepard et al., 2016). On the whole, vector-borne diseases diseases pose serious public health problems and high economic costs in many regions of the world.

Besides, it has been suggested that insects destroy about 20% of the annual production of crops worldwide (Sharma et al., 2017). The agricultural damage caused by insects may be direct, as well as indirect, through the transmission of plant diseases (Oerke, 2006). Two factors contribute to the importance of insects as agricultural pests: their diversity —two thirds of known species, around 600,000, are phytophagous—, and the fact that practically all plant species are consumed by at least one species of phytophagous insect— even some agricultural pests can hit many species of plants (Douglas, 2018). The issues induced by agricultural pests are therefore a challenge for

global food production.

The most commonly used methods to suppress or reduce insect populations are based on chemical treatment. The conventional control strategy of mosquito populations use larvicides and/or adulticides (Shaw WR, 2019). However, this strategy is affected by the evolution of resistance (Hemingway and Ranson, 2000) which reduces the efficiency of the chemical control campaigns and their lifespan (Koella et al., 2009a). Nowadays, in addition to an alarming propagation of vectors, most of the species involved are showing resistance to many kinds of insecticides (Vontas et al., 2012b). Resistance not only reduces the efficiency of chemical control methods, but may also perturb the application of other control methods, like biological and genetic controls, through the undesired fitness advantage that it provides to the local mosquito species (Garcia et al., 2020).

2.1.2 Modelling of insecticide resistance evolution

Resistance to insecticides is a human-made example of selection (Daborn et al., 2004). This occurs when the environment is changed artificially by impregnation with an insecticide that increases the mortality of a target species, in such a way that some genetic variants survive better than others.

The issue of insecticide resistance provides a contemporary natural model to study how new adaptations evolve by selection: the selection agent is known —as an example a given insecticide—, the evolution is recent and rapid —few years after the application—, and the biological and genetic mechanisms are often known —many insect genes that code the targets for insecticides have been identified and cloned (Labbé et al., 2011). In this regard, due to the cost, risk and logistical difficulties in the field study of resistance evolution, mathematical models may help to improve management strategies of insecticides, apart from allowing them to learn more about adaptive evolution in the context of complex life history.

Literature related to models of evolution by selection is quite extensive. For an overview of the state of knowledge, the reader is referred to the following classical texts (Hofbauer and Sigmund, 1998; Ewens, 2011; Schuster, 2011a,b; Bürger, 2011). Reproduction and natural selection involve inherently stochastic effects, and a typical modeling approach includes stochastic time-discrete processes (Huillet and Martinez, 2011), which may however present considerable mathematical complexity (Bürger, 2011). In classical population genetics selection models, it is common to appeal to the law of large numbers and assume an infinite population size, to omit the effect of stochasticity and to focus the mathematical analysis on the evolution of the allelic and genotypic

relative frequencies by selection. This is the case of the Fisher selection equation (see (Schuster and Sigmund, 1983; Hofbauer et al., 1982; Hofbauer and Sigmund, 1998)), generally framed in evolutionary game theory as a replicator equation, to describe the allelic or genotype evolution of relative frequencies (Schuster, 2011a; Schuster and Sigmund, 1983). In this context, (Hofbauer and Sigmund, 1998) provides models and analytical results of selection for some game dynamics equations, including continuous selection dynamics models such as: independent and density-dependent Malthusian fitness, additive and multiplicative fertility, and Mendelian populations.

For simplicity, it is common in population geneticsno to specify the elementary mechanisms by which fitness reduces (Barbosa and Hastings, 2012; Levick et al., 2017). On the other hand, the use of larvicides and/or adulticides for the control of mosquitoes affects the viability differently in the pre-reproductive and reproductive phases. In addition, viability may decrease in a growing population due to the limitation of some resources by competition, and may depend on density, which in turn may affect different classes of individuals in the population in a non-homogeneous way.

Several approaches have been proposed in the literature to model insecticide resistance, with several objectives. In (Taylor and Headley, 1975) a time-discrete model is presented for three genotypes that considers a resistance allele with intermediate dominance in an autosomal locus. A time-discrete model of insecticide resistance is developed in (Comins, 1977) that includes migration, in order to understand variations in the time required for insects to develop resistance. Likewise, (Taylor and Georghiou, 1979) explored a model proposed in (Crow et al., 1970) to quantify changes in gene frequency between zygotes in each generation. The model in question is time-discrete, with intermediate dominance alleles in an autosomal locus, and assumes migration and a density-dependent growth of the population. On the other hand, (Curtis, 1985) and (Mani, 1985) used time-discrete models classical in populations genetics to show the essential characteristics of the selection dynamics for resistance by one or two insecticides on two autosomal loci. More recently, this line of research was explored again (Levick et al., 2017; South and Hastings, 2018). Also, (Barbosa and Hastings, 2012) developed genetic models to predict changes in the fitness and frequency of resistance alleles in synergistic scenarios. All these models consider Mendelian inheritance, but do not take into account the existence of several stages of life, and different selective pressure for each phase.

Furthermore, models have been proposed to develop new approaches, such as the idea of evolution-proof insecticides (Koella et al., 2009a; Read et al., 2009; Gourley et al., 2011). In particular, these models were developed to explore the control of

malaria vector mosquito. Since the malaria parasite requires a mosquito with a long life expectancy, these authors explore strategies to slow down the evolution of resistance using combinations of larvicides and late-life-acting insecticides. In this regard a classical population genetics model is used in (Read et al., 2009) to quantify the change in the relative frequency of a resistant allele, assuming a constant population of adults. A population genetics model that considers the change in relative frequency of a resistance allele in different age classes is considered in (Koella et al., 2009a). The two works cited above differ from (Gourley et al., 2011), in which an aged-structured population of variable size is modeled by delay differential equations. However, this model does not possess an inheritance mechanism for autosomal genes.

A non-conventional approach to resistance models was given in (Langemann et al., 2013). Inspired by the study of herbicide resistant weed, this Chapter proposed a continuous-time deterministic model that combines the logistic growth in a population with the rearrangement of alleles in the genotypes given by inheritance. In addition, the model applies to cases of multiple loci using the tensor product and extends to polyploid and other numbers of alleles. However, it does not allow to model the several life phases, which present different selective pressures in their respective ecological niches.

In (Schechtman and Souza, 2015) a compartmental model with age-structure was proposed to quantify the time required to reverse resistance in a dengue vector mosquito. They introduced a 15 dimensional (five life stages for three genotypes) model and conducted numerical simulations to evaluate the loss of resistance, assuming that in the absence of insecticide, the resistant genotype has lower fitness.

Finally, some recent studies have emphasized the need for models to have an integrated analysis of various control strategies simultaneously. For example, (Li and Liu, 2020) proposed a model for control mosquito-borne diseases including insecticides and *Wolbachia*, a maternally inherited bacterium with the potential to reduce vector competence. However, the model proposed is limited to an insecticide susceptible mosquito population. Based on empirical evidence, models have been proposed that analyze the synergy between insecticide resistance in chemical control strategies for mosquito epidemics with the use of *Wolbachia* (Garcia et al., 2020).

2.1.3 The proposed modelling approach

Our goal in the present Chapter is to provide a class of simple models able to account for the evolution of resistance to larvicides and/or adulticides on an autosomal gene for an insect population, taking into account the life history complexity, and to show that

the latter possess key properties that we are entitled to expect from such models. This work is viewed as paving the way towards the construction of more complex ad hoc models, describing more involved situations and useful for various situations involving biological control of vectors. A typical example is the release of *Wolbachia* infected mosquitoes in presence of, possibly undesired, insecticide. Elaborating and analyzing release strategies for such situations requires a mix of population dynamics, population genetics and control theory. Work built up upon the models and analysis provided here, will be presented in a forthcoming Chapter.

Insects are diploid organisms with sexual reproduction and usually with several phases of life. In many cases the genes involved in insecticides resistance are autosomal and follow the principles of Mendelian inheritance. Furthermore, they have a pre-reproductive and a reproductive phases, and quite frequently, as in the case of holometabolism, the immature stages are well differentiated from the mature stages. In such cases the larvae do not compete with adults, since they are found in different ecological niches, and are consequently subject to different selective pressures —*e.g.* larvicides and adulticides factors. In response to the aforementioned, we propose:

- a continuous-time compartmental model based on a life history with two leading phases, a pre-reproductive and reproductive;
- a reproductive phase that includes a heredity function for Mendelian inheritance given by an autosomal gene;
- and selective pressures of larvicides and/or adulticides for each genotype that may affect fertility and density-dependent viability in each life phase.

The life cycle of an insect may be seen analogously to a sequence of chemical modifications that sustenance goes through. Like in a chemical reaction network (Klonowski, 1983), some stages of life are slower than others. This last feature opens up the possibility of using slow manifold theory to deduce simpler inheritance models. The modelling framework presented below is based on this principle. More precisely, according to whether the reproductive phase is fast or slow with respect to the pre-reproductive one, we obtain two distinct class of models. This simplification, achieved via slow manifold theory, yields two different classes of Mendelian inheritance models, which present density-dependent recruitment and mortality rates in a non-conventional way.

We show that these models fulfil several fundamental properties. Most importantly, in the absence of selection they evolve in compliance with the Hardy-Weinberg law; while in the presence of selection and in the dominant or codominant cases, they globally converge towards the disappearance of all genotypes except the fittest homozygous

one. Mendelian inheritance is easily incorporated into population dynamics in the modeling framework proposed here. This is achieved through inheritance matrices deduced from probability principles, allowing for modeling and analysis of the evolution in more complicated situations.

The Chapter is organized as follows. The modelling framework is presented in Section 2.2, departing from a general two life phase model. A single locus trait heredity function that formalizes Mendel's first law is described in Section 2.2.1. In Sections 2.2.2.1 and 2.2.2.2, slow manifold theory is used to deduce two classes of models describing the evolution of three genotypes of a population having inheritable attributes and density-dependent recruitment and mortality rates. These two classes correspond respectively to the limit of fast and slow reproductive phase. We extend in Section 2.3 the latter to two general classes of models, namely (**F**) (*Fast*) and (**S**) (*Slow*), which are studied afterwards. The assumptions necessary to this study are given in Section 2.3.1, and useful technical results are put in Section 2.3.2 (their proofs are in Appendix 2.8). Well-posedness of these models and other qualitative results are considered in Section 2.4.

The asymptotic behavior is then studied. The case where no fitness difference exists between the different genotypes is considered in Section 2.5. In this case, Hardy-Weinberg law is shown to hold for the considered classes of models (Theorem 2.13). In Section 2.6 is studied the case of dominant and codominant selection regimes. Asymptotic convergence to the homozygote with higher fitness is demonstrated in such conditions for models (**F**) and (**S**) (Theorem 2.14). Last, concluding remarks are made in Section 2.7.

2.2 Modelling

In this section is introduced the approach leading to the models. The latter is introduced in Section 2.3 and studied afterward We begin by listing some of the main constitutive hypotheses made to obtain these models of life history for a diploid population obeying Mendel's laws of inheritance and submitted to selection.

- No distinction is made between male and female individuals. In particular the fertility and mortality are considered identical for males and females. It is possible to consider this abstraction when the sex ratio is constant and absolute fitness is independent of sex.

- The mortality rates in each life phase are increasing functions of the population density.

- The fertility rates are constant, *i.e.* they are independent of the population density.
- The differences in fertility or mortality between different genotypes result from an artificial, stationary, modification of the environment *e.g.* by a constant lethal dose application of an insecticide.
- The differences in inheritable attributes that modify the fitness with respect to natality and mortality are determined by a unique autosomal locus.
- There are two different types of alleles in this locus, namely s and r.

In chemical control, the applied lethal dose of insecticide can vary over time, affecting fertility and mortality in different ways. In the models introduced in the sequel, we do not treat explicitly this time-dependence, and assume that to every given insecticide lethal dose density correspond fixed characteristic fertility and mortality. Once this dependence is modelled, describing intermittent application of insecticide is done by introducing time-dependence of the insecticide density. This aspect is not explored further in this Chapter, which instead focuses on asymptotic properties in stationary environment.

As a consequence of the setting of the two alleles in a single locus of a diploid population, we have three different genotypes, namely:

$$\{r, s\} \times \{r, s\} = \{(r, r), (s, r), (s, s)\}$$

as no difference exists between the genotypes (s, r) and (r, s). In the sequel, the index $i = 1, 2, 3$ will be used to identify the *genotypes*, while generally speaking the index $j = r, s$ will refer to the *alleles*. The latter are designated r, s as *resistant* and *susceptible*.

As mentioned before, we are interested in the representation of a population with two life phases. This depiction is quite straightforward for insects with complex life cycles, but covers broad distinctions like pre-reproductive phase, subject to food and space limitation, and reproductive phase with different niches and potential selective pressures. As a starting point to represent such life history, we begin with the following compartmental models:

$$\dot{L}_i = \alpha_i(F\hat{A}(t)) - \mu_i(v^\intercal L(t))L_i(t) - \nu_i L_i(t) \tag{2.1a}$$

$$\dot{\hat{A}}_i = \nu_i L_i(t) - \hat{\mu}_i(\hat{w}^\intercal \hat{A}(t))\hat{A}_i(t), \tag{2.1b}$$

for $i = 1, 2, 3$. The quantities L_i (*Larvae*) represent the density of genotypes ($i = 1, 2, 3$), in pre-reproductive phase, and $\hat{A}_i$ (*Adults*) the corresponding density of reproductive individuals. The parameters involved in (2.1) have the following meaning.

- The mortality functions μ_i and $\hat{\mu}_i$ depend on the density, through the use by a population of certain recourse, typically food or space. We assume that these mortality rates are all *increasing functions of the density*. On the other hand, we want to allow each genotype to have its proper consumption needs. This is done by introducing *weighted sums* $v^\intercal L$ and $\hat{w}^\intercal \hat{A}$ as argument of the functions μ_i and $\hat{\mu}_i$, for given *positive vectors* $v, \hat{w}$.

- The functions α_i account for the mechanism of Mendelian inheritance, presented in detail in Section 2.2.1; while, for positive f_i, $i = 1, 2, 3$, the diagonal matrix $F := \mathtt{diag}\{f_i\}$ represents multiplicative symmetry fertility rates of genotypes (Felsenstein, 2005). The "symmetry" here refers to the fact that the numbers of births resulting from a given genotypic crossing $i \times i'$ are identical whether females carry the genotype i and males the genotype i' or the opposite. Modeling of non-symmetric fertilities of mating pairs in one-locus genetics yields quite complicated models (Hofbauer and Sigmund, 1998).

- Last, the ν_i describe constant maturity rates from pre-reproductive to reproductive phase.

Defining $A := F\hat{A}$, that is $A_i := f_i \hat{A}_i$, system (2.1) rewrites as

$$\dot{L}_i = \alpha_i(A(t)) - \mu_i(v^\intercal L(t))L_i(t) - \nu_i L_i(t) \tag{2.2a}$$

$$\dot{A}_i = \hat{\nu}_i L_i(t) - \hat{\mu}_i(w^\intercal A(t))A_i(t), \tag{2.2b}$$

for $i = 1, 2, 3$, where by definition

$$\hat{\nu}_i := f_i \nu_i, \qquad w_i = f_i^{-1} \hat{w}_i. \tag{2.3}$$

2.2.1 Single locus trait inheritance

In this section, we present the heredity functions α_i used to model Mendelian inheritance. As already said, in this Chapter we consider a general diploid population composed of three genotypes and assume no distinction between male and female individuals.

We associate in the sequel to $A_1(t)$ (resp. $A_2(t)$, resp. $A_3(t)$) the density of individuals with genotype (r,r) (resp. (r,s), resp. (s,s)) at time t in the population: the two homozygous genotypes are represented by A_1 and A_3, while A_2 represents the heterozygous genotype.

Considering all possible crosses given random mating, the expected frequency of two allele combinations in a diploid population is obtained from a *Punnett Square* (Edwards, 2012) and is represented in the following table:

Offspring	♂ \ ♀	$A_1\,(r,r)$	$A_2\,(r,s)$	$A_3\,(s,s)$
(r,r)	A_1	1	1/2	0
	A_2	1/2	1/4	0
	A_3	0	0	0
(r,s)	A_1	0	1/2	1
	A_2	1/2	1/2	1/2
	A_3	1	1/2	0
(s,s)	A_1	0	0	0
	A_2	0	1/4	1/2
	A_3	0	1/2	1

Defining the vectors

$$u_r := \begin{pmatrix} 1 \\ \frac{1}{2} \\ 0 \end{pmatrix}, \quad u_s := \begin{pmatrix} 0 \\ \frac{1}{2} \\ 1 \end{pmatrix}, \quad \mathbf{1} := \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} = u_r + u_s, \tag{2.4}$$

the *relative frequency* of the genotype i, $i = 1,2,3$, in the offspring produced by the population density A is given by

$$\frac{(u_r^\intercal A)^2}{(\mathbf{1}^\intercal A)^2}, \qquad 2\frac{(u_r^\intercal A)(u_s^\intercal A)}{(\mathbf{1}^\intercal A)^2}, \qquad \frac{(u_s^\intercal A)^2}{(\mathbf{1}^\intercal A)^2}\,.$$

Making the normalization hypothesis that the total density of offsprings (of all genotypes) hatched by time unit equals the total density of adults of all genotypes, that is $\alpha_1(A) + \alpha_2(A) + \alpha_3(A) = A_1 + A_2 + A_3$ for any $A \in \mathbb{R}^3_+$, their genotypic density repartition is therefore given by:

$$\alpha_1(A) := \frac{(u_r^\intercal A)^2}{\mathbf{1}^\intercal A}, \qquad \alpha_2(A) := 2\frac{(u_r^\intercal A)(u_s^\intercal A)}{\mathbf{1}^\intercal A}, \qquad \alpha_3(A) := \frac{(u_s^\intercal A)^2}{\mathbf{1}^\intercal A}, \tag{2.5}$$

(see 2.8.1) or equivalently

$$\alpha_i(A) := \frac{1}{\mathbf{1}^\intercal A} A^\intercal G_i A, \qquad i = 1, 2, 3, \tag{2.6}$$

with *inheritance matrices* G_i, $i = 1, 2, 3$, defined by

$$G_1 = u_r u_r^\intercal = \begin{pmatrix} 1 & 1/2 & 0 \\ 1/2 & 1/4 & 0 \\ 0 & 0 & 0 \end{pmatrix},$$

$$G_2 = u_r u_s^\intercal + u_s u_r^\intercal = \begin{pmatrix} 0 & 1/2 & 1 \\ 1/2 & 1/2 & 1/2 \\ 1 & 1/2 & 0 \end{pmatrix},$$

$$G_3 = u_s u_s^\intercal = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 1/4 & 1/2 \\ 0 & 1/2 & 1 \end{pmatrix}.$$

We also define the operator $\alpha : \mathbb{R}^3_+ \setminus \{0_3\} \to \mathbb{R}^3_+ \setminus \{0_3\}$ as

$$\alpha(A) := \begin{pmatrix} \alpha_1(A) \\ \alpha_2(A) \\ \alpha_3(A) \end{pmatrix}. \tag{2.7}$$

Coming back to the initial setting of (2.2a), one sees that the expected frequency of the zygotes depend upon the crossings, through the diagonal matrix F multiplying the unnormalized vector of adult densities $\hat{A}$. This setting represents indeed symmetric multiplicative fertility (Felsenstein, 2005).

A quite similar matrix setting was introduced by Langemann *et al.* (Langemann et al., 2013) to model the evolution of herbicide resistance, in the case of single and multiple loci. It is well fitted to this purpose, with the G_i matrix materializing the inheritance mechanisms expressed by the first Mendel's Law (Law of Segregation of genes). Notice also that the outer product between the probability vectors $u_j u_{j'}^\intercal$ corresponds to the encounters of a sex with the opposite. Other inheritance mechanisms may be modelled in this framework, including mechanisms that involve multiple loci (Langemann et al., 2013).

2.2.2 Fast-slow models of population dynamics

The life history of organisms in general and insect in particular is quite different from one to the other. Some mature early and reproduce quickly, while others mature late and reproduce slowly. An extreme example is the arachnids *Adactylidium sp.*, which are born mature and, having hatched inside their mother, mate with their brothers (Elbadry and Tawfik, 1966; Gould, 2010). The insects *Ephemeroptera* constitute another extreme case: the life of an adult mayfly is very short and has essentially the primary function of reproduction (Welch, 1998).

We consider in the sequel the cases where one of the life phases is sensibly faster than the other one, in other words that a fast dynamics and a slow dynamics are present in (2.2). In such conditions, it is reasonable to expect that the fast variable in (2.2) should evolve rapidly and reach a unique equilibrium value, depending upon the value of the slow variable, as if the latter was frozen; and that the global evolution could be described by the evolution of the slow variable alone, taking for the fast one the previous equilibrium value. This heuristic, consisting in approximating the initial fast-slow system by a smaller slow system, may indeed be firmly justified, by applying singular perturbation methods (O'Malley Jr, 1991). The latter simplifies the dimension of the system analyzed and preserves the parameters and properties of the original system. Under adequate assumptions, when the equilibrium value is asymptotically stable, then the approximation holds on any finite time interval, and even on infinite time intervals when the slow system has an asymptotically stable equilibrium, see e.g. (Tikhonov et al., 1980; Carr, 2012) for details.

Depending on which of the phases is faster, applying singular perturbation yields two different classes of models. We show in Sections 2.2.2.1 (fast reproductive phase) and 2.2.2.2 (slow reproductive phase) how these two classes are obtained.

2.2.2.1 Fast reproductive phase population dynamics

We consider here the case of an organism with a reproductive phase faster than the pre-reproductive phase. As said before, the mortality rates are increasing, and this is specially true for $\hat{\mu}_i$ in (2.2b). Therefore, for any *fixed* L, equation (2.2b) possesses a unique, globally asymptotically stable, equilibrium $A(L)$, given implicitly by

$$0 = \hat{\nu}_i L_i - \hat{\mu}_i(w^\intercal A)A_i, \qquad i = 1, 2, 3\ . \tag{2.8}$$

Equation (2.8) yields the following algebraic relationship between L_i and A_i:

$$A_i = \frac{\hat{\nu}_i}{\hat{\mu}_i(w^\intercal A)} L_i, \qquad i = 1, 2, 3$$

which necessarily implies that $b := w^\intercal A$ fulfills the identity

$$b = \sum_{i=1}^{3} \frac{w_i \hat{\nu}_i}{\hat{\mu}_i(b)} L_i \tag{2.9}$$

Now, the mortality $\hat{\mu}_i$ is increasing with the total population, so for all $L \in \mathbb{R}^3_+ \setminus \{0\}$, the map

$$b \mapsto \sum_{i=1}^{3} \frac{w_i \hat{\nu}_i}{\hat{\mu}_i(b)} L_i \tag{2.10}$$

is decreasing and may be inverted, providing a unique solution, denoted $b^*(L)$, to equation (2.9). For any given nonnegative vector L, the unique solution of (2.8) is then given as

$$A_i = \frac{\hat{\nu}_i}{\hat{\mu}_i(b^*(L))} L_i, \qquad i = 1, 2, 3 \ . \tag{2.11}$$

In the limiting case where the duration of the mature phase is sensibly faster than the immature one, one may approximate equation (2.2) through slow manifold theory (O'Malley Jr, 1991), and the asymptotic evolution is then expressed by the algebro-differential system

$$\dot{L}_i = \alpha_i(A) - \mu_i(v^\intercal L) L_i - \nu_i L_i, \qquad A_i = \frac{\hat{\nu}_i}{\hat{\mu}_i(b^*(L))} L_i, \qquad i = 1, 2, 3 \ . \tag{2.12}$$

Defining for any nonnegative scalar b, $m_i(b) := \dfrac{\hat{\nu}_i}{\hat{\mu}_i(b)}$, one then ends up with the system

$$\dot{L}_i = \alpha_i \left(\mathtt{diag}\{m_i(b^*(L))\} L \right) - (\nu_i + \mu_i(v^\intercal L)) L_i, \qquad i = 1, 2, 3 \tag{2.13a}$$

where, for any $L \in \mathbb{R}^3_+$, $b^*(L)$ is defined implicitly by the identity:

$$b^*(L) = \sum_{i=1}^{3} w_i m_i(b^*(L)) L_i \ . \tag{2.13b}$$

In (2.13a), $\mathtt{diag}\{m_i(b^*(L))\}$ denotes the diagonal matrix formed with the scalar coefficients $m_i(b^*(L))$, $i = 1, 2, 3$. Notice that by construction the functions m_i present in (2.13) are *decreasing*. The scalar $b^*(L)$ represents the weighted density of adults $w^\intercal A$ corresponding to steady-state population L in pre-reproductive stage. There is no difficulty in expressing the functions and coefficients of system (2.13) in terms of

the initial problem (2.1), through the above formulas and the identities in (2.3).

2.2.2.2 Slow reproductive phase population dynamics

Consider now the opposite situation, of an reproductive phase comparatively much slow than the pre-reproductive one. In this case, the same argument than before leads similarly to consider instead of system (2.2) the algebro-differential model:

$$0 = \alpha_i(A) - \mu_i(v^\intercal L)L_i - \nu_i L_i, \qquad \dot{A}_i = \hat{\nu}_i L_i - \hat{\mu}_i(w^\intercal A)A_i, \qquad i = 1,2,3 \tag{2.14}$$

The algebraic relationship in equation (2.14) provides the identities

$$L_i = \frac{1}{\nu_i + \mu_i(v^\intercal L)}\alpha_i(A), \qquad i = 1,2,3 \tag{2.15}$$

and thus $b := v^\intercal L$ necessarily fulfils the condition:

$$b = \sum_{i=1}^{3} \frac{v_i}{\nu_i + \mu_i(b)}\alpha_i(A) \tag{2.16}$$

From the increasingness of the mortality functions, one deduces as before that, for all $A \in \mathbb{R}^3_+ \setminus \{0\}$, the right-hand side of (2.16) is decreasing, and this relation may thus be inverted. This operation yields a unique solution to equation (2.16), which is denoted $b^*(\alpha(A))$, using α defined in (2.7). With this, for any nonnegative A, (2.15) has a unique solution $L(A)$, which writes

$$L_i = \frac{1}{\nu_i + \mu_i(b^*(\alpha(A)))}\alpha_i(A), i = 1,2,3 \ .$$

Defining here for any nonnegative scalar b, (decreasing) functions $m_i(b) := \dfrac{\hat{\nu}_i}{\nu_i + \mu_i(b)}$, one obtains finally the model:

$$\dot{A}_i = \alpha_i(A)m_i(b^*(\alpha(A))) - \hat{\mu}_i(w^\intercal A)A_i, \quad i = 1,2,3 \tag{2.17a}$$

where, for any $A \in \mathbb{R}^3_+$, $b^*(A)$ is defined implicitly by

$$b^*(A) = \sum_{i=1}^{3} \frac{v_i}{\hat{\nu}_i} m_i(b^*(A))A_i \ . \tag{2.17b}$$

Equation (2.17) is quite similar to, but different from, equation (2.13) obtained in the case of a fast reproductive phase. Here, the scalar $b^*(A)$ is the weighted density $w^\intercal L$

of individuals in the pre-reproductive phase that corresponds to steady-state population A in reproductive stage. As in Section 2.2.2.1, there is no specific difficulty here in expressing the functions and coefficients of system (2.17) in terms of the initial problem (2.1), using the above transformations and the identities in (2.3).

As can be seen from the derivations of (2.13) and (2.17), monotonicity assumptions on the mortality rates are necessary, in order to obtain the perturbed systems. For this reason, we postpone the formal statement of the models studied in the sequel to Section 2.3, where all the assumptions are introduced.

2.3 Preliminaries

2.3.1 Assumptions

We now introduce the two general classes of equations studied in this Chapter. The latter extend in particular the systems (2.13) and (2.17) obtained previously as models for fast and slow reproductive phase populations. The notations are inspired from these preliminary examples and generalised.

We first introduce functions m_i and μ_i to model the *recruitment* and *mortality* rates, and v, w two vectors permitting to define their arguments. The following series of assumptions will be made on these objects.

Assumption 1. *For any $i = 1, 2, 3$, the functions $m_i : \mathbb{R}_+ \to \mathbb{R}_+$ are locally Lipschitz decreasing functions; the functions $\mu_i : \mathbb{R}_+ \to \mathbb{R}_+$ are locally Lipschitz increasing functions. The vectors $v, w \in \mathbb{R}^3$ have positive components.*

Assumption 1 assumes that the recruitment rates are decreasing functions, while the mortality rates are increasing functions, as is the case for the Verhulst logistic equation and other conventional population dynamics models. As a central consequence, this allows to give sense to the function b^* that naturally appeared in Sections 2.2.2.1 and 2.2.2.2, as shown by the following result, whose proof is in Appendix 2.8.2. The values v_i that appear in the statement are the components of the vector v introduced in Assumption 1.

Lemma 2.1. *Let Assumption 1 holds. Then, for any $x \in \mathbb{R}^3_+$, there exists a unique solution $b^*(x) \in \mathbb{R}_+$, to the scalar equation*

$$b = \sum_{i=1}^{3} v_i m_i(b) x_i. \tag{2.18}$$

Moreover, $b^*(x) > 0$ *if* $x \in \mathbb{R}^3_+ \setminus \{0_3\}$, $b^*(0_3) = 0$ *and* $b^* : \mathbb{R}^3_+ \to \mathbb{R}_+$ *has the same regularity than the functions* m_i.

As explained in Sections 2.2.2.1 and 2.2.2.2, for any density $x \in \mathbb{R}^3_+ \setminus \{0_3\}$, the scalar $b^*(x)$ in Lemma 2.1 represents the total effective density of individuals present in the other life stage, reached here infinitely fast. Notice that the map b^* depends upon the vector v.

With this done, we are finally in position to introduce the two classes of models studied in this Chapter. For any $x \in \mathbb{R}^3_+$ and $z \in \mathbb{R}_+$, define the *positive diagonal matrices* $M(x)$ and $\mu(z)$ by:

$$M(x) = \texttt{diag}\{m_i(b^*(x))\}, \qquad \mu(z) = \texttt{diag}\{\mu_i(z)\}.$$

The two classes of models we will be interested in are expressed as follows:

$$\dot{x} = \alpha(M(x)x) - \mu(w^\intercal x)x \ , \tag{\textbf{F}}$$

$$\dot{x} = M(\alpha(x))\alpha(x) - \mu(w^\intercal x)x \ . \tag{\textbf{S}}$$

Equations (**F**) and (**S**) can be described as a class of inheritance models where population dynamics is governed by density-dependent recruitment and mortality. The first terms in the right hand side of these equations models recruitment, while the second term models mortality. Conventional population dynamics models implicitly assume that all individuals have on average the same fertility and viability. However, it is clear that this condition may vary according to heritable traits, *e.g.* resistance to an insecticide. The class of inheritance models proposed generalizes a conventional population dynamics system for the case of three genotypes governed by a locus, such that selective pressure can affect recruitment or mortality.

Recall that the map α is defined in (2.7). In developed form, these equations write respectively

$$\dot{x}_1 = \frac{(u_r^\intercal M(x)x)^2}{\mathbf{1}^\intercal M(x)x} - \mu_1(w^\intercal x)x_1 \tag{\textbf{F.a}}$$

$$\dot{x}_2 = 2\frac{(u_r^\intercal M(x)x)(u_s^\intercal M(x)x)}{\mathbf{1}^\intercal M(x)x} - \mu_2(w^\intercal x)x_2 \tag{\textbf{F.b}}$$

$$\dot{x}_3 = \frac{(u_s^\intercal M(x)x)^2}{\mathbf{1}^\intercal M(x)x} - \mu_3(w^\intercal x)x_3 \tag{\textbf{F.c}}$$

and

$$\dot{x}_1 = \frac{(u_r^\intercal x)^2}{\mathbf{1}^\intercal x} m_1(b^*(\alpha(x))) - \mu_1(w^\intercal x)x_1 \tag{S.a}$$

$$\dot{x}_2 = 2\frac{(u_r^\intercal x)(u_s^\intercal x)}{\mathbf{1}^\intercal x} m_2(b^*(\alpha(x))) - \mu_2(w^\intercal x)x_2 \tag{S.b}$$

$$\dot{x}_3 = \frac{(u_s^\intercal x)^2}{\mathbf{1}^\intercal x} m_3(b^*(\alpha(x))) - \mu_3(w^\intercal x)x_3 \ . \tag{S.c}$$

Manifestly, equations (**F**) and (**S**) contain as particular cases the equations (2.13) and (2.17), obtained by applying singular perturbation to the normalized system (2.1). One shows easily that the system (2.13) that emerged in the case of fast reproductive phase (Section 2.2.2.1) is system (**F**) with the recruitment rates m_i and the mortality rates μ_i

$$\frac{f_i\nu_i}{\hat{\mu}_i(\cdot)} \qquad \text{and} \qquad \nu_i + \mu_i(\cdot) \ .$$

The variable x represents the pre-adult populations in the original model. On the other hand, system (2.17) appeared in the slow reproductive phase (Section 2.2.2.2) corresponds to (**S**) with recruitment and mortality rates

$$\frac{f_i\nu_i}{\nu_i + \mu_i(\cdot)} \qquad \text{and} \qquad \hat{\mu}_i(\cdot) \ ,$$

and x now represents the adult populations. Expressed in terms of the coefficients of the starting model (2.1), the recruitment rate in systems (2.13) and (2.17) depends jointly upon the genotype fertility f_i, the maturation rate ν_i and the density-dependent mortality in the corresponding life phase.

The population dynamics under selective pressure (in adaptation) implies a difference in fitness between genetically distinct individuals, either in the recruitment or mortality rate. The following supplementary assumptions will be used to study adaptation.

Assumption 2. *The functions m_i, μ_i satisfy*

$$\forall x \in \mathbb{R}^3_+, \quad m_1(b^*(x)) \geq m_2(b^*(x)) \geq m_3(b^*(x)) \qquad \textit{and} \qquad \forall z \geq 0, \quad \mu_1(z) \leq \mu_2(z) \leq \mu_3(z) \tag{2.19}$$

Moreover, for any $x \in \mathbb{R}^3_+$,

- $m_1(b^*(x)) - m_3(b^*(x)) + \mu_3(w^\intercal x) - \mu_1(w^\intercal x) > 0$ *for system* (**F**)*;*
- $m_1(b^*(\alpha(x))) - m_3(b^*(\alpha(x))) + \mu_3(w^\intercal x) - \mu_1(w^\intercal x) > 0$ *for system* (**S**)*.*

Assumption 3. *The following inequality holds*

$$m_1(0) > \mu_1(0) \tag{2.20}$$

Assumption 4. *For any $x \in \mathbb{R}^3_+ \setminus \{0_3\}$, the following limits exist and satisfy*

$$0 \leq \lim_{\lambda \to +\infty} m_i(\lambda x) < \lim_{\lambda \to +\infty} \mu_i(\lambda) \leq +\infty, \qquad i = 1, 2, 3. \tag{2.21}$$

Assumption 2 imposes a relative ordering of the fitnesses of the three genotypes, associated with corresponding increasing mortality rates or decreasing recruitment rates.Two distinct important situations are covered: the cases of *codominance* or *incomplete dominance*, when the fitness of the two homozygotes and of the heterozygote are strictly ordered according to (2.19) —*e.g.* $m_1 > m_2 > m_3$ and $\mu_1 < \mu_2 < \mu_3$); and the case of *dominance*, where the heterozygote has the same fitness than one of the two homozygotes —*e.g.* $m_1 = m_2 = m_3$, and $\mu_1 < \mu_2 = \mu_3$ or $\mu_1 = \mu_2 < \mu_3$; or $\mu_1 = \mu_2 = \mu_3$, and $m_1 > m_2 = m_3$ or $m_1 = m_2 > m_3$. Notice that the *selectively neutral* case, where the fitness of all genotypes is equal, is excluded by the positivity requirement contained in Assumption 2.

Assumption 3 ensures that at least genotype 1, with highest fitness, is viable. Last, Assumption 4 indicates that in any sufficiently large population, the mortality rates are greater than the recruitment rates for each genotype, and this overpopulation effect will limit the population growth.

2.3.2 Technical lemmas

Before proceeding to the analysis of results in Section 2.4, we now state now two technical lemmas useful in the sequel. By definition, e_i, $i = 1, 2, 3$, represents the ith unit vector of $\mathbb{R}^3$.

Lemma 2.2. *For any $x \in \mathbb{R}^3_+ \setminus \{0_3\}$ and any $\lambda > 0$, the following properties are fulfilled*

1. $u_j^\intercal \alpha(x) = u_j^\intercal x, \ j = r, s;$
2. $\mathbf{1}^\intercal \alpha(x) = \mathbf{1}^\intercal x;$
3. $\alpha(\lambda x) = \lambda \alpha(x);$
4. $\alpha(e_i) = e_i, \ i = 1, 3.$

Recall that the map α is defined in (2.7), and that the vectors u_r, u_s and $\mathbf{1}$ come from (2.72). We explain now the meaning of these properties. Point 1 manifests that the density of each allele hatched per time unit is equal to its density, as a consequence of the mechanisms of Mendelian inheritance, and therefore the same property holds for the global population (Point 2). This is a consequence of the normalization exposed in Section 2.2.1. Point 3 indicates that the operator α is *homogeneous of degree 1*: the zygote repartition in the offspring only depends upon the zygotic *proportion* of adults, while the offspring birth density is proportional to the adult density. Last, Point 4 states that a homogeneous population of one of the homozygotes only gives birth to homozygotes of the same genotype.

Lemma 2.3. *Let $x \in \mathbb{R}^3_+ \setminus \{0\}$.*

1. *The following properties are satisfied*

$$\lim_{\lambda \to +\infty} b^*(\lambda x) = +\infty, \tag{2.22}$$

$$\lim_{\lambda \to +\infty} m_i(b^*(\lambda x)) < \lim_{\lambda \to +\infty} \mu_i(\lambda), \quad i = 1, 2, 3. \tag{2.23}$$

   Moreover, for both limits the convergence is uniform in the set $\{x \in \mathbb{R}^3_+ : w^\intercal x = 1\}$.

2. *The map $\lambda \mapsto b^*(\lambda x)$ is increasing on $[0, +\infty)$.*

Proofs of Lemmas 2.2 and 2.3 are given in Appendices 2.8.3 and 2.8.4. Point 1 indicates that, for any population x of the slow phase, the population $b^*(\lambda x)$ of the fast phase grows unbounded when λ goes to infinity; and that, the birth rate $m_i(b^*(\lambda x))$ in the slow life stage i is smaller than the mortality rate $\mu_i(\lambda)$ when λ goes to infinity. Both these properties are uniform with respect to the genotypic repartition in the population x. Point 1 states that the map, for given slow phase population x, the fast phase population $b^*(\lambda x)$ increases with λ. Notice however that the map $x \mapsto b^*(x)$ itself is not increasing.

2.4 Well-posedness and qualitative results

We provide here the first results concerning the solutions of systems (**F**) and (**S**). Firsst, we prove well-posedness of these systems of nonlinear ordinary differential equations is proved in Section 2.4.1. The qualitative properties that relate to the existence of

monomorphic and *polymorphic states*, and *trajectories* are studied in section 4.2. Last, we show in Section 2.4.3 that quite natural notions of *mean allelic recruitment rate* and *mean allelic mortality rate* may be introduced for each system, which will prove quite useful in establishing the forthcoming asymptotic results.

2.4.1 Well-posedness of the models

Well-posedness for the models (**F**) and (**S**) is supplied by the following statement.

Theorem 2.4 (Well-posedness and boundedness of the solutions)**.** *Assume Assumption* 1 *is fulfilled. Then, for any nonnegative initial condition, there exists a unique solution* x *of* (**F**)*, resp.* (**S**)*, on* $[0, +\infty)$*, continuous with respect to the initial condition. Its coordinates are nonnegative for any* $t \geq 0$*.*

If moreover Assumption 4 *is fulfilled, then*

$$0 \leq \liminf_{t\to+\infty} \mathbf{1}^\intercal x(t) \leq \limsup_{t\to+\infty} \mathbf{1}^\intercal x(t) \leq c^*_{\mathbf{F}}, \qquad \textit{resp. } c^*_{\mathbf{S}} \tag{2.24}$$

where by definition $c^*_{\mathbf{F}}$*, resp.* $c^*_{\mathbf{S}}$*, is the largest* $c \geq 0$ *such that*

$$\begin{aligned} \max\left\{ \max_i \frac{m_i(b^*(cx))}{\mu_i(c)} \ : \ w^\intercal x = 1 \right\} \leq 1, \\ \textit{resp. } \max\left\{ \max_i \frac{m_i(b^*(c\alpha(x)))}{\mu_i(c)} \ : \ w^\intercal x = 1 \right\} \leq 1 \end{aligned} \tag{2.25}$$

Formula (2.24) guarantees that the unique solution corresponding to a given initial condition, takes on nonnegative values and is asymptotically bounded from above by a constant value, independent of the trajectory. Inequality (2.25) provides an estimate of this bound. This differs from the conventional dynamics for Mendelian populations continuous model —see Chapters 19 and 22 in (Hofbauer and Sigmund, 1998), in which the population is governed by a Malthusian fitness and goes exponentially towards infinity together with all alleles of the gene pool.

Proof.

• The equations (**F**) and (**S**) are meaningful as soon as Assumption 1 holds, as the latter permits to define b^* (through Lemma 2.1). The well-posedness of both systems comes from the Lipschitzness of their right-hand side. The fact that the trajectories do not escape the nonnegative quadrant comes from the fact that $\dot{x}_i(t) \geq 0$ whenever $x_i(t) = 0$, $i = 1, 2, 3$.

• We first demonstrate that the definition of $c^*_{\mathbf{F}}$ as stated in the statement is meaningful. Indeed, for any $x \in \mathbb{R}^3_+ \setminus \{0_3\}$, due to Lemma 2.3 the map

$$c \mapsto \max_{i=1,2,3} \frac{m_i(b^*(cx))}{\mu_i(c)}$$

is decreasing and, due to Assumption 4, it satisfies:

$$\lim_{c\to+\infty} \max_{i=1,2,3} \frac{m_i(b^*(cx))}{\mu_i(c)} < 1.$$

As the convergence of this limit is uniform in the set $\{x \in \mathbb{R}^3_+ : w^\intercal x = 1\}$, the map

$$c \mapsto \max\left\{ \max_{i=1,2,3} \frac{m_i(b^*(cx))}{\mu_i(c)} : w^\intercal x = 1 \right\}$$

admits values smaller than 1 for sufficiently large $c > 0$. Therefore, $c^*_{\mathbf{F}}$ as given in the statement is well defined, too.

Slight adaptation of the same argument demonstrates that $c^*_{\mathbf{S}}$ too is well defined.

• Summing up the three equations in (**F**), we have

$$\begin{aligned}
\mathbf{1}^\intercal \dot{x} &= \mathbf{1}^\intercal \alpha(M(x)x) - \mathbf{1}^\intercal \mu(w^\intercal x)x \\
&= \mathbf{1}^\intercal M(x)x - \mathbf{1}^\intercal \mu(w^\intercal x)x \qquad \text{(by Property } \textit{2} \text{ in Lemma 2.2)} \\
&= \sum_{i=1}^{3} (m_i(b^*(x)) - \mu_i(w^\intercal x))x_i \\
&\leq \left(\max_i \{m_i(b^*(x)) - \mu_i(w^\intercal x)\} \right) \mathbf{1}^\intercal x, \quad i = 1, 2, 3.
\end{aligned}$$

The vector $\frac{x}{w^\intercal x} = 1$ is normalised, in the sense that $w^\intercal \frac{x}{w^\intercal x} = 1$. As $m_i(b^*(x)) = m_i(b^*(w^\intercal x \frac{x}{w^\intercal x}))$, one gets by definition of $c^*_{\mathbf{F}}$ that $\max_i\{m_i(b^*(x)) - \mu_i(w^\intercal x)\} < 0$ whenever $w^\intercal x > c^*_{\mathbf{F}}$.

Essentially the same argument provides the corresponding result for system (**S**), and this proves (2.24) and (2.25), and achieves the demonstration of Theorem 2.4. □

2.4.2 Monomorphism and polymorphism

Variability is essential for the selection to operate in a population. With this in mind, we introduce some related notions.

Definition 2.5 (Monomorphic, polymorphic and "holomorphic" states)**.** *A* nonzero *population state $x \in \mathbb{R}^3_+$ is called* monomorphic *if it consists of a single homozygous*

genotype, that is $x = ce_i$ *for* $i = 1$ *or* 3 *and a certain* $c > 0$*. Otherwise it is called* polymorphic*, and "holomorphic" if all the genotypes are present.*

We exhibit now the possible values of a homozygous equilibrium point.

Lemma 2.6 (Monomorphic equilibria)**.** *Assume Assumptions* 1 *and* 4 *are fulfilled. For any* $i \in \{1, 3\}$*,* $c_i^* e_i$ *is a monomorphic equilibrium, where*

- *If* $m_i(0) > \mu_i(0)$*,* $c_i^* \in \mathbb{R}_+$ *is the unique positive solution to the scalar equation*

$$m_i(b^*(c_i e_i)) = \mu_i(c_i w_i) \ . \tag{2.26}$$

- *If* $m_i(0) \leq \mu_i(0)$*, we let* $c_i^* := 0$*.*

Recall that e_i denotes the ith unit vector.

Proof. Notice that the functions defined on $\mathbb{R}^+$ by $c \mapsto m_i(b^*(ce_i))$, $i = 1, 2, 3$, are decreasing, due to Assumption 1 and property *2* in Lemma 2.3, while the functions $c \mapsto \mu_i(cw_i)$, $i = 1, 2, 3$, are increasing. Therefore for $m_i(0) > \mu_i(0)$, (2.26) admits a unique, positive, solution. □

The following lemma shows that the trajectories of (**F**) and (**S**) initially originated from a monomorphic population converge to the corresponding monomorphic equilibrium.

Lemma 2.7 (Monomorphic trajectories)**.** *Assume Assumptions* 1 *and* 4 *are fulfilled. Then any trajectory originating from a monomorphic state, say of homozygote* $i \in \{1, 3\}$*, stays monomorphic and converges towards the corresponding equilibrium point* $c_i^* e_i$*, with* c_i^* *given by Lemma* 2.6*.*

The positive numbers c_i^* represent the carrying capacities corresponding to each monomorphic homozygous population.

Proof. Clearly when only one allele is initially present, *i.e.* when the heterozygous genotype and one of the two homozygous ones are initially absent, this property remains true throughout time. The dynamics of (**F**) or (**S**) then occurs in the one-dimensional space that corresponds to this homozygous genotype, and it is easily shown that the evolution obeys the law:

$$\dot{x}_i = \Big(m_i(b^*(x_i e_i)) - \mu_i(w_i x_i)\Big)\, x_i \ .$$

In the case where c_i^* is such that $m_i(b^*(c_i^* e_i)) - \mu_i(w_i c_i^*) = 0$, that is when $i = 1$, or when $i = 3$ and $m_3(0) > \mu_3(0)$, then c_i^* is the unique globally asymptotically stable equilibrium of this system.

When $m_3(0) \leq \mu_3(0)$, all trajectories converge towards the globally asymptotically equilibrium $0 = c_3^* e_3$, as in this case $c_3^* = 0$. □

We now consider trajectories of (**F**) and (**S**) such that $u_r^\intercal x(0) \neq 0$ *and* $u_s^\intercal x(0) \neq 0$. The following result shows that in such cases all alleles, *but also all genotypes*, are present for positive times: extinction of a genotype (in the selection case) may only occur asymptotically in time. In other words, *polymorphic* trajectories are also "holomorphic" trajectories: immediately after the initial time, they contain all genotypes.

Lemma 2.8 (Polymorphic trajectories)**.** *Assume Assumption* 1 *is fulfilled. Then for any trajectory such that* $u_r^\intercal x(0) \neq 0$ *and* $u_s^\intercal x(0) \neq 0$*, we have*

$$\forall t > 0, \qquad x_i(t) > 0, \qquad i = 1, 2, 3 \ . \tag{2.27}$$

Proof of Lemma 2.8. If $x_i(0) = 0$ for $i = 1$ or 3, and $x_2(0) > 0$, then the corresponding derivative $\dot{x}_i$ is positive at time $t = 0$, and thus x_i takes on positive values at the right of 0. Similarly, if $x_i(0) > 0$ for $i = 1$ and 3, and $x_2(0) = 0$, the same occurs for the derivative $\dot{x}_2$, and x_2 is also positive at the right of 0.

On the other hand, one sees that, for any $t \geq 0$ and $i = 1, 2, 3$,

$$\dot{x_i} \geq -\mu_i(w^\intercal x) x_i \ .$$

Therefore

$$\forall t \geq t' \geq 0, \ x_i(t) \geq x_i(t') \ \exp\left(- \int_{t'}^{t} \mu_i(w^\intercal x(s)) \ \mathrm{d}s \right)$$

which is positive whenever $x_i(t') > 0$. This establishes the desired inequality. □

In view of Lemma 2.8, we put

Definition 2.9 (Polymorphic trajectories)**.** *Any trajectory such that* $u_r^\intercal x(0) \neq 0$ *and* $u_s^\intercal x(0) \neq 0$ *is called a* polymorphic trajectory.

Due to Lemma 2.8, any polymorphic trajectory is constituted of holomorphic states, except possibly at its initial point.

2.4.3 Mean allelic mortality and recruitment rates

In order to study selection in Section 2.6, we associate here to each of the systems (**F**) and (**S**) two *mean allelic rates*, which are defined *at any polymorphic state*. Due

to Lemma 2.8 and property *1* in Lemma 2.2, these rates are well defined along any polymorphic trajectory.

Definition 2.10 (Mean allelic mortality and recruitment rates)**.**
• **System (F).** *For any polymorphic state* $x \in \mathbb{R}^3_+$*, define the* mean allelic recruitment rates $\tilde{m}_{\mathbf{F},j}(x)$*:*

$$\tilde{m}_{\mathbf{F},j}(x) := \frac{u_j^\intercal M(x)x}{u_j^\intercal x}, \qquad j = r, s \tag{2.28a}$$

and the mean allelic mortality rates $\tilde{\mu}_{\mathbf{F},j}(x)$*:*

$$\tilde{\mu}_{\mathbf{F},j}(x) := \frac{u_j^\intercal \mu(w^\intercal x)x}{u_j^\intercal x}, \qquad j = r, s. \tag{2.28b}$$

• **System (S).** *For any polymorphic state* $x \in \mathbb{R}^3_+$*, define the* mean allelic recruitment rates $\tilde{m}_{\mathbf{S},j}(x)$*:*

$$\tilde{m}_{\mathbf{S},j}(x) := \frac{u_j^\intercal M(\alpha(x))\alpha(x)}{u_j^\intercal x}, \qquad j = r, s \tag{2.29a}$$

and the mean allelic mortality rates $\tilde{\mu}_{\mathbf{S},j}(x)$*:*

$$\tilde{\mu}_{\mathbf{S},j}(x) := \frac{u_j^\intercal \mu(w^\intercal x)x}{u_j^\intercal x}, \qquad j = r, s. \tag{2.29b}$$

The fundamental interest of the previous definitions is to allow writing the evolution of the allelic populations *along any polymorphic trajectory* as:

$$\begin{aligned} u_j^\intercal \dot{x} &= u_j^\intercal \left(\alpha(M(x)x) - \mu(w^\intercal x)x\right) = u_j^\intercal M(x) - \tilde{\mu}_{\mathbf{F},j}(x) u_j^\intercal x \\ &= \left(\tilde{m}_{\mathbf{F},j}(x) - \tilde{\mu}_{\mathbf{F},j}(x)\right) u_j^\intercal x, \qquad j = r, s \end{aligned} \tag{2.30a}$$

for system (**F**); and similarly for system (**S**):

$$\begin{aligned} u_j^\intercal \dot{x} &= u_j^\intercal \left(M(\alpha(x))\alpha(x) - \mu(w^\intercal x)x\right) = \left(\frac{u_j^\intercal M(\alpha(x))\alpha(x)}{u_j^\intercal \alpha(x)} - \tilde{\mu}_{\mathbf{S},j}(x)\right) u_j^\intercal x \\ &= \left(\tilde{m}_{\mathbf{S},j}(x) - \tilde{\mu}_{\mathbf{S},j}(x)\right) u_j^\intercal x, \qquad j = r, s. \end{aligned} \tag{2.30b}$$

(Property *1* of Lemma 2.2 was used in the previous deductions).

A key characteristic of the mean rates introduced in Definition 2.10 is summarized in the following lemma.

Lemma 2.11 (Ordering of the mean allelic rates)**.** *Assume Assumptions* 1 *and* 2 *are*

fulfilled. Then for any polymorphic state $x \in \mathbb{R}^3_+$, one has

$$m_1(b^*(x)) \geq \tilde{m}_{\mathbf{F},r}(x) \geq m_2(b^*(x)) \geq \tilde{m}_{\mathbf{F},s}(x) \geq m_3(b^*(x)) \ , \tag{2.31a}$$

$$m_1(b^*(\alpha(x))) \geq \tilde{m}_{\mathbf{S},r}(x) \geq m_2(b^*(\alpha(x))) \geq \tilde{m}_{\mathbf{S},s}(x) \geq m_3(b^*(\alpha(x))) \tag{2.31b}$$

and

$$\mu_1(w^\mathsf{T}x) \leq \tilde{\mu}_{\mathbf{F},r}(x) \leq \mu_2(w^\mathsf{T}x) \leq \tilde{\mu}_{\mathbf{F},s}(x) \leq \mu_3(w^\mathsf{T}x) \ , \tag{2.32a}$$

$$\mu_1(w^\mathsf{T}x) \leq \tilde{\mu}_{\mathbf{S},r}(x) \leq \mu_2(w^\mathsf{T}x) \leq \tilde{\mu}_{\mathbf{S},s}(x) \leq \mu_3(w^\mathsf{T}x) \tag{2.32b}$$

Proof. For some $j \in \{r, s\}$ consider *e.g.* the map $\tilde{\mu}_{\mathbf{F},j}$. One has

$$\tilde{\mu}_{\mathbf{F},j}(x) := \frac{u_j^\mathsf{T}\mu(w^\mathsf{T}x)x}{u_j^\mathsf{T}x}$$

and thus

$$\tilde{\mu}_{\mathbf{F},1}(x) = \frac{\mu_1(w^\mathsf{T}x)x_1 + \frac{1}{2}\mu_2(w^\mathsf{T}x)x_2}{x_1 + \frac{1}{2}x_2}, \qquad \tilde{\mu}_{\mathbf{F},3}(x) = \frac{\mu_3(w^\mathsf{T}x)x_3 + \frac{1}{2}\mu_2(w^\mathsf{T}x)x_2}{x_1 + \frac{1}{2}x_2}$$

and Assumption 2 yields immediately (2.32a). The three other formulas are proved in the same way. □

2.5 Analysis of the selectively neutral case

An inheritable variant is selectively neutral when the phenotypic manifestations of certain mutant alleles are equivalent to those of the wild type allele in their fitness (fertility and viability). Neutrality is considered the null hypothesis of evolution in the study of adaptation (Duret, 2008), since when this is not fulfilled, the selection operates.

We consider here the *selectively neutral* case, where recruitment and mortality rates are identical for all genotypes. Write in this case $\mu_{\text{sn}} := \mu_i$, $m_{\text{sn}} := m_i$ for $i = 1, 2, 3$. In particular, Assumption 2 doesn't hold here. As a consequence of Assumption 1, m_{sn} is decreasing and μ_{sn} increasing. Equation (2.18) here writes

$$b = m_{\text{sn}}(b)v^\mathsf{T}x$$

and its unique scalar solution clearly depends upon x only through the quantity $v^\mathsf{T}x$. To emphasize this fact, it is denoted $b_{\text{sn}}(v^\mathsf{T}x)$, rather than $b^*(x)$. As a direct consequence

of Lemma 2.1, $b_{\rm sn}$ is null at zero and takes on positive values otherwise. Also, it comes from the second point of Lemma 2.3 that $b_{\rm sn}$ is increasing. The following result for (**F**) and (**S**) then presents no difficulty.

Lemma 2.12. *Assume Assumptions* 1, 3 *and* 4 *are fulfilled. For any* $x \in \mathbb{R}^3_+ \setminus \{0\}$, *there exists a unique solution, denoted* $c^*_{\rm sn}(x)$ *in the sequel, of the equation*

$$m_{\rm sn}(b_{\rm sn}(cv^\intercal x)) = \mu_{\rm sn}(cw^\intercal x). \tag{2.33}$$

The latter is such that the vector $c^*_{\rm sn}(x)x$ *is an equilibrium.*

Proof. Due to Assumption 1, the map $c \mapsto m_{\rm sn} \circ b_{\rm sn}(cv^\intercal x)$ is decreasing, while the map $c \mapsto \mu_{\rm sn}(cw^\intercal x)$ is increasing. On the other hand, $m_{\rm sn}(b_{\rm sn}(0)) = m_{\rm sn}(0) > \mu_{\rm sn}(0)$ from Assumption 3; and $0 \leq \lim_{z\to+\infty} m_{\rm sn}(z) < \lim_{z\to+\infty} \mu_{\rm sn}(z) \leq +\infty$ due to Assumption 4. This demonstrates Lemma 2.12. □

Both systems (**F**) and (**S**) now reduce to the equation

$$\dot{x} = m_{\rm sn}(b_{\rm sn}(v^\intercal x))\alpha(x) - \mu_{\rm sn}(w^\intercal x)x \ . \tag{2.34}$$

The asymptotic behaviour of the solutions of (2.34) is completely described by the following fundamental result. In particular, its proof makes clear that the total population follows a variant of Verhulst's logistic growth equation (Wilson and Bossert, 1971).

Theorem 2.13 (The Hardy-Weinberg law in selectively neutral evolution)**.** *Assume Assumptions* 1, 3 *and* 4 *are fulfilled, and that the recruitment and mortality rates are the same for all genotypes. Then for any nonzero initial condition, the solutions of* (**F**), *resp.* (**S**), *satisfy*

$$\forall t \geq 0, \ \frac{u_j^\intercal x(t)}{\mathbf{1}^\intercal x(t)} = \frac{u_j^\intercal x(0)}{\mathbf{1}^\intercal x(0)} := p_j, \qquad j = r, s \tag{2.35}$$

where $p_r + p_s = 1$, *and*

$$\lim_{t\to+\infty} x(t) = c^*_{\rm sn}(p)\, p \tag{2.36}$$

for $c^*_{\rm sn}$ *defined in Lemma* 2.12 *and the vector* p *defined by* $p^\intercal := (p_r^2 \ \ 2p_rp_s \ \ p_s^2)$.

As is clear from the statement, Assumption 2, which implies fitness ordering, is *not* made here. Theorem 2.13 establishes that in absence of asymmetric fitness among genotypes, systems (**F**) and (**S**) fulfill the Hardy-Weinberg principle: the allele frequencies remain constant over time and determine the asymptotic genotype frequencies, see

(2.35), while the total density of individuals converges to the unique population level, defined by the solution of (2.33), which forms the carrying capacity for this relative frequency. This is a “null model" of the behavior of genes frequency in a population (Freeman and Herron, 2007), obtained as a consequence of the random mating and the absence of selection in the population.

Proof of Theorem 2.13. • For any $j = r, s$, one has

$$u_j^\intercal \dot{x} = u_j^\intercal \left(m_{\mathrm{sn}}(b_{\mathrm{sn}}(v^\intercal x))\alpha(x) - \mu_{\mathrm{sn}}(w^\intercal x)x\right) = \Big(m_{\mathrm{sn}}(b_{\mathrm{sn}}(v^\intercal x)) - \mu_{\mathrm{sn}}(w^\intercal x)\Big)\, u_j^\intercal x$$

using property *1* in Lemma 2.2. Therefore

$$\mathbf{1}^\intercal \dot{x} = (u_r + u_s)^\intercal \dot{x} = (m_{\mathrm{sn}}(b_{\mathrm{sn}}(v^\intercal x)) - \mu_{\mathrm{sn}}(w^\intercal x))\mathbf{1}^\intercal x$$

The two ratios $\dfrac{u_j^\intercal x(t)}{\mathbf{1}^\intercal x(t)}$ are defined for any $t \geq 0$ and differentiable with respect to time, with

$$\begin{aligned}\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{u_j^\intercal x}{\mathbf{1}^\intercal x}\right) &= \frac{(u_j^\intercal \dot{x})(\mathbf{1}^\intercal x) - (u_j^\intercal x)(\mathbf{1}^\intercal \dot{x})}{(\mathbf{1}^\intercal x)^2} \\ &= (m_{\mathrm{sn}}(b_{\mathrm{sn}}(v^\intercal x)) - \mu_{\mathrm{sn}}(w^\intercal x))\frac{(u_j^\intercal x)(\mathbf{1}^\intercal x) - (u_j^\intercal x)(\mathbf{1}^\intercal x)}{(\mathbf{1}^\intercal x)^2} = 0\end{aligned}$$

which yields (2.35) by integration.

• One now studies the evolution of the components of the vector x. ite One may rewrite formally (2.34) as

$$\dot{x} = \hat{m}(t)\alpha(x) - \hat{\mu}(t)x \tag{2.37}$$

where for simplicity we put the scalar functions $\hat{m}(t) := m_{\mathrm{sn}}(b_{\mathrm{sn}}(v^\intercal x(t)))$ and $\hat{\mu}(t) := \mu_{\mathrm{sn}}(w^\intercal x(t))$. Using (2.35), which has just been demonstrated, one may write, *for any* $t \geq 0$,

$$\alpha(x(t)) = \frac{1}{\mathbf{1}^\intercal x(t)} \begin{pmatrix} (u_r^\intercal x(t))^2 \\ 2(u_r^\intercal x(t))(u_s^\intercal x(t)) \\ (u_s^\intercal x(t))^2 \end{pmatrix} = (\mathbf{1}^\intercal x(t))p,$$

for the vector p defined in the statement. Consequently, one obtains from (2.37) the

identities:

$$\begin{aligned}\forall t \geq 0,\ \hat{m}(t)(\mathbf{1}^{\mathsf{T}} x(t)) &= \frac{1}{p_r^2}\left(\dot{x}_1 + \hat{\mu}(t)x_1(t)\right) \\ &= \frac{1}{2p_r p_s}\left(\dot{x}_2 + \hat{\mu}(t)x_2(t)\right) \\ &= \frac{1}{p_s^2}\left(\dot{x}_3 + \hat{\mu}(t)x_3(t)\right)\end{aligned}$$

One then deduces that

$$\frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{x_1}{p_r^2} - \frac{x_2}{2p_r p_s}\right) + \hat{\mu}(t)\left(\frac{x_1}{p_r^2} - \frac{x_2}{2p_r p_s}\right) = \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{x_3}{p_s^2} - \frac{x_2}{2p_r p_s}\right) + \hat{\mu}(t)\left(\frac{x_3}{p_s^2} - \frac{x_2}{2p_r p_s}\right) = 0\ . \tag{2.38}$$

The function $\hat{\mu}(t)$ is uniformly bounded from below by a positive constant on the set $\{x \in \mathbb{R}^3_+\ :\ \mathbf{1}^{\mathsf{T}} x \leq c^*\}$, due to Theorem 2.4. Thus $\int_0^{+\infty} \hat{\mu}(t)\ dt = +\infty$, and one deduces by integration of (2.38) that the limits in the following formula exist, and consequently that the identities themselves are true:

$$\lim_{t\to+\infty}\left(\frac{x_1(t)}{p_r^2} - \frac{x_2(t)}{2p_r p_s}\right) = \lim_{t\to+\infty}\left(\frac{x_3(t)}{p_s^2} - \frac{x_2(t)}{2p_r p_s}\right) = 0\ .$$

Therefore, the evolution occurs asymptotically on the half-line

$$\left\{x \in \mathbb{R}^3_+\ :\ \exists c > 0,\ x = cp\right\}\ .$$

• Now, the evolution of the state $x(t) = c(t)p$ on the previous half-line is dictated by the evolution of $c(t)$. The fact that $p_r + p_s = 1$ implies that $\mathbf{1}^{\mathsf{T}} x(t) = c(t)$, and the function c fulfils the scalar differential equation

$$\dot{c} = (\hat{m}(t) - \hat{\mu}(t))c(t) = \left(m_{\mathrm{sn}} \circ b_{\mathrm{sn}}\left(c(t)v^{\mathsf{T}}p\right) - \mu_{\mathrm{sn}}\left(c(t)w^{\mathsf{T}}p\right)\right)c(t).$$

The latter possesses two points of equilibrium, namely 0 and $c^*_{\mathrm{sn}}(p)$ by definition of the map c^*_{sn} —see Lemma 2.12. Due to Assumption 3, one has $m_{\mathrm{sn}}(0) > \mu_{\mathrm{sn}}(0)$, so the first equilibrium is unstable, while the second one is globally asymptotically stable. This achieves the proof of Theorem 2.13. □

2.6 Analysis of the selection case

We now state the result that describes the asymptotic behaviour in the *dominant* and *codominant* cases.

Theorem 2.14 (Asymptotic convergence to the homozygous equilibrium with higher fitness)**.** *Assume Assumptions* 1*,* 2*,* 3 *and* 4 *are fulfilled. Then, for any nonzero initial condition, the solution of* (**F**)*, resp.* (**S**)*, satisfies*

$$\lim_{t\to+\infty} x(t) = c_1^* e_1 \tag{2.39}$$

if allele r *is initially present, and otherwise*

$$\lim_{t\to+\infty} x(t) = c_3^* e_3 \ . \tag{2.40}$$

Theorem 2.14 states that, provided that the allele r is initially present, the system converges asymptotically towards the homozygous equilibrium of strictly higher fitness. When only the allele s is present, it goes towards the other homozygous nonzero equilibrium, or towards extinction if the latter does not exist. In both cases, the asymptotic population levels c_j^*, $j = r = 1$ and $j = s = 3$, correspond to the monomorphic equilibria defined in Lemma 2.6.

Theorem 2.14 is a central result in the context of the evolution of resistance. It is important to emphasize that a scenario of resistance reversal would be covered by turning in the direction of the order relationship for the fitness components. From a biological point of view, the latter implies homogeneous modifications in the environment —in space and time interval— that condition heterogeneous fitness in a target population. This last Theorem guarantees that the selection can lead to total saturation, that is, to the fixing of the resistance and total adaptation of the population. Lemmas 2.17 and 2.18 guarantee the extinction of the susceptible allele. The latter is a fundamental difference in relation to the models derived from the conventional definition of Malthusian fitness, where all alleles grow exponentially unless they are assumed to be unviable (birth less than mortality), *e.g.* dynamics for Mendelian populations model presented in (Hofbauer and Sigmund, 1998).

The case of monomorphic trajectories has been already studied in Lemma 2.7. The proof of Theorem 2.14 in the general case of polymorphic trajectories is conducted in the remaining part of the present section, based on careful study of the evolution of each allele $j = r, s$ in the population, and then of the evolution of each genotypic population $i = 1, 2, 3$. Central use will be made of the notions of mean allelic rates and of the formulas (2.30), introduced in Section 2.4.3. Most of the demonstration steps below are similar for (**F**) and (**S**), and will be treated altogether for both systems. For simplicity we drop, whenever possible, the indices referring to the system considered,

and simply write the allelic evolution

$$u_j^\intercal \dot{x} = \left(\tilde{m}_j(x(t)) - \tilde{\mu}_j(x(t))\right) u_j^\intercal x(t), \qquad j = r, s \ . \tag{2.41}$$

We first demonstrate in the following result that the ratio of the allelic frequencies evolves in a monotone way. More precisely, the ratio of the densities of the ("susceptible") allele s over the ("resistant") allele r is non increasing.

Lemma 2.15. *For any polymorphic trajectory,*

$$\forall t \geq 0, \quad \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)}\right) = \left(\tilde{m}_s(x(t)) - \tilde{\mu}_s(x(t)) - \tilde{m}_r(x(t)) + \tilde{\mu}_r(x(t))\right)\left(\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)}\right) \leq 0, \tag{2.42}$$

and the previous inequality is strict *for any $t > 0$.*

Proof.

• As a consequence of Lemma 2.8, the ratio $\dfrac{u_s^\intercal x(t)}{u_r^\intercal x(t)}$ is defined for any $t \geq 0$ along a polymorphic trajectory, and it is differentiable with respect to time. One has therefore

$$\forall t \geq 0, \qquad \frac{\mathrm{d}}{\mathrm{d}t}\left(\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)}\right) = \left(\frac{u_s^\intercal \dot{x}}{u_s^\intercal x(t)} - \frac{u_r^\intercal \dot{x}}{u_r^\intercal x(t)}\right)\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)} \tag{2.43}$$

which, thanks to (2.41), gives the equality part of (2.42). Formulas (2.31) and (2.32) provide the non-strict version of (2.42).

• To prove the *strict* inequality, consider first system (**F**). One has

$$\begin{aligned}(\tilde{m}_{\mathbf{F},r}(x) - \tilde{\mu}_{\mathbf{F},r}(x) - \tilde{m}_{\mathbf{F},s}(x) + \tilde{\mu}_{\mathbf{F},s}(x)) \\ &= (\tilde{m}_{\mathbf{F},r}(x) - m_2(b^*(x)) - \tilde{\mu}_{\mathbf{F},r}(x) + \mu_2(w^\intercal x)) \\ &\qquad + (m_2(b^*(x)) - \tilde{m}_{\mathbf{F},s}(x) + \tilde{\mu}_{\mathbf{F},s}(x) - \mu_2(w^\intercal x))\end{aligned} \tag{2.44}$$

and due to Lemma 2.11, each of the two expressions between parentheses in the right-hand side of (2.44) is *nonnegative*.

Moreover, at any polymorphic point, one has —see the definitions in (2.28):

$$\begin{aligned}\tilde{m}_{\mathbf{F},r}(x) - m_2(b^*(x)) - \tilde{\mu}_{\mathbf{F},r}(x) + \mu_2(w^\intercal x) \\ &= \frac{x_1}{u_r^\intercal x}\left(m_1(b^*(x)) - m_2(b^*(x)) + \mu_2(w^\intercal x) - \mu_1(w^\intercal x)\right) \\ &\qquad m_2(b^*(x)) - \tilde{m}_{\mathbf{F},s}(x) + \tilde{\mu}_{\mathbf{F},s}(x) - \mu_2(w^\intercal x) \\ &\qquad = \frac{x_3}{u_s^\intercal x}\left(m_2(b^*(x)) - m_3(b^*(x)) + \mu_3(w^\intercal x) - \mu_2(w^\intercal x)\right)\end{aligned} \tag{2.45}$$

A fundamental point now is that, due to the fact that $x_1 \neq 0$ and $x_3 \neq 0$ at any polymorphic point, one deduces from the second part of Assumption 2 that *at least one of the two nonnegative expressions* $m_1(b^*(x)) - m_2(b^*(x)) + \mu_2(w^\intercal x) - \mu_1(w^\intercal x)$ *and* $m_2(b^*(x)) - m_3(b^*(x)) + \mu_3(w^\intercal x) - \mu_2(w^\intercal x)$ *is positive*. Notice that Assumption 2 is crucial here for nonnegativity.

As all genotypes are present along a polymorphic trajectory when $t > 0$ —see Lemma 2.8, one gets that, along any polymorphic trajectory, at least one of the two nonnegative expressions

$$\frac{x_1(t)}{u_r^\intercal x(t)} \left(m_1(b^*(x(t))) - m_2(b^*(x(t))) + \mu_2(w^\intercal x(t)) - \mu_1(w^\intercal x(t))\right)$$

and

$$\frac{x_3(t)}{u_s^\intercal x(t)} \left(m_2(b^*(x(t))) - m_3(b^*(x(t))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t))\right)$$

is indeed *positive* whenever $t > 0$. This in turn shows that along any polymorphic trajectory of equation $(\mathbf{F})$, $\left(\tilde{m}_{\mathbf{F},a}(x(t)) - \tilde{\mu}_{\mathbf{F},a}(x(t)) - \tilde{m}_{\mathbf{F},A}(x(t)) + \tilde{\mu}_{\mathbf{F},A}(x(t))\right) < 0$ for any $t > 0$, and thus the strict inequality in (2.42). This achieves the proof of Lemma 2.15 in the case of equation $(\mathbf{F})$.

• The same argument holds for system $(\mathbf{S})$. The counterpart of the formulas (2.45) is obtained by noticing that, at any polymorphic point, one has (see (2.29)):

$$\begin{aligned}
&\tilde{m}_{\mathbf{S},r}(x) - m_2(b^*(\alpha(x))) - \tilde{\mu}_{\mathbf{S},r}(x) + \mu_2(w^\intercal x) \\
&\quad = \frac{\alpha_1(x)}{\alpha_1(x) + \frac{1}{2}\alpha_2(x)} \left(m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x)))\right) + \frac{x_1}{u_r^\intercal x}(\mu_2(w^\intercal x) - \mu_1(w^\intercal x)) \\
&\quad = \frac{u_r^\intercal x}{\mathbf{1}^\intercal x} \left(m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x)))\right) + \frac{x_1}{u_r^\intercal x}(\mu_2(w^\intercal x) - \mu_1(w^\intercal x)) \qquad (2.46a)
\end{aligned}$$

and similarly

$$\begin{aligned}
&m_2(b^*(\alpha(x))) - \tilde{m}_{\mathbf{S},s}(x) + \tilde{\mu}_{\mathbf{S},s}(x) - \mu_2(w^\intercal x) \\
&\qquad = \frac{u_s^\intercal x}{\mathbf{1}^\intercal x} \left(m_2(b^*(\alpha(x))) - m_3(b^*(\alpha(x)))\right) + \frac{x_3}{u_s^\intercal x}(\mu_3(w^\intercal x) - \mu_2(w^\intercal x)) \ . \qquad (2.46b)
\end{aligned}$$

Using the adequate version of the second part of Assumption 2 allows to obtain in the same manner than before the strict inequality in (2.42) for equation $(\mathbf{S})$, and finally achieves the proof of Lemma 2.15. □

We gather in the following result a series of estimates related to the genotypic frequencies.

Lemma 2.16. *For any polymorphic trajectory, there exists $c_1 > 0$ such that*

$$u_s^\intercal x(t) \leq c_1(u_r^\intercal x(t)), \qquad \forall t \geq 0. \tag{2.47}$$

Moreover, for any $\varepsilon > 0$, there exist $c_2, c_3 \geq 0$ such that $\forall t \geq \varepsilon$

$$x_2(t) \leq c_2 x_1(t), \quad x_3(t) \leq c_3 x_2(t), \quad \frac{x_1(t)}{u_r^\intercal x(t)} \geq \frac{1}{1+\frac{1}{2}c_2}, \quad \frac{x_3(t)}{u_s^\intercal x(t)} \leq \frac{c_3}{c_3+\frac{1}{2}} \tag{2.48}$$

Lemma 2.16 establishes that along any polymorphic trajectory, the ratio of the densities of susceptible over the density of resistants is bounded from above.

Proof.

• Formula (2.47) comes as direct consequence of Lemma 2.15. As a matter of fact, integrating (2.42) yields

$$\begin{aligned} \left(\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)}\right) &= \exp\left(\int_0^t (\tilde{m}_s(x(t)) - \tilde{\mu}_r(x(t)) - \tilde{m}_r(x(t)) + \ \tilde{\mu}_r(x(t)))\, dt\right)\left(\frac{u_s^\intercal x(0)}{u_r^\intercal x(0)}\right) \\ &\leq \left(\frac{u_s^\intercal x(0)}{u_r^\intercal x(0)}\right) \end{aligned} \tag{2.49}$$

for any $t \geq 0$, and therefore

$$u_s^\intercal x(t) \leq \frac{u_s^\intercal x(0)}{u_r^\intercal x(0)}(u_r^\intercal x(t)) := c_1(u_r^\intercal x(t)), \qquad \forall t \geq 0.$$

• Consider first system (**F**). For any polymorphic trajectory one has $x_1(\varepsilon) > 0$ for any $\varepsilon > 0$, see the proof of Lemma 2.8. Within the present demonstration, one assumes for simplicity that ε may be taken as zero, i.e. $x_1(0) > 0$. Choose then positive constants c_2, c_3 such that

$$c_2 > \max\left\{\frac{x_2(0)}{x_1(0)}; 2c_1\right\}, \qquad c_3 < \max\left\{\frac{x_2(0)}{x_3(0)}; \frac{2}{c_1}\right\} \tag{2.50}$$

where c_1 is the positive constant in (2.47). One deduces successively from Assumption

2 and (2.47) that

$$\begin{aligned} u_s^\intercal M(x)x &= \frac{1}{2}m_2(b^*(x))x_2 + m_3(b^*(x))x_3 \\ &\leq \frac{1}{2}m_2(b^*(x))x_2 + m_2(b^*(x))x_3 \\ &= m_2(b^*(x))(u_s^\intercal x) \\ &\leq c_1 m_2(b^*(x))(u_r^\intercal x) \\ &= c_1 m_2(b^*(x))\left(x_1 + \frac{1}{2}x_2\right) \\ &\leq c_1\left(m_1(b^*(x))x_1 + \frac{1}{2}m_2(b^*(x))x_2\right) \\ &= c_1(u_r^\intercal M(x)x) \end{aligned} \tag{2.51}$$

Using by turns (**F.b**), (2.51), (2.50) and (**F.a**), one deduces

$$\begin{aligned} \dot{x}_2 &= \frac{2}{\mathbf{1}^\intercal M(x)x}(u_r^\intercal M(x)x)(u_s^\intercal M(x)x) - \mu_2(w^\intercal x)x_2 \\ &\leq 2c_1\frac{1}{\mathbf{1}^\intercal M(x)x}(u_r^\intercal M(x)x)^2 - \mu_2(w^\intercal x)x_2 \\ &\leq c_2\frac{1}{\mathbf{1}^\intercal M(x)x}(u_r^\intercal M(x)x)^2 - \mu_2(w^\intercal x)x_2 \\ &= c_2\left(\dot{x}_1 + \mu_1(w^\intercal x)x_1\right) - \mu_2(w^\intercal x)x_2 \end{aligned}$$

Therefore,

$$\begin{aligned} \dot{x}_2 - c_2\dot{x}_1 &\leq c_2\mu_1(w^\intercal x)x_1 - \mu_2(w^\intercal x)x_2 \\ &= -\mu_1(w^\intercal x)\left(x_2 - c_2x_1\right) + \left(\mu_1(w^\intercal x) - \mu_2(w^\intercal x)\right)x_2 \\ &\leq -\mu_1(w^\intercal x)\left(x_2 - c_2x_1\right) \end{aligned} \tag{2.52}$$

where the last inequality has been deduced from the fact that $\mu_2 \geq \mu_1$, see Assumption 2. Integrating inequality (2.52) and using (2.50) yields for any $t \geq 0$:

$$x_2(t) - c_2x_1(t) \leq \exp\left(-\int_0^t \mu_1(w^\intercal x(s))\,\mathrm{d}s\right)\left(x_2(0) - c_2x_1(0)\right) \leq 0$$

and the first part of (2.48).

On the other hand, one also deduces from (**F.b**), (2.51), (**F.c**) and the fact that

$\mu_3 \geq \mu_2$,

$$\begin{aligned}
\dot{x}_2 &= \frac{2}{\mathbf{1}^\mathsf{T} M(x)x}(u_r^\mathsf{T} M(x)x)(u_s^\mathsf{T} M(x)x) - \mu_2(w^\mathsf{T} x)x_2 \\
&\geq \frac{2}{c_1}\frac{1}{\mathbf{1}^\mathsf{T} M(x)x}(u_s^\mathsf{T} M(x)x)^2 - \mu_2(w^\mathsf{T} x)x_2 \\
&\geq c_3\frac{1}{\mathbf{1}^\mathsf{T} M(x)x}(u_s^\mathsf{T} M(x)x)^2 - \mu_2(w^\mathsf{T} x)x_2 \\
&= c_3(\dot{x}_3 + \mu_3(w^\mathsf{T} x)x_3) - \mu_2(w^\mathsf{T} x)x_2 \\
&\geq c_3\dot{x}_3 + \mu_3(w^\mathsf{T} x)\,(c_3x_3 - x_2)
\end{aligned}$$

Therefore

$$\dot{x}_2 - c_3\dot{x}_3 \geq -\mu_3(w^\mathsf{T} x)\,(x_2 - c_3x_3) \tag{2.53}$$

which, taking into account the fact that $c_3 < \dfrac{x_2(0)}{x_3(0)}$, yields

$$\forall t \geq 0, \qquad x_2(t) - c_3x_3(t) \geq 0\ .$$

This proves the second inequality in (2.48). The last two inequalities come as a consequence, using the fact that

$$\frac{x_1(t)}{u_r^\mathsf{T} x(t)} = \frac{x_1(t)}{x_1(t) + \frac{1}{2}x_2(t)}, \qquad \frac{x_3(t)}{u_s^\mathsf{T} x(t)} = \frac{x_3(t)}{x_3(t) + \frac{1}{2}x_2(t)}\ .$$

This concludes the proof of Lemma 2.16 in the case of system (**F**).

• The proof is conducted similarly for system (**S**). We just quote here step by step the differences in the computations. The analogue of formulas (2.52) and (2.53) is proved as follows. Using (**S.b**), Assumption 2, (2.47) and (**S.a**), one deduces that

$$\begin{aligned}
\dot{x}_2 &= \frac{2}{\mathbf{1}^\mathsf{T} x}(u_r^\mathsf{T} x)(u_s^\mathsf{T} x)m_2(b^*(\alpha(x))) - \mu_2(w^\mathsf{T} x)x_2 \\
&\leq 2c_1\frac{(u_r^\mathsf{T} x)^2}{\mathbf{1}^\mathsf{T} x}m_1(b^*(\alpha(x))) - \mu_2(w^\mathsf{T} x)x_2 \\
&\leq c_2\frac{(u_r^\mathsf{T} x)^2}{\mathbf{1}^\mathsf{T} x}m_1(b^*(\alpha(x))) - \mu_2(w^\mathsf{T} x)x_2 \\
&= c_2\,(\dot{x}_1 + \mu_1(w^\mathsf{T} x)x_1) - \mu_2(w^\mathsf{T} x)x_2
\end{aligned}$$

and therefore

$$\begin{aligned}\dot{x}_2 - c_2\dot{x}_1 &\leq c_2\mu_1(w^\intercal x)x_1 - \mu_2(w^\intercal x)x_2 \\ &= -\mu_1(w^\intercal x)\left(x_2 - c_2x_1\right) + \left(\mu_1(w^\intercal x) - \mu_2(w^\intercal x)\right)x_2 \\ &\leq -\mu_1(w^\intercal x)\left(x_2 - c_2x_1\right)\end{aligned}$$

On the other hand, the fact that $m_3 \leq m_2$ and $\mu_3 \geq \mu_2$ yields

$$\begin{aligned}\dot{x}_2 &= \frac{2}{\mathbf{1}^\intercal x}(u_r^\intercal x)(u_s^\intercal x)m_2(b^*(\alpha(x))) - \mu_2(w^\intercal x)x_2 \\ &\geq \frac{2}{c_1}\frac{(u_s^\intercal x)^2}{\mathbf{1}^\intercal x}m_3(b^*(\alpha(x))) - \mu_2(w^\intercal x)x_2 \\ &\geq \frac{1}{c_3}\frac{(u_s^\intercal x)^2}{\mathbf{1}^\intercal x}m_3(b^*(\alpha(x))) - \mu_2(w^\intercal x)x_2 \\ &= \frac{1}{c_3}(\dot{x}_3 + \mu_3(w^\intercal x)x_3) - \mu_2(w^\intercal x)x_2 \\ &\geq \frac{1}{c_3}\dot{x}_3 + \mu_3(w^\intercal x)\left(\frac{1}{c_3}x_3 - x_2\right)\end{aligned}$$

which is the counterpart of (2.53). The other steps of the proof are similar to the case of system (**F**), and not repeated for the sake of space. This concludes the proof of Lemma 2.16. □

We are now in position to show that the ratio of the allelic frequencies not only decreases, as demonstrated by the previous result, but also vanishes asymptotically. Of course Assumption 2, which orders the different recruitment and mortality rates, is crucial to this Lemma.

Lemma 2.17. *For any polymorphic trajectory,*

$$\lim_{t\to+\infty}\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)} = 0\ . \tag{2.54}$$

Proof. We consider in the whole demonstration a given polymorphic trajectory —either of system (**F**) or of system (**S**) according to the context.

The ratio of allelic frequencies being decreasing, as a consequence of Lemma 2.15, there exists a nonnegative scalar λ such that

$$\lim_{t\to+\infty}\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)} = \lambda\ . \tag{2.55}$$

Due to the fact that $u_s^\intercal x + u_r^\intercal x = \mathbf{1}^\intercal x$, one may deduce from (2.55) that the allelic

frequencies also converge, namely:

$$\lim_{t\to+\infty} \frac{u_s^\intercal x(t)}{\mathbf{1}^\intercal x(t)} = \frac{\lambda}{1+\lambda}, \qquad \lim_{t\to+\infty} \frac{u_r^\intercal x(t)}{\mathbf{1}^\intercal x(t)} = \frac{1}{1+\lambda} \ .$$

We assume by contradiction that

$$\lambda > 0 \ . \tag{2.56}$$

Our aim is to show that (2.56) is wrong, i.e. that $\lambda = 0$.

• By Theorem 2.4, the trajectories are uniformly bounded. Therefore, by compactness, Assumption 2 guarantees the existence of a certain $\zeta > 0$ such that

$$\forall t > 0, \qquad m_1(b^*(x(t))) - m_3(b^*(x(t))) + \mu_3(w^\intercal x(t)) - \mu_1(w^\intercal x(t)) > \zeta \tag{2.57a}$$

for system (**F**); and

$$\forall t > 0, \qquad m_1(b^*(\alpha(x(t)))) - m_3(b^*(\alpha(x(t)))) + \mu_3(w^\intercal x(t)) - \mu_1(w^\intercal x(t)) > \zeta \tag{2.57b}$$

for system (**S**). For the considered trajectory and the corresponding value ζ, let the set X be defined as

$$X := \left\{ x \in \mathbb{R}^3_+ : \ m_1(b^*(x)) - m_2(b^*(x)) + \mu_2(w^\intercal x) - \mu_1(w^\intercal x) > \frac{\zeta}{2} \right\} \tag{2.58a}$$

for the case of system (**F**), and as

$$X := \left\{ x \in \mathbb{R}^3_+ : \ m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x))) + \mu_2(w^\intercal x) - \mu_1(w^\intercal x) > \frac{\zeta}{2} \right\} \tag{2.58b}$$

for system (**S**). Notice that, due to (2.57),

$$x(t) \notin X \ \Rightarrow \ m_2(b^*(x(t))) - m_3(b^*(x(t))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t)) > \frac{\zeta}{2} \tag{2.59a}$$

for (**F**), and for (**S**):

$$x(t) \notin X \ \Rightarrow \ m_2(b^*(\alpha(x(t)))) - m_3(b^*(\alpha(x(t)))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t)) > \frac{\zeta}{2} \ . \tag{2.59b}$$

Now, observe that the derivative of $\dfrac{u_s^\intercal x}{u_r^\intercal x}$ appears in (2.42) as a *locally Lipschitz*

function of the state variable x; and that along any polymorphic trajectory, the latter is *uniformly bounded* with *uniformly bounded time derivative*. From this, we may deduce that this derivative is *uniformly continuous* with respect to the time variable. As the convergence property (2.55) holds, Barbalat's lemma (Barbalat, 1959; Farkas and Wegner, 2016), establishes that the derivative converges to zero when $t \to +\infty$. Inserting in the expression of the latter (see (2.42)), the decomposition in two nonnegative terms obtained in (2.44) and (2.45) for (**F**), and in (2.46) for (**S**), one concludes by use of the hypothesis (2.56), that

$$\lim_{t\to+\infty} \frac{x_1(t)}{u_r^\intercal x(t)} \left(m_1(b^*(x(t))) - m_2(b^*(x(t))) + \mu_2(w^\intercal x(t)) - \mu_1(w^\intercal x(t))\right) = 0$$
$$\lim_{t\to+\infty} \frac{x_3(t)}{u_s^\intercal x(t)} \left(m_2(b^*(x(t))) - m_3(b^*(x(t))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t))\right) = 0$$

• Assume first that, for the considered polymorphic trajectory and the set X defined in (2.58),

$$\text{meas}\left\{t > 0 \ : \ x(t) \in X\right\} = +\infty \ , \tag{2.61}$$

where meas denotes the Lebesgue measure.

Consider primarily the case of system (**F**). One derives from (2.45), (2.48) and the definition of X in (2.58), that

$$\begin{aligned}
&\tilde{m}_{\mathbf{F},s}(x(t)) - \tilde{\mu}_{\mathbf{F},s}(x(t)) - \tilde{m}_{\mathbf{F},r}(x(t)) + \ \tilde{\mu}_{\mathbf{F},r}(x(t)) \\
&\quad\leq \ -\frac{x_1(t)}{u_r^\intercal x(t)} \Big(m_1(b^*(x(t))) - m_2(b^*(x(t))) + \mu_2(w^\intercal x(t)) - \mu_1(w^\intercal x(t))\Big) \\
&\quad\leq \ -\frac{1}{1+\frac{1}{2}c_2}\frac{\zeta}{2}\ \chi_{x^{-1}(X)}(t)
\end{aligned} \tag{2.62}$$

where by definition the characteristic function $\chi_{x^{-1}(X)}(t)$ is equal to 1 if $x(t) \in X$, 0 otherwise. Integrating now this inequality as in (2.49), one gets for any $t \geq 0$,

$$\left(\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)}\right) \leq \left(\frac{u_s^\intercal x(0)}{u_r^\intercal x(0)}\right) \exp\left(-\frac{1}{1+\frac{1}{2}c_2}\frac{\zeta}{2}\ \text{meas}\left\{s \in (0,t) \ : \ x(s) \in X\right\}\right)$$

Due to the hypothesis made in (2.61), the previous expression converges towards 0 when $t \to +\infty$. Therefore $\lambda = \lim_{t\to+\infty} \dfrac{u_s^\intercal x(t)}{u_r^\intercal x(t)} = 0$, which contradicts (2.56). This latter formula is thus wrong, which establishes (2.54) by contradiction.

The case of (**S**) is quite similar. Due to (2.47), one has for any $t \geq 0$,

$$\frac{u_r^\intercal x(t)}{\mathbf{1}^\intercal x(t)} \geq \frac{1}{1+c_1} \qquad \text{and} \qquad \frac{u_s^\intercal x(t)}{\mathbf{1}^\intercal x(t)} \leq \frac{c_1}{1+c_1} \ .$$

From (2.46a), one derives here

$$\begin{aligned}
&\tilde{m}_{\mathbf{S},s}(x(t)) - \tilde{\mu}_{\mathbf{S},s}(x(t)) - \tilde{m}_{\mathbf{S},r}(x(t)) + \ \tilde{\mu}_{\mathbf{S},r}(x(t)) \\
&\leq \ -\frac{u_r^\intercal x}{\mathbf{1}^\intercal x}\left(m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x)))\right) - \frac{x_1}{u_r^\intercal x}(\mu_2(w^\intercal x) - \mu_1(w^\intercal x)) \\
&\leq \ -\frac{1}{1+c_1}\left(m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x)))\right) - \frac{1}{1+\frac{1}{2}c_2}(\mu_2(w^\intercal x) - \mu_1(w^\intercal x)) \\
&\leq \ -\min\left\{\frac{1}{1+c_1}; \frac{1}{1+\frac{1}{2}c_2}\right\}\frac{\zeta}{2}\ \chi_{x^{-1}(X)}(t)
\end{aligned}$$

which is analogous to (2.62). The demonstration is then conducted in the same way and yields similarly $\lambda = 0$. By contradiction with (2.56), this shows identity (2.54).

• We now treat the case where (2.61) does not hold, that is:

$$\text{meas}\left\{t > 0 \ : \ x(t) \in X\right\} < +\infty \ . \tag{2.63}$$

It is not possible to use here the same argument than previously, because the quantity $\dfrac{x_3(t)}{u_s^\intercal x(t)}$ is bounded *from above*, contrary to $\dfrac{x_1(t)}{u_r^\intercal x(t)}$ which is bounded *from below*, see (2.48). The measure of the set $\{t > 0 \ : \ x(t) \notin X\}$ is now infinite, and as a consequence of (2.59), one deduces that

$$\text{meas}\left\{t \geq 0 \ : \ m_2(b^*(x(t))) - m_3(b^*(x(t))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t)) > \frac{\zeta}{2}\right\} = +\infty \tag{2.64a}$$

for (**F**), and for (**S**):

$$\begin{aligned}
&\text{meas}\left\{t \geq 0 : m_2(b^*(\alpha(x(t)))) - m_3(b^*(\alpha(x(t)))) + \mu_3(w^\intercal x(t)) - \mu_2(w^\intercal x(t)) > \frac{\zeta}{2}\right\} \\
&\qquad\qquad = +\infty. \qquad\qquad (2.64b)
\end{aligned}$$

From (2.60) and (2.64), one obtains here that necessarily:

$$\lim_{t\to+\infty} \frac{x_3(t)}{u_s^\intercal x(t)} = 0 \ ,$$

and thus

$$\lim_{t\to+\infty} x_3(t) = 0 \ . \tag{2.65}$$

In view of the equations (**F.c**) for system (**F**) and (**S.c**) for system (**S**), one deduces by invoking newly Barbalat's lemma that

$$\lim_{t\to+\infty} \dot{x}_3(t) = 0 \ . \tag{2.66}$$

By considering again the right-hand side of (**F.c**), resp. (**S.c**), one then gets from (2.65) and (2.66) that

$$\lim_{t\to+\infty} u_s^{\intercal} M(x(t))x(t) = 0, \qquad \text{resp. } \lim_{t\to+\infty} u_s^{\intercal} x(t) = 0 \ ,$$

and therefore

$$\lim_{t\to+\infty} x_2(t) = 0 \ . \tag{2.67}$$

But (2.65) and (2.67) together yield

$$\lambda = \lim_{t\to+\infty} \frac{u_s^{\intercal} x(t)}{\mathbf{1}^{\intercal} x(t)} = 0 \ ,$$

which contradicts (2.56). The latter is therefore wrong. This establishes (2.54) in the case where (2.63) holds, and finally concludes the proof of Lemma 2.17. □

As a remark, notice that using the techniques in the proof of Lemma 2.17, one may show that the convergence is *exponential* in (2.54) whenever the following stronger form of Assumption 2 holds: $m_1(b^*(x)) - m_2(b^*(x)) + \mu_2(w^{\intercal}x) - \mu_1(w^{\intercal}x) > 0$ for system (**F**), or $m_1(b^*(\alpha(x))) - m_2(b^*(\alpha(x))) + \mu_2(w^{\intercal}x) - \mu_1(w^{\intercal}x) > 0$ for system (**S**). Indeed (2.61) always holds in such cases. On the contrary, there is no indication that the same property holds when $m_2(b^*(x)) - m_3(b^*(x)) + \mu_3(w^{\intercal}x) - \mu_2(w^{\intercal}x) > 0$ for system (**F**), or $m_2(b^*(\alpha(x))) - m_3(b^*(\alpha(x))) + \mu_3(w^{\intercal}x) - \mu_2(w^{\intercal}x) > 0$ for system (**S**).

The asymptotic behavior of the ratio of allelic populations given in Lemma 2.17 is sufficient to assert the asymptotics of the *genotypic* relative frequencies in (**F**) and (**S**), as shown now.

Lemma 2.18. *For any polymorphic trajectory,*

$$\lim_{t\to+\infty} \frac{x_1(t)}{\mathbf{1}^{\intercal} x(t)} = 1, \qquad \lim_{t\to+\infty} \frac{x_2(t)}{\mathbf{1}^{\intercal} x(t)} = \lim_{t\to+\infty} \frac{x_3(t)}{\mathbf{1}^{\intercal} x(t)} = 0 \ . \tag{2.68}$$

Proof. Recall that by definition

$$\frac{u_s^\intercal x(t)}{u_r^\intercal x(t)} = \frac{\frac{1}{2}x_2(t) + x_3(t)}{x_1(t) + \frac{1}{2}x_2(t)} \geq \frac{\frac{1}{2}x_2(t) + x_3(t)}{x_1(t) + x_2(t) + x_3(t)}$$

which is larger than or equal to both nonnegative expressions

$$\frac{1}{2}\frac{x_2(t)}{x_1(t) + x_2(t) + x_3(t)} \qquad \text{and} \qquad \frac{x_3(t)}{x_1(t) + x_2(t) + x_3(t)}$$

Lemma 2.17 implies that both these ratios converge towards 0 when $t \to +\infty$ and this permits to conclude the proof of Lemma 2.18. □

Due to Lemma 2.18 and the fact that the trajectories are bounded (see Theorem 2.4), x_2 and x_3 converge towards 0. We are finally in the position to establish the asymptotic behaviour of the population size for each genotype.

Lemma 2.19. *For any polymorphic trajectory,*

$$\lim_{t\to+\infty} x_1(t) = c_1^*, \qquad \lim_{t\to+\infty} x_2(t) = \lim_{t\to+\infty} x_3(t) = 0 \ . \tag{2.69}$$

Proof. Consider *e.g.* system (**F**). Equation (**F.a**) may be written as

$$\dot{x}_1 = \frac{(u_r^\intercal M(x)x)^2}{\mathbf{1}^\intercal M(x)x} - \mu_1(w^\intercal x)x_1 = \left(\frac{(u_r^\intercal M(x)x)^2}{(\mathbf{1}^\intercal M(x)x)x_1} - \mu_1(w^\intercal x)\right) x_1 \ .$$

Due to (2.68),

$$\lim_{t\to+\infty} \eta(t) = 0, \quad \eta(t) := \left(\frac{(u_r^\intercal M(x)x)^2}{(\mathbf{1}^\intercal M(x)x)x_1} - \mu_1(w^\intercal x) - m_1(b^*(x_1(t)e_1)) + \mu_1(w_1x_1(t))\right) \ .$$

Thus, for any polymorphic trajectory of (**F**) and any $\bar{\eta} > 0$, there exists $T_{\bar{\eta}} > 0$ such that, for any $t \geq T_{\bar{\eta}}$,

$$\Big(m_1(b^*(x_1(t)e_1)) - \mu_1(w_1x_1(t)) - \bar{\eta}\Big)\, x_1 \leq \dot{x}_1 \leq \Big(m_1(b^*(x_1(t)e_1)) - \mu_1(w_1x_1(t)) + \bar{\eta}\Big)\, x_1. \tag{2.70}$$

For $\bar{\eta} > 0$ sufficiently small, let $c_{\bar{\eta}}^{\pm}$ be the unique positive scalars such that

$$m_1(b^*(c_{\bar{\eta}}^{\pm}e_1)) - \mu_1(w_1c_{\bar{\eta}}^{\pm}) \pm \bar{\eta} = 0 \ .$$

By definition of c_1^*, see Lemma 2.6, one has

$$c_{\bar\eta}^- < c_1^* < c_{\bar\eta}^+, \qquad \lim_{\bar\eta\to 0^+} c_{\bar\eta}^{\pm} = c_1^* \ . \tag{2.71}$$

By (2.70), one deduces that, for any sufficiently small $\bar\eta > 0$,

$$c_{\bar\eta}^- \le \liminf_{t\to+\infty} x_1(t) \le \limsup_{t\to+\infty} x_1(t) \le c_{\bar\eta}^+ \ ,$$

and finally

$$\liminf_{t\to+\infty} x_1(t) = \limsup_{t\to+\infty} x_1(t) \le c_1^* \ ,$$

by doing $\bar\eta \to 0^+$ and using (2.71). This demonstrates Lemma 2.19 in the case of system (**F**). System (**S**) is treated analogously. □

With the proof of Lemma 2.19, the proof of Theorem 2.14 is now complete.

2.7 Conclusion and future issues

We proposed a class of Mendelian inheritance models that considers the complexity of the life history of insects and its selective pressures. These models describe the evolution in continuous time of a population with two main life phases, governed by birth of the three genotypes of two alleles, density-dependent mortality rates and constant rate of passage to reproductive phase. Each model is represented by a system of six scalar ordinary differential equations, one for each genotype in each life phase.

This starting system has been simplified using slow manifold theory, to obtain two classes of Mendelian inheritance models of dimension 3. Both classes were derived from assuming one of the phases slower than the other.

We proved that, under realistic assumptions, the proposed models demonstrate several fundamental properties expected in population dynamics and population genetics. In fact, in a selectively neutral scenario, the population converges asymptotically to the carrying capacity, while the Hardy-Weinberg law is valid: the allele frequencies in the polymorphic population are constant, and determine the asymptotic value of the genotypic relative frequencies. In presence of selective pressures —*i.e.* an ordering of the recruitment or mortality functions according to genotype—, adaptive evolution occurs, and in case of dominance or codominance, the population is asymptotically made of individuals of the homozygous genotype having the highest fitness, at the corresponding carrying capacity.

The evolution described above take place as consequence of a stationary environment. On the other hand, introducing time-dependence in the model parameters offers the possibility to describe a variety of evolving phenomena, such as *e.g.* emergence and reversal of resistance evolution as a result of intermittent pesticide applications. Also, these models allow to analyze selective pressure situations faced by genotypes during life phases occurring in different ecological niches.

The proposed classes of models permit, possibly through minor extensions, to study several issues of importance related to the use of insecticides and other adaptive phenomena. Simple extensions of the models to incorporate migration would allow to evaluate the consequences of the natural or artificial addition of susceptible genotypes in the evolution of insecticide resistance, following the proposals made in (Comins, 1977) and (Taylor and Georghiou, 1979). Also, one could explore the consequences of the use of a larvicide and adulticide in the context of an evolution-proof insecticide following the line developed in (Read et al., 2009; Koella et al., 2009a; Gourley et al., 2011), —partitioning the adult phase into younger adults and less vigorous old adults, with a mortality rate in the last phase more affected by the adulticide. Further, the proposed models can be used to explore how dominance levels given by the dose of insecticide (Priester and Georghiou, 1978; Curtis et al., 1978; Taylor and Georghiou, 1979; Bourguet et al., 2000) affect the speed of settlement of resistance evolution (Dawson, 1970; Freeman and Herron, 2007; Helps et al., 2017). In addition, in situations where the application of the insecticide is interrupted and the resistance has a fitness cost, the models may be used to estimate the time taken by a resistant population to revert to a susceptible one, as done in (Kliot and Ghanim, 2012; Schechtman and Souza, 2015).

Looking forward, as most traits of evolutionary or economic importance are determined by several genes, an adequate understanding of the evolution of such traits may require the study of multi-locus models (Bürger, 2011). It turns out that the heredity function which models the births is constructed in such a way as to allow extensions to more than two alleles, multiple loci —by means of Kronecker product between inheritance matrices— or polyploid cases. The modelling procedure presented in the present paper thus offers the ability to accommodate more complicated inheritance configurations, with two or more loci with autosomal inheritance, accounting for *e.g.* sequential or mixed use of insecticides (Curtis, 1985; Mani, 1985; Levick et al., 2017; South and Hastings, 2018), non-genetic inheritance, unified maternal and autosomal inheritance as autosomal resistance and *Wolbachia* for biological control —a bacterium of maternal inheritance related to mitochondria with the potential to suppress vector capacity in

mosquitoes (Hoffmann and Turelli, 2013a; Garcia et al., 2020).

As a last remark, notice that models of species having more than two main phases may be considered too, for example in the case of a holometabolous insect for which the phases of embryo, larva and pupa are all quite fast compared to the adult phase. Note also that organism models having two life phases do not concern only insects. Even in plants it is possible to describe pre-reproductive and reproductive phases with different periods. For instance, weedy ephemerals (a very common weed) are very short-lived plants that reproduce rapidly after human disturbance from plowing (Keddy, 2007). This means that the models proposed here could cover problems related to resistance to herbicides, where chemical control can occur in the seedling phase or in the reproductive phase (see (Langemann et al., 2013)), which are supposed to slow down or even reverse the development of resistances due to the interruption or modification of the application of pesticide lethal doses in the environment.

Mathematical models played a decisive role in reconciling Mendelian genetics with Darwin's theory of adaptive evolution (Ewens, 2011). In regard to inheritance models, the biological or genetic control for insect pest raises new issues with potentially valuable applications (Alphey, 2014; Hoffmann et al., 2015). We think that the modeling strategy presented here may help in this task, for which extensions of these models may help to design, analyze, dimension and simulate release strategies.

2.8 Appendix — proof of technical results

2.8.1 Heredity functions

In order to have the mathematics come out simply —see (Felsenstein, 2005), one can consider a multiplicative fertility independent of sex. We note that, the absolute number of births for a genotype in given interval of time for a given $x_i \times x_{i'}$ crosses will jointly depends on the fraction of $x_{i'}$ individuals of a sex and the number of x_i individuals of the opposite one that can produce an expected frequency of this kind offspring. As a possibility, let us suppose that there exist different average fertility f_i over each genotype in the population.

Defining the vectors:

$$u_r := \begin{pmatrix} 1 \\ \frac{1}{2} \\ 0 \end{pmatrix}, \quad u_s := \begin{pmatrix} 0 \\ \frac{1}{2} \\ 1 \end{pmatrix}, \quad \mathbf{1} := \begin{pmatrix} 1 \\ 1 \\ 1 \end{pmatrix} = u_r + u_s. \tag{2.72}$$

Thereby, considering the zygotes expected frequency of a genotype resulting from the crossing $x_i \times x_{i'}$ as shown in the table above, one has for $i = 1, 2, 3$ respectively

$$\begin{aligned}
\alpha_1(Fx) &= \frac{f_1 x_1}{\mathbf{1}^\intercal Fx} f_1 x_1 + \frac{1}{2}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_1 x_1 + \frac{1}{2}\frac{f_1 x_1}{\mathbf{1}^\intercal Fx} f_2 x_2 + \frac{1}{4}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_2 x_2 \\
&= \frac{(f_1 x_1 + \frac{1}{2} f_2 x_2)^2}{\mathbf{1}^\intercal Fx} \\
&= \frac{(u_r^\intercal Fx)^2}{\mathbf{1}^\intercal Fx}
\end{aligned} \tag{2.73}$$

$$\begin{aligned}
\alpha_2(Fx) &= \frac{1}{2}\frac{f_1 x_1}{\mathbf{1}^\intercal Fx} f_2 x_3 + \frac{1}{2}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_1 x_1 + \frac{1}{2}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_2 x_2 + \frac{f_1 x_1}{\mathbf{1}^\intercal Fx} f_3 x_3 \\
&+ \frac{f_3 x_3}{\mathbf{1}^\intercal Fx} f_1 x_1 + \frac{1}{2}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_3 x_3 + \frac{1}{2}\frac{f_3 x_3}{\mathbf{1}^\intercal Fx} f_2 x_2 \\
&= 2\frac{(u_r^\intercal Fx)(u_s^\intercal Fx)}{\mathbf{1}^\intercal Fx}
\end{aligned} \tag{2.74}$$

$$\begin{aligned}
\alpha_3(Fx) &= \frac{f_3 x_3}{\mathbf{1}^\intercal Fx} f_3 x_3 + \frac{1}{2}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_3 x_3 + \frac{1}{2}\frac{f_3 x_3}{\mathbf{1}^\intercal Fx} f_2 x_2 + \frac{1}{4}\frac{f_2 x_2}{\mathbf{1}^\intercal Fx} f_2 x_2 \\
&= \frac{(f_1 x_1 + \frac{1}{2} f_2 x_2)^2}{\mathbf{1}^\intercal Fx} \\
&= \frac{(u_s^\intercal Fx)^2}{\mathbf{1}^\intercal Fx}
\end{aligned} \tag{2.75}$$

2.8.2 Proof of Lemma 2.1

The left-hand side of (2.18) is an increasing function of b and varies from 0 to $+\infty$; while the right-hand side is null if $x = 0_3$ and a decreasing function otherwise. Therefore, by the Implicit function Theorem, there exists a unique solution $b^*(x)$ to the scalar equation

$$b - \sum_{i=1}^{3} v_i m_i(b) x_i = 0$$

which is of class C^p if every function m_i is of class C^p, $p \in \mathbb{N}$. □

2.8.3 Proof of Lemma 2.2

For Property *1*, one can see that, for any $j = r, s$,

$$u_j^\intercal \alpha(x) = \frac{1}{\mathbf{1}^\intercal x}((u_j^\intercal x)^2 + (u_r^\intercal x)(u_s^\intercal x)) = \frac{1}{\mathbf{1}^\intercal x}(u_r^\intercal x + u_s^\intercal x) u_j^\intercal x = u_j^\intercal x. \tag{2.76}$$

as $u_r + u_s = \mathbf{1}$. Using again this identify, property *2* is deduced from the previous one, as:

$$\mathbf{1}^\intercal \alpha(x) = u_r^\intercal \alpha(x) + u_s^\intercal \alpha(x) = u_r^\intercal x + u_s^\intercal x = \mathbf{1}^\intercal x. \tag{2.77}$$

Property *3* is trivial, and expresses the homogeneity of the function α. To show Property *4*, notice that for any $(j,k) \in \{1,3\} \times \{r,s\}$, $u_k^\intercal e_j = 1$ if $(j,k) = (1,r)$ or $(3,s)$, and 0 otherwise; and on the other hand that $\mathbf{1}^\intercal e_j = 1$. Therefore

$$\alpha(e_j) = \frac{1}{\mathbf{1}^\intercal e_j} \begin{pmatrix} (u_r^\intercal e_j)^2 \\ 2(u_r^\intercal e_j)(u_s^\intercal e_j) \\ (u_s^\intercal e_j)^2 \end{pmatrix} = e_j \tag{2.78}$$

for any $j = r = 1$, $j = s = 3$. □

2.8.4 Proof of Lemma 2.3

• Let $x \in \mathbb{R}^3_+ \setminus \{0_3\}$ and $\lambda > 0$. By definition (see the statement of Lemma 2.1),

$$b^*(\lambda x) = \lambda \sum_{i=1}^{3} v_i m_i(b^*(\lambda x)) x_i. \tag{2.79}$$

Therefore

$$\lambda \min_{i=1,2,3}\{v_i/w_i\} \min_{i=1,2,3}\{m_i(b^*(\lambda x))\} w^\intercal x \le b^*(\lambda x) \le \lambda \max_{i=1,2,3}\{v_i/w_i\} \max_{i=1,2,3}\{m_i(b^*(\lambda x))\} w^\intercal x. \tag{2.80}$$

which may be rewritten as an inequality on $\lambda(w^\intercal x)$:

$$\frac{b^*(\lambda x)}{\max_i\{v_i/w_i\} \max_i\{m_i(b^*(\lambda x))\}} \le \lambda(w^\intercal x) \le \frac{b^*(\lambda x)}{\min_i\{v_i/w_i\} \min_i\{m_i(b^*(\lambda x))\}} \tag{2.81}$$

Therefore, when $\lambda \to +\infty$, one has $\dfrac{b^*(\lambda x)}{\min_i\{v_i/w_i\} \min_i\{m_i(b^*(\lambda x))\}} \to +\infty$, and the convergence is uniform with respect to x such that $w^\intercal x = 1$. Consequently, $b^*(\lambda x) \to +\infty$ uniformly in x such that $w^\intercal x = 1$.

From this one deduces that $\lim_{\lambda \to +\infty} m_i(b^*(\lambda x)) < \lim_{\lambda \to +\infty} \mu_i(\lambda)$, because m_i decreases, μ_i increases and Assumption 4 holds.

• Let us now show the second property on b^*. By definition one has, for any $x \in \mathbb{R}^3_+ \setminus \{0\}$,

$$b^*(x) = \sum_{i=1}^{3} v_i m_i(b^*(x)) x_i.$$

Therefore, for any $\lambda, \lambda' \geq 0$,

$$\lambda \sum_{i=1}^{3} v_i m_i(b^*(\lambda x))x_i - \lambda' \sum_{i=1}^{3} v_i m_i(b^*(\lambda' x))x_i = b^*(\lambda x) - b^*(\lambda' x)$$

Subtracting and adding the term $\lambda \sum_{i=1}^{3} v_i m_i(b^*(\lambda' x))x_i$, one gets

$$\lambda \sum_{i=1}^{3} v_i \Big(m_i(b^*(\lambda x)) - m_i(b^*(\lambda' x)) \Big) x_i + (\lambda - \lambda') \sum_{i=1}^{3} v_i m_i(b^*(\lambda' x))x_i = b^*(\lambda x) - b^*(\lambda' x)$$

that is

$$(\lambda - \lambda') \sum_{i=1}^{3} v_i m_i(b^*(\lambda' x))x_i = b^*(\lambda x) - b^*(\lambda' x) - \lambda \sum_{i=1}^{3} v_i \Big(m_i(b^*(\lambda x)) - m_i(b^*(\lambda' x)) \Big) x_i$$

Assume *e.g.* $b^*(\lambda x) > b^*(\lambda' x)$. Due to Assumption 1, the functions m_i, $i = 1, 2, 3$, decrease. Therefore $m_i(b^*(\lambda x)) - m_i(b^*(\lambda' x)) < 0$, and we deduce from the previous identity that $\lambda > \lambda'$.

One shows similarly that $b^*(\lambda x) < b^*(\lambda' x)$ implies $\lambda < \lambda'$. In conclusion, $\lambda < \lambda' \Leftrightarrow b^*(\lambda x) < b^*(\lambda' x)$, and this shows that b^* is increasing. □

Chapter 3

Simulation of evolutionary scenarios for a Mendelian population

3.1 Introduction

3.1.1 Population dynamics and genetic evolution

Population genetics is a field of biology that integrates Mendelian genetic with the theory of evolution by selection. According to (Freeman and Herron, 2007), the most important idea of population genetics is that changes in the relative abundance of traits in a population can be related to changes in the relative frequency of alleles that regulate them. Under this perspective, theoretical models of population genetics focused on changing relative allele frequencies have been generated.

From a classical perspective, population genetics models are constructed with assumptions such as large constant populations (infinite). In contrast, it is common in population dynamics to focus on the changes in population size, eluding variations between individuals. In addition, in many cases the effect of different phases of life is often considered —see (Wilson and Bossert, 1971).

We believe that models that unify the fundamental principles of both population dynamics and population genetics are necessary for the problem of vector mosquito control. Without delving into an extensive review we illustrated better this need in some recently published works (Langemann et al., 2013; Schechtman and Souza, 2015; Edgington and Alphey, 2018; Unckless et al., 2017). We think that, in the context of the genetics of a population, general enough models to cover of life history of insects, such as, mosquitoes with phases of life in different ecological niches (e.g. aquatic and air) could better illustrate phenomena related to applied problems such as population

control. However, taking into account the genetic aspects, the mathematical analysis of these models becomes complicated. In this sense, Chapter 2 shows how slow manifold theory facilitates to reach analytical results.

In this Chapter, we present a simulation of the population model (introduced in Chapter 2) differentiated in genotypes governed by Mendelian inheritance in which it is considered a pre-reproductive and reproductive phase of life. Then, the two simplified models introduced in Chapter 2 are provided. Simulations of different evolutionary scenarios are presented using the two-life phase model. Finally, the model of two life phases is compared through numerical simulations, with the simplified models by singular perturbation and assuming regular perturbation.

3.1.2 Fast and slow phases in evolutionary systems

As already mentioned in Charter 2, the life history of organisms is quite different from one to the other. Some mature early and reproduce quickly, while others mature late and reproduce slowly. An extreme example is the arachnids *Adactylidium sp.*, which are born mature and, having hatched inside their mother, mate with their brothers (Elbadry and Tawfik, 1966; Gould, 2010). The insects *Ephemeroptera* constitute another extreme case: the life of an adult mayfly is very short and has essentially the primary function of reproduction (Welch, 1998). The life cycle may be seen analogously to a sequence of chemical modifications that a sustenance goes through. Like in a chemical reaction network (Klonowski, 1983), some phase of life are slower than others. This last feature opens up the possibility of using slow manifold theory to deduce simpler population models.

Explicit models deduced in this chapter also consider the cases where one of the two life phases is sensibly faster than the other one, in other words that a fast dynamics and a slow dynamics are present in a diploid population. Depending on which of the phases is faster, this assumption yields through singular perturbation (O'Malley Jr, 1991) two different inheritance models. As mentioned in Chapter 2, these inheritance models represent a population dynamic of density-dependent recruitment and mortality.

3.1.3 Hypothetical evolutionary scenarios

Simulation results are presented for Mendelian population dynamic with two life stages. Starting from a series of in silico experiments, we studied different hypothetical evolutionary scenarios for trait governed by a genetic locus with two alleles. In the following, we give a commented list of scenarios to consider.

1. Selectively neutral genotypes.
   That is, a scenario where all genotypes have exactly the same viability.

2. Monomorphic of the allele with the highest fitness.
   This is a scenario where only the homozygous genotype given by the allele with the highest fitness is present.

3. Monomorphic of the allele with the lowest fitness.
   This is a scenario where only the homozygous genotype given by the allele with the lowest fitness is present.

4. All unviable genotypes.
   It is a scenario where given the environmental conditions the population is going towards extinction.

5. Incomplete dominance with selection in the adult phase.
   In this scenario a heterozygous individual combines the traits. In the case of selection, it is interpreted here that the viability in the adult phase has an intermediate value —*e.g.* when heterozygote are moderately susceptible to an adulticide.

6. Incomplete dominance with selection in the pre-adult phase.
   Unlike the previous case, the intermediate value of the viability is given in the pre-adult phase —*e.g.* by larvicide application.

7. Complete dominance of allele with the highest fitness with selection in pre-adult phase.
   This scenario occurs when the heterozygous expresses the phenotype of one homozygotes, in this case, the homozygous with highest fitness —*e.g.* insecticide resistance phenotype.

8. Complete dominance of allele with the lowest fitness with selection in the pre-adult phase.
   This case is genetically the same as the previous one, however heterozygote are equal to homozygotes with the lowest fitness —*e.g.* insecticide susceptibility phenotype.

9. Overdominance with selection in the pre-adult phase.
   This scenario occurs when the heterozygous has highest fitness compared to homozygotes.

10. Underdominance with selection in the pre-adult phase 1.
    This scenario occurs when the heterozygous has lower fitness compared to homozygotes.

11. Underdominance with selection in the pre-adult phase 2.
    This scenario is the same type as the previous one but illustrates a different qualitative behavior.

The simulated scenarios represent cases without selection, directional selection, stabilizing (overdominance) and disruptive selection (underdominance). In particular, it shows a potential application for the control of insect populations to stop the transmission of diseases (Reeves et al., 2014; Edgington and Alphey, 2018). In the same direction, the scenarios 4 to 8 for directional selection have particular application in cases of pest control in which it is desired to maintain a population level below a threshold —*e.g.* economic threshold or economic injury levels (Tang and Cheke, 2008). For example, in the case of chemical control through a pesticide, the evolution of resistance compromises application time, which in turn may be conditioned by the lethal dose used and the degree of genetic dominance of the alleles involved (Taylor and Georghiou, 1979).

In the above list and throughout the document it is not considered an explicit mathematical definition of fitness. The terms "highest fitness" and "lowest fitness" should be interpreted as a qualitative appellation that refers to the absolute reproductive efficacy or absolute viability of a genotype in the population.

3.2 Mathematical models

Here we recall a population dynamic model with two life phases (introduced in Chapter 2), one reproductive and the other pre-reproductive. The model assumes that the two phases live in independent niches, consequently admitting different life parameters. From this model, two simpler models are deduced by singular perturbation: one in which it is assumed that the pre-reproductive phase is faster than the reproductive one and another in which is assumed that the pre-reproductive phase is slower than the reproductive one. The two-life phase model is then used to simulate hypothetical evolutionary scenarios. Finally, are provide a comparison between the three models, the two-phase life model without singular perturbation, with regular disturbance, and the two models with singular perturbation.

3.2.1 Two phases compartmental model (2.1)

We recall the compartmental model with two phases of life (pre-adult and adult) previously presented —see Section 2.2 in Chapter 2. The modeled population differs in three genotypes given by two autosomal alleles.

We will make everywhere in the sequel the following assumption. The main benefit is to allow an explicit computation of the functions b^* that are used to define the singularly perturbed models.

Assumption 5. *For any $b \in \mathbb{R}_+$, the mortality rate functions verify*

$$\mu_i(b) = \mu_{i0}(1 + \mu b), \qquad i = 1, 2, 3 \tag{3.1a}$$

$$\hat{\mu}_i(b) + \nu_i = \hat{\mu}_{i0}(1 + \hat{\mu} b), \qquad i = 1, 2, 3 \tag{3.1b}$$

for positive $\mu, \hat{\mu}$ and $\mu_{i0}, \hat{\mu}_{i0}$, $i = 1, 2, 3$.

3.2.2 Fast reproductive phase model

We consider here the case of an organism with a mature phase shorter than the immature phase. For any fixed L, considering Assumption 5 and assuming (2.1b) at equilibrium one gets

$$0 = \nu_i L_i - \hat{\mu}_{i0}(1 + \hat{\mu} w^\intercal A) A_i, \qquad i = 1, 2, 3 \ . \tag{3.2}$$

This equation allows establishing a relationship between L_i and A_i:

$$A_i = \frac{\nu_i}{\hat{\mu}_{i0}(1 + \hat{\mu} w^\intercal A)} L_i, \qquad i = 1, 2, 3 \tag{3.3}$$

which necessarily implies that $b := w^\intercal A$ fulfils the identity

$$b = \sum_{i=1}^{3} \frac{w_i \nu_i}{\hat{\mu}_{i0}(1 + \hat{\mu} b)} L_i \tag{3.4}$$

Now, the mortality $\hat{\mu}_i$ is increasing with the total population, so for all $L \in \mathbb{R}^3_+ \setminus \{0\}$, the map

$$b \mapsto \sum_{i=1}^{3} \frac{w_i \nu_i}{\hat{\mu}_{i0}(1 + \hat{\mu} b)} L_i \tag{3.5}$$

is decreasing and may be inverted, providing a unique solution, denoted $b^*(L)$. Indeed, from equation (3.3) one obtains

$$0 = \sum_{i=1}^{3} \frac{w_i \nu_i}{\hat{\mu}_{i0}} L_i - b - \hat{\mu} b^2 \ . \tag{3.6}$$

Thus, one obtains from (3.6) the explicit solution

$$b^*(L) = w^\intercal A = \frac{-1 \pm \sqrt{1 + 4\hat{\mu}\varpi^\intercal L}}{2\hat{\mu}}, \qquad \varpi := \begin{pmatrix} \frac{w_1\nu_1}{\hat{\mu}_{10}} & \frac{w_2\nu_2}{\hat{\mu}_{20}} & \frac{w_3\nu_3}{\hat{\mu}_{30}} \end{pmatrix}^\intercal \tag{3.7}$$

Hence, for any given nonnegative vector L, the unique solution of (3.2) is then given as

$$A_i = \frac{2\nu_i}{\hat{\mu}_{i0}\left(1 + \sqrt{1 + 4\hat{\mu}\varpi^\intercal L}\right)} L_i, \qquad i = 1, 2, 3 \tag{3.8}$$

One then ends up with the system

$$\dot{L}_i = \alpha_i \left(M(L)L\right) - (\nu_i + \mu_i(v^\intercal \hat{L}))L_i, \qquad i = 1, 2, 3 \tag{3.9a}$$

where, for any nonnegative scalar b, one defines

$$m_i(b) := \frac{\nu_i}{\hat{\mu}_i(b)}, \quad i = 1, 2, 3, \qquad M(L) := \mathtt{diag}\{m_i(b^*(L))\} \tag{3.9b}$$

3.2.3 Slow reproductive phase model

Consider now the opposite situation, of an adult phase comparatively much longer than the pre-adult one. Following similar reasoning to the previous case from the system (2.1), considering Assumption 5, one has

$$0 = \alpha_i(A) - \mu_{i0}(1 + \mu v^\intercal \hat{L})L_i, \qquad \dot{A}_i = \hat{\nu}_i L_i - \hat{\mu}_{i0}(1 + \hat{\mu} w^\intercal A)A_i, \qquad i = 1, 2, 3 \tag{3.10}$$

The algebraic relationship in equation (3.10) provides the identities

$$L_i = \frac{1}{\mu_{i0}(1 + \mu v^\intercal \hat{L})} \alpha_i(A), \qquad i = 1, 2, 3 \tag{3.11}$$

and thus $b := v^\intercal \hat{L}$ necessarily fulfills the condition:

$$b = \frac{1}{(1+\mu b)} \sum_{i=1}^{3} \frac{v_i}{\mu_{i0}} \alpha_i(A) \tag{3.12}$$

From the increasing of the mortality functions, one deduces as before that, for all $A \in \mathbb{R}^3_+ \setminus \{0\}$, the right-hand side of (3.12) is decreasing, and this relation may thus be inverted. This operation yields a unique solution to equation (3.12), which is denoted $b^*(\alpha(A))$ (using α defined in (2.7)). As a matter of fact, one has the following polynomial equation

$$0 = \vartheta^\intercal \alpha(A) - b - \mu b^2 \ , \qquad \vartheta := \begin{pmatrix} \frac{v_1}{\mu_{10}} & \frac{v_2}{\mu_{20}} & \frac{v_3}{\mu_{30}} \end{pmatrix}^\intercal \tag{3.13}$$

and from this identity one deduces explicitly the value of b^*,

$$b^*(A) := \frac{-1 \pm \sqrt{1 + 4\mu \vartheta^\intercal A}}{2\mu}. \tag{3.14}$$

Namely,

$$v^\intercal L = b^*(\alpha(A)) = \frac{-1 + \sqrt{1 + 4\mu \vartheta^\intercal \alpha(A)}}{2\mu}. \tag{3.15}$$

With this, for any nonnegative A, (3.11) has a unique solution, which writes

$$\hat{L}_i = \frac{2}{\mu_{i0}(1 + \sqrt{1 + 4\mu \vartheta^\intercal \alpha(A)})} \alpha_i(A), \qquad i = 1, 2, 3 \tag{3.16}$$

Defining here for any nonnegative scalar b, the (decreasing) functions

$$m_i(b) := \frac{\nu_i}{\mu_{i0}(1+\mu b)} \ , \tag{3.17a}$$

one obtains finally the model:

$$\dot{A}_i = \alpha_i(A) m_i(b^*(\alpha(A))) - \hat{\mu}_i(w^\intercal A) A_i, \quad i = 1, 2, 3 \ . \tag{3.17b}$$

3.3 Numerical simulations

All the simulations were done with the free and open-source programming language Scilab. In order to ensure the reproducibility of the results, we developed a code with GUI.The details of the source code and how to use it are in Appendix A.

3.3.1 Parameters possible values

The baseline domain of parameter values used for the simulation correspond to the *Aedes aegypti* mosquito population dynamics (all units in days^{-1}). *Aedes aegypti* has been selected as a case study in this chapter for the purpose of providing complementary understanding to subsequent chapters. Furthermore, these mosquitoes are vectors of diseases that cause a significant public health stress and show an evolution to insecticide resistance.

- The rate of transfer to the adult (ν_i) presents values in $[14^{-1}, 10^{-1}]$ (Walker et al., 2011a; Hoffmann et al., 2014a; Koiller et al., 2014a; Adekunle et al., 2019).

- The mortality rate for susceptible homozygous larvae presents value in $[0.1, 0.2]$ (Koiller et al., 2014a; Xue et al., 2017; Adekunle et al., 2019). Here the mutant allele of resistance contributes to a decrease in mortality and depends on some degree of allelic dominance. In consequence, the mortality rate for L_1 ($\hat{\mu}_{10}$) take values in $\hat{\mu}_{30}(1-\hat{d}_1)$, while the mortality rates for L_2 ($\hat{\mu}_{20}$) take values in $\hat{\mu}_{30}(1-\hat{h}_1\hat{d}_1)$. Where, $\hat{h}_i, \hat{d}_i \in [0,1]$, such that $\hat{d}_i$ is a proportion decrease in the mortality rate and $\hat{h}_i$ is the degree of allelic dominance, similar to (Gillespie, 2004) population genetic model —see (Luz et al., 2009).

- The density-dependence mortality parameter ($\hat{\mu}, \mu$) depends on the availability of resources in the system and consequently impacts on the load capacity. The relative density between larvae and adults depends on this parameter.

- The mortality rate for susceptible homozygous adult (μ_3) presents values in $[0.02, 0.09]$ (Koiller et al., 2014a; Xue et al., 2017; Adekunle et al., 2019); while the mortality rates for A_1 (μ_{10}) take values in $\mu_3(1-d_1)$ and the mortality rates for A_2 (μ_2) in $\mu_3(1-h_1d_1)$ for $h_i^\eta, d_i \in [0,1]$.

- The fecundity rate of A_i (f_i) presents values in $[4, 18]$ (Koiller et al., 2014a; Hoffmann et al., 2014a; McMeniman et al., 2009; McMeniman and O'Neill, 2010; Adekunle et al., 2019).

3.3.2 Simulation of several evolutionary scenarios

We present here simulations using the two phase compartmental model (2.1). In Tables 3.1 and 3.2, we present the initial conditions and baseline parameters assumed for the simulated scenarios. Parameter configurations represent hypothetical evolutionary

scenarios, the purpose of these settings is to show the capacity of the model to describe well-known situations.

The simulations from setting 1 to 8 presented below are supported by the analytical results of Chapter 2. Among them, the simulations for setting 5, 6, 7 and 8 are scenarios of directional selection. On the other hand, the scenarios given for setting 9 to 11 (overdominance and underdominance) correspond respectively to stabilizing selection and disruptive selection.

Table 3.1: Setting for initial conditions under different evolutionary hypothetical scenarios.

Setting	L_{1_0}	L_{2_0}	L_{3_0}	A_{1_0}	A_{2_0}	A_{3_0}
1	0	0	0	10	40	20
2	0	0	0	10	0	0
3	0	0	0	0	0	10
4	0	0	0	10	40	30
5	18	0	70000	0	0	50000
6	18	0	70000	0	0	50000
7	18	0	70000	0	0	50000
8	1000	0	70000	0	0	50000
9	0	18	70000	0	18	50000
10	1000	100	1000	1000	100	1000
11	5000	5000	30000	5000	10000	30000

Table 3.2: Setting for parameters under directional selection hypothetical scenarios.

Setting	d_1	h_1	$\hat{d}_1$	$\hat{h}_1$	μ_{30}	$\hat{\mu}_{30}$
1	0	0	0	0	0.2	0.09
2	0.03	0.5	0	0	0.3	0.09
3	0.03	0.5	0	0	0.3	0.09
4	0.03	0.5	0	0	1.2	1.09
5	0	0	0.03	0.5	0.2	0.09
6	0.03	0.5	0	0	0.2	0.09
7	0.03	1	0	0	0.2	0.09
8	0.03	0	0	0	0.2	0.09

In all cases: $\mu = 1.e-5$, $\hat{\mu} = 1.e-2$, $\mu_{10} = \mu_{30}(1-d_1)$, $\mu_{20} = \mu_{30}(1-h_1 d_1)$, $\hat{\mu}_{10} = \hat{\mu}_{30}(1-\hat{d}_1)$, $\hat{\mu}_{20} = \hat{\mu}_{30}(1-\hat{h}_1\hat{d}_1)$, $f_i = 18$, $\nu_i = 18 \times 0.1$, $v_i = 1$ and $w_i = 1/18$.

3.3.2.1 Selectively neutral genotypes.

The first illustrated numerical result is a scenario without selection (Figure 3.1). This result is obtained from the assumption that all genotypes have the same viability in the

Table 3.3: Setting for parameters under stabilizing selection and disruptive selection hypothetical scenarios.

Setting	μ_{30}	μ_{20}	μ_{10}	$\hat{\mu}_{30}$	$\hat{\mu}_{20}$	$\hat{\mu}_{10}$
9	0.2	$\mu_{30}(1-0.015)$	μ_{30}	0.09	0.09	0.09
10	0.2	$\mu_{30}(1+0.03)$	μ_{30}	0.09	0.09	0.09
11	0.2	$\mu_{30}(1+0.1)$	μ_{30}	0.09	0.09	0.09

In all cases: $\mu = 1.e-5$, $\hat{\mu} = 1.e-2$, $f_i = 18$, $\nu_i = 18 \times 0.1$, $v_i = 1$ and $w_i = 1/18$.

two life phases. Given this assumption, in absence of selection the population grows until reaching a stable non-trivial polymorphic equilibrium with the three genotypes.

Note that the allele frequencies remain constant along time and equal for the two phases (no selection), according to Theorem 2.13 p. 33 and the Hardy-Weinberg principle. All other examples provided below present selection situations.

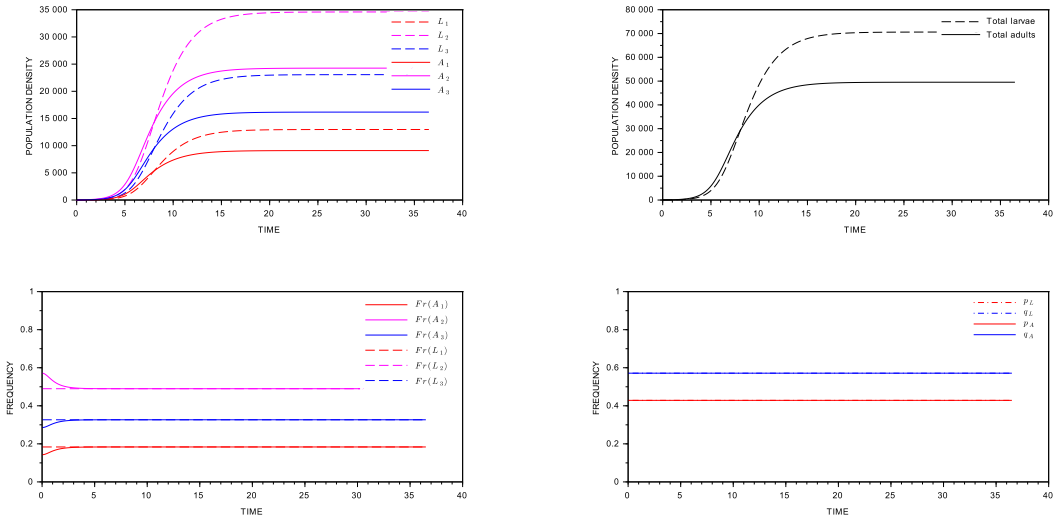


Figure 3.1: Selectively neutral genotypes trajectory of larvae and adults is shown when it is assumed that there are no differences in viability between genotypes (left). The alleles relative frequencies remain constant over time (right). Setting for simulation 1 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.1.

3.3.2.2 Monomorphic trajectories with highest or lowest fitness.

Figure 3.2 shows monomorphic trajectories —see Definition 2.5— for a system submitted to selection. In this case, regardless of the configuration of parameters, when the initially existing genotype is viable, the trajectory converges to a stable non-zero equilibrium, even if the corresponding genotype has the lowest fitness.

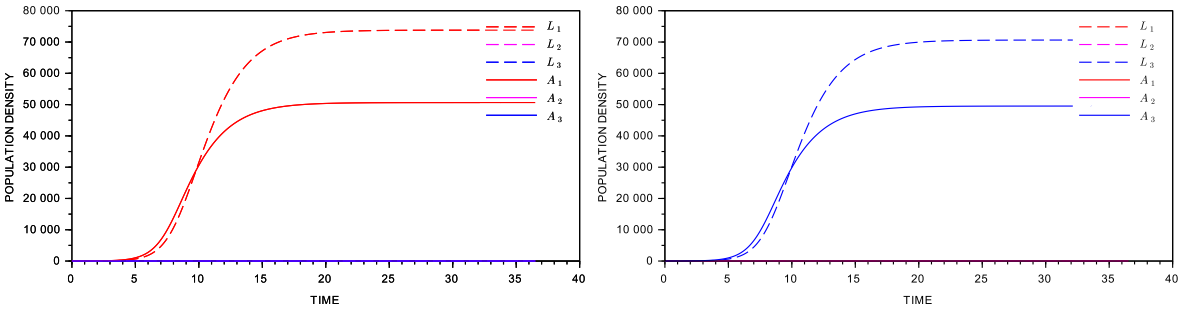


Figure 3.2: Monomorphic trajectory of the allele with the lowest fitness (left) and monomorphic trajectory of the allele with the highest fitness (right). Setting for simulation 2 and 3 respectively are given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.2.

3.3.2.3 All inviable genotypes.

Contrary to the previous case, if all genotypes are inviable for a given niche, for any initial condition, a trivial equilibrium point is achieved. Indeed, an unviable population is assumed and, consequently, it extinguishes as one can see in Figure 3.3. Note that unlike a standard population genetics model that assumes infinite population sizes and focuses on changing frequencies, from an appropriate parameter setting the simulated model here is capable of representing scenarios of extinction population. These types of scenarios are useful, for example, in cases where one wishes to completely eliminate a pathogen, even when there are differences in the fitness of genotypes. As states (Bull et al., 2007), extinction is a demographic phenomenon that depends on absolute fitness. Consequently for this case population genetics models based on relative fitness are useless.

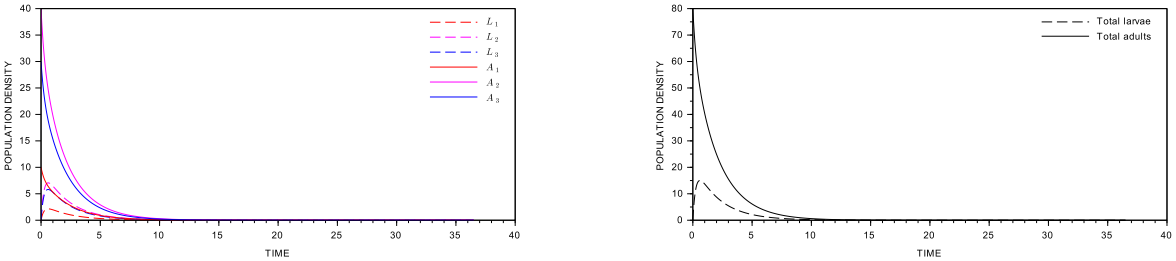


Figure 3.3: Unviable population. Setting for simulation 4 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.3.

3.3.2.4 Incomplete dominance with selection.

Figures 3.4 and 3.5 illustrate cases of incomplete dominance where each genotype corresponds to a different and ordered fitness in a viable population. In the parameter setting, genotype 1 has a viability strictly greater than genotype 2 and this by its

turns, it in is strictly greater than genotype 3. In Figure 3.4, these differences are given in terms of adult mortality such that $\hat{\mu}_{10} < \hat{\mu}_{20} < \hat{\mu}_{30}$, whereas in Figure 3.5 the differences in viability are given in terms of larva mortality terms such that $\mu_{10} < \mu_{20} < \mu_{30}$. In Figure 3.4 initial condition is near the carrying capacity reached in the monomorphic case of genotype with the lower fitness —see Figure 3.2, right—, but also with $L_{1_0} = 1$ for the highest fitness genotype. In fact, given an initial polymorphic state for these two cases (5, 6), given an initial polymorphic state, the population converges asymptotically to a stable monomorphic equilibrium where the genotype with the lower fitness disappears. Note that with the parameter settings for mosquito populations, the insecticide is no longer effective after approximately 5 years of use.

One can see (Figure 3.4 and 3.5) that even from a sufficiently large population in the presence of polymorphism and directional selection, the final maximal population size is determined by the highest fitness. Consequently, for the model in question the notion of invariant population and directional selection are exclusive. An example would be the evolution of resistance resulting from the use of chemical larvicides or adulticides to control disease-carrying mosquitoes. It is said that a population is in an "evolutionarily stable state" if its genetic composition is restored after a small perturbation (Smith et al., 1982). As illustrated in Figures 3.2 and 3.4, we can say that an evolutionarily stable state is reached under conditions 3 (this is a scenario where only the homozygous genotype given by the allele with the lowest fitness is present.) and 6 (It is a scenario where given the environmental conditions the population is going towards extinction), but not under condition 2 (This is a scenario where only the homozygous genotype given by the allele with the highest fitness is present).

3.3.2.5 Complete dominance of allele with the highest or lowest fitness.

Now, we show cases of complete dominance in the population dynamic with selection in pre-adult phase. In such a case, the heterozygous genotype expresses the same phenotype as one of the two homozygotes and, hence consequently the same fitness. Figure 3.6 shows a scenario with complete dominance of the allele with highest fitness: $\mu_{10} = \mu_{20} < \mu_{30}$. This is a case of selection against the recessive allele and in favor of the dominant one. Figure 3.7 shows a scenario with complete dominance of the allele with lowest fitness: $\mu_{10} < \mu_{20} = \mu_{30}$. This is a case of *selection in favor of the recessive allele and against the dominant.* As a matter of fact, one can see that just like in the scenarios 5 and 6, in 7 and 8 given a polymorphic initial condition, a stable monomorphic equilibrium is reached corresponding to the homozygous genotype with higher fitness.

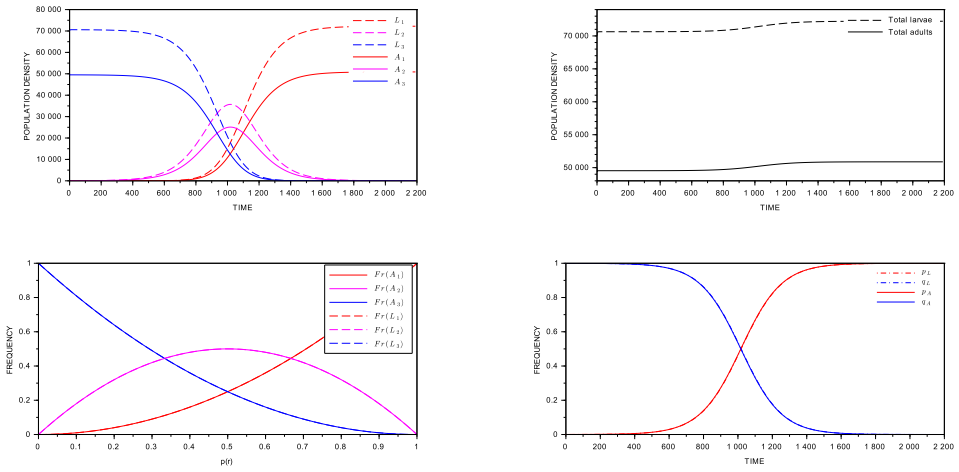


Figure 3.4: Incomplete dominance for selection in the adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies over time (bottom-right). The genotype relative frequencies given highest fitness alleles relative frequencies (bottom-left). Setting for simulation 5 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.4.

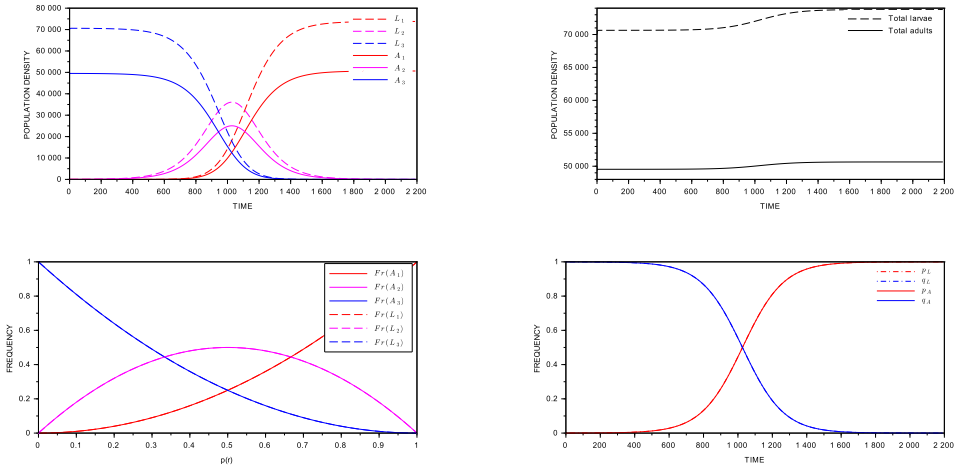


Figure 3.5: Incomplete dominance for selection in the pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies over time (bottom-right).The genotype relative frequencies given highest fitness alleles relative frequencies (bottom-left). Setting for simulation 6 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.4.

Comparing the dynamics illustrated in Figures 3.3, 3.4 and 3.5 one can observe a clear effect of genetic dominance on the disappearance of polymorphism in the population. The data published by Dawson (Dawson, 1970) are an example of how recessiveness and genetic dominance affects evolution. Freeman and Herron (Freeman and Herron, 2007) provide a detailed explanation of this type of evolutionary scenario. In

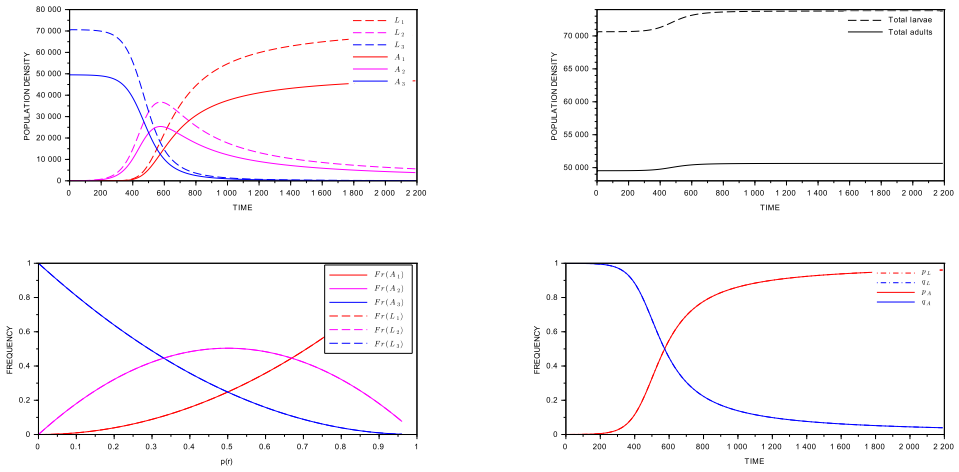


Figure 3.6: Complete dominance of allele with the highest fitness with selection in pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies over time (bottom-right). The genotype relative frequencies given highest fitness alleles relative frequencies (bottom-left). Setting for simulation 7 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.5.

Figure 3.5 one can see how the selection is less potent when acting against frequent dominant alleles and in favor of rare recessive alleles. This last prediction is consistent with that observed by the aforementioned authors. At the same time, this effect impacts on the total population size of the two life phases.

Note that from the same initial state configuration (Table 3.2: 3, 5, 6) there are two distinguishable moments in the three figures for the maximum population: the first with predominance of the allele with lowest fitness and the second with predominance of the allele with highest fitness to which the population finally converges. When the complete genetic dominance is for the allele with highest fitness (Figure 3.4) the duration of allele predominance with lowest fitness is reduced by almost half compared to the case of intermediate dominance (Figure 3.3). On the other hand, when the complete genetic dominance is of the allele with lowest fitness the predominance of alleles with lowest fitness is more durable (Figure 3.5), at least more larger than in the case of incomplete dominance (Figure 3.3). In the two cases of complete domination illustrated, the polymorphic trajectory in the population extends over the time. These results have a particular relevance in situations where it is desired to establish a threshold in the population through chemical control, also, the evolution of resistance appears and the degree of dominance allele can be altered by the lethal dose used —see (Taylor and Georghiou, 1979) and the next Chapter in this thesis.

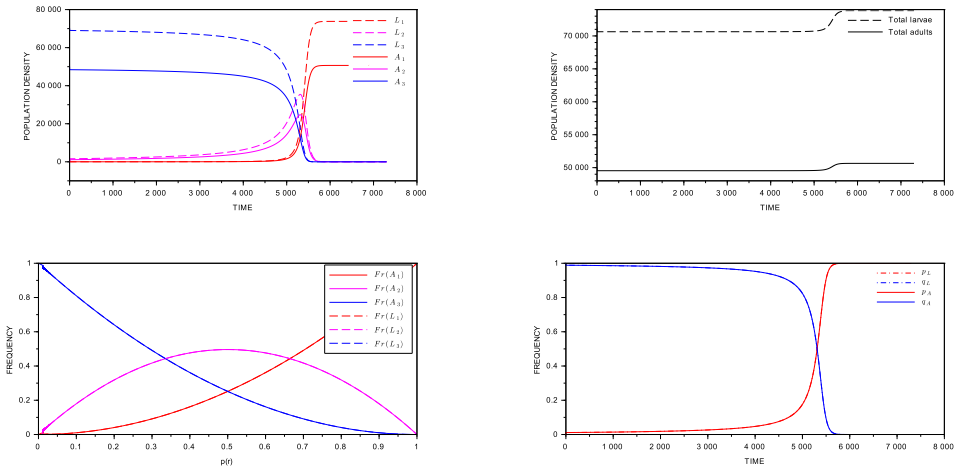


Figure 3.7: Complete dominance of allele with the lowest fitness with selection in pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies over time (bottom-right). The genotype relative frequencies given highest fitness alleles relative frequencies (bottom-left). Setting for simulation 8 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.5.

3.3.2.6 Overdominance with selection in the pre-adult phase.

Such simulations correspond to cases of stabilizing selection, described as an advantage of heterozygotes over homozygotes. In setting 9, heterozygous advantage is caused by lower mortality in the pre-adult phase: $\mu_2 < \mu_1, \mu_3$. In this case, whenever the initial condition of the system is polymorphic, the population converges asymptotically to a stable polymorphic equilibrium point and to a stable allele frequency (Figure 3.8).

3.3.2.7 Underdominance with selection in the pre-adult phase.

The next described simulations correspond to cases of disruptive selection. It is the cases for heterozygote disadvantage, known as underdominance. In setting 10 and 11, the heterozygous disadvantage is caused by a higher mortality in the pre-adult phase: $\mu_2 > \mu_1, \mu_3$. Figure 3.9 represents convergence towards a polymorphic state. In setting 11 is considered a small perturbation that changes the initial allelic frequencies. Besides, in Figure 3.10 one can see how the homozygous genotype with the most frequent initial allele reaches a monomorphic equilibrium. In the case of underdominance, one allele increases in frequency if it is common or decreases in frequency if it is rare. The critical point between the two regions in which the allele increases or vanishes, is an *unstable polymorphic equilibrium.*

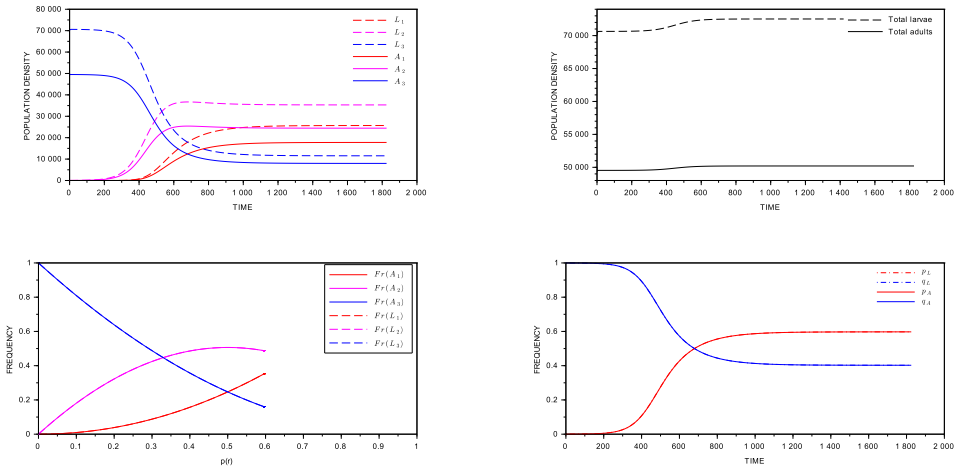


Figure 3.8: Overdominance with selection in pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies for any time (bottom-right). The genotype relative frequencies for any time (bottom-left). Setting for simulation 9 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.6.

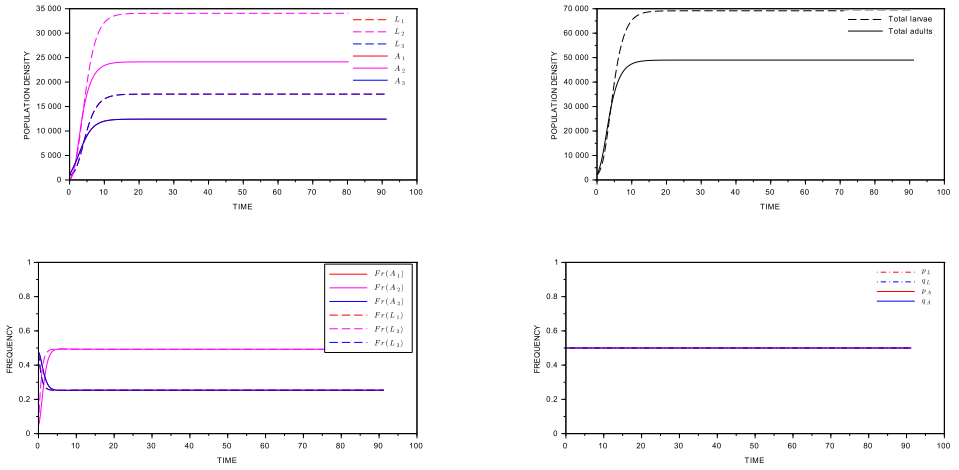


Figure 3.9: Underdominance 1 with selection in pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies for any time (bottom-right). The genotype relative frequencies for any time (bottom-left). Setting for simulation 10 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.7.

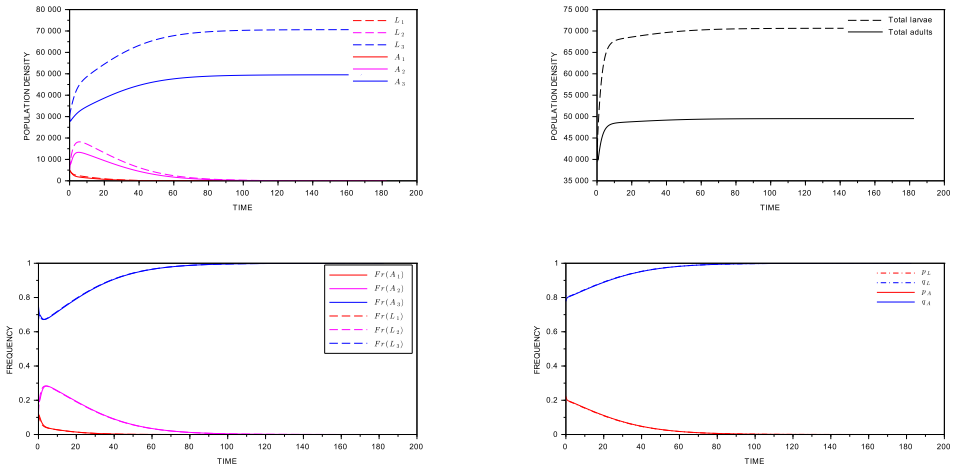


Figure 3.10: Underdominance 2 with selection in pre-adult phase. Genotype trajectory for larvae and adult (top-left). Total population larva and adult (top-right). The alleles relative frequencies for any time (bottom-right). The genotype relative frequencies for any time (bottom-left). Setting for simulation 9 is given in Tables 3.1 and 3.2. See further explanations in Section 3.3.2.7.

3.3.3 Comparison between the singular perturbed and unperturbed models

In order to show the effects of the change in dynamics, we introduce the following variants of (2.1):

$$\varepsilon_L \dot{L}_i = \alpha_i(A(t)) - \mu_i(v^\mathsf{T} L(t))L_i(t) - \nu_i L_i(t), \qquad i = 1,2,3 \tag{3.18a}$$

$$\varepsilon_A \dot{A}_i = \nu_i L_i(t) - \hat{\mu}_i(w^\mathsf{T} A(t))A_i(t), \qquad i = 1,2,3 \tag{3.18b}$$

for nonnegative values of $\varepsilon_L, \varepsilon_A$. System (2.1) is obtained in the case where $\varepsilon_L = \varepsilon_A = 1$.

In the context of fast and slow phases in evolutionary systems, we show here comparisons of several simulations: the *Full model* (2.1), the *Fast reproductive phase model* (3.9) and the *Slow reproductive phase model* (3.17) deduced by singular perturbation, and the model (3.18) with different choices of $\varepsilon_L, \varepsilon_A$. With a special interest in the analytical formulations and demonstrations presented in (P.E. Perez-Estigarribia, 2019a) about selectively neutral evolution and directional selection for class (3.9a) and (3.17b) models, we are interested in numerically illustrating what happens when one phase of life tends to be noticeably faster with respect to another, e.g. $\varepsilon_L \to 0$ and $\varepsilon_A = 1$ or $\varepsilon_L = 1$ and $\varepsilon_A \to 0$.

Starting from setting 6 given in Tables 3.1 and 3.2, Figure 3.11 compares cases where the adult phase is faster than the pre-adult one. Here, the dynamics of pre-

adult phase genotypes is illustrated in the Figures a, b, c, while, the dynamics of adult phase genotypes is illustrated in the Figures d, e, f, such that $\varepsilon_L = 0.9$ and $\varepsilon_A = 1$. The row three and four of the Figures g, h, i and j, k, l correspond to the genotypes of the pre-adult and adult phase respectively such that $\varepsilon_L = 0.1$ and $\varepsilon_A = 1$.

Similarly, Figure 3.12 shows regular perturbations of the pre-adult phase. The first two rows of the figure correspond to setting $\varepsilon_L = 1$ and $\varepsilon_A = 0.9$, rows three and four are given by setting $\varepsilon_L = 1$ and $\varepsilon_A = 0.1$.

For all cases in Figures 3.11 and 3.12, it can be seen that to the extent that ε approaches zero the curves of system with regular perturbation move away from the numerical solution of the full model and approach the solution of the models deduced by singular perturbation. We can observes that, given the same initial condition and the same parameter setting, *all four models show the same qualitative behavior*. That is, for the same initial conditions and setting of parameters, they represent the same types of evolutionary phenomena.

3.4 Conclusions and future issues

Inspired by the modeling and analysis in Chapter 2, we have presented an explicit model of population dynamics with Mendelian inheritance representing two phases of life: a pre-reproductive and other reproductive. The proposed model unifies the fundamental principles of population dynamics and population genetics, and as shown in numerical simulations, with the appropriate setting of parameters and initial conditions, it can describe different evolutionary scenarios.

In addition, assuming both fast and slow phases, two simple models of a dynamic governed by recruitment and mortality in a single phase of life have been deduced from the complete model. In this respect, numerical simulations show that, given the same set of parameters and initial conditions, the two-phase compartmentalized model and the two simpler models derived by slow manifold theory show the same qualitative behavior.

These classes of models are applicable in situations where life phases occupy different ecological niches —*e.g.* aquatic and aerial as the case of mosquitoes, and consequently each phase of life can be subjected to different selective pressures that impact on population dynamics —*e.g.*, agents larvicide and/or adulticide.

As future issues, we are interested in studying the capacity of extensions the proposed inheritance systems to model phenomena that involve combinations of attributes governed by multiple loci.

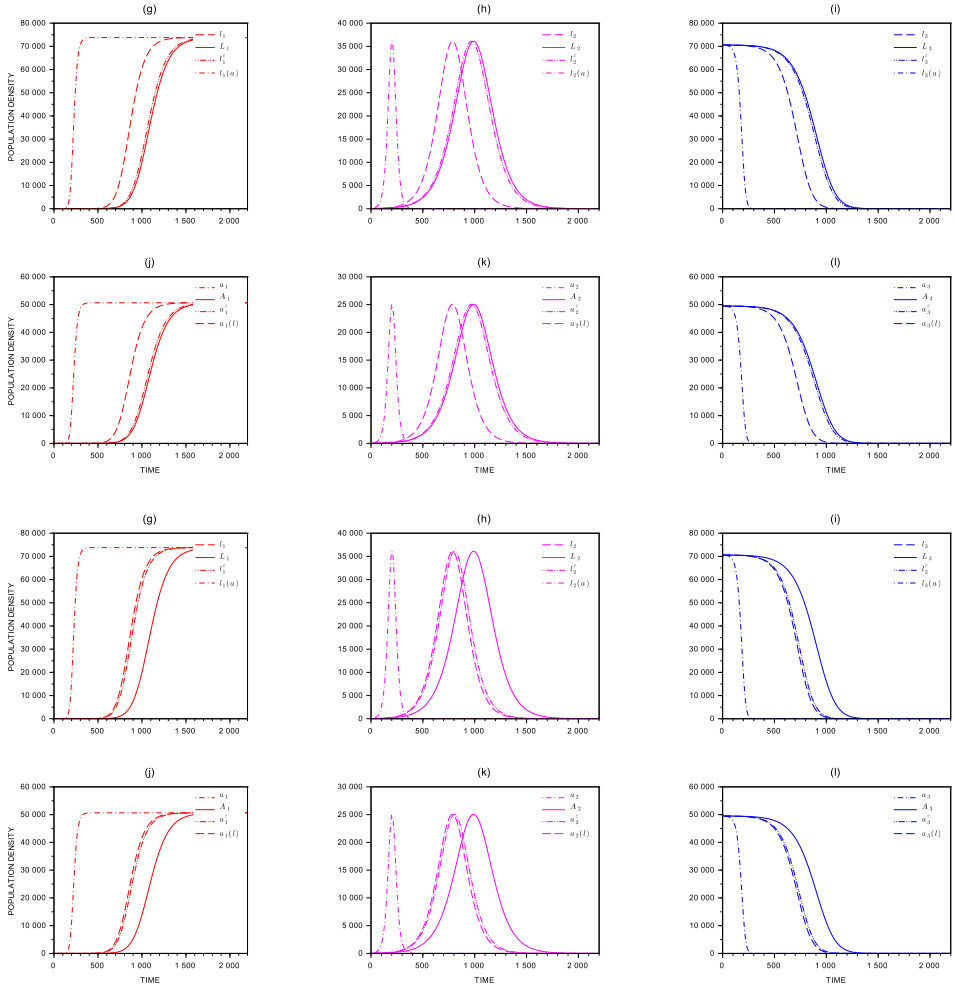


Figure 3.11: The curves of four simulations are compared, the full model (continuous line), Fast reproductive phase model (interrupted line), Slow reproductive phase model (line interrupted by a point) and simulations for different magnitudes of regular perturbation in the adult phase (line interrupted by two points). See further explanations in Section 3.3.3.

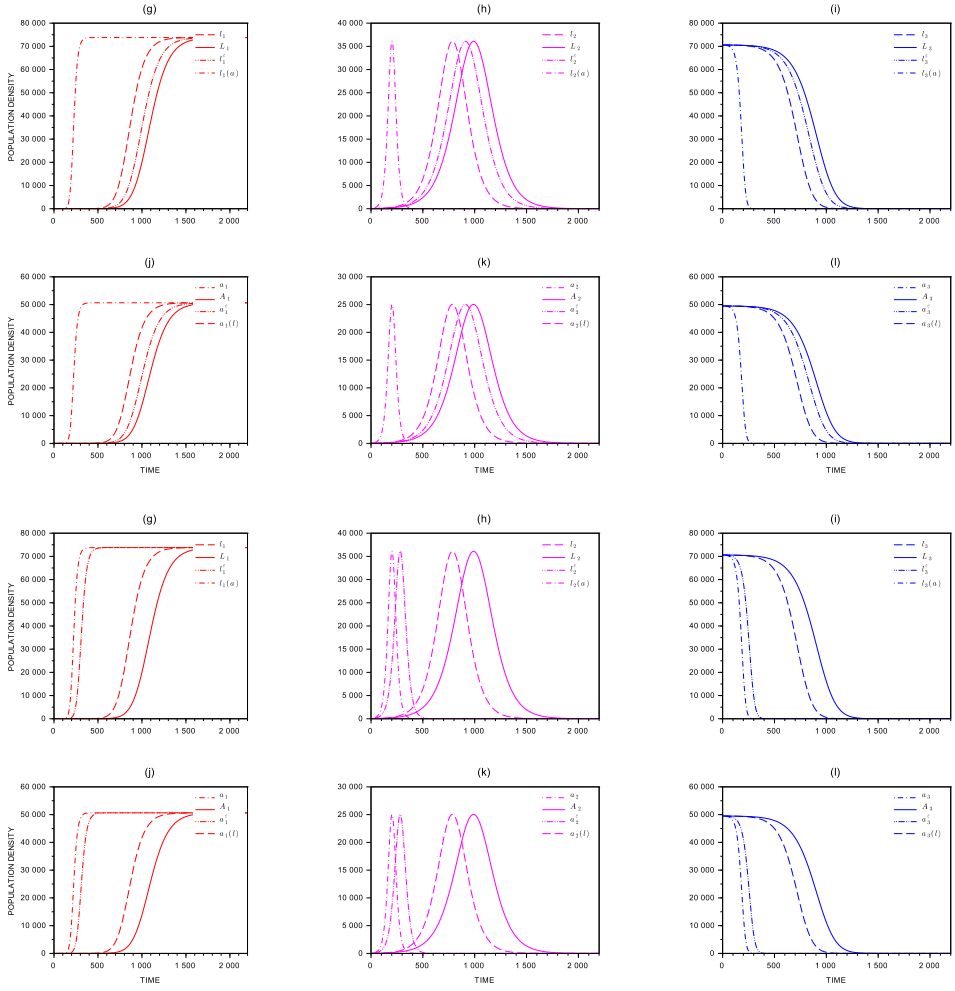


Figure 3.12: The curves of four simulations are compared, the full model (continuous line), Fast reproductive phase model (interrupted line), Slow reproductive phase model (line interrupted by a point) and simulations for different magnitudes of regular perturbation in the larvae phase (line interrupted by two points). See further explanations in Section 3.3.3.

Chapter 4

Levels of dominance and the reversal of insecticide resistance

4.1 Introduction

The evolution of resistance to insecticide is a recurring problem in agronomy and public health. As mentioned in Chapters 1 and 2, pest control through the use of larvicides or adulticides is a widely used strategy. In agronomy, insect pests can damage agricultural production. While for Public Health, they pose the risk of creating an epidemic of some insect-borne diseases.

The increase in frequency of resistant individuals due to the use of insecticides is a case of directional selection caused by humans. Chemical resistance can be regulated by different genetic mechanisms, either by multiple loci or a single locus in the genome. A mechanism regulated by diallelic genes resistant and susceptible in a locus is represented in Mendelian genetic by three genotypes, however, in these cases the number of phenotypes is given by the dominance level of the alleles and it may be governed by the insecticide lethal dose (Taylor and Georghiou, 1979; Bourguet et al., 2000).

As a matter of fact, the dominance or recessivity of resistance to an insecticide is not necessarily beyond the reach of human control (Curtis et al., 1978). The empirical support of this property of insecticide resistance is the toxicological essays is given by dose mortality that proves homozygous resistance, heterozygous and susceptibility under controlled laboratory conditions —see (Priester and Georghiou, 1978; Curtis et al., 1978; Taylor and Georghiou, 1979; Bourguet et al., 2000). As is known, the purpose of chemical resistance management strategies is to maintain a null or low resistance frequency and thereby prolong its effectiveness. The dominance or genetic recessiveness alters the speed with which the selection acts (Dawson, 1970; Freeman

and Herron, 2007). In that matter, being able to quantify the effect of dominance level on changes in frequency by selection can help to search better strategies for the management of resistance evolution.

On the other hand, stopping the use of an insecticide can change the parameters of life history to the detriment of resistant genotypes. This effect is known as resistance fitness cost and it can have the effect of reverting the frequency of resistance genes in a population. There have been reports on insecticide resistance fitness costs in many species of insects (Kliot and Ghanim, 2012). Once a resistant mutant is introduced into a population, this attribute can spread very quickly, for example, in the case of *Aedes aegypti* there are reports of populations where the frequency of the 1534Cys mutant allele is above 95%, however, also there is evidence of slow reversal in the absence of insecticidal pressure (Garcia et al., 2012). In fact, under certain circumstances, the persistence of resistance to an insecticide in a population may be constrained by resistance fitness cost (Schechtman and Souza, 2015).

The potential to slow down or even stop the evolution of resistance through evolution-proof insecticides is a hot topic explored through mathematical models (Koella et al., 2009b; Read et al., 2009; Gourley et al., 2011). In this regards, the application of insecticides that exert directional selection at an early or late phase of life (Gourley et al., 2011), the cost of fitness (Koella et al., 2009b; Schechtman and Souza, 2015), or the level of resistance dominance associated with the lethal dose (Helps et al., 2017) are aspects that may affect the speed of evolution by selection.

In the context of insecticide resistance reversal in this chapter through simulation, the following questions are addressed:

1. How does the level of allelic dominance dependent on lethal dose of adulticide or larvicide affect the evolution of resistance?

2. How does the level of a lethal-dose-dependent allelic dominance affect the reversal of resistance?

3. How can levels of dominance and the reversal be used in the management of insecticide resistance?

For this purpose, the model introduced and analyzed in Chapter 2, and implemented for the simulations presented in Chapter 3.

4.2 The two phases model

The model used here corresponds to the two life phases implemented for the simulations in Charter 3 and analyzed in Chapter 2. In that sense, recall that dynamics is governed by

$$\begin{aligned}\dot{L}_i &= \frac{1}{\mathbf{1}^\intercal F A(t)}(FA(t))^\intercal G_i F A(t) - \mu_i(v^\intercal L(t))L_i(t) - \nu_i L_i(t)\\ \dot{A}_i &= \nu_i L_i(t) - \hat{\mu}_i(w^\intercal A(t))A_i(t),\end{aligned}$$

for $i = 1, 2, 3$. This formulation is identical to the equation (2.1), p. 15.

The quantities L_i (*Larvae*) represent the number of individuals of the genotypes ($i = 1, 2, 3$), in pre-adult phase, and A_i (*Adults*) the corresponding number of adult individuals.

The parameters involved in (2.1) have the following meaning. The mortality functions $\mu_i(v^\intercal L)$ and $\hat{\mu}_i(w^\intercal A)$ depend upon the density, through the use by the population of a certain resource (typically food or space). Here v, w are *positive vectors* that allow each genotype to have its proper consumption needs. The quantities ν_i describe a constant maturation rate from the pre-adult to the adult phase. The fertility for each genotypes is given by the positive diagonal matrix $F := \mathtt{diag}\{f_i\}$ for $i = 1, 2, 3$.

Notice that the heredity functions, represented by the additive expression on the right side of equation (2.1a) which gives births by genotypes, represents a rate of crosses of males with females, and G_i is an inheritance matrix deduced from the mechanism considered. Using $u_r = (1 \quad \frac{1}{2} \quad 0)^\intercal$ and $u_s = (0 \quad \frac{1}{2} \quad 1)^\intercal$ one may define Mendelian inheritance matrices $G_i \in \mathbb{R}_+^{3\times 3}$ as

$$\begin{aligned}G_1 &:= u_r u_r^\intercal,\\ G_2 &:= u_r u_s^\intercal + u_s u_r^\intercal,\\ G_3 &:= u_s u_s^\intercal.\end{aligned}$$

For the mortality functions, the explicit form introduced in Chapter 3 (Assumption 5, p.58) is retained. Namely, for any $z \in \mathbb{R}_+$, the mortality rate functions verify

$$\begin{aligned}\mu_i(z) &= \mu_{i0}(1 + \mu z), \qquad i = 1, 2, 3\\ \hat{\mu}_i(z) + \nu_i &= \hat{\mu}_{i0}(1 + \hat{\mu} z), \qquad i = 1, 2, 3\end{aligned}$$

for positive $\mu, \hat{\mu}$ and $\mu_{i0}, \hat{\mu}_{i0}$, $i = 1, 2, 3$. For more details on the deduction, analysis

and additional numerical simulations in the context of evolution of this model one can consult Chapters 2 and 3 of this Thesis.

4.3 Implementation issues

All the simulations were done with the free and open-source programming language Scilab. To ensure the reproducibility of the results, we developed a code with GUI.The details of the source code, and how to use it are provided in the Appendix A. The simulation results presented here were visualized with the ggplot2 library implemented in R.

In all simulations presented in this chapter, we assume that:

- Insecticides do not affect the fertility of genotypes (absence of fertility selection).
- Resistance genes reduce mortality, *e.i.*, insecticides affect the survival of genotypes —see (Luz et al., 2009).

The initial condition and parameter settings for the simulations are presented in Table 4.1 and 4.2 respectively. We chose these values to illustrate numerical examples that help to answer the questions above. The baseline value domains for the parameters used here were introduced and referenced in the previous chapter.

Settings I and II have been used to answer Question 1, considering the use of larvicide and adulticide scenarios respectively. In these cases the level of dominance is defined by h in $0 \leq h \leq 1$. More precisely, to portray the effect of dominance levels on the evolution of resistance, we considered that the survival of genotypes in the model (2.1) could be affected by a larvicide (in (4.2)) such that

$$\mu_{10} = \mu_{30}(1-\delta) \leq \mu_{20} = \mu_{30}(1-h\delta) \leq \mu_{30} \tag{4.3}$$

for any $0 \leq \delta \leq 1$. As formulated in the previous chapter, here the mutant allele of resistance contributes to a decrease in mortality and depends on some degree of allelic dominance. In consequence, let $h, \delta \in [0,1]$ be, such that δ is a proportion decrease in the mortality rate and h is the degree of allelic dominance, similar to (Gillespie, 2004) population genetic model —see (Luz et al., 2009). In this formulation, $h = 0$ corresponds to the genetic resistance dominance, $h = 1$ represents recessive resistance and the successive values of $0 < h < 1$ correspond to cases of incomplete dominance. Successive values in $0 \leq h \leq 1$ have been selected for an in-silico experiment for independent simulations —see Table 4.2, in empirical terms these values should be

given by lethal doses of an insecticide that induce different levels of dominance —see (Priester and Georghiou, 1978; Curtis et al., 1978; Taylor and Georghiou, 1979; Bourguet et al., 2000).

A similar formulation is used in the case of adulticide (in (4.2)), namely

$$\hat{\mu}_{10} = \hat{\mu}_{30}(1-\hat{\delta}) \leq \hat{\mu}_{20} = \hat{\mu}_{30}(1-\hat{h}\hat{\delta}) \leq \hat{\mu}_{30}. \tag{4.4}$$

To simulate the reversal resistance, we considered fitness cost, therefore, we interpret that interrupting the use of insecticides induces a higher survival of susceptible phenotypes compared to resistant ones. We have used setting III, IV, and V to answer Question 2, for these cases, the switch $\kappa \in [-1, 1]$ control the fitness cost on the resistance phenotype by interrupting temporally the insecticide —see Table 4.2.

Setting VI has been used to explore options in the context of Question 3. The presented numerical example illustrates a case of adulticide use in rectangular wave pulses.

Table 4.1: Setting for initial conditions under different evolutionary hypothetical scenarios.

Setting	L_{1_0}	L_{2_0}	L_{3_0}	A_{1_0}	A_{2_0}	A_{3_0}
I-VI	180	0	70000	180	0	50000

In all cases: $\mu = 1.e-5$, $\hat{\mu} = 1.e-2$, $\mu_{10} = \mu_{30}(1-\delta)$, $\mu_{20} = \mu_{30}(1-h\delta)$, $\hat{\mu}_{10} = \hat{\mu}_{30}(1-\hat{\delta})$, $\hat{\mu}_{20} = \hat{\mu}_{30}(1-\hat{h}\hat{\delta})$, $f_i = 18$, $\nu_i = 18 \times 0.1$, $v_i = 1$ and $w_i = 1/18$. In I and II, let be $0 \leq h \leq 1$ or $0 \leq \hat{h} \leq 1$ such that take successive values in $D = \{0, 0.001, 0.01, 0.2, 1\}$ for different dominance level. The switch $\kappa \in [-1, 1]$ controls the fitness cost on resistance by interrupting temporally the insecticide, $\kappa = 1$ is when the insecticide is applied, $\kappa = 0$ is when the insecticide is not applied and conditions are selectively neutral, and $-1 \leq \kappa < 0$ is when the insecticide is not applied and there is a metabolic cost for the resistance genotype.

Table 4.2: Setting for parameters under different evolutionary hypothetical scenarios.

Setting	κ	δ	h	μ_{30}	$\hat{\delta}$	$\hat{h}$	$\hat{\mu}_{30}$
I	1	0.2κ	D	0.2	0	0	0.09
II	1	0	0	0.2	0.2κ	D	0.09
III	$\{-0.2, 1\}$	0	0	0.2	0.2κ	0.5	0.09
IV	$\{-0.2, 1\}$	0	0	0.2	0.2κ	1	0.09
V	$\{-0.2, 1\}$	0	0	0.2	0.2κ	0	0.09
VI	$\{-0.2, 1\}$	0	0	0.2	0.2κ	0.5	0.09

4.4 Numerical simulations

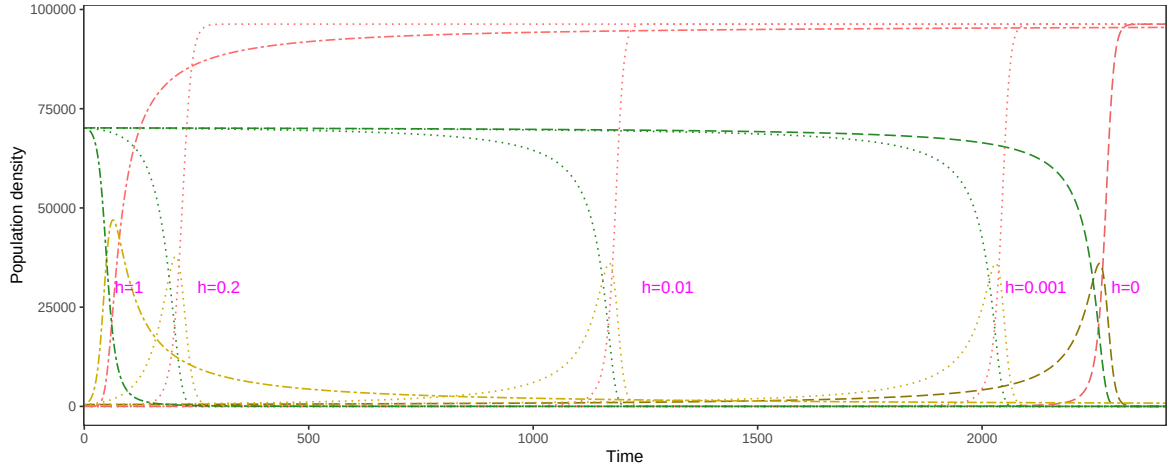
4.4.1 Resistance to larvicide under dominance levels effect.

The evolution of insecticide resistance is a case of directional selection. In the case presented below, the selection is governed by a difference in the survival in favor of the resistant phenotype and against the susceptible phenotype due to the lethal dose used. In these cases, as demonstrated in Chapter 2 and illustrated numerically in Chapter 3, the system converges asymptotically to a monomorphic non-trivial equilibrium point with only resistant individuals.

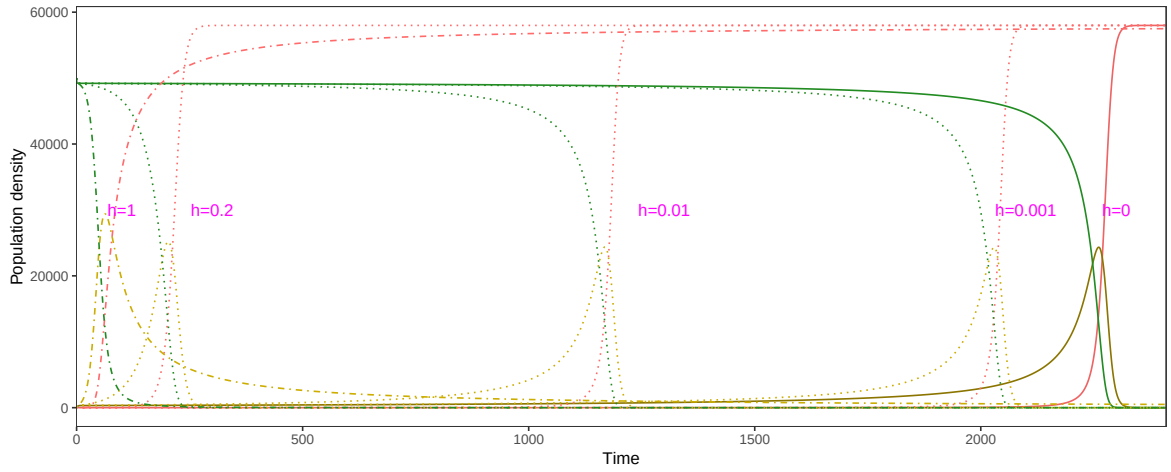
In the Figure 4.1 are illustrate the dynamics of genotypes when the differences in survival are determined by the use of a larvicide —see (Norgaard, 1976). Figure 4.1a shows larvae dynamics and the Figure 4.1b shows adult. Dashed and solid lines show dynamics when larvicide resistance is dominant ($h = 1$), such that differences in survival fulfill $\mu_{10} = \mu_{20} < \mu_{30}$. The dot-dashed lines illustrate the dynamics when larvicide resistance is recessive ($h = 0$) such that differences in survival fulfill $\mu_{10} < \mu_{20} = \mu_{30}$. While, dotted lines show successive levels of incomplete dominance such that the differences in larvicide survival fulfill $\mu_{10} < \mu_{20} < \mu_{30}$, when it is assumed that dominance level can be controlled by the lethal dose of an insecticide —*e.g.* (Curtis et al., 1978; Bourguet et al., 2000). The same scheme applies to adulticide. This is achieved by setting in (4.3) or (4.4) the successive values of $h \in \{0, 0.001, 0.01, 0.2, 1\}$ for independent simulations, such that one represent different levels of dominance. Note that to the extent that resistance becomes recessive ($h \to 0$ or $\hat{h} \to 0$), one can see that the decrease of susceptible density occurs later.

The rising frequency of resistance alleles computed from genotypes dynamics (in Figure 4.1) is illustrated in Figure 4.2. The dashed lines in the larval 4.2a and solid lines in adult 4.2b phase correspond to the case of complete resistance recessive ($h, \hat{h} = 0$). The dot-dashed lines correspond to the case of dominant resistance ($h, \hat{h} = 1$). While, the successive dotted lines illustrate intermediate levels of dominance. In this in-silico experiment, it is observed that the replacement of a majority-susceptible population to a majority-resistant population is delayed to the extent that $h \to 0$ in $\mu_{10} = \mu_{30}(1-\delta) \leq \mu_{20} = \mu_{30}(1 - h\delta) \leq \mu_{30}$ for any $0 < \delta$, namely, resistance is setting recessive. In short, the directional selection is slower when the heterozygous has a worse fitness.

Chemical insect control usually aims to keep pest population below a threshold. The total larvae and adults population density computed from the dynamics of genotypes is illustrated in Figure 4.3. The horizontal dashed line represents a hypothetical damage threshold, solid line corresponds to the dynamic in case of recessive resistance, the dot-



(a) Larvae



(b) Adult

Figure 4.1: Dynamic of Mendelian genotypes with larvicide resistance for different dominance levels of alleles. Red line represented resistance genotype, golden line correspond to heterozygote, while green line is susceptible genotype. Let be $0 \leq h \leq 1$ such that take successive values in $h \in \{0, 0.001, 0.01, 0.2, 1\}$ for different dominance level. The dashed line in 4.1a correspond to larvae genotype for recessive resistance allele ($h = 0$ in equation (4.3)). The solid line in 4.1b is adult genotype for recessive resistance allele. The dot-dashed line illustrated the dynamic for dominant resistance allele ($h = 1$ in equations (4.3)). The dotted line correspond for different resistance values of levels of dominance ($0 < h < 1$ in equation (4.3)). See further explanations in Section 4.4.1.

dashed line corresponds to the case of dominant resistance, while the successive dotted lines correspond to different levels of intermediate dominance. One can observe that to the extent that dominant resistance becomes recessive, it is possible to maintain for more time total population below the hypothetical damage threshold.

4.4.2 Resistance to adulticide under dominance levels effect

The use of adulticide or larvicide can have a different impact in the fixation time of an attribute, for example resistance to an insecticide and consequently impact on its effectiveness in the population. In Figure 4.4 the effect of an adulticide (setting II table 4.2) with the same magnitude as the larvicide (setting I table 4.2) on the dynamics of genotypes is illustrated. Note that, as in the case of larvicide —see Figure 4.1—, the noticeable reduction of susceptible genotypes (green line) is delayed to the extent that resistance becomes recessive. However, it can be seen that the use of adulticide anticipates the extinction of susceptible genotypes when compared with the simulated dynamics for the use of larvicide for cases of intermediate dominance (dotted line) and recessive resistance (dot-dashed line).

The rate of fixation of an allele is a fundamental issue when studying evolution. In the case of resistance evolution, the fixation of a resistance allele means the total loss of insecticide effectiveness. Figure 4.5 shows the impact of an adulticide on this allele fixation rate by directional selection. The numerical simulations predict that the fixation of resistance alleles occur faster when using adulticides —see 4.2 for larvicide effect.

As mentioned before, in cases of pest control, it is desired to maintain a population level below a threshold —*e.g.* economic threshold or economic injury levels (Tang and Cheke, 2008). Figure 4.6 illustrates the effect of using adulticide use on the total population computed from genotype dynamic when the evolution of resistance advances. Note that for cases of intermediate dominance tending to recessive resistance, the time during which the population remains below an hypothetical damage threshold is significantly reduced compared to the use of larvicide illustrated in Figure 4.3.

4.4.3 Level of dominance and the reversal of resistance by interrupted use of adulticide.

In this class of systems, whenever insecticide resistance is associated with a fitness cost, it is expected that interruption of the application causes a reversal of resistance.

Figures 4.7, 4.8 and 4.9 illustrates numerical examples for different level of dominance case with a fitness cost for the resistance (setting III, IV and V in table 4.2) in which the application of an adulticide is suddenly interrupted. In the case of incomplete dominance 4.7, the use of insecticide is interrupted just before the fixation of resistance, reaching a reversion of approximately 100% is observed at a period greater than insecticide application. On the other hand, in numerical example for the case of recessive

resistance 4.8 a reversion close to 100 % susceptible is achieved in an approximate period of 4 year. In contrast, for the numerical example of the dominant resistance 4.9, the period required approximately 3 year no application a reversion close to 100% is achieved. Note that to revert a majority-resistant population to a majority-susceptible population, more time is required for the case of recessive resistance —heterozygous with worse fitness in the period without insecticide— in contrast to dominant resistance —heterozygous with best fitness in the period without insecticide.

4.4.4 Alternatives to prolong insecticides effectiveness.

In this section we present exploratory results for use of dominance levels and the reversal resistance for the chemical control of a population and the management of resistance evolution. This simulated scenario aims to explore the potential of discontinuous use of a chemical agent with the property of the reversal in context of evolution-proof insecticide —see (Koella et al., 2009b; Read et al., 2009).

For this purpose we have simulated a scenario with pulses rectangular waveform use larvicide 4.10. The numerical example illustrates a scenario of dominant resistance —see setting VI in table 4.2. Figures 4.10a and 4.10c show genotype dynamics and allele frequency respectively.

Regarding total population (Figure 4.10c), one can see marked increases given by the insecticide application and the resistance evolution. As can be seen, the emergence and evolution towards resistance changes the equilibrium point of the total population towards a higher one. In this scenario, sustained application of an insecticide runs counter to the goal of suppressing population size.

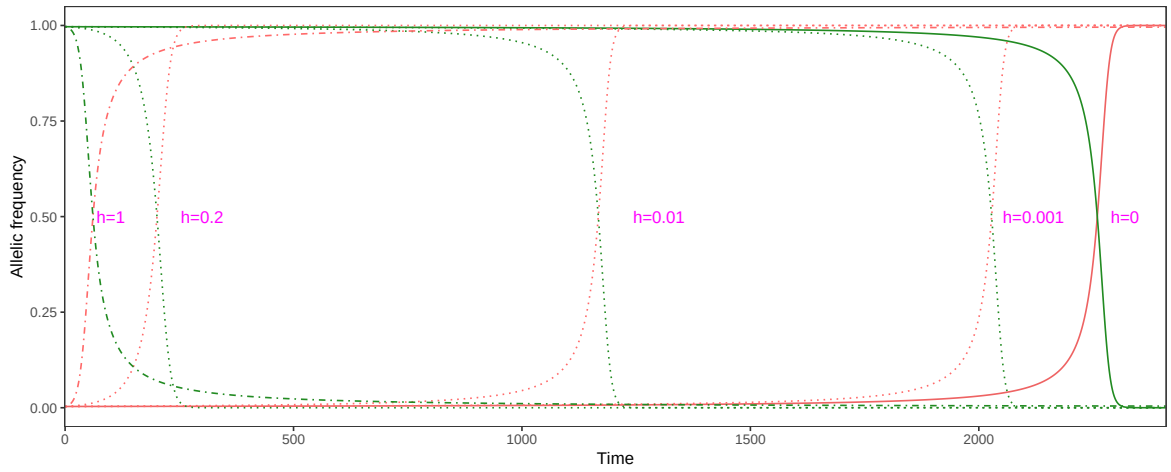
4.5 Conclusions and future issues

The presented non-trivial numerical solutions of directional selection show that, on a microevolution scale, a model of population dynamics that integrates the fundamentals of population genetics can provide applicable knowledge for the management of resistance evolution.

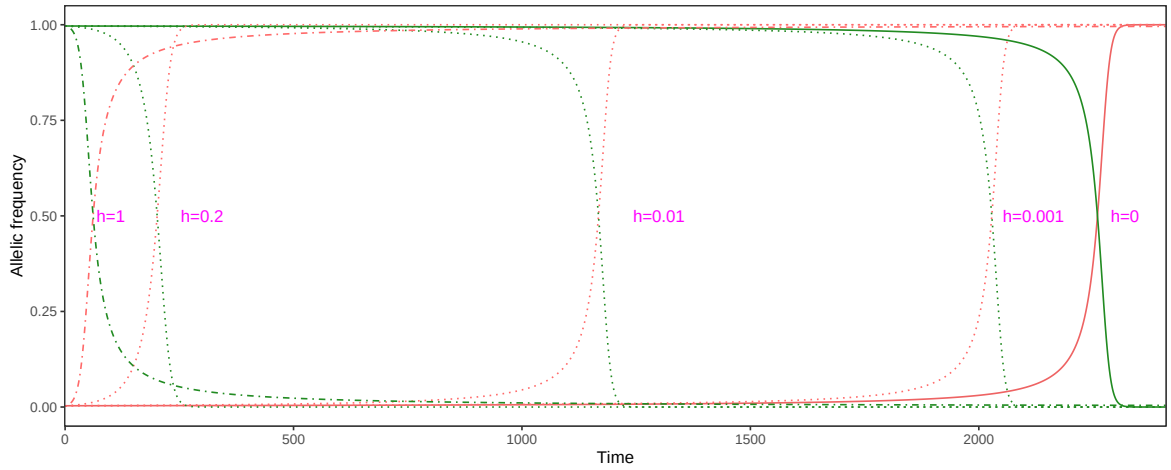
The simulations presented predict that the levels of dominance —that may depend on the lethal dose and the insecticide used— alter the speed of allele fixation and in turn this depends on whether the selection is given in the pre-reproductive phase —by use of larvicide—, or the reproductive phase —by use of adulticide.

As a general aspect, the numerical examples predict that the selection is slower when heterozygous present the worst fitness. This last determines resistance reversibil-

ity speed, such that given a fitness cost for the resistance in periods of insecticide application interruption, the reversal of resistant allele frequency is slower when the resistant allele is dominant.

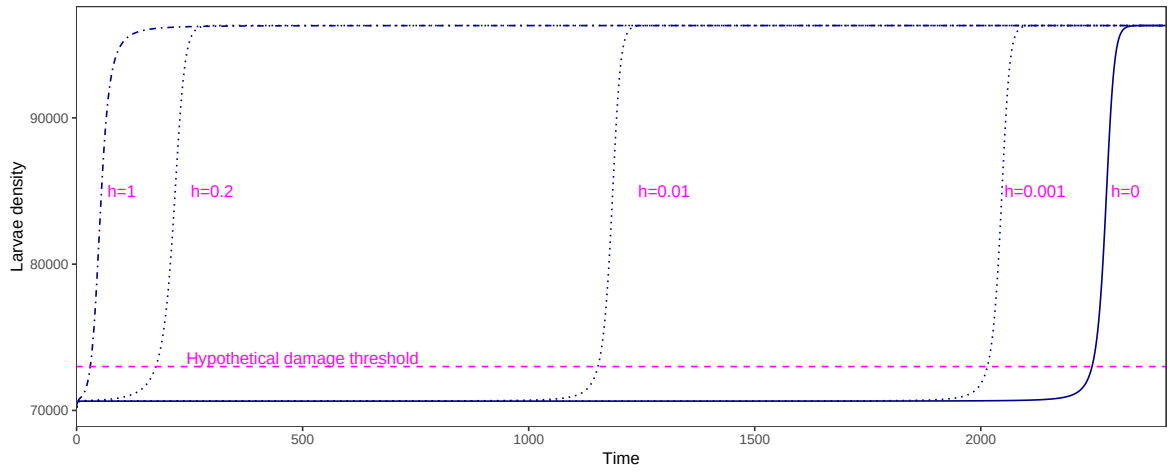


(a) Larvae

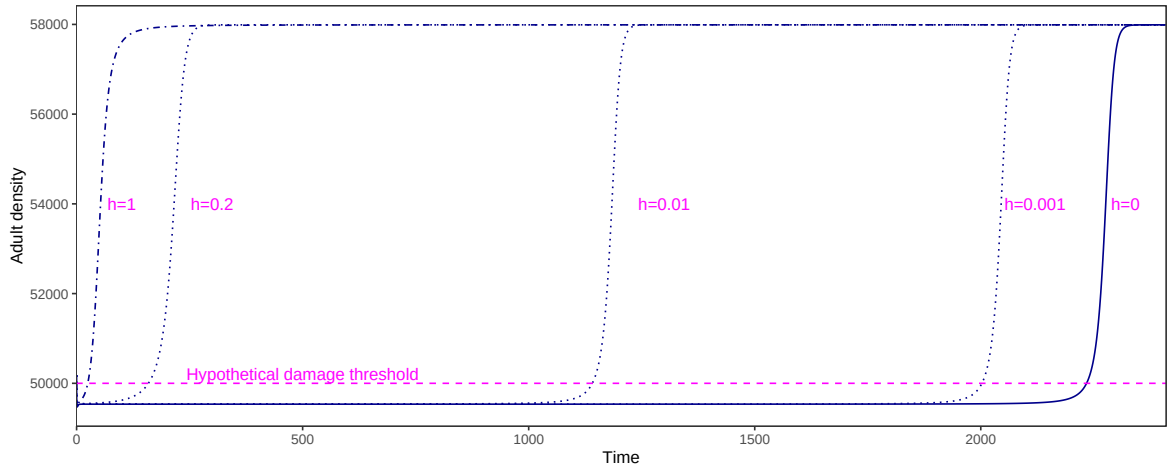


(b) Adult

Figure 4.2: Changes in allele frequencies by larvicide effect is calculated from the dynamics of genotypes. The red line represents the resistance allele in both larvae 4.2a and adults 4.2b, while the green line represents the frequency of susceptible alleles. Let be $0 \leq h \leq 1$ such that take successive values in D for different dominance level. The solid line corresponds to the case in which the resistant allele is recessive ($h = 0$ in equation (4.3)), the dot-dashed line corresponds to the case of dominant resistance ($h = 1$ in equation (4.3)), while the dotted lines represent successive levels of dominance ($0 < h < 1$ in equation (4.3)). See further explanations in Section 4.4.1.

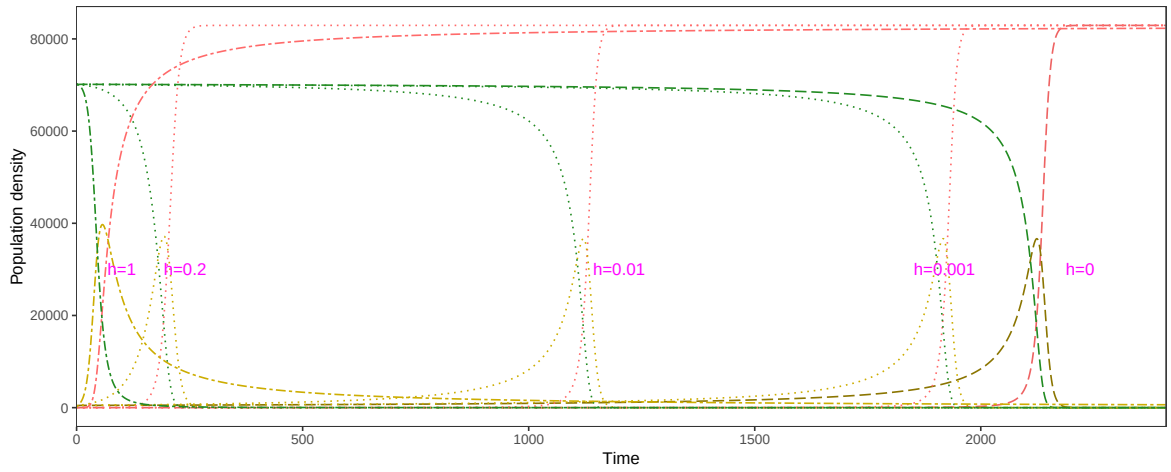


(a) Larvae

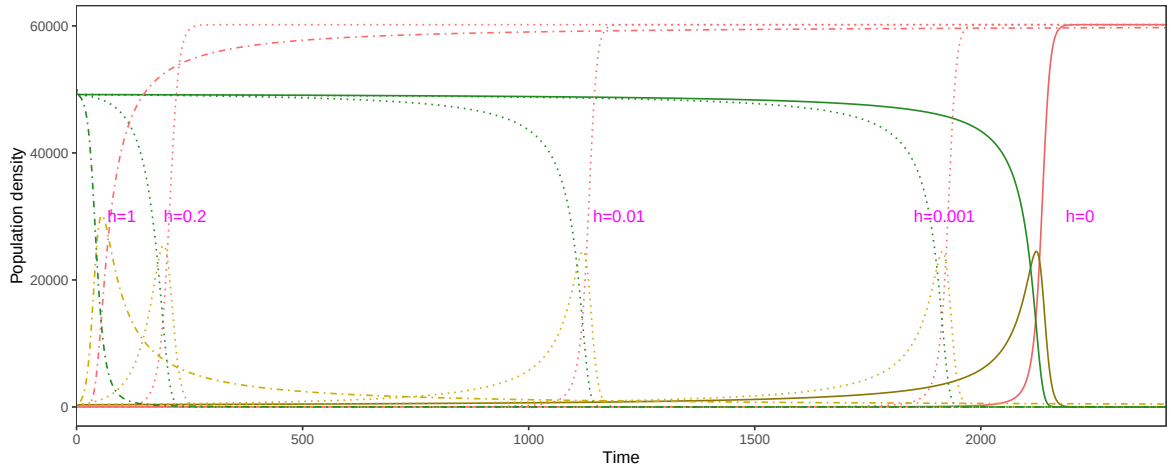


(b) Adult

Figure 4.3: The dynamics of total population under larvicide effect in larvae and adults calculated from genotypes are illustrated. Let be $0 \leq h \leq 1$ such that take successive values in D for different dominance level. The solid line is for the case of recessive resistance ($h = 0$ in equation (4.3)), the dot-dashed line corresponds to the case of dominant resistance ($h = 1$ in equation (4.3)), while the dotted lines are cases corresponding to successive levels of dominance ($0 < h < 1$ in equation (4.3)). The horizontal interrupted line represents a hypothetical damage threshold. See further explanations in Section 4.4.1.

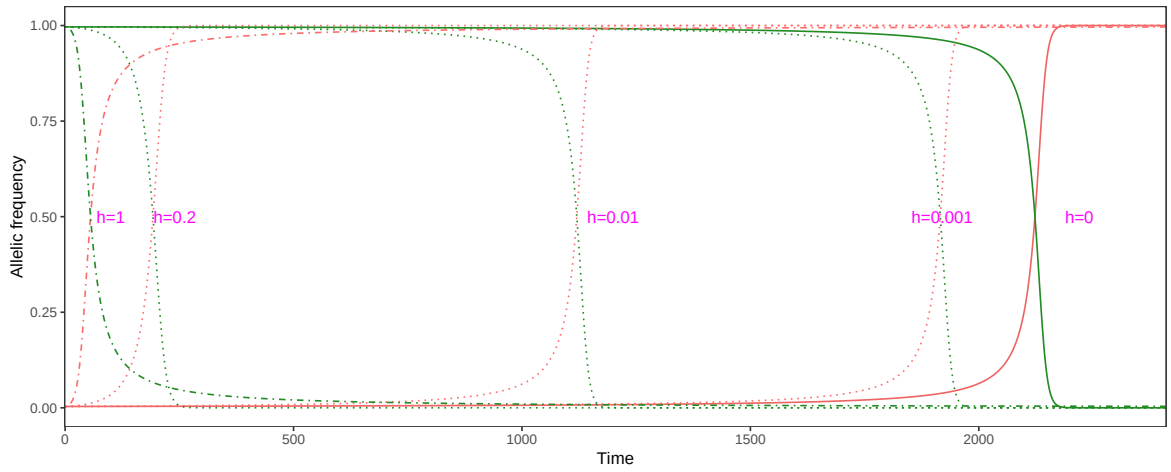


(a) Larvae

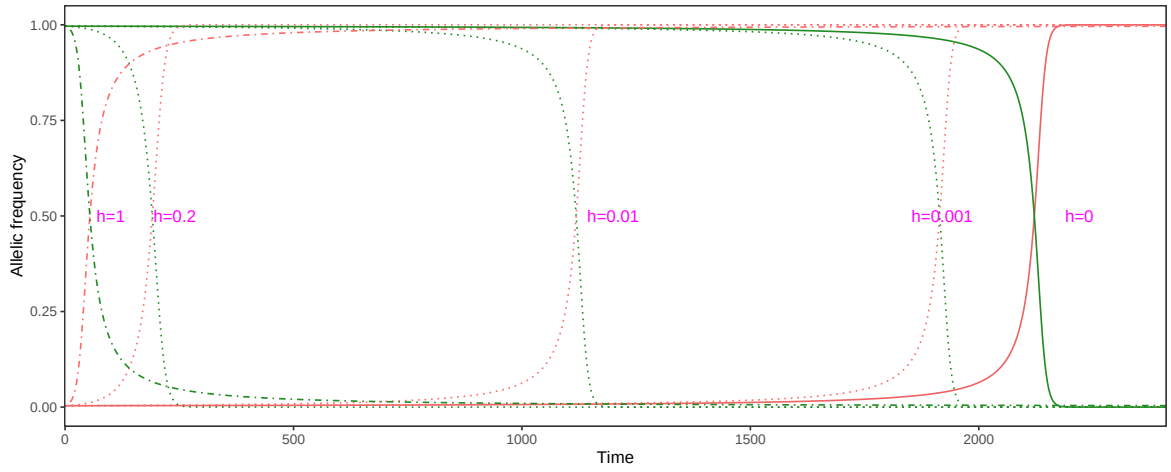


(b) Adult

Figure 4.4: Dynamic of Mendelian genotypes with adulticide resistance (with the same intensity as the previous case of larvicide) for different dominance levels of alleles. The red line represented resistance genotype, golden line corresponds to heterozygote, while green line is susceptible genotype. Let be $0 \leq \hat{h} \leq 1$ such that take successive values in D for different dominance level. The dashed line in 4.4a corresponds to larvae genotype for recessive resistance allele ($\hat{h} = 0$ in equation (4.4)). The solid line in 4.4b represents adult genotype for recessive resistance allele. The dot-dashed line illustrates the dynamic for dominant resistance allele ($\hat{h} = 1$ in equation (4.4)). The dotted line corresponds to successive levels of dominance ($0 < \hat{h} < 1$ in equation (4.4)). See further explanations in Section 4.4.2

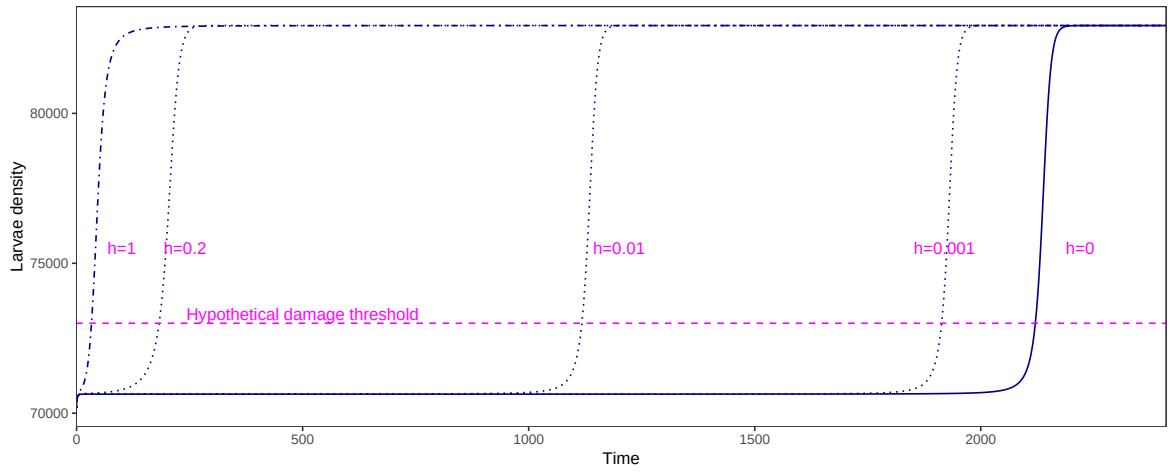


(a) Larvae

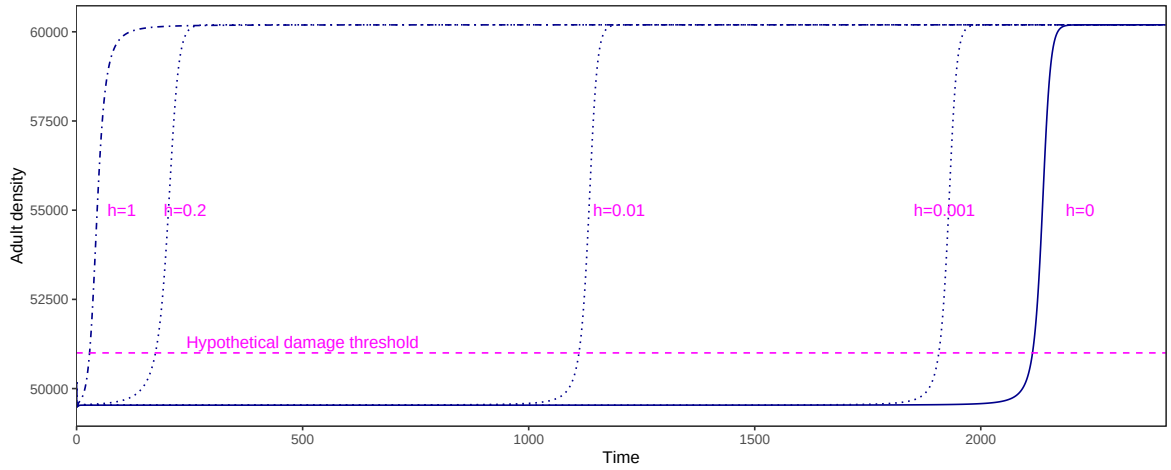


(b) Adult

Figure 4.5: Changes in allele frequencies by adulticide effect (with the same intensity as the previous case of larvicide) is calculated from the dynamics of genotypes. The red line represents the resistance allele in both larvae 4.5a and adults 4.5b, while the green line represents the frequency of susceptible alleles. The solid line corresponds to the case in which the resistant allele is recessive ($\hat{h} = 0$ in equation (4.4)), the dot-dashed line corresponds to the case of dominant resistance ($\hat{h} = 1$ in equation (4.4)), while the dotted lines represent successive levels of dominance ($0 < \hat{h} < 1$ in equation (4.4)). See further explanations in Section 4.4.2.

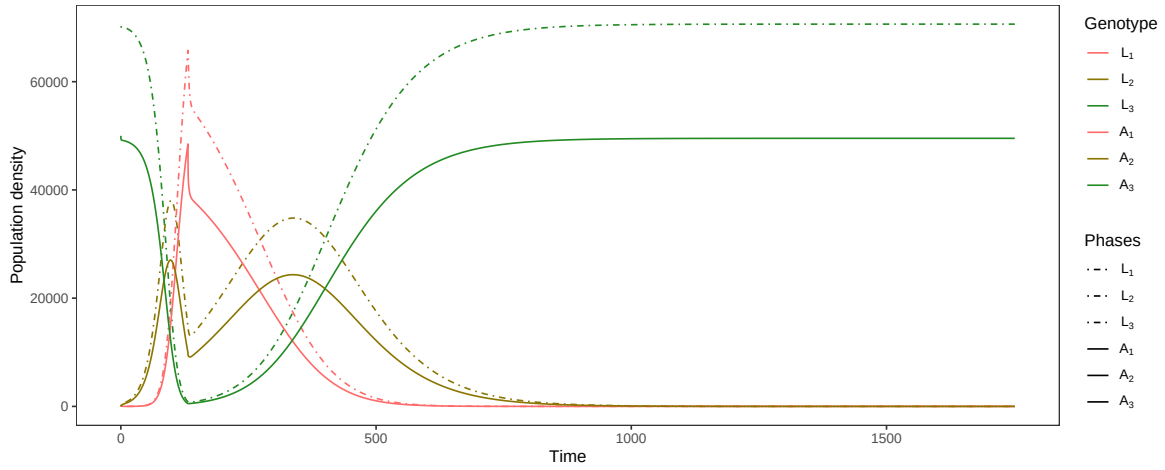


(a) Larvae

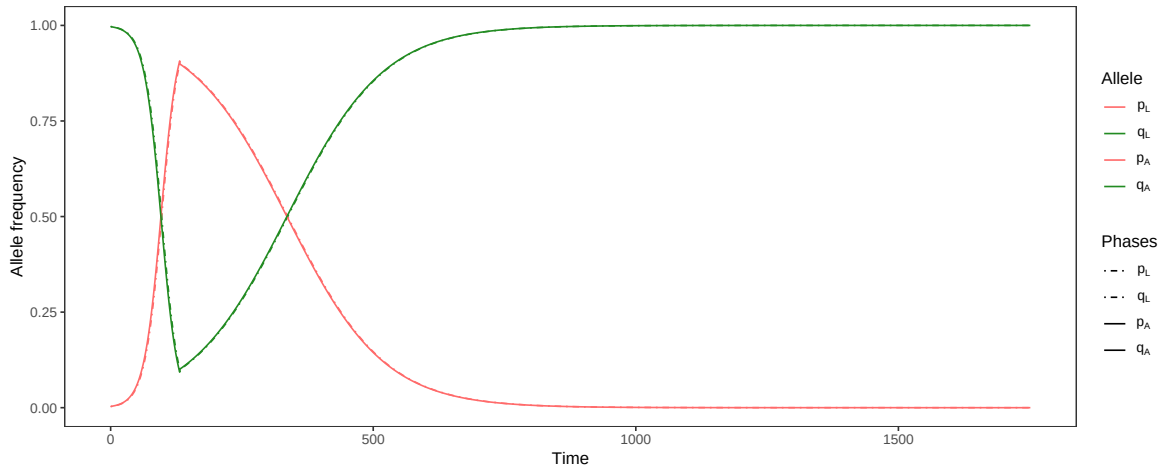


(b) Adult

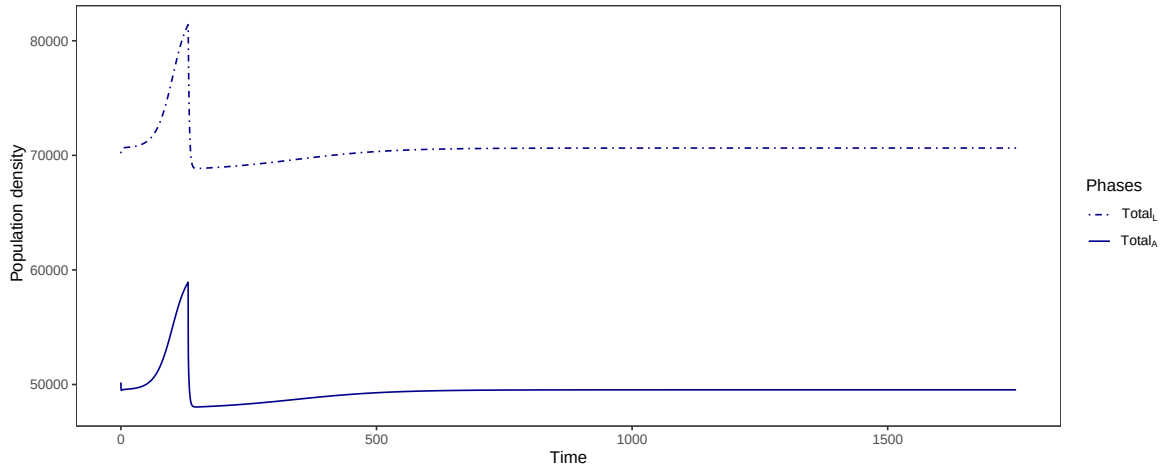
Figure 4.6: The dynamics of total population under adulticide effect (with the same intensity as the previous case of larvicide) in larvae and adults calculated from genotypes are illustrated. The solid line is for the case of recessive resistance ($\hat{h} = 0$ in equation (4.4)), the dot-dashed line corresponds to the case of dominant resistance ($\hat{h} = 1$ in equation (4.4)), while the dotted lines are cases corresponding to successive levels of dominance ($0 < \hat{h} < 1$ in equation (4.4)). The horizontal interrupted line represents a hypothetical damage threshold. See further explanations in Section 4.4.2.



(a) Genotype

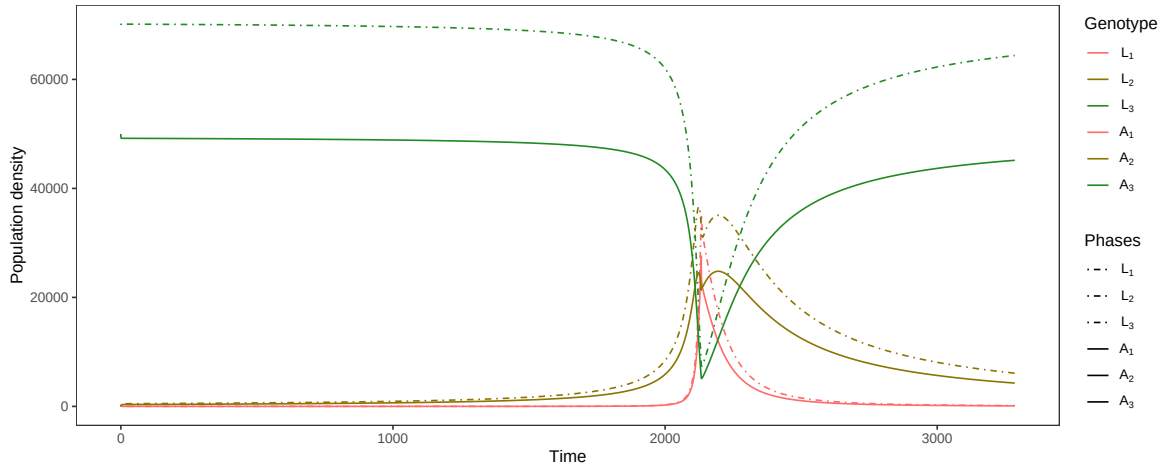


(b) Allele

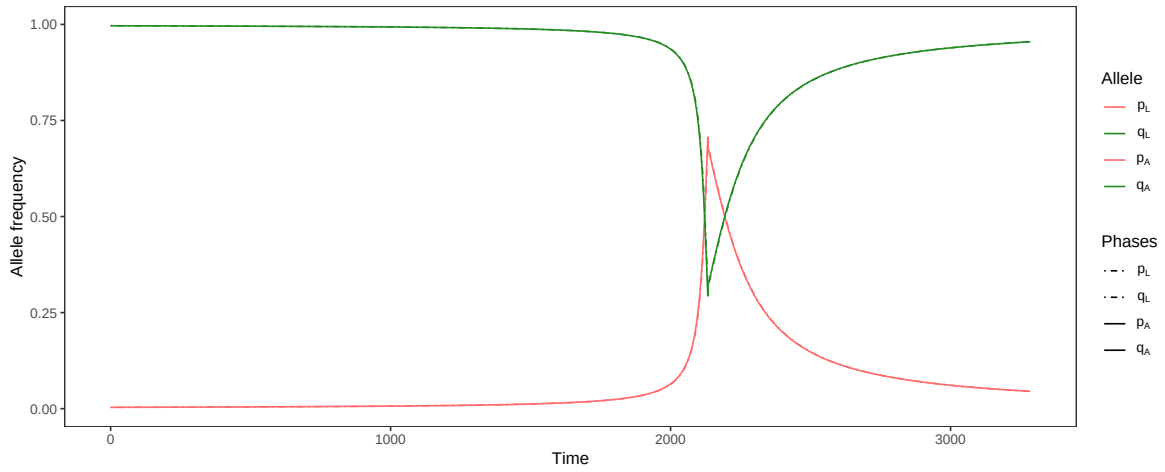


(c) Total population

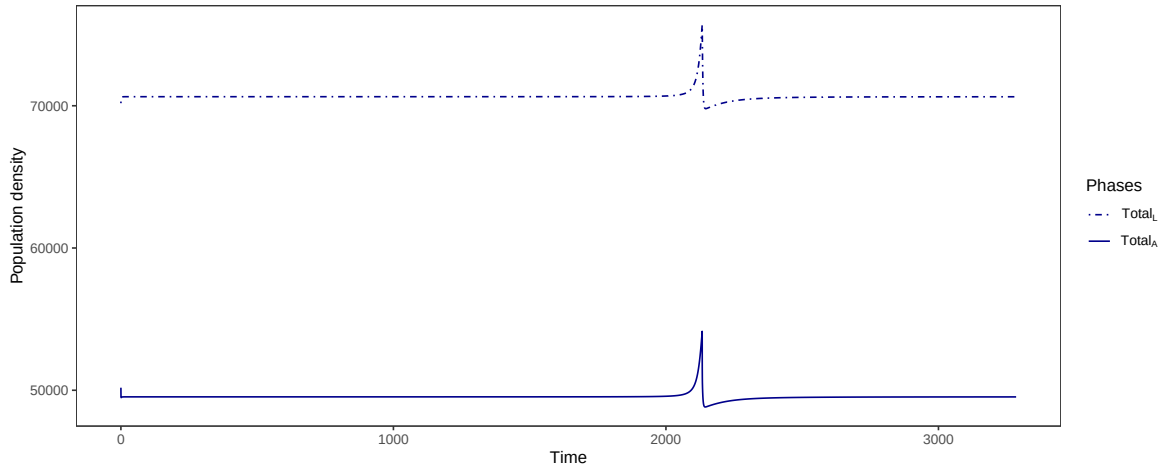
Figure 4.7: Reversal process of incomplete dominant resistance cases by interrupted use of adulticide (vertical dashed line) is illustrated. In the Figure 4.7a the genotypes dynamic is presented. In the Figure 4.7b the allele frequency calculate from genotype dynamic is illustrated. Finally, the Figure 4.7c represent the total population dynamic under the mentioned condition. See further explanations in Section 4.4.3.



(a) Genotype

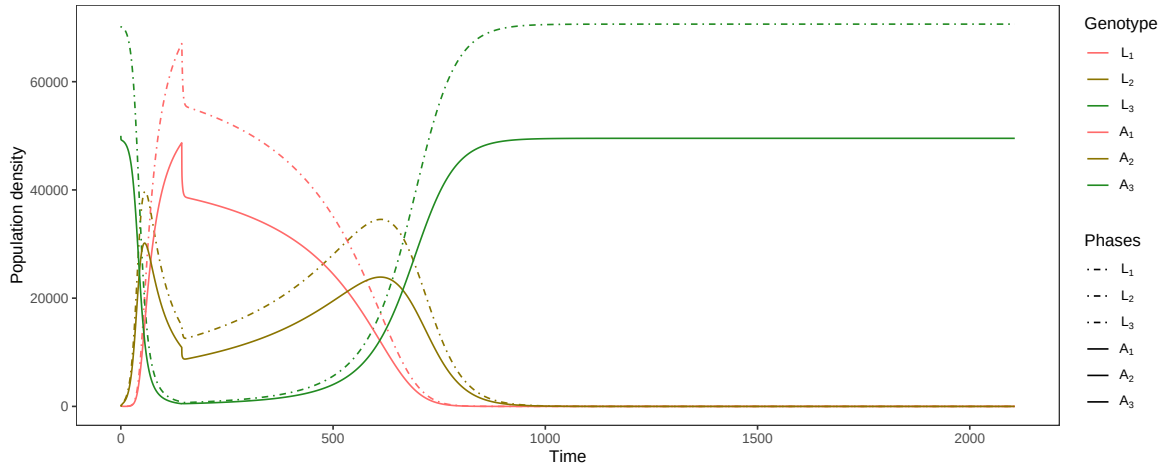


(b) Allele

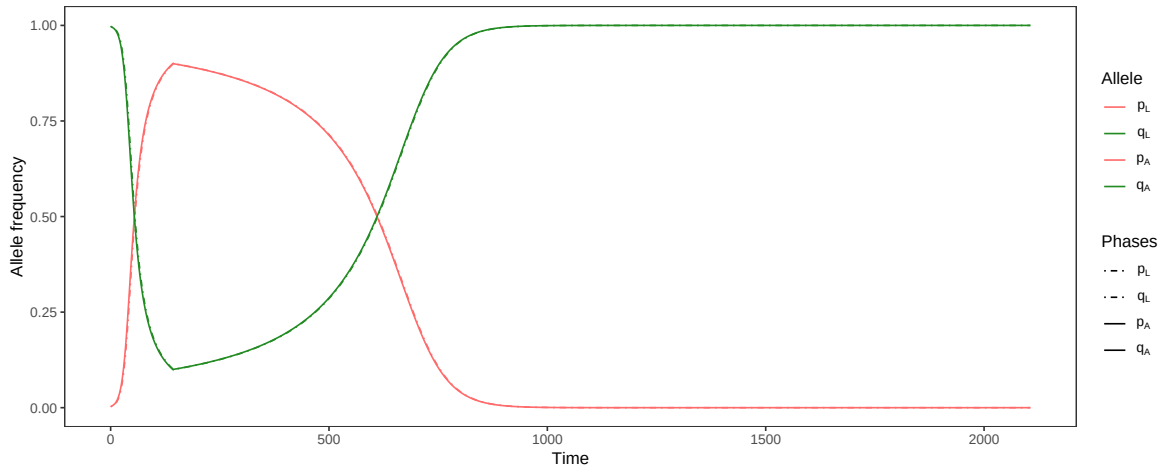


(c) Total population

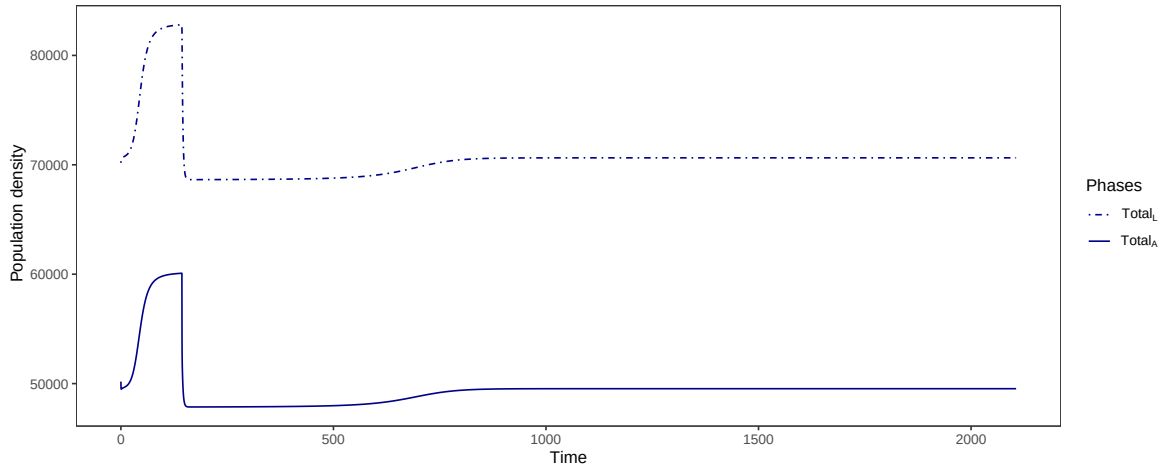
Figure 4.8: Reversal process of recessive resistance cases by interrupted use of adulticide (vertical dashed line) is illustrated. In the Figure 4.8a the genotypes dynamic is presented. In the Figure 4.8b the allele frequency calculate from genotype dynamic is illustrated. Finally, the Figure 4.8c represent the total population dynamic under the mentioned condition. See further explanations in Section 4.4.3.



(a) Genotype

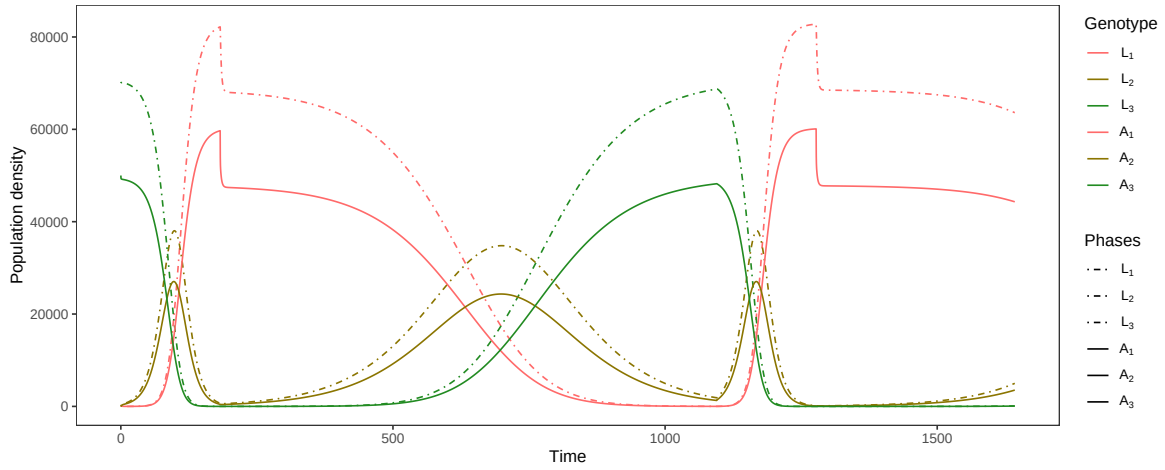


(b) Allele.

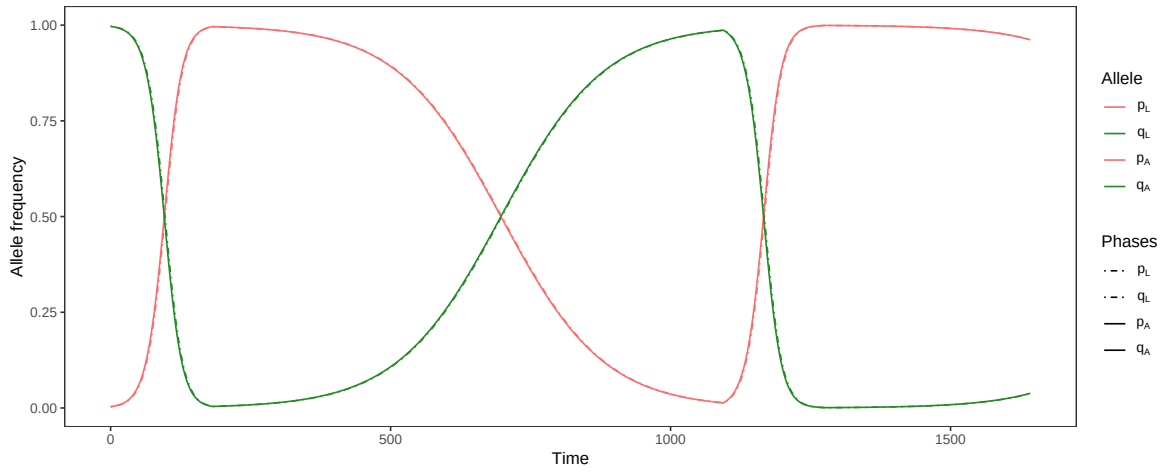


(c) Total population

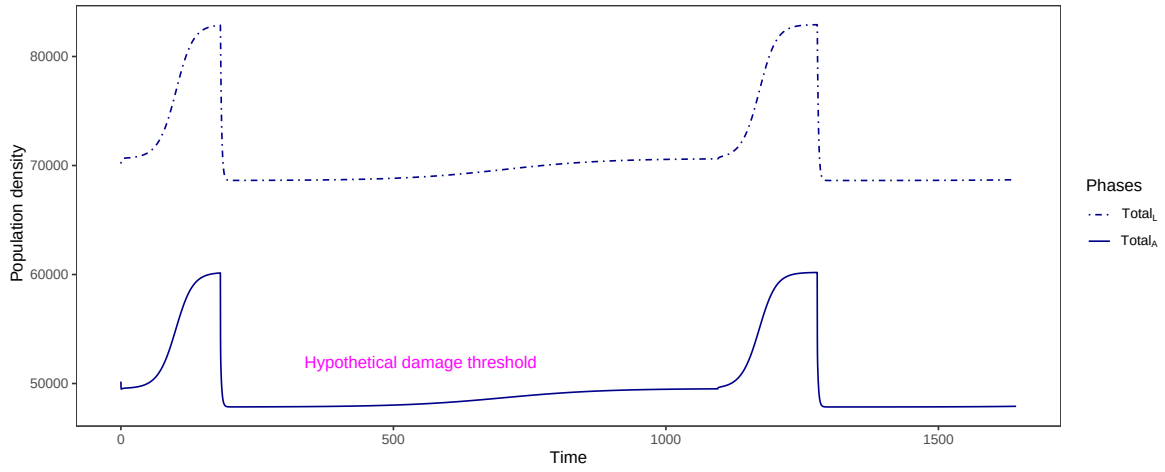
Figure 4.9: Reversal process of dominant resistance cases by interrupted use of adulticide (vertical dashed line) is illustrated. In the Figure 4.9a the genotypes dynamic is presented. In the Figure 4.9b the allele frequency calculate from genotype dynamic is illustrated. Finally, the Figure 4.9c represent the total population dynamic under the mentioned condition. See further explanations in Section 4.4.3.



(a) Genotype



(b) Allele



(c) Total population

Figure 4.10: A hypothetical case of insecticide resistance management by pulses of rectangular waveform use larvicide is illustrate. In the Figure 4.10a the genotypes dynamic is presented. In the Figure 4.10b the allele frequency calculate from genotype dynamic is illustrated. Finally, the Figure 4.10c represent the total population dynamic under the mentioned condition. See further explanations in Section 4.4.4.

Chapter 5

Modeling Wolbachia infection in presence of insecticide and resistance

5.1 Introduction

Due to the problems on mosquitoes population control associated with the use of insecticides —*e.g.* the resistance evolution (Brown, 1986; Hemingway and Ranson, 2000; Schechtman and Souza, 2015; Levick et al., 2017) and potential ecological damages (Oosthoek, 2013), in the last fifteen years progress has been made in the development of alternative strategies ranging from biological control methods to modification genetics of insect (McGraw and O'Neill, 2013; Kean et al., 2015). These control technologies may have the purpose of suppressing a population as insecticides do, or replacing by mosquitoes with reduced or null vector competence (Walker et al., 2011b; Alphey, 2014; Leftwich et al., 2016). Among these are the innovations known as genetic control, which are defined as biological control methods that depend on the spread of hereditary factors that reduce the damage of pests (Alphey, 2014). In this regards, understand and anticipate the limitations and potential of the simultaneous or independent use some of these strategies represents a recent challenge.

One of the promising new strategies is the use of *Wolbachia* —a intracellular bacterium inherited in the insect from the mother to her offspring like his phylogenetic relatives, the mitochondria (Emelyanov, 2003). Depending on the strain it can suppress mosquito population size or reduce its vector competence (McMeniman et al., 2009; Hoffmann et al., 2011). In this sense, several mathematical models have been proposed for releases mosquitoes infected by *Wolbachia*, see (Keeling et al., 2003; Farkas and Hinow, 2010; Zheng et al., 2014; Yakob et al., 2017; Xue et al., 2017; Campo-Duarte et al., 2017, 2018; Bliman et al., 2018a; Almeida et al., 2019) and (Hughes and Britton,

2013; Koiller et al., 2014a; Ndii et al., 2015) in the context of dengue epidemic.

Modeling a *Wolbachia* infection with intersection on Population Genetics predicts that the success of replacement strategies is influenced by chemical control in an insecticide resistance population (Hoffmann and Turelli, 2013a). These authors proposed a diploid population discrete time model that involves infected and uninfected mosquitoes, resistant, moderately susceptible and susceptible to an insecticide to show how the use of chemical control can facilitate the incorporation of *Wolbachia* into a population.

The use of chemical control has been mentioned as a way to facilitate the incorporation of *Wolbachia* into a population (Hoffmann and Turelli, 2013b). On the other hand, it has been reported that undesired exposition to insecticide may weaken the action of released susceptible mosquitoes against resistant wild population (Garcia, 2012; Garcia et al., 2017, 2019).

Indeed, according to the life history of mosquitoes, the contribution of this chapter is the continuous time model for a diploid population with two life phases of individuals infected and uninfected by *Wolbachia* with three genotypes given by two alleles, one of resistance and another of susceptibility to an insecticidal agent. In this model, a Mendelian inheritance mechanism for resistance and maternal inheritance mechanisms for *Wolbachia* is considered. In addition, we also consider density-dependent mortality in the aquatic phase. The model that results from this complicated combination of attributes is 12-dimensional. However, using *slow manifold theory* and assuming that the larval phase is significantly faster than the adult phase, we can obtain for the three genotypes a simpler 6-dimensional model represented by recruitment and mortality of infected and uninfected mosquitoes.

The main result of this chapter is a control law to guarantee the infection of a population by release of infected individuals, even if the infected mosquitoes released are susceptible and unviable. In addition, we present analytical results that describe the qualitative behavior of the system at both population and genetic levels. The numerical simulations not only illustrate the analytical results, but also the expected scenarios by the influence of some factors in the release campaigns of mosquitoes infected with *Wolbachia*. These factors are: the released genotype, the use of larvicides or adulticides, the level of allelic dominance, increased competition in the larval phase, and an incomplete cytoplasmic incompatibility.

5.2 A 12-dimensional controlled model

5.2.1 Notations (vectors/matrices/state variables)

- Generally speaking, in all the sequel the *exponent* U, W refers to uninfected (U) and *Wolbachia*-infected (W) populations; while the *index* $i = 1, 2, 3$ refers to the three genotypes, and the *index* $j = r, s$ to the two alleles.
- $e^U := \begin{pmatrix} 1 \\ 0 \end{pmatrix}$, $e^W := \begin{pmatrix} 0 \\ 1 \end{pmatrix}$, $e_1 := \begin{pmatrix} 1 \\ 0 \\ 0 \end{pmatrix}$, $e_2 := \begin{pmatrix} 0 \\ 1 \\ 0 \end{pmatrix}$, $e_3 := \begin{pmatrix} 0 \\ 0 \\ 1 \end{pmatrix}$
- $\mathbf{1}_2 := \begin{pmatrix} 1 & 1 \end{pmatrix}^\intercal$, $\mathbf{1}_3 := \begin{pmatrix} 1 & 1 & 1 \end{pmatrix}^\intercal$, $\mathbf{1}_6 := \mathbf{1}_2 \otimes \mathbf{1}_3$
- $G^U := \mathbf{1}_2 e^{U\intercal} - \sigma e^W e^{U\intercal}$, $G^W := \mathbf{1}_2 e^{W\intercal}$, that is

$$G^U = \begin{pmatrix} 1 & 0 \\ 1-\sigma & 0 \end{pmatrix}, \qquad G^W = \begin{pmatrix} 0 & 1 \\ 0 & 1 \end{pmatrix} \tag{5.1}$$

  The constant $\sigma \in [0, 1]$ will characterize the efficiency of the cytoplasmic incompatibility: $\sigma = 0$ in absence of incompatibility (only non-infected offsprings hatch from an encounter between a non-infected female and an infected male), $\sigma = 1$ when the incompatibility is complete (no viable offspring hatch in the same conditions).
- $u_r := \begin{pmatrix} 1 \\ 1/2 \\ 0 \end{pmatrix}$, $u_s := \begin{pmatrix} 0 \\ 1/2 \\ 1 \end{pmatrix}$. Notice that $u_r + u_s = \mathbf{1}_3$.
- $G_1 := u_r u_r^\intercal, G_2 := u_r u_s^\intercal + u_s u_r^\intercal, G_3 := u_s u_s^\intercal$, that is:

$$G_1 = \begin{pmatrix} 1 & 1/2 & 0 \\ 1/2 & 1/4 & 0 \\ 0 & 0 & 0 \end{pmatrix}, \quad G_2 = \begin{pmatrix} 0 & 1/2 & 1 \\ 1/2 & 1/2 & 1/2 \\ 1 & 1/2 & 0 \end{pmatrix}, \quad G_3 = \begin{pmatrix} 0 & 0 & 0 \\ 0 & 1/4 & 1/2 \\ 0 & 1/2 & 1 \end{pmatrix} \tag{5.2}$$

  Notice that $G_1 + G_2 + G_3 = \mathbf{1}_3 \mathbf{1}_3^\intercal$.
- We will use six-dimensional nonnegative vectors A and L to represent the states of the adult and larval populations. More precisely, for $\eta \in \{U, W\}$ and $i \in \{1, 2, 3\}$, one will denote A_i^η the number of adults of genotype i that are uninfected

($\eta = U$) or *Wolbachia*-infected ($\eta = W$). One adopts consequently the following definitions, concerning *vectors* and *norms*: for any $A \in \mathbb{R}^6_+$, let

$$A := \begin{pmatrix} A_1^U \\ A_2^U \\ A_3^U \\ A_1^W \\ A_2^W \\ A_3^W \end{pmatrix}, \quad |A| := \mathbf{1}_6^\intercal A, \tag{5.3a}$$

$$A^\eta := \begin{pmatrix} A_1^\eta \\ A_2^\eta \\ A_3^\eta \end{pmatrix}, \quad |A^\eta| := \mathbf{1}_3^\intercal A^\eta = A_1^\eta + A_2^\eta + A_3^\eta, \qquad \eta = U, W, \tag{5.3b}$$

$$A_i := \begin{pmatrix} A_i^U \\ A_i^W \end{pmatrix}, \quad |A_i| := \mathbf{1}_2^\intercal A_i = A_i^U + A_i^W, \qquad i = 1, 2, 3, \tag{5.3c}$$

Clearly, the vector A^η gathers the numbers of non-infected ($\eta = U$) or *Wolbachia*-infected ($\eta = W$) individuals of each genotype; while the vector A_i gathers the numbers of individuals of genotype i of each infection status. The norm $|A^\eta|$ represents the total number of non-infected ($\eta = U$) or *Wolbachia*-infected ($\eta = W$) adults, and the norm $|A_i|$ the total number of adults of genotype i. The quantity $|A|$ is the total number of adults, and of course

$$|A| = |A_1| + |A_2| + |A_3| = |A^U| + |A^W|. \tag{5.3d}$$

The following decomposition formulas may be easily shown and will be useful in the sequel:

$$A = \sum_{i=1}^{3} (A_i \otimes e_i) = \sum_{\eta = U, W} (e^\eta \otimes A^\eta). \tag{5.3e}$$

We will also consider the number of alleles in the infected and non-infected populations, namely

$$A_r^\eta := A_1^\eta + \frac{1}{2} A_2^\eta, \;\; A_s^\eta := A_3^\eta + \frac{1}{2} A_2^\eta, \qquad \eta = U, W \tag{5.4a}$$

and the associated vectors

$$A_j := \begin{pmatrix} A_j^U \\ A_j^W \end{pmatrix}, \qquad j = r, s \tag{5.4b}$$

In this way, one has the *vectorial* identities

$$A_r = A_1 + \frac{1}{2}A_2, \qquad A_s = A_3 + \frac{1}{2}A_2 \tag{5.5}$$

where the vectors A_i, $i = 1, 2, 3$, have been defined in (5.3c). In the sequel, we will in general write formulas such as (5.5) in the following form:

$$A_j = A_i + \frac{1}{2}A_2 \tag{5.6}$$

adopting the convention that $i = 1$ (resp. $i = 3$) whenever $j = r$ (resp. $j = s$). Coherently with the previous notations, one defines the norms

$$|A_j| := A_j^U + A_j^W, \qquad j = r, s \tag{5.7}$$

Clearly, $|A_j| = |A_i| + \frac{1}{2}|A_2|$.

One introduces similar notations for the components L_i^η of the preliminary phase.

- Define first the scalar functions $\alpha_i^\eta : \mathbb{R}_+^6 \setminus \{0_6\} \to \mathbb{R}_+$ by

$$\alpha_i^\eta(A) := \frac{1}{|A|}A^\intercal(G^\eta \otimes G_i)A \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.8}$$

Then, define the vectorial function $\alpha(A) : \mathbb{R}_+^6 \setminus \{0_6\} \to \mathbb{R}_+^6$ by

$$\alpha(A) := \sum_{\eta=U,W} \sum_{i=1,2,3} \alpha_i^\eta(A)(e^\eta \otimes e_i) \tag{5.9}$$

where $\otimes$ denotes the Kronecker product. One extends to 0_6 the previous definitions by continuity, putting

$$\alpha_i^\eta(0_6) := 0, \qquad \eta = U, W,\ i = 1, 2, 3$$

and thus $\alpha(0_6) = 0_6$. Observe that α so defined is *positively homogeneous of degree* 1: for any $A \in \mathbb{R}_+^6 \setminus \{0_6\}$, for any $\lambda > 0$, $\alpha(\lambda A) = \lambda A$.

- Kronecker symbol: for any indexes a, b, $\delta_a^b = 1$ if $a = b$, $\delta_a^b = 0$ otherwise.

- For any $z \in \mathbb{R}$, define the positive and negative parts of z as the nonnegative scalars $|z|_\pm$ given by

$$|z|_+ := \max\{z; 0\}, \qquad |z|_- := -\min\{z; 0\}$$

In this way, one has $z = |z|_+ - |z|_-$ for any $z \in \mathbb{R}$.

Last, we make the following qualitative definitions.

Definition 5.1 (Monomorphic and polymorphic states)**.** *Any point $A \in \mathbb{R}^6_+$ is called a* monomorphic state *if it contains only one allele, that is $A_1^\eta > 0 = A_2^\eta = A_3^\eta$ for some $\eta = U, W$, or $A_1^\eta = A_2^\eta = 0 < A_3^\eta$ for some $\eta = U, W$. A point that is* not *monomorphic is called* polymorphic*.*

Definition 5.2 (Homogeneous and heterogeneous states)**.** *Any point $A \in \mathbb{R}^6_+$ is called a* homogeneous state *if it contains only uninfected populations, that is $A_i^W = 0$, $i = 1, 2, 3$; or if it contains only* Wolbachia *infected populations, that is $A_i^U = 0$, $i = 1, 2, 3$. A point that is* not *homogeneous is called* heterogeneous*.*

5.2.2 A model of *Wolbachia* infection in presence of insecticide and resistance

Introducing input variables v_{Li}, v_{Ai} corresponding to releases of infected larvae or adults of genotypes 1, 2 or 3, yields the following *controlled* system:

$$\dot{L}_i^\eta = r^\eta \alpha_i^\eta(A) - \hat{\mu}_i^\eta(|L|) L_i^\eta - \nu L_i^\eta + \delta_\eta^W v_{Li}, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.10a}$$

$$\dot{A}_i^\eta = \nu L_i^\eta - \mu_i^\eta A_i^\eta + \delta_\eta^W v_{Ai}, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.10b}$$

where the maps α_i^η are defined in (5.8).

One can notice that the model (5.10) is governed by a dynamic similar to the model (2.1) introduced in Chapter 2, p.15. However, in this model, adult mortality does not depend on density.

From now on, we will suppose that only *adult* mosquitoes are introduced, that is $v_{Li} \equiv 0$, $i = 1, 2, 3$.

5.3 Singularly perturbed system

5.3.1 The proposed model

The pre-adult phase being relatively faster than the adult one, one approximates the system by singular perturbation. One considers instead of (5.10a) the algebraic formula

$$r^\eta \alpha_i^\eta(A) - \hat{\mu}_i^\eta(|L|) L_i^\eta - \nu L_i^\eta = 0, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.11}$$

To inverse (5.11) and express the L_i^η as functions of the components A_i^η, we first deduce

$$L_i^\eta = \frac{r^\eta \alpha_i^\eta(A)}{\hat{\mu}_i^\eta(|L|) + \nu}, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.12}$$

Summing up the six previous expressions yields

$$|L| = \sum_{i=1}^{3} \sum_{\eta=U,W} \frac{r^\eta \alpha_i^\eta(A)}{\hat{\mu}_i^\eta(|L|) + \nu}\ , \tag{5.13}$$

which provides an equation in the unknown $|L|$. Due to the assumption that the functions $\hat{\mu}_i^\eta$ are increasing, for any vector $A \in \mathbb{R}_+^6$, the right-hand side of (5.13) is a decreasing function of $|L|$, while its left-hand side is increasing and takes on any value from 0 to $+\infty$. Therefore, there exists a unique nonnegative scalar, denoted $b^*(\alpha(A))$, solution of the equation(5.13). By definition, the map b^* defined in this way is such that, for any $A \in \mathbb{R}_+^6$,

$$b^*(A) = \sum_{i=1}^{3} \sum_{\eta=U,W} \frac{r^\eta A_i^\eta}{\hat{\mu}_i^\eta(b^*(A)) + \nu}\ . \tag{5.14}$$

In view of this value, the components L_i^η are given (in view of (5.12)) as

$$L_i^\eta = \frac{r^\eta \alpha_i^\eta(A)}{\hat{\mu}_i^\eta(b^*(\alpha(A))) + \nu}, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.15}$$

Introducing this value in (5.10b) yields

$$\dot{A}_i^\eta = m_i^\eta(b^*(\alpha(A)))\, \alpha_i^\eta(A) - \mu_i^\eta A_i^\eta + \delta_\eta^W v_{Ai}, \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.16a}$$

where the map b^* has been defined by the implicit relation (5.14), and by definition, for any $b \in \mathbb{R}_+$,

$$m_i^\eta(b) := \frac{\nu r^\eta}{\hat{\mu}_i^\eta(b) + \nu} \tag{5.16b}$$

System (5.16) is written compactly under vector form as

$$\dot{A} = m(b^*(\alpha(A)))\, \alpha(A) - \mu A + \begin{pmatrix} 0_3 \\ v_A(t) \end{pmatrix}, \qquad m(b) := \mathtt{diag}\{m_i^\eta(b)\},\ \mu := \mathtt{diag}\{\mu_i^\eta\} \tag{5.17}$$

and an equivalent developed form of the nonlinear controlled system (5.16) is as follows:

$$
\begin{aligned}
\dot{A}_1^U &= \frac{m_1^U(b^*(\alpha(A)))}{|A|}\left(A_1^U+\frac{1}{2}A_2^U+(1-\sigma)\left(A_1^W+\frac{1}{2}A_2^W\right)\right)\left(A_1^U+\frac{1}{2}A_2^U\right)\\
&- \mu_1^U A_1^U \qquad (5.18a)\\
\dot{A}_2^U &= \frac{m_2^U(b^*(\alpha(A)))}{|A|}\left(A_3^U+\frac{1}{2}A_2^U+(1-\sigma)\left(A_3^W+\frac{1}{2}A_2^W\right)\right)\left(A_1^U+\frac{1}{2}A_2^U\right)\\
&+\frac{m_2^U(b^*(\alpha(A)))}{|A|}\left(A_1^U+\frac{1}{2}A_2^U+(1-\sigma)\left(A_1^W+\frac{1}{2}A_2^W\right)\right)\left(A_3^U+\frac{1}{2}A_2^U\right)\\
&- \mu_2^U A_2^U \qquad (5.18b)\\
\dot{A}_3^U &= \frac{m_3^U(b^*(\alpha(A)))}{|A|}\left(A_3^U+\frac{1}{2}A_2^U+(1-\sigma)\left(A_3^W+\frac{1}{2}A_2^W\right)\right)\left(A_3^U+\frac{1}{2}A_2^U\right)\\
&- \mu_3^U A_3^U \qquad (5.18c)\\
\dot{A}_1^W &= \frac{m_1^W(b^*(\alpha(A)))}{|A|}\left(A_1^U+\frac{1}{2}A_2^U+A_1^W+\frac{1}{2}A_2^W\right)\left(A_1^W+\frac{1}{2}A_2^W\right)\\
&- \mu_1^W A_1^W + v_{A1}(t) \qquad (5.18d)\\
\dot{A}_2^W &= \frac{m_2^W(b^*(\alpha(A)))}{|A|}\left(A_3^U+\frac{1}{2}A_2^U+A_3^W+\frac{1}{2}A_2^W\right)\left(A_1^W+\frac{1}{2}A_2^W\right)\\
&+\frac{m_2^W(b^*(\alpha(A)))}{|A|}\left(A_1^U+\frac{1}{2}A_2^U+A_1^W+\frac{1}{2}A_2^W\right)\left(A_3^W+\frac{1}{2}A_2^W\right)\\
&- \mu_2^W A_2^W + v_{A2}(t) \qquad (5.18e)\\
\dot{A}_3^W &= \frac{m_3^W(b^*(\alpha(A)))}{|A|}\left(A_3^U+\frac{1}{2}A_2^U+A_3^W+\frac{1}{2}A_2^W\right)\left(A_3^W+\frac{1}{2}A_2^W\right)\\
&- \mu_3^W A_3^W + v_{A3}(t) \qquad (5.18f)
\end{aligned}
$$

5.3.2 General hypotheses

We make the following general hypotheses on the dynamical system (5.17), saying essentially that the fitness of uninfected (resp. susceptible) is lower than of infected (resp. resistant) (Walker et al., 2011c; Hoffmann et al., 2014b; Koiller et al., 2014c; Bliman et al., 2018b). For $\eta = U, W$, $i, i' = 1, 2, 3$,

- $\mu_i^\eta : \mathbb{R}_+ \to \mathbb{R}_+$ non-decreasing; $\hat{\mu}_i^\eta : \mathbb{R}_+ \to \mathbb{R}_+$ increasing and unbounded
- $i < i'$ implies $\hat{\mu}_i^\eta \leq \hat{\mu}_{i'}^\eta$ and $\mu_i^\eta \leq \mu_{i'}^\eta$
- $\hat{\mu}_i^U \leq \hat{\mu}_i^W$ and $\mu_i^U \leq \mu_i^W$

Moreover, we assume that some of the previous inequalities are *strict*,by assuming that

- $\mu_1^U < \mu_2^W$.

From these hypotheses it is possible to deduce the following properties that will be useful later to describe the qualitative behavior of the studied model.

Lemma 5.3. *Assuming the hypotheses in Section* 5.3.2*, one has, for any* $\eta = U, W$*, for any* $i, i' = 1, 2, 3$*,*

- $m_i^\eta : \mathbb{R}_+ \to \mathbb{R}_+$ *decreasing with limit zero*
- $i \leq i'$ *implies* $m_i^\eta \geq m_{i'}^\eta$
- $m_i^U \geq m_i^W$

Due to the strict inequalities assumed before, a stronger property holds here, namely: either $m_1^\eta > m_2^\eta$ or $m_2^\eta > m_3^\eta$.

The parameters that govern the dynamics (mortality and birth) of mosquitoes can be affected by genetic factors, the strain of *Wolbachia* that infects, or by endogenous factors such as weather time-dependence (e.g. temperature, precipitation, etc.). These factors can even affect biological parameters jointly. However, like a laboratory experimental design in a modeling framework, one can neglect the effect of these factors to focus on the questions of interest. In the model introduced in the sequel, we do not explicitly address this time-dependence, and we assume that for each given insecticide, the lethal dose density corresponds to the fixed characteristic fertility and mortality, as well as the effect of the Wolbachia strains used and environmental conditions. This aspect is not explored further in this chapter, which instead focuses on asymptotic properties in a stationary environment.

5.3.3 Well-posedness and invariance properties

We assume in the sequel that the control input is locally integrable and almost everywhere positive. Under such conditions, showing the well-posed character of the controlled system (5.17) presents no specific difficulty.

We show now several properties of the model. The first result establishes that any genotype once present may only disappear in infinite time, whatever the control input.

Theorem 5.4 (Polymorphic trajectories, heterogeneous trajectories)**.** *Whatever the (nonnegative-valued) input signal* v_A*, all trajectories of system* (5.17) *fulfil the following properties.*

1. *For any trajectory such that* $A_i^\eta(0) > 0$ *for some* $\eta = U, W$*,* $i = 1, 2, 3$*, one has* $A_i^\eta(t) > 0$ *for any* $t \geq 0$*.*

2. *Any trajectory originating from a monomorphic (resp. homogeneous) state remains monomorphic (resp. homogeneous) for any $t \geq 0$ if no other genotype (resp. no population with other infection status) is introduced in the input.*

3. *Any trajectory originating from a polymorphic (resp. heterogeneous) state remains polymorphic (resp. heterogeneous) for any $t \geq 0$.*

As a consequence of this result, one may talk about homogeneous or heterogeneous trajectories, and similarly about monomorphic or polymorphic trajectories.

Proof of Theorem 5.4. The first property comes from integrating the differential inequality

$$\dot{A}_i^\eta \geq -\mu_i^\eta A_i^\eta,$$

easily deduced from (5.16a), which yields $A_i^\eta(t) \geq A_i^\eta(0)e^{-\mu_i^\eta t} > 0$. The second property is a straightforward property of system (5.17), which comes as direct consequence of (5.5) and (5.6) in Lemma 5.15. The third property is a consequence of the first one. □

The next result shows that the trajectories of system (5.17) are bounded.

Theorem 5.5 (Trajectory boundedness)**.** *Assume the input control v_A uniformly bounded on $[0, +\infty)$. Then all trajectories of* (5.17) *are uniformly ultimately bounded.*

Proof. Summing up all equations in (5.17) yields

$$\frac{d|A|}{dt} = \tilde{m}(t) \sum_{\eta=U,W} \sum_{i=1}^{3} \alpha_i^\eta(A) - \tilde{\mu}(t) \sum_{\eta=U,W} \sum_{i=1}^{3} A_i^\eta + |v_A|, \tag{5.19}$$

where by definition

$$\tilde{m}(t) := \frac{\sum_{\eta=U,W} \sum_{i=1}^{3} m_i^\eta(b^*(\alpha(A)))\alpha_i^\eta(A)}{\sum_{\eta=U,W} \sum_{i=1}^{3} \alpha_i^\eta(A)} \leq m_1^U(t), \quad \tilde{\mu}(t) := \frac{\sum_{\eta=U,W} \sum_{i=1}^{3} \mu_i^\eta A_i^\eta}{\sum_{\eta=U,W} \sum_{i=1}^{3} A_i^\eta} \geq \mu_1^U.$$

On the other hand, at any $A \in \mathbb{R}_+^6$, one has

$$|\alpha(A)| = \sum_{\eta=U,W} \sum_{i=1}^{3} \alpha_i^\eta(A) = \frac{1}{|A|} A^\intercal \left(\sum_{\eta=U,W} G^\eta \otimes \sum_{i=1}^{3} G_i \right) A \leq \frac{1}{|A|} A^\intercal \left(\mathbf{1}_2 \mathbf{1}_2^\intercal \otimes \mathbf{1}_3 \mathbf{1}_3^\intercal \right) A = |A|$$

Therefore,

$$\frac{d|A|}{dt} \leq \left(m_1^U(b^*(\alpha(A))) - \mu_1^U \right) |A| + \|v_A\|_{L^\infty}.$$

Due to the fact that $m_1^U(b)$ is decreasing with zero limit at infinity, the function in the right-hand side of the previous formula is negative for sufficiently large values of $|A|$. This permits to conclude the proof of Theorem 5.5. □

The last result of this paragraph unveils more precise properties of the trajectories, which are characteristic of the underlying genetic mechanisms involved.

Theorem 5.6 (Genotypic properties)**.** *Whatever the nonnegative-valued input signal, all trajectories of system* (5.17) *fulfil the following properties.*

1. *If both alleles are present at $t = 0$ in the non-infected (resp. infected) population, then all genotypes are present in the non-infected (resp. infected) population for any $t > 0$.*

2. *If some allele is present at $t = 0$ in the non-infected population and the other one in the infected, then all genotypes are present in the* infected *population for any $t > 0$.*

3. *Assume $\sigma = 1$. If only the allele j, $j = r, s$, is present at $t = 0$ in the* non-infected *population (that is $A_1^U(0) > 0 = A_2^U(0) = A_3^U(0)$ if $j = r$, or $A_1^U(0) = A_2^U(0) = 0 < A_3^U(0)$ if $j = s$), then the same holds true for any $t \geq 0$.*

Proof of Theorem 5.6. The first point comes from (5.7) and Theorem 5.4, which guarantees that any population present at a certain time persists after any finite time. The second point is constructed similarly, using (5.8) instead of (5.7). If $\alpha_{i''}^W(A) > 0$, then one argues as before; while if $\alpha_{i''}^W(\alpha(A)) > 0$, then indeed (see the proof of Lemma 5.15) $\alpha_2^W(A) > 0$, which implies the appearance of infected heterozygous for $t > 0$, and finally the appearance of every infected genotypes.

Last, the third point of the statement comes from applying formula (5.9). This achieves the proof of Theorem 5.6. □

5.3.4 Problem under study

The problem we consider in the sequel is the synthesis of control laws that permit to bring the system in the state of full infection, with a control effort that vanishes asymptotically. We show below that, under suitable assumptions, we may realize this, not only by introducing resistant *Wolbachia* infected mosquitoes but also, by introducing susceptible *Wolbachia* infected mosquitoes, even if the latter is not viable. However, the simulations conducted with this model show that the latter possibility needs to release more mosquitoes.

5.4 Balance equations

By sommation of the equations in (5.16), one obtains on the one hand equations describing the evolution of the non-infected and infected total populations $|A^\eta|$, $\eta = U, W$; and on the other hand equations describing the evolution of each genotype $|A_i|$, $i = 1, 2, 3$, and of each allele $|A_j|$, $j = r, s$. These balance equations will be used in the sequel and are believed to be of independent interest. Notice that none of them takes the form of a replicator equation (Hofbauer and Sigmund, 1998).

5.4.1 Non-infected/infected balance equation

For $\eta = U, W$, the evolution of $|A^\eta| = A_1^\eta + A_2^\eta + A_3^\eta$ obeys the following equation:

$$\begin{aligned} \frac{d|A^\eta|}{dt} &= \sum_{i=1}^{3} \dot{A}_i^\eta = \sum_{i=1}^{3} \left(m_i^\eta(b^*(\alpha(A)))\, \alpha_i^\eta(A) - \mu_i^\eta A_i^\eta + \ \delta_\eta^W v_{Ai} \right) \\ &= \tilde{m}^\eta(t) \sum_{i=1}^{3} \alpha_i^\eta(A) - \tilde{\mu}^\eta(t) \sum_{i=1}^{3} A_i^\eta + \ \delta_\eta^W |v_A| \end{aligned} \tag{5.20}$$

where by definition $|v_A| := \sum_{i=1}^{3} v_{Ai}$ and

$$\tilde{m}^\eta(t) := \frac{\sum_{i=1}^3 m_i^\eta(b^*(\alpha(A)))\alpha_i^\eta(A)}{\sum_{i=1}^3 \alpha_i^\eta(A)}, \qquad \tilde{\mu}^\eta(t) := \frac{\sum_{i=1}^3 \mu_i^\eta A_i^\eta}{\sum_{i=1}^3 A_i^\eta}, \qquad \eta = U, W \tag{5.21}$$

One may write under matrix form

$$\sum_{i=1}^{3} \alpha_i^\eta(A) = \frac{1}{|A|} \sum_{i=1}^{3} A^\intercal (G^\eta \otimes G_i) A = \frac{1}{|A^U| + |A^W|} \begin{pmatrix} |A^U| \\ |A^W| \end{pmatrix}^\intercal G^\eta \begin{pmatrix} |A^U| \\ |A^W| \end{pmatrix} \tag{5.22}$$

$$:= \alpha^\eta(A) \tag{5.23}$$

and formula (5.20) may then be expressed as

$$\frac{d|A^\eta|}{dt} = \tilde{m}^\eta(t)\alpha^\eta(A) - \tilde{\mu}^\eta(t)|A^\eta| + \ \delta_\eta^W |v_A|, \qquad \eta = U, W \tag{5.24}$$

or again, using (5.2c), as

$$\frac{d|A^U|}{dt} = \left(\tilde{m}^U(t)\frac{|A^U| + (1-\sigma)|A^W|}{|A^U| + |A^W|} - \tilde{\mu}^U(t)\right)|A^U| \tag{5.25a}$$

$$\frac{d|A^W|}{dt} = (\tilde{m}^W(t) - \tilde{\mu}^W(t))|A^W| + \ |v_A| \tag{5.25b}$$

One checks easily from the hypotheses and (5.21) that $\tilde{m}^U \geq \tilde{m}^W$ and $\tilde{\mu}^U \leq \tilde{\mu}^W$. Formally, one may thus interpret (5.24) as describing the interaction between two, non-infected and infected, homogeneous populations. Notice that one also has

$$m_1^\eta \leq \tilde{m}^\eta \leq m_3^\eta, \quad \mu_3^\eta \leq \tilde{\mu}^\eta \leq \mu_1^\eta, \qquad \eta = U, W \ . \tag{5.26}$$

5.4.2 Genotypic balance equation

Similarly, one may consider the evolution of the different genotypes, independently of their infection status. Let $i = 1, 2, 3$.

$$\begin{aligned}\frac{d|A_i|}{dt} &= \sum_{\eta=U,W} \dot{A}_i^\eta = \sum_{\eta=U,W} \left(m_i^\eta(b^*(\alpha(A)))\,\alpha_i^\eta(A) - \mu_i^\eta A_i^\eta + \ \delta_\eta^W v_{Ai}\right) \\ &= \tilde{m}_i(t) \sum_{\eta=U,W} \alpha_i^\eta(A) - \tilde{\mu}_i(t) \sum_{\eta=U,W} A_i^\eta + \ v_{Ai}\end{aligned} \tag{5.27}$$

with here

$$\tilde{m}_i(t) := \frac{\sum_{\eta=U,W} m_i^\eta(b^*(\alpha(A)))\alpha_i^\eta(A)}{\sum_{\eta=U,W} \alpha_i^\eta(A)}, \qquad \tilde{\mu}_i(t) := \frac{\sum_{\eta=U,W} \mu_i^\eta A_i^\eta}{\sum_{\eta=U,W} A_i^\eta}, \qquad i = 1, 2, 3 \tag{5.28}$$

One may write under matrix form

$$\begin{aligned}\sum_{\eta=U,W} \alpha_i^\eta(A) &= \frac{1}{|A|} \sum_{\eta=U,W} A^\intercal (G^\eta \otimes G_i) A \\ &= \frac{1}{|A_1| + |A_2| + |A_3|} \left(\begin{pmatrix} |A_1| \\ |A_2| \\ |A_3| \end{pmatrix}^\intercal G_i \begin{pmatrix} |A_1| \\ |A_2| \\ |A_3| \end{pmatrix} - \sigma A^{U\intercal} G_i A^W \right) := \alpha_i(A)\,,\end{aligned} \tag{5.29}$$

which may be expressed explicitly by use of (5.2e) and (5.2f).

Formula (5.27) then writes

$$\frac{d|A_i|}{dt} = \tilde{m}_i(t)\alpha_i(A) - \tilde{\mu}_i(t)|A_i| + \ v_{Ai}, \qquad i = 1, 2, 3 \tag{5.30}$$

Here, $\tilde{m}_1 \geq \tilde{m}_2 \geq \tilde{m}_3$ and $\tilde{\mu}_1 \leq \tilde{\mu}_2 \leq \tilde{\mu}_3$, and formally one may see in (5.30) the evolution of three homogeneous genotypes. Notice that one also has

$$m_i^W \leq \tilde{m}_i \leq m_i^U, \quad \mu_i^U \leq \tilde{\mu}_i \leq \mu_i^W, \qquad i = 1, 2, 3 \ . \tag{5.31}$$

5.4.3 Allelic equations and allelic balance

It is quite interesting to write the 6-dimensional system (5.17) in terms of allelic evolution, expressed by a 4-dimensional equation.

Using (5.2a), (5.2b) and the same convention than the one used in Lemma 5.14 (i.e. $i = 1$ for $j = r$, $i = 3$ for $j = s$), one deduces from (5.29), (5.30):

$$\frac{d|A_j|}{dt} = \tilde{m}_j(t)\left(\alpha_i(A) + \frac{1}{2}\alpha_2(A)\right) - \tilde{\mu}_j(t)\left(|A_i| + \frac{1}{2}|A_2|\right) + \delta_j^r v_{Ar} + \delta_j^s v_{As}, \quad j = r, s \tag{5.32}$$

where the mean allelic rates are defined by

$$\tilde{\mu}_j(t) := \frac{\alpha_i(A)\tilde{\mu}_i(t) + \frac{1}{2}\alpha_2(A)\tilde{\mu}_2(t)}{\alpha_i(A) + \frac{1}{2}\alpha_2(A)}, \quad \tilde{m}_j(t) := \frac{|A_i|\tilde{m}_i(t) + \frac{1}{2}|A_2|\tilde{m}_2(t)}{|A_i| + \frac{1}{2}|A_2|}, \quad j = r, s \tag{5.33}$$

and $v_{AX} := v_{A1} + \frac{1}{2}v_{A2}$, $v_{Ax} := v_{A3} + \frac{1}{2}v_{A2}$.

The term $|A_i| + \frac{1}{2}|A_2|$ in (5.32) is equal to $|A_j|$ (see the comment after formula (5.7)). On the other hand, summing up (5.2a) and (5.2b) yields

$$\begin{aligned}
\alpha_i(A) + \frac{1}{2}\alpha_2(A) &= \frac{1}{2|A|}A^\intercal\left(\left(\mathbf{1}_2\mathbf{1}_2^\intercal - \sigma e^W e^{U\intercal}\right) \otimes \left(u_j\mathbf{1}_3^\intercal + \mathbf{1}_3 u_j^\intercal\right)\right)A^\intercal \\
&= \frac{1}{2|A|}A^\intercal\Big((\mathbf{1}_2 \otimes u_j)\mathbf{1}_6^\intercal + \mathbf{1}_6(\mathbf{1}_2 \otimes u_j)^\intercal - \sigma(e^W \otimes u_j)(e^U \otimes \mathbf{1}_3)^\intercal \\
&\qquad -\sigma(e^W \otimes \mathbf{1}_3)(e^U \otimes u_j)^\intercal\Big)A \\
&= |A_j| - \frac{\sigma}{2|A|}\left(|A^U|A_j^W + |A^W|A_j^U\right)
\end{aligned} \tag{5.34}$$

In view of this, one deduces the following equivalent form of (5.32):

$$\frac{d|A_j|}{dt} = \tilde{m}_j(t)\left(|A_j| - \frac{\sigma}{2|A|}\left(|A^U|A_j^W + |A^W|A_j^U\right)\right) - \tilde{\mu}_j(t)|A_j| + \delta_j^r v_{Ar} + \delta_j^s v_{As}, \quad j = r, s \tag{5.35}$$

We now consider the equations at the description level of the 4 variables A_j^η, $\eta =$

U, W, $j = r, s$. From (5.16a) and with the definitions in (5.4a), one gets by summation

$$\dot{A}_j^\eta = \tilde{m}_j^\eta(t) \left(A_i^\eta + \frac{1}{2} A_2^\eta \right) - \tilde{\mu}_j^\eta(t) A_j^\eta + \delta_\eta^W v_{Ai}, \qquad \eta = U, W, \ j = r, s \tag{5.36}$$

where by definition

$$\tilde{m}_j^\eta(t) := \frac{\alpha_i^\eta(A) m_i^\eta(b^*(\alpha(A))) + \frac{1}{2}\alpha_2^\eta(A) m_2^\eta(b^*(\alpha(A)))}{\alpha_i^\eta(A) + \frac{1}{2}\alpha_2^\eta(A)}, \qquad \eta = U, W, \ j = r, s \tag{5.37a}$$

$$\tilde{\mu}_j^\eta(t) := \frac{A_i^\eta \mu_i^\eta + \frac{1}{2} A_2^\eta \tilde{\mu}_2^\eta}{A_i^\eta + \frac{1}{2} A_2^\eta}, \qquad \eta = U, W, \ j = r, s \tag{5.37b}$$

Again, we used here the convention exposed in Lemma 5.14: $i = 1$ for $j = r$, $i = 3$ for $j = s$.

Using (5.2a), (5.2b), one may express the previous system as

$$\dot{A}_j^U = \frac{1}{2} \tilde{m}_j^U(t) \left(\left(1 - \sigma \frac{|A^W|}{|A|} \right) A_j^U + \frac{|A_j| - \sigma A_j^W}{|A|} |A^U| \right) - \tilde{\mu}_j^U(t) A_j^U, \qquad j = r, s \tag{5.38a}$$

$$\dot{A}_j^W = \frac{1}{2} \tilde{m}_j^W(t) \left(A_j^W + \frac{|A_j||A^W|}{|A|} \right) - \tilde{\mu}_j^W(t) A_j^W + v_{Aj}, \qquad j = r, s \tag{5.38b}$$

5.5 Equilibrium points for the uncontrolled system

We study here the number and properties of the equilibrium points of the uncontrolled system. We consider here and in the remaining of the paper the case of *complete cytoplasmic incompatibility*, that is:

$$\sigma = 1 \ . \tag{5.39}$$

When this is verified, (5.38) reduces to

$$\dot{A}_j^U = \left(\tilde{m}_j^U(t) \frac{|A^U|}{|A|} - \tilde{\mu}_j^U(t) \right) A_j^U, \qquad j = r, s \tag{5.40a}$$

$$\dot{A}_j^W = \frac{1}{2} \tilde{m}_j^W(t) \left(A_j^W + \frac{|A_j||A^W|}{|A|} \right) - \tilde{\mu}_j^W(t) A_j^W + v_{Aj}, \qquad j = r, s \tag{5.40b}$$

or in expanded form:

$$\dot{A}_r^U = \left(\tilde{m}_r^U(t)\frac{|A^U|}{|A|} - \tilde{\mu}_r^U(t)\right) A_r^U \tag{5.41a}$$

$$\dot{A}_s^U = \left(\tilde{m}_s^U(t)\frac{|A^U|}{|A|} - \tilde{\mu}_s^U(t)\right) A_s^U \tag{5.41b}$$

$$\dot{A}_r^W = \frac{1}{2}\tilde{m}_r^W(t)\left(A_r^W + \frac{|A_r||A^W|}{|A|}\right) - \tilde{\mu}_r^W(t)A_r^W + v_{Ar} \tag{5.41c}$$

$$\dot{A}_s^W = \frac{1}{2}\tilde{m}_s^W(t)\left(A_s^W + \frac{|A_s||A^W|}{|A|}\right) - \tilde{\mu}_s^W(t)A_s^W + v_{As} \tag{5.41d}$$

5.5.1 Existence of equilibrium points

The following result exposes the situation concerning the equilibrium points of the system under study in absence of release.

Theorem 5.7 (Equilibrium points of uncontrolled system (5.16))**.** *Apart from the* extinction equilibrium 0_6 *which always exists, the equilibrium points of the* uncontrolled *(i.e. with $v_A \equiv 0$) system* (5.16) *fulfil the following properties.*

- *There are* at most six monomorphic equilibrium points*, that decompose as follows.*
  - *At most four* monomorphic, homogeneous, equilibria*, equal to the vectors*

$$A_j^{\eta *}(e^\eta \otimes e_i), \qquad \eta = U, W,\ j = r, s\ , \tag{5.42a}$$

  where $A_j^{\eta *}$ is the unique positive solution of the scalar equation

$$m_i^\eta \left(b^*(A_j^{\eta *}\alpha(e^\eta \otimes e_i))\right)\ \alpha_i^\eta(e^\eta \otimes e_i) = \mu_i^\eta; \tag{5.42b}$$

  - *two* monomorphic, heterogeneous, coexistence equilibria

$$A_j^{U**}(e^U \otimes e_i) + A_j^{W**}(e^W \otimes e_i), \qquad j = r, s, \tag{5.43a}$$

  where the positive pair (A_j^{U**}, A_j^{W**}) constitutes the unique solution of

$$\frac{m_i^W(b^*(\alpha(A_j^{U**}(e^U \otimes e_i) + A_j^{W**}(e^W \otimes e_i))))}{\mu_i^W} = 1, \tag{5.43b}$$

$$\frac{A_j^{W**}}{A_j^{U**}} = \frac{m_i^U(b^*(\alpha(A_j^{U**}(e^U \otimes e_i) + A_j^{W**}(e^W \otimes e_i))))}{\mu_i^U} - 1. \tag{5.43c}$$

By convention, in (5.42) *and* (5.43)*, $i = 1$ (resp. $i = 3$) when $j = r$ (resp. $j = s$).*

- *Any possible* polymorphic equilibrium *fulfils*

$$A_3^U, A_1^W, A_2^W, A_3^W > 0, \qquad A_1^U = A_2^U = 0. \tag{5.44}$$

The previous results provide a complete characterization for the monomorphic equilibrium. Each of the *monomorphic homogeneous equilibria* is distinct from the zero equilibrium *if and only if* (5.42b) admits positive solution, that is *if and only if*

$$m_i^\eta(0) > \mu_i^\eta. \tag{5.45}$$

This condition expresses that the "recruitment rate for zero population" is larger than the mortality rate, or in other terms that the corresponding homozygous non-infected or infected population is viable for a certain population level (which is then unique).

Similarly, each of the *monomorphic heterogeneous equilibria* is distinct from zero *iff* (5.43b) admits a positive solution, that is *iff* (5.45) holds for $\eta = W$. In such a case, the value of $b^*(\alpha(A_j^{U**}(e^U \otimes e_i) + A_j^{W**}(e^W \otimes e_i)))$ is uniquely determined by (5.43b), and the ratio between A_j^{W**} and A_j^{U**} as well, through (5.43c). With these two information, there is therefore at most one such equilibrium for each allele. Notice that if (5.45) holds for $\eta = W$, it also holds for $\eta = U$, due to the hypotheses (see also Lemma 5.3 and the comments given afterwards).

On the contrary, the result concerning the *polymorphic equilibria* is partial: it establishes the possible general form of such a point, but does not decide about existence or uniqueness.

At last, notice that the equilibrium points of system (5.10) being in one-to-one correspondence with the equilibrium points of the singularly perturbed system (5.16), the previous result also provides information on the former system.

Proof of Theorem 5.7.

• Looking for homogeneous monomorphic equilibria of the type $c(e^\eta \otimes e_j)$, $\eta = U, W$, $j = r, s$ for some $c \geq 0$ yields (at most) four equilibria *for each allele* r and s: two monomorphic equilibria, a coexistence equilibrium, and the extinction equilibrium (which is of course the same for r and s). As a matter of fact, the population level corresponding to the homogeneous monomorphic direction $e^\eta \otimes e_j$ should fulfil (5.42), and by a monotonicity argument, this equation admits at most one positive solution. For the heterogeneous monomorphic equilibria, the comments after the statement also explains the uniqueness. Notice that some of the previous equilibria are zero, if the previous population level is zero (apparent mortality larger than apparent recruitment

for this direction). So we have at least the six monomorphic equilibria depicted in the statement —of which some are identical in case of nullity.

• Let us now consider the issue of existence of *polymorphic* equilibria. Let A be such a point. A key argument is that, from the nullity of the right-hand side of equations (5.41a) and (5.41b) and the inequalities on the recruitment and mortality rates, one may deduce that either $A_r^U = 0$ or $A_s^U = 0$. As a matter of fact, one has

$$\frac{\tilde{\mu}_r^U}{\tilde{m}_r^U} \leq \frac{\mu_2^U}{m_2^U(b^*(\alpha(A)))} \leq \frac{\tilde{\mu}_s^U}{\tilde{m}_s^U} \tag{5.46}$$

with two equalities *iff* $A_1^U = A_3^U = 0$. Then $A_2^U > 0$, because otherwise the whole population would be infected, which contradicts the fact that the equilibrium is heterogeneous. But this situation (that is: $A_1^U = A_3^U = 0 < A_2^U$) is impossible at equilibrium, as the presence of non-infected heterozygous induces the presence of both homozygous. This is indeed a consequence of point 3 in Lemma 5.15. Therefore, one of the two inequalities is strict in (5.46), and the right-hand sides of (5.41a) and (5.41b) are not zero simultaneously. This shows the alternative enunciated above.

Assume now by contradiction that $A_s^U = 0$. One thus has $A_r^U > 0$, and more precisely, $A_1^U > 0$, $A_2^U = A_3^U = 0$. In such a case, then

$$|A^U| = A_r^U + A_s^U = A_r^U, \qquad |A_s| = A_s^U + A_s^W = A_s^W. \tag{5.47}$$

Therefore, at equilibrium one gets from (5.41c) and (5.41d):

$$\dot{A}_r^W \equiv 0 = \left(\frac{1}{2}\tilde{m}_r^W\left(1 + \frac{|A_r||A^W|}{A_r^W|A|}\right) - \tilde{\mu}_r^W\right)A_r^W \tag{5.48a}$$

$$\dot{A}_s^W \equiv 0 = \left(\frac{1}{2}\tilde{m}_s^W\left(1 + \frac{|A^W|}{|A|}\right) - \tilde{\mu}_s^W\right)A_s^W \tag{5.48b}$$

Being at a *polymorphic* equilibrium such that $A_1^U > 0$, $A_2^U = A_3^U = 0$, one should necessarily have $A_s^W > 0$, and this in turn implies that $A_i^W > 0$, $i = 1, 2, 3$, due to point 4 in Lemma 5.15. Identities (5.48a), (5.48b) then yields

$$\frac{1}{2}\tilde{m}_r^W\left(1 + \frac{|A_r||A^W|}{A_r^W|A|}\right) - \tilde{\mu}_r^W = \frac{1}{2}\tilde{m}_s^W\left(1 + \frac{|A^W|}{|A|}\right) - \tilde{\mu}_s^W = 0, \tag{5.49}$$

that is:

$$\frac{\tilde{\mu}_r^W}{\tilde{m}_r^W} = \frac{1}{2}\left(1 + \frac{|A_r||A^W|}{A_r^W|A|}\right), \qquad \frac{\tilde{\mu}_s^W}{\tilde{m}_s^W} = \frac{1}{2}\left(1 + \frac{|A^W|}{|A|}\right). \tag{5.50}$$

Now, similarly to (5.46), one has here:

$$\frac{\tilde{\mu}_r^W}{\tilde{m}_r^W} \leq \frac{\mu_2^W}{m_2^W(b^*(\alpha(A)))} \leq \frac{\tilde{\mu}_s^W}{\tilde{m}_s^W}, \tag{5.51}$$

while in the same time, the fact that $A_r^W < A_r^U + A_r^W = |A_r|$ implies

$$\frac{1}{2}\left(1 + \frac{|A_r||A^W|}{A_r^W|A|}\right) > \frac{1}{2}\left(1 + \frac{|A^W|}{|A|}\right) \tag{5.52}$$

This yields a contradiction: one cannot have $A_s^U = 0$.

The only possible polymorphic equilibria are thus such that $A_r^U = 0 < A_s^U$, and more precisely such that $A_1^U = A_2^U = 0$, $A_3^U > 0$. One shows in a similar way than in the preceding case, that here $A_1^W, A_2^W, A_3^W > 0$. Any possible polymorphic equilibrium is thus of the type (5.44). This achieves the proof of Theorem 5.7. □

5.5.2 Stability of the equilibrium points

Here we study the stability of the equilibrium points exhibited in Theorem 5.7.

Theorem 5.8 (Stability of the equilibrium points of uncontrolled system (5.16))**.** *All possible equilibrium points of system* (5.16) *are unstable, except the two homogenous resistant monomorphic equilibria* $A_r^{\eta*}(e^\eta \otimes e_1)$, $\eta = U, W$, *which are locally asymptotically stable.*

Proof.

• It is easy to show that, due to the assumed viability of the resistant populations, the extinction equilibrium is unstable.

• Also, as shown in Chapter 2, any trajectory departing from a *homogenous, polymorphic*, state converges towards the corresponding *homogenous, monomorphic (resistant)*, equilibrium $A_r^{\eta*}(e^W \otimes e_1)$, as the latter has higher fitness than the other homozygous $A_s^{\eta*}(e^W \otimes e_3)$. The latter points are thus unstable in the forward-invariant space of the corresponding homogeneous states, and therefore unstable. The same argument applies to the case of the coexistence equilibria.

• On the other hand, any polymorphic equilibrium is unstable. As a matter of fact, we have established in Theorem 5.7 that any such point writes as in (5.44). For any infinitesimal perturbation of the component A_1^U, the argument applied in the proof of this result applies, and shows that

$$\frac{d}{dt}\left[\ln\left(\frac{A_r^U}{A_s^U}\right)\right] > 0.$$

In such a case, one then has

$$A_r^U(t) > \frac{A_r^U(0)}{A_s^U(0)} A_s^U(t), \qquad t \geq 0$$

which certainly forbids stability of such a point. Therefore, the polymorphic equilibria are unstable.

• It remains to show the local asymptotic stability of the homogenous monomorphic equilibria $A_r^{\eta *}(e^\eta \otimes e_1)$, $\eta = U, W$. This is done by direct inspection of the Jacobian matrices, exploiting the computations from Section 5.10.2 and 5.10.3. Notice that, due to Lemma 5.13,

$$\alpha(A_r^{\eta *}(e^\eta \otimes e_1)) = A_r^{\eta *}(e^\eta \otimes e_1), \qquad \eta = U, W.$$

◦ Consider first the case $\eta = U, i = 1$. By application of Lemma 5.16, one has at the point $A^* := A_r^{U*}(e^U \otimes e_1)$,

$$J_\alpha(A^*) = -\frac{1}{|A^*|}\alpha(A^*)\mathbf{1}_6^\intercal + \frac{1}{|A^*|}\beta(A^*)$$

where

$$\frac{1}{|A^*|}\alpha(A^*)\mathbf{1}_6^\intercal = (e^U \otimes e_1)\mathbf{1}_6^\intercal \tag{5.53a}$$

and

$$\begin{aligned}\frac{1}{|A^*|}\beta(A^*) &= \sum_{\eta,\eta',i,i'} (e^U \otimes e_1)^\intercal \left((G^\eta + G^{\eta\intercal})e^{\eta'} \otimes G_i e_{i'}\right) \ (e^\eta \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal \\ &= \sum_{\eta,\eta',i,i'} \left((e^{U\intercal}(G^\eta + G^{\eta\intercal})e^{\eta'} \otimes e_1^\intercal G_i e_{i'}\right) \ (e^\eta \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal. \end{aligned} \tag{5.53b}$$

Now, one shows easily that

$$e^{U\intercal}G^W = e^{W\intercal}, \quad e^{U\intercal}G^{W\intercal} = 0_{1\times 2}, \quad \text{and} \quad \sigma = 1 \quad \Rightarrow \quad e^{U\intercal}G^U = e^{U\intercal}G^{U\intercal} = e^{U\intercal}; \tag{5.54}$$

and that

$$e_1^\intercal G_1 e_i = u_r^\intercal e_i, \ e_1^\intercal G_2 e_i = u_s^\intercal e_i, \ e_1^\intercal G_3 e_i = 0, \qquad i = 1, 2, 3. \tag{5.55}$$

One then educes from (5.53a) and (5.53b) and by use of (5.54), that

$$\begin{aligned} J_\alpha(A^*) &= -(e^U \otimes e_1)\mathbf{1}_6^\intercal + \sum_{\eta,\eta',i,i'} (e^{\eta\intercal} e^{\eta'} \otimes e_1^\intercal G_i e_{i'})\ (e^\eta \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal \\ &\quad + \sum_{\eta',i,i'} (e^{U\intercal} G^{U\intercal} e^{\eta'} \otimes e_1^\intercal G_i e_{i'})\ (e^U \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal \\ &= -(e^U \otimes e_1)\mathbf{1}_6^\intercal + \sum_{\eta,i,i'} (e_1^\intercal G_i e_{i'})\ (e^\eta \otimes e_i)(e^\eta \otimes e_{i'})^\intercal \\ &\quad + \sum_{i,i'} (e_1^\intercal G_i e_{i'})\ (e^U \otimes e_i)(e^U \otimes e_{i'})^\intercal \\ &= -(e^U \otimes e_1)\mathbf{1}_6^\intercal + \sum_{i,i'} (e_1^\intercal G_i e_{i'})\ \left((2e^U e^{U\intercal} + e^W e^{W\intercal}) \otimes (e_i e_{i'}^\intercal)\right) \end{aligned} \tag{5.56}$$

Using the formulas in (5.2) as well as (5.55), one shows that

$$\sum_{i,i'} (e_1^\intercal G_i e_{i'})(e_i e_{i'}^\intercal) = \sum_{i'} \left((u_r^\intercal e_{i'})(e_1 e_{i'}^\intercal) + (u_s^\intercal e_{i'})(e_2 e_{i'}^\intercal)\right) = \begin{pmatrix} 1 & \frac{1}{2} & 0 \\ 0 & \frac{1}{2} & 1 \\ 0 & 0 & 0 \end{pmatrix}. \tag{5.57}$$

In these conditions, one shows in particular that

$$(e^W \otimes I_3)^\intercal J_\alpha(A^*)(e^U \otimes I_3) = 0_{3\times 3},$$

due to the fact that $e^{W\intercal} e^U = 0$. The matrix $J_\alpha(A^*)$ is thus *upper block-triangular*, a property which will allow to factorize the determinant of the system linearized around the equilibrium under study.

In view of (5.17), the system linearized around A^* writes

$$\dot{M} = (\nabla b^*(A^*) \cdot M)\, \mathtt{diag}\{m'(b^*(\alpha(A^*)))\} A^* + \mathtt{diag}\{m(b^*(\alpha(A^*)))\} J_\alpha(A^*) M - \mu M. \tag{5.58}$$

Due to the previous consideration, the matrix appearing in the right-hand side is upper block-triangular. By use of Lemmas 5.16 and 5.17, one deduces that the characteristic polynomial of the linearized system is the product of the two determinants

$$\left| \lambda I_3 - \begin{pmatrix} m_1^{U\prime} A_1^{U*} \delta_1 + m_1^U - \mu_1^U & m_1^{U\prime} A_1^{U*} \delta_2 + m_1^U & m_1^{U\prime} A_1^{U*} \delta_3 \\ 0 & m_2^U - \mu_2^U & 2m_2^U \\ 0 & 0 & -\mu_3^U \end{pmatrix} \right|$$

and

$$\left|\lambda I_3 - \begin{pmatrix} m_1^W - \mu_1^W & \frac{1}{2}m_1^W & 0 \\ 0 & \frac{1}{2}m_2^W - \mu_2^W & m_2^W \\ 0 & 0 & -\mu_3^W \end{pmatrix}\right|,$$

In the preceding formulas, m_i^η and $m_i^{\eta\prime}$ are shorthands for the value of the function m_i^η and its derivative $m_i^{\eta\prime}$, taken at the point $b^*(\alpha(A))$, while $\delta_i := (\nabla b^*(A^*)\cdot(e^U \otimes e_i)) > 0$, $i = 1, 2, 3$.

Now, at the equilibrium $A^* = A_r^{U*}(e^U \otimes e_1)$, one has

$$0 = m_1^U(b^*(\alpha(A^*))) - \mu_1^U > m_2^U(b^*(\alpha(A^*))) - \mu_2^U > m_3^U(b^*(\alpha(A^*))) - \mu_3^U$$

and

$$0 = m_1^U(b^*(\alpha(A^*))) - \mu_1^U > m_1^W(b^*(\alpha(A^*))) - \mu_1^W > m_2^W(b^*(\alpha(A^*))) - \mu_2^W$$

$$> m_3^W(b^*(\alpha(A^*))) - \mu_3^W.$$

From the fact that the derivative $m_1^{U\prime}$ takes on negative values, one deduces that all six zeros of the preceding characteristic polynomial are real and negative. This shows the local asymptotic stability of the equilibrium point $A_r^{U*}(e^U \otimes e_1)$.

∘ Let us now prove the same stability property for the equilibrium $A^* := A_r^{W*}(e^W \otimes e_1)$. One has here

$$J_\alpha(A^*) = -(e^W \otimes e_1)\mathbf{1}_6^\intercal + \sum_{\eta,\eta',i,i'} \left(e^{W\intercal}(G^\eta + G^{\eta\intercal})e^{\eta'} \otimes e_1^\intercal G_i e_{i'}\right) (e^\eta \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal \quad (5.59)$$

and from the fact that

$$e^{W\intercal}G^W = e^{W\intercal}, \quad e^{W\intercal}G^{W\intercal} = \mathbf{1}_2^\intercal, \quad \text{and} \quad \sigma = 1 \quad \Rightarrow \quad e^{W\intercal}G^U = e^{W\intercal}G^{U\intercal} = 0_{1\times 2}, \quad (5.60)$$

this implies

$$\begin{aligned} J_\alpha(A^*) &= -(e^W \otimes e_1)\mathbf{1}_6^\intercal \\ &\quad + \sum_{\eta',i,i'} \Big((e^{W\intercal} e^{\eta'} \otimes e_1^\intercal G_i e_{i'}) + (\mathbf{1}_2^\intercal e^{\eta'} \otimes e_1^\intercal G_i e_{i'}) \Big) \ (e^W \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal \\ &= -(e^W \otimes e_1)\mathbf{1}_6^\intercal + \sum_{i,i'} (e_1^\intercal G_i e_{i'}) \ (e^W \otimes e_i)(e^W \otimes e_{i'})^\intercal \\ &\quad + \sum_{i,i'} (e_1^\intercal G_i e_{i'}) \ (e^W \otimes e_i)((e^U + e^W) \otimes e_{i'})^\intercal \\ &= -(e^W \otimes e_1)\mathbf{1}_6^\intercal + \sum_{i,i'} (e_1^\intercal G_i e_{i'}) \ \Big((e^W (e^U + 2e^W)^\intercal) \otimes (e_i e_{i'}^\intercal) \Big) \end{aligned} \tag{5.61}$$

One observes here that $(e^U \otimes I_3)^\intercal J_\alpha(A^*) = 0_{3\times 6}$, and the characteristic polynomial of (5.58) at $A^* = A_r^{W*}(e^W \otimes e_1)$ is the product of the two determinants

$$\left| \lambda I_3 - \begin{pmatrix} -\mu_1^U & 0 & 0 \\ 0 & -\mu_2^U & 0 \\ 0 & 0 & -\mu_3^U \end{pmatrix} \right|$$

and

$$\left| \lambda I_3 - \begin{pmatrix} m_1^{W\prime} A_1^{W*} \delta_1 + m_1^W - \mu_1^W & m_1^{W\prime} A_1^{W*} \delta_2 + m_1^W & m_1^{W\prime} A_1^{W*} \delta_3 \\ 0 & m_2^W - \mu_2^W & 2m_2^W \\ 0 & 0 & -\mu_3^W \end{pmatrix} \right|,$$

where now $\delta_i := (\nabla b^*(A^*) \cdot (e^W \otimes e_i)) > 0$, $i = 1, 2, 3$.

Its spectrum is real and negative, and the local asymptotic stability of the equilibrium $A_r^{W*}(e^W \otimes e_1)$ comes as a consequence. This achieves the demonstration of Theorem 5.8. □

5.6 State-feedback stabilization

We consider now the issue of synthesizing state-feedback law able to drive the system from any nonzero initial state towards the desired resistant, fully-infected, equilibrium previously denoted $A_1^{W*}(e^W \otimes e_1)$. As already announced in the beginning of Section 5.5, we assume here full cytoplasmic incompatibility ($\sigma = 1$), Also, we make here and in the sequel of the paper the following hypothesis:

$$\lim_{c\to 0^+} m_1^\eta(b^*(c(e^\eta \otimes e_1))) > \mu_1^\eta, \qquad \lim_{c\to 0^+} m_3^\eta(b^*(c(e^\eta \otimes e_1))) < \mu_3^\eta, \qquad \eta = U, W. \tag{5.62}$$

In other words, it is assumed from now on that both *resistant* homozygous genotypes are viable, while the *susceptible* homozygous ones are not. (No specific assumption is made at this step about the heterozygous, whose fitness lies between the two homozygous ones.) This is typical of the situation one wishes to model here, of treatment by *Wolbachia* in an environment containing insecticide. As a consequence of (5.62), among the *monomorphic* equilibria exhibited previously in Theorem 5.7, only the *resistant* ones are indeed distinct from zero, that is the two homogeneous $A_r^{\eta *}(e^\eta \otimes e_1)$, $\eta = U, W$, and the coexistence equilibrium $A_r^{U**}(e^U \otimes e_1) + A_r^{W**}(e^W \otimes e_1)$.

We recall the following inequalities, valid at each instant along the trajectories, and easily deduced from the assumptions:

$$m_3^\eta(b^*(\alpha(A))) \leq \tilde{m}_s^\eta \leq m_2^\eta(b^*(\alpha(A))) \leq \tilde{m}_r^\eta \leq m_1^\eta(b^*(\alpha(A))), \qquad \eta = U, W \tag{5.63a}$$

$$\mu_1^\eta \leq \tilde{\mu}_r^\eta \leq \mu_2^\eta \leq \tilde{\mu}_s^\eta \leq \mu_3^\eta, \qquad \eta = U, W \tag{5.63b}$$

$$\tilde{m}_j^W \leq \tilde{m}_j^U, \quad \tilde{\mu}_j^U \leq \tilde{\mu}_j^W, \qquad j = r, s \tag{5.63c}$$

Our aim is to control the system and reach the monomorphic equilibrium

$$(A_r^U, A_s^U, A_r^W, A_s^W) = (0, 0, A_1^{W*}, 0), \tag{5.64a}$$

typically (but not only) departing from the other monomorphic equilibrium

$$(A_r^U, A_s^U, A_r^W, A_s^W) = (A_1^{U*}, 0, 0, 0). \tag{5.64b}$$

In (5.64a), (5.64b), one has used the equilibrium values $A_i^{\eta *}$, $\eta = U, W$, $i = 1, 2, 3$, defined in Theorem 5.7. Notice that the values in (5.64a), (5.64b) are "pseudo states", which correspond to the two different homogeneous monomorphic equilibria of resistant alleles for the underlying system (5.16a), the switch being thought of across release of infected alleles in (5.41d) or (5.41d). They constitute equilibrium points for system (5.40)/(5.41), given that the time-varying coefficients $\tilde{m}_j^\eta(t), \tilde{\mu}_j^\eta(t)$, $\eta = U, W$, $j = r, s$ are in fact state-dependent quantities[1].

5.6.1 Growth rate comparison and evolution of uninfected population

The following simple result is central to study growth rate comparison.

[1]Using Control theory terminology, system (5.40)/(5.41) may be seen as a *controlled, autonomous, nonlinear parameter-varying system.*

Proposition 5.9 (Growth rate dominance)**.** *Consider two positive, absolutely continuous, scalar functions y, z defined on $[0, +\infty)$. Assume that, for some $\varepsilon > 0$ and $T \geq 0$,*

$$\frac{\dot{y}(t)}{y(t)} - \frac{\dot{z}(t)}{z(t)} \geq \varepsilon > 0 \tag{5.65}$$

holds for almost any $t \geq T$. Then, for any $t \geq T$,

$$0 \leq \frac{z(t)}{y(t)} \leq \frac{z(T)}{y(T)} e^{-\varepsilon(t-T)} \tag{5.66}$$

Moreover, if y is bounded, one has

$$\lim_{t \to +\infty} z(t) = 0 \ . \tag{5.67}$$

Proof. Formula (5.65) writes

$$\frac{d}{dt}\left[\ln\left(\frac{y}{z}\right)\right] \geq \varepsilon$$

and (5.66) is deduced by integration. Formula (5.67) then comes as an immediate consequence of the boundedness of y. □

We deduce from Proposition 5.9 an important auxiliary result on the evolution of the uninfected population, somehow reminiscent of the Lemmas 16, 17, 18 in (P.E. Perez-Estigarribia, 2019b).

Proposition 5.10 (Asymptotic predominance of resistant among the uninfected)**.** *For any heterogeneous initial point $A(0)$ containing uninfected, $|A^U|$ is uniformly bounded along time,*

$$\lim_{t \to +\infty} \frac{A_1^U}{|A^U|} = 1, \tag{5.68}$$

and

$$\lim_{t \to +\infty} A_2^U = \lim_{t \to +\infty} A_3^U = 0. \tag{5.69}$$

In spite of its proximity with results from Chapter 2, the result in Proposition 5.10 is in a sense *stronger*. It says that the growth of the number of alleles r pertaining to non infected is larger than the growth of the number of alleles s pertaining to non infected. This effect is insensitive to release of infected mosquitoes, including say "massive" introductions of infected homozygous with genotype (s, s). This property is a consequence of the involved mechanisms of genetic transmission.

Proof of Proposition 5.10. Equations (5.41a), (5.41b) show that

$$\frac{\dot{A}_r^U}{A_r^U} - \frac{\dot{A}_s^U}{A_s^U} > 0, \tag{5.70}$$

and indeed that

$$\frac{\dot{A}_r^U}{A_r^U} - \frac{\dot{A}_s^U}{A_s^U} > \varepsilon \tag{5.71}$$

for some $\varepsilon > 0$, arguing as in Chapter 2. Applying Proposition 5.9 shows that $\frac{A_s^U}{A_r^U}$ decreases exponentially to zero, and the same holds true for $\frac{A_s^U}{|A^U|} = \frac{A_s^U}{A_r^U + A_s^U}$. This yields (5.68) as a consequence.

On the other hand, considering (5.25a) with $\sigma = 1$, one gets

$$\frac{d|A^U|}{dt} = \left(\tilde{m}^U(t)\frac{|A^U|}{|A|} - \tilde{\mu}^U(t)\right)|A^U| \leq \left(\tilde{m}^U(t) - \tilde{\mu}^U(t)\right)|A^U| \leq \left(\tilde{m}_1^U(b^*(\alpha(A))) - \tilde{\mu}_1^U\right)|A^U| \tag{5.72}$$

which, due to the properties of the recruitment and mortality rates, establishes that

$$\limsup_{t\to+\infty} |A^U(t)| \leq A_1^{U*} \ , \tag{5.73}$$

A_1^{U*} being the equilibrium level defined in Theorem 5.7. Consequently, $|A^U|$ is bounded, and Proposition 5.9 implies:

$$\lim_{t\to+\infty} A_s^U(t) = 0 \tag{5.74}$$

which provides (5.69). This achieves the proof of Proposition 5.10. □

5.6.2 Control laws and stabilisation results

We now present the main result of this note. The stabilisation method is based on (5.25), which, due to the fact that $\sigma = 1$, rewrites as follows:

$$\frac{d|A^U|}{dt} = \left(\tilde{m}^U(t)\frac{|A^U|}{|A^U| + |A^W|} - \tilde{\mu}^U(t)\right)|A^U|, \qquad \frac{d|A^W|}{dt} = (\tilde{m}^W(t) - \tilde{\mu}^W(t))|A^W| + |v_A| \tag{5.75}$$

The maps $\tilde{m}^U, \tilde{\mu}^U, \tilde{m}^W, \tilde{\mu}^W$ have been defined in (5.21).

The result, inspired by the ideas developed in (Bliman, 2019), is the following.

Theorem 5.11 (Infection by release of susceptible infected)**.** *Assume*

$$\mu_1^U + m_3^W(0) - \mu_3^W > 0. \tag{5.76}$$

Let $v_{A3} > 0$ be an input control such that, for some $\varepsilon \in (0, \mu_1^U + m_3^W(0) - \mu_3^W) \cap (0, \mu_3^U)$, $v_{A1} = v_{A2} = 0$ and some $T > 0$,

$$|v_A(t)| \geq \left| \tilde{m}^U(t) \frac{|A^U|}{|A^U| + |A^W|} - \tilde{\mu}^U(t) - \tilde{m}^W(t) + \tilde{\mu}^W(t) + \varepsilon \right|_+ |A^W|, \qquad t \geq T, \tag{5.77}$$

with equality except on a bounded subinterval of $[T, +\infty)$.

Then the solution of (5.17) *satisfies*

$$\lim_{t \to +\infty} A(t) = A_1^{W*}(e^W \otimes e_1) \tag{5.78}$$

and there exists $T' \geq T$ such that $|v_A|_{[T', +\infty)} \equiv 0$.

Provided that (5.76) holds, Theorem 5.11 provides a way to reach full infection by use of a control law which vanishes after finite time. As is clear from (5.77), Theorem 5.11 prescribes only a minimal value for the global release rate of infected mosquitoes of all genotypes. However, successful infection by release of susceptible mosquitoes or of resistant mosquitoes necessitates different quantities of insects, as illustrated numerically below in Section 5.7.3.1.

When (5.77) applies, then in view of (5.75), for any $t \geq T$,

$$\begin{aligned} \frac{1}{|A^W|} \frac{d|A^W|}{dt} &\geq \tilde{m}^W(t) - \tilde{\mu}^W(t) + \left| \tilde{m}^U(t) \frac{|A^U|}{|A^U| + |A^W|} - \tilde{\mu}^U(t) - \tilde{m}^W(t) + \tilde{\mu}^W(t) + \varepsilon \right|_+ \\ &\geq \max \left\{ \tilde{m}^U(t) \frac{|A^U|}{|A^U| + |A^W|} - \tilde{\mu}^U(t) + \varepsilon, \tilde{m}^W(t) - \tilde{\mu}^W(t) \right\} \\ &\geq \max \left\{ \frac{1}{|A^U|} \frac{d|A^U|}{dt} + \varepsilon, \tilde{m}^W(t) - \tilde{\mu}^W(t) \right\} \end{aligned} \tag{5.79}$$

with equality *iff* equality holds in (5.77). Therefore the mean growth rate of the *Wolbachia* infected is kept unchanged when larger than the mean growth rate of the uninfected plus ε, and changed to this value otherwise. This is the principle of the feedback.

Notice that applying (5.77) with equality everywhere causes no release if A^W is initially zero, and the infection then does not occur. On the contrary, departing from any state containing infectious and taking equality in (5.77) yields convergence to the desired equilibrium, and no input is indeed necessary after a finite time.

Proof of Theorem 5.11. From (5.79) one has that, for any $t \geq T$,

$$\frac{1}{|A^W|} \frac{d|A^W|}{dt} \geq \frac{1}{|A^U|} \frac{d|A^U|}{dt} + \varepsilon. \tag{5.80}$$

In particular,

$$\max\left\{\frac{1}{|A^U|}\frac{d|A^U|}{dt},\frac{1}{|A^W|}\frac{d|A^W|}{dt}\right\}=\max\left\{\tilde{m}^U(t)\frac{|A^U|}{|A^U|+|A^W|}-\tilde{\mu}^U(t)+\varepsilon,\tilde{m}^W(t)-\tilde{\mu}^W(t)\right\} \tag{5.81}$$

As the functions m_1^η, $\eta=U,W$, vanish at infinity, one deduces from (5.81) that all trajectories of the controlled system are uniformly ultimately bounded, see Theorem 5.5. From this boundedness property and inequality (5.80), one derives from Proposition 5.9 that

$$\lim_{t\to+\infty}A^U(t)=0_3. \tag{5.82}$$

On the other hand, Proposition 5.10 implies that

$$\tilde{\mu}^U(t)=\frac{\sum_{i=1}^3\mu_i^UA_i^U(t)}{\sum_{i=1}^3A_i^U(t)}\longrightarrow\mu_1^U\text{ when }t\to+\infty. \tag{5.83}$$

Putting together (5.82) and (5.83), one deduces that

$$\tilde{m}^U(t)\frac{|A^U|}{|A^U|+|A^W|}-\tilde{\mu}^U(t)\longrightarrow-\mu_1^U\text{ when }t\to+\infty. \tag{5.84}$$

Let us now compare the asymptotic behaviour of the growth rates for the *Wolbachia* infected allelic populations. From the previous deductions one has that

$$\lim_{t\to+\infty}\Big(|A_j(t)|-A_j^W(t)\Big)=\lim_{t\to+\infty}A_j^U(t)=0,\qquad j=r,s,$$

and therefore one may infer from (5.41c) and (5.41d) that

$$\lim_{t\to+\infty}\left|\frac{1}{|A^W|}\frac{d|A^W|}{dt}-\Big(\tilde{m}_r^W(t)-\tilde{\mu}_r^W(t)\Big)\right|_-=0 \tag{5.85a}$$

$$\lim_{t\to+\infty}\left|\frac{\dot{A}_s^W}{A_s^W}-\left(\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)+\Big|-\mu_1^U-\tilde{m}^W(t)+\tilde{\mu}^W(t)+\varepsilon\Big|_+\right)\right|_+=0 \tag{5.85b}$$

Now, using the fact that

$$\tilde{m}^W(t)=\frac{A_r^W\tilde{m}_r^W(t)+A_s^W\tilde{m}_s^W(t)}{A_r^W+A_s^W},\qquad\tilde{\mu}^W(t)=\frac{A_r^W\tilde{\mu}_r^W(t)+A_s^W\tilde{\mu}_s^W(t)}{A_r^W+A_s^W} \tag{5.86}$$

one has

$$\begin{aligned}
&\tilde{m}_s^W(t) - \tilde{\mu}_s^W(t) + \left|-\mu_1^U - \tilde{m}^W(t) + \tilde{\mu}^W(t) + \varepsilon\right|_+ \\
&= \tilde{m}_s^W(t) - \tilde{\mu}_s^W(t) + \max\left\{-\mu_1^U - \frac{A_r^W(\tilde{m}_r^W(t) - \tilde{\mu}_r^W(t)) + A_s^W(\tilde{m}_s^W(t) - \tilde{\mu}_s^W(t))}{A_r^W + A_s^W} + \varepsilon; 0\right\} \\
&= \max\left\{-\mu_1^U + \frac{A_r^W}{A_r^W + A_s^W}\left(\tilde{m}_s^W(t) - \tilde{\mu}_s^W(t) - \tilde{m}_r^W(t) + \tilde{\mu}_r^W(t)\right) + \varepsilon; \tilde{m}_s^W(t) - \tilde{\mu}_s^W(t)\right\} \\
&\leq \max\left\{-\mu_1^U + \varepsilon; \tilde{m}_s^W(t) - \tilde{\mu}_s^W(t)\right\} \\
&\leq \max\left\{-\mu_1^U + \varepsilon; m_3^W(0) - \mu_3^W\right\} \\
&= m_3^W(0) - \mu_3^W \qquad \text{(due to (5.76))} \\
&< \tilde{m}_r^W(t) - \tilde{\mu}_r^W(t) \qquad (5.87)
\end{aligned}$$

The quantity

$$\begin{aligned}
\frac{1}{|A^W|}\frac{d|A^W|}{dt} - \frac{\dot{A}_s^W}{A_s^W} \;=\; & \frac{1}{|A^W|}\frac{d|A^W|}{dt} - \left(\tilde{m}_r^W(t) - \tilde{\mu}_r^W(t)\right) \qquad (5.88) \\
& + \left(\tilde{m}_r^W(t) - \tilde{\mu}_r^W(t)\right) \\
& - \left(\tilde{m}_s^W(t) - \tilde{\mu}_s^W(t) + \left|-\mu_1^U - \tilde{m}^W(t) + \tilde{\mu}^W(t) + \varepsilon\right|_+\right) \\
& + \left(\tilde{m}_s^W(t) - \tilde{\mu}_s^W(t) + \left|-\mu_1^U - \tilde{m}^W(t) + \tilde{\mu}^W(t) + \varepsilon\right|_+\right) - \frac{\dot{A}_s^W}{A_s^W}
\end{aligned}$$

then appears as positive asymptotically, due to (5.85a), (5.87), (5.85b). The comparison of the asymptotic growth rates of A_r^W and A_s^W then yields

$$\lim_{t\to+\infty} \frac{A_s^W}{A_r^W + A_s^W} = 0, \qquad (5.89)$$

due to Proposition 5.9, and then

$$\lim_{t\to+\infty} \frac{A_1^W}{|A^W|} = 1 \qquad (5.90)$$

In turn this implies that A_1^W behaves asymptotically in such a way that

$$\lim_{t\to+\infty} \left(\dot{A}_1^W - \left(m_1^W(b^*(A_1^W(e^W \otimes e_1))) - \mu_1^W\right) A_1^W\right) = 0 \qquad (5.91)$$

which implies (5.78).

Last, this induces that

$$\lim_{t\to+\infty}\left(\tilde{m}^W(t)-\tilde{\mu}^W(t)\right)=m_1^W(b^*(A_1^{W*}(e^W\otimes e_1)))-\mu_1^W=0 \tag{5.92}$$

and finally

$$\tilde{m}^U(t)\frac{|A^U|}{|A^U|+|A^W|}-\tilde{\mu}^U(t)-\tilde{m}^W(t)+\tilde{\mu}^W(t)+\varepsilon\to-\mu_1^U+\varepsilon<0 \qquad \text{when } t\to+\infty \tag{5.93}$$

One has used here the fact that $\varepsilon<\mu_1^U$. Now, as $v_{A3}(t)$ is equal to the *positive value* of the previous expression, this quantity vanishes in finite time. This achieves the proof of Theorem 5.11. □

Choosing control (5.77) thus allows to reach full infection by use of control vanishing in finite time. Theorem 5.12 is analogous, with *resistant* mosquitoes, which is formally expressed below. Of course, releasing susceptible or resistant requires different quantities of insects to achieve infection.

Theorem 5.12 (Infection by release of resistant infected)**.** *Assume*

$$\mu_1^U+m_2^W(0)-\mu_2^W>0. \tag{5.94}$$

Let $v_{A1}>0$ be an input control such that, for some $\varepsilon\in(0,\mu_1^U+m_2^W(0)-\mu_2^W)\cap(0,\mu_2^U)$, $v_{A3}=v_{A2}=0$, some $T>0$ and equation (5.77) *with equality except on a bounded subinterval of $[T,+\infty)$. Then the solution of* (5.17) *satisfies* (5.77) *and there exists $T'\geq T$ such that $|v_A|_{[T',+\infty)}\equiv 0$.*

Proof of Theorem 5.12. The proof of this theorem is achieved by following steps analogous to the previous one. In contrast the previous, for this case in the step corresponding to the equation (5.87) we have

$$\begin{aligned}
&\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)+\left|-\mu_1^U-\tilde{m}^W(t)+\tilde{\mu}^W(t)+\varepsilon\right|_+\\
&\quad=\ \tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)+\max\left\{-\mu_1^U-\frac{A_r^W(\tilde{m}_r^W(t)-\tilde{\mu}_r^W(t))+A_s^W(\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t))}{A_r^W+A_s^W}+\varepsilon;0\right\}\\
&\quad=\ \max\left\{-\mu_1^U+\frac{A_r^W}{A_r^W+A_s^W}\left(\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)-\tilde{m}_r^W(t)+\tilde{\mu}_r^W(t)\right)+\varepsilon;\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)\right\}\\
&\quad\leq\ \max\left\{-\mu_1^U+\varepsilon;\tilde{m}_s^W(t)-\tilde{\mu}_s^W(t)\right\}\\
&\quad\leq\ \max\left\{-\mu_1^U+\varepsilon;m_2^W(0)-\mu_2^W\right\}\\
&\quad=\ m_2^W(0)-\mu_2^W \qquad \text{(due to (5.94))}\\
&\quad<\ \tilde{m}_r^W(t)-\tilde{\mu}_r^W(t).
\end{aligned}$$

The remaining steps of the previous Theorem 5.11 proof are also satisfied for this case. □

As a final remark on Theorems 5.11 and 5.12, recall that these results apply to the singularly perturbed system (5.17). However, they extend to 12-dimensional systems similar to (5.10), with $\dot{L}_i^\eta$ in (5.10a) replaced by $\varepsilon\dot{L}_i^\eta$ for small enough $\varepsilon > 0$. This corresponds to pre-adult phase evolving faster than the adult one, but with finite evolution speed.

5.7 Numerical simulations

All the simulations were done with the free and open-source programming language Scilab. In order to ensure the reproducibility of the results, we provide the details of the implemented source code in Appendix A.

5.7.1 Model implemented for numerical simulations

For the simulations we use the same Assumption 5 introduced in Section 3.2.1, p. 58 on the explicit form of larvae mortality function. Namely, for any $b \in \mathbb{R}_+$, the mortality rate functions verify

$$\hat{\mu}_i^\eta(b) + \nu = \hat{\mu}_{i0}^\eta(1 + \hat{\mu}b) \tag{5.95}$$

for given positive $\hat{\mu}$ and $\hat{\mu}_{i0}^\eta$ with $i = 1, 2, 3$ and $\eta = U, W$. This formulation determines the survival conditions in a given ecological niche. The parameter $\hat{\mu}_{i0}$ define baseline multiplicative constant death rate for each genotype, while, slope $\hat{\mu}$ is the baseline per capita intra-specific death rate given by scramble competition —*e.g.* due to the restricted availability of breeding site space. As a matter of fact, any natural or human factor that causes a reduction in the number of breeding sites induces an increase in scramble competition and an increase in density dependent mortality by competition. This phenomenon is captured by an increase in the constant $\hat{\mu}$.

Following the reasoning presented in Section 5.3, given equations 5.95, the equation (5.13) takes the form

$$|L| = \frac{1}{(1 + \hat{\mu}|L|)} \sum_{i=1}^{3} \sum_{\eta=U,W} \frac{r^\eta}{\hat{\mu}_{i0}^\eta} \alpha_i^\eta(A) \ . \tag{5.96}$$

Hence, considering $b := |L|$, from equations (5.14) and (5.96) one can deduce the

following polynomial equation

$$0 = \vartheta^{\intercal}\alpha(A) - b - \mu b^2, \qquad \vartheta := \sum_{\eta=U,W}\sum_{i=1}^{3} \frac{r^{\eta}}{\hat{\mu}_{i0}^{\eta}}(e^{\eta} \otimes e_i) \ . \tag{5.97}$$

Let be $A \in \mathbb{R}_{+}^{6}$, from the identity (5.97) one deduces explicitly the value of b^* such that

$$b^*(A) = \frac{-1 \pm \sqrt{1 + 4\hat{\mu}\vartheta^{\intercal}A}}{2\hat{\mu}}. \tag{5.98}$$

Therefore, one has

$$|L| = b^*(\alpha(A)) = \frac{-1 + \sqrt{1 + 4\hat{\mu}\vartheta^{\intercal}\alpha(A)}}{2\hat{\mu}}. \tag{5.99}$$

Now, from the explicit solution (5.98), one can see that for any $b \in \mathbb{R}_{+}$, the function m_i^{η} introduced in (5.16a) can be computed as

$$m_i^{\eta}(b) := \frac{\nu r^{\eta}}{\hat{\mu}_{i0}^{\eta}(1 + \hat{\mu}b)} \ . \tag{5.100}$$

This allows us to achieve an explicit formulation for the implementation and simulation of the model (5.17).

Note also that from this last result, replacing equation (5.100) in the expression (5.42b), from successive algebraic operations one has

$$\begin{aligned} \mu_i^{\eta} &= m_i^{\eta}(b^*(\alpha(A))) \\ \mu_i^{\eta} &= \frac{\nu r^{\eta}}{\hat{\mu}_{i0}^{\eta}(1 + \hat{\mu}b^*(\alpha(A)))} \\ b^*(\alpha(A)) &= \frac{1}{\hat{\mu}}\left(\frac{\nu r^{\eta}}{\hat{\mu}_{i0}^{\eta}\mu_i^{\eta}} - 1\right) \end{aligned}$$

Then, replacing $b^*(\alpha(A))$ in the last equality with the equation (5.98) evaluated in the

homogeneous monomorphic equilibrium $A_i^{\eta*}$ one has

$$\begin{aligned}
\frac{-1+\sqrt{1+4\hat{\mu}A_i^{\eta*}\vartheta^{\intercal}(e_\eta\otimes e_i)}}{2\hat{\mu}} &= \frac{1}{\hat{\mu}}\left(\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}-1\right)\\
1+4\hat{\mu}A_i^{\eta*}\vartheta^{\intercal}(e_\eta\otimes e_i) &= \left(2\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}-1\right)^2\\
1+4\hat{\mu}A_i^{\eta*}\vartheta^{\intercal}(e_\eta\otimes e_i) &= 4\left(\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}\right)^2-4\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}+1\\
\hat{\mu}A_i^{\eta*}\vartheta^{\intercal}(e_\eta\otimes e_i) &= \left(\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}\right)^2-\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}\\
\hat{\mu}\frac{r^\eta}{\hat{\mu}_{i0}^\eta}A_i^{\eta*} &= \frac{\nu}{\mu_i^\eta}\frac{r^\eta}{\hat{\mu}_{i0}^\eta}\left(\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}-1\right)\ .
\end{aligned}$$

Thus, the explicit value of this equilibrium is

$$A_i^{\eta*}=\left|\frac{\nu}{\hat{\mu}\mu_i^\eta}\left(\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta}-1\right)\right|_+,\quad i=1,3,\quad \eta=U,W. \tag{5.101}$$

Note that defining the basic reproductive number of an infected or uninfected genotype as

$$\mathbf{R}_{0i}^\eta:=\frac{\nu r^\eta}{\hat{\mu}_{i0}^\eta\mu_i^\eta},\quad i=1,3,\quad \eta=U,W. \tag{5.102}$$

Thus, the equation (5.103) can be written as

$$A_i^{\eta*}=\left|\frac{\nu}{\hat{\mu}\mu_i^\eta}\left(\mathbf{R}_{0i}^\eta-1\right)\right|_+,\quad i=1,3,\quad \eta=U,W. \tag{5.103}$$

Hence the population is viable if and only if $\mathbf{R}_{0i}^\eta>1$ for $i=1,3$, and $\eta=U,W$.

5.7.2 Parameters possible values

Below are ranges of entomological parameter values for *Aedes aegypti* provided in the literature (all units in days^{-1}).

- The rate of transfer to the adult (ν) presents values in $[14^{-1},10^{-1}]$ (Walker et al., 2011a; Hoffmann et al., 2014a; Koiller et al., 2014a; Adekunle et al., 2019).
- The mortality rate for L_3^U ($\hat{\mu}_{30}^U$) presents value in $[0.1,0.2]$ (Koiller et al., 2014a; Xue et al., 2017; Adekunle et al., 2019). Here the mutant allele of resistance contributes to a decrease in mortality and depends on some degree of allelic

dominance. In consequence, the mortality rate for L_1^U ($\hat{\mu}_{10}^U$) take values in $\hat{\mu}_{30}^U(1-\hat{d}_1^U)$, while the mortality rates for L_2^U ($\hat{\mu}_{20}^U$) take values in $\hat{\mu}_{30}^U(1-\hat{h}_1^U\hat{d}_1^U)$. Where, $\hat{h}_i^\eta, \hat{d}_i^\eta \in [0,1]$, such that $\hat{d}_i^\eta$ is a proportion decrease in the mortality rate and $\hat{h}_i^\eta$ is the degree of allelic dominance, similar to (Gillespie, 2004) population genetic model —see (Luz et al., 2009).

- The mortality rate for L_3^W ($\hat{\mu}_{30}^W$) presents values in $[0.1, 0.2]$ (Koiller et al., 2014a; Xue et al., 2017; Adekunle et al., 2019); while the mortality rates for L_1^W ($\hat{\mu}_{10}^W$) take values in $\hat{\mu}_{30}^W(1-\hat{d}_1^W)$ and the mortality rates for L_2^W ($\hat{\mu}_{20}^W$) in $\hat{\mu}_{30}^W(1-\hat{h}_1^W\hat{d}_1^W)$ for $\hat{h}_i^\eta, \hat{d}_i^\eta \in [0,1]$.

- The density-dependence mortality for L_i^η ($\hat{\mu}$) take values in $[0.01, 0.02]$ (Bliman et al., 2018a; Koiller et al., 2014a; Adekunle et al., 2019).

- The mortality rate for A_3^U (μ_3^U) presents values in $[0.02, 0.09]$ (Koiller et al., 2014a; Xue et al., 2017; Adekunle et al., 2019); while the mortality rates for A_1^U (μ_{10}^U) take values in $\mu_3^U(1-d_1^U)$ and the mortality rates for A_2^U (μ_2^U) in $\mu_3^U(1-h_1^U d_1^U)$ for $h_i^\eta, d_i^\eta \in [0,1]$.

- The mortality rate for A_3^W (μ_3^W) presents values in $[0.03, 0.14]$ (Styer et al., 2007; Walker et al., 2011a; Bliman et al., 2018a; Adekunle et al., 2019); while the mortality rates for A_1^W (μ_{10}^W) take values in $\mu_3^U(1-d_1^W)$ and the mortality rates for A_2^W (μ_2^W) in $\mu_3^W(1-h_1^W d_1^W)$ for $h_i^\eta, d_i^\eta \in [0,1]$.

- The fecundity rate of A_i^U (r^U) presents values in $[4, 18]$ (Koiller et al., 2014a; Hoffmann et al., 2014a; McMeniman et al., 2009; McMeniman and O'Neill, 2010; Adekunle et al., 2019); while, the fecundity rate of A_i^U (r^W) presents values in $[3.8, 12]$ (Walker et al., 2011a; Hoffmann et al., 2014a; Bliman et al., 2018a; Adekunle et al., 2019).

- The Cytoplasmic Incompatibility level (σ dimensionless) presents values in $[0.9, 1]$ (Walker et al., 2011a; Koiller et al., 2014a; Bliman et al., 2018a; Adekunle et al., 2019).

5.7.3 *Wolbachia* release scenarios

Using the system (5.17) coupled to the proposed Control Law (5.77) in a computational implementation, a series of in-silico experiment are presented in order to illustrate the analytical results. Also, the simulated scenarios listed below are intended to illustrate

the effect that certain inheritance and population dynamic factors have on the control by *Wolbachia*. The numerical results provided later show robustness of the stabilizing effect of the control law, against variations of these factors and in which scenarios it fails. The following simulations have been completed:

1. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide and larvicide, assuming allelic incomplete dominance. For this scenario, it is assumed in the parameter setting 5% of relative increase in mortality of infected larvae $\hat{\mu}_{i0}^{W} = \hat{\mu}_{i0}^{U}(1 + 0.05)$ and adult $\mu_{i0}^{W} = \mu_{i0}^{U}(1 + 0.05)$, 7% relative mortality decrease by the resistance in larvae $\hat{\mu}_{10}^{\eta} = \hat{\mu}_{30}^{\eta}(1-0.07)$ and adult $\mu_{10}^{\eta} = \mu_{30}^{\eta}(1-0.07)$ and 0.5 for the level of dominance of resistance in larvae $\hat{\mu}_{20}^{\eta} = \hat{\mu}_{30}^{\eta}(1-0.07\times0.05)$ and adult $\mu_{20}^{\eta} = \mu_{30}^{\eta}(1-0.07\times0.05)$ for heterozygotes (Figure 5.1).

2. Release of homozygous insecticide-resistance mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide and larvicide. The same parameter setting as the previous case is assumed (Figure 5.2).

3. Release of heterozygous mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide and larvicide, assuming allelic incomplete dominance.The same parameter setting as in the two previous cases is preserved (Figure 5.3).

4. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to a larvicide, assuming allelic incomplete dominance. It is assumed in the parameter setting 5% of relative increase in mortality of infected larvae and adult, 7% relative mortality decrease by the resistance in L_1^{η} and 0.5 for the level of dominance of resistance in larvae for heterozygotes (Figure 5.4).

5. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide, assuming allelic incomplete dominance. It is assumed in the parameter setting 5% of relative increase in mortality of infected larvae and adult, 7% relative mortality decrease by the resistance in A_1^{η} and 0.5 for the level of dominance of resistance in adult for heterozygotes (Figure 5.5).

6. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide, assuming genetic recessiveness for resistance. It is assumed in the parameter setting 5% of relative increase in mortality of infected larvae and adult, 7% relative mortality decrease by the resistance

in A_1^η and 0 for the level of dominance of resistance in adult for heterozygotes (Figure 5.6).

7. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide, assuming genetic dominance for resistance.It is assumed in the parameter setting 5% of relative increase in mortality of infected larvae and adult, 7% relative mortality decrease by the resistance in A_1^η and 1 for the level of dominance of resistance in adult for heterozygotes (Figure 5.7).

8. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to an adulticide, assuming allelic incomplete dominance and high scramble competition effect in larvae. It is assumed in the parameter setting of 80% of relative increase in larvae mortality by complete symmetric competition (Figure 5.8).

9. Release of homozygous insecticide-susceptible mosquitoes infected with *Wolbachia* whit 0.8 incomplete cytoplasmic incompatibility in an environment subjected to an adulticide, assuming allelic incomplete dominance (Figure 5.9).

10. Release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* with 0.65 incomplete cytoplasmic incompatibility in an environment subjected to an adulticide, assuming allelic incomplete dominance (Figure 5.10).

11. Insufficient release of homozygous insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to a strong effect of adulticide, assuming allelic incomplete dominance (such that assumption (5.76) in Theorem 5.11 is not satisfied). Parameter setting on 40% relative mortality decrease by the resistance in A_1^η and 0.5 for the level of dominance of resistance in adult for heterozygotes (Figure 5.11).

The parameter settings for each simulation are shown in Table 5.1, while the initial conditions are shown in Table 5.2. In all cases in Table 5.2 ϵ is proportional to A_1^{U*}, this amounts to take initial input $|v_A(t)|$ equal to a Dirac perturbation at zero of amplitude ϵ.

The total control effort made can be calculated in each simulated scenario using the expression $\int_0^{t_{max}} |v_A(t)|dt + \epsilon$. The numerical results of this computation are presented in Table 5.3 and are discussed in the following sections.

Table 5.1: Setting for parameters under different evolutionary hypothetical scenarios.

Sim	1,2, 3	4	5	6	7	8	9	10	11
ν	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$\hat{\mu}_{10}^{U}$	0.093	0.093	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$\hat{\mu}_{20}^{U}$	0.096	0.096	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$\hat{\mu}_{30}^{U}$	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
$\hat{\mu}_{10}^{W}$	0.097	0.098	0.105	0.105	0.105	0.105	0.105	0.1	0.1
$\hat{\mu}_{20}^{W}$	0.101	0.101	0.105	0.105	0.105	0.105	0.105	0.105	0.1
$\hat{\mu}_{30}^{W}$	0.105	0.105	0.105	0.105	0.105	0.105	0.105	0.105	0.1
$\hat{\mu}$	0.01	0.01	0.01	0.01	0.01	0.018	0.01	0.01	0.01
μ_1^U	0.057	0.061	0.057	0.057	0.057	0.057	0.057	0.057	0.037
μ_2^U	0.058	0.061	0.059	0.061	0.057	0.059	0.059	0.059	0.049
μ_3^U	0.061	0.061	0.061	0.061	0.061	0.061	0.061	0.061	0.061
μ_1^W	0.059	0.064	0.059	0.059	0.059	0.059	0.059	0.059	0.038
μ_2^W	0.062	0.064	0.062	0.064	0.059	0.062	0.061	0.061	0.051
μ_3^W	0.064	0.064	0.064	0.064	0.064	0.064	0.064	0.064	0.064
r^U	18	18	18	18	18	18	18	18	18
r^W	12	12	12	12	12	12	12	12	12
σ	1	1	1	1	1	1	0.8	0.5	1

Table 5.2: Setting for initial conditions.

Sim	$A_1^U(T_c)$	$A_2^U(T_c)$	$A_3^U(T_c)$	$A_1^W(T_c)$	$A_2^W(T_c)$	$A_3^W(T_c)$
1	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
2	A_1^{U*}	0	0	$1/3A_1^{U*}$	0	0
3	A_1^{U*}	0	0	0	$1/3A_1^{U*}$	0
4	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
5	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
6	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
7	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
8	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
9	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
10	A_1^{U*}	0	0	0	0	$1/3A_1^{U*}$
11	A_1^{U*}	0	0	0	0	A_1^{U*}

In all cases, $A_1^U(0) = A_1^{U*}$ given by equation (5.103).

5.7.3.1 Influence by released genotype

Simulations scenario 1, 2 and 3, illustrates the influence of genotype infected with *Wolbachia* released at the time of fixation and control effort given the proposed control law (see Figures 5.1, 5.2 and 5.3 respectively). In these three cases the change from an initial uninfected homogenous resistant monomorphic population to a finally infected homogenous resistant monomorphic population is achieved. Comparing simulation

Table 5.3: Total control effort comparison.

Sim	$\|A(0)\|$	$\mathbf{R}_{01}^{U}$	$\mathbf{R}_{02}^{U}$	$\mathbf{R}_{03}^{U}$	$\mathbf{R}_{01}^{W}$	$\mathbf{R}_{02}^{W}$	$\mathbf{R}_{03}^{W}$	Initial release	Control effort
1	59964	341	317	295	206	192	178	19988	73430
2	59964	341	317	295	206	192	178	19988	72953
3	59964	341	317	295	206	192	178	19988	72755
4	51851	317	306	295	192	185	178	17284	63248
5	55754	317	306	295	192	185	178	18585	67680
6	55754	317	295	295	192	178	178	18585	69335
7	55754	317	317	295	192	192	178	18585	65986
8	30974	317	306	295	192	185	178	10325	37600
9	55754	317	306	295	192	185	178	18585	79895
10	55754	317	306	295	192	185	178	18585	418887
11	134099	492	369	295	297	223	178	134099	321519

In all cases, $\mathbf{R}_{0i}^{\eta}$ is given by equation (5.102).

5.1b, 5.2b and 5.3b it can be seen that the control effort calculated by $\int_0^{t_{max}} |v_A(t)|dt+\epsilon$ is greater when susceptible homozygotes mosquitoes are released in comparison to resistant homozygotes (Table 5.3). Also, the release of susceptible mosquitoes gives a control effort bigger than heterozygotes. It can also be observed that the time required for the control effort is greater when the mosquitoes released are susceptible. In contrast, when the released mosquitoes are not susceptible, the control effort guarantees success in less time. The observed difference may vary depending on the difference in the basic reproductive number between infected and uninfected genotypes and the initial proportion of infected mosquitoes released. It is important to mention that it was observed that the success of the replacement, the effort and control time required depends not only on the genotype released, but also on the initial perturbance as discussed in Section 5.7.3.5.

Regarding to total population dynamics, Figures 5.1c, 5.2c and 5.2c show the changes induced by the control law, in all three cases there is an increase in population size with the initial control law increases, it is followed by a population decrease which is greater in the case of release of susceptible homozygous mosquitoes. Finally, the population size increases and converges to a value below the initial total population.

Concerning population genetics, Figures 5.1d and 5.3d illustrate the changes in genotypic frequencies induced by the control. The fixation of a total infected population from an uninfected population is illustrated in Figures 5.1e, 5.2d and 5.3e. Note that the release of susceptible genotype postpones the fixation of an infected population. While, Figures 5.1f and 5.3f show changes in allelic frequencies for mosquitoes infected and uninfected by *Wolbachia*, note that due to complete cytoplasmic incompatibility

the flow of alleles occurs unidirectionally from uninfected to infected mosquitoes and not in opposite direction.

In summary, whatever the case of *Wolbachia*-infected genotype released, under a scenario of insecticide application and resistance evolution —*i.e.* population adaptation— as previously demonstrated, the simulations illustrate how the proposed control law in Theorem 5.11 and 5.12 guarantees population convergence to a homogeneous infected equilibrium.

5.7.3.2 Influence by larvicides or adulticides

Chemical control strategies may involve the use of substances with direct or indirect effect larvicide and adulticide. However, there are some insecticides that only have the adulticidal or the larvicidal. It is difficult to establish in advance how will the use of these substances affect the biological controls by *Wolbachia*.

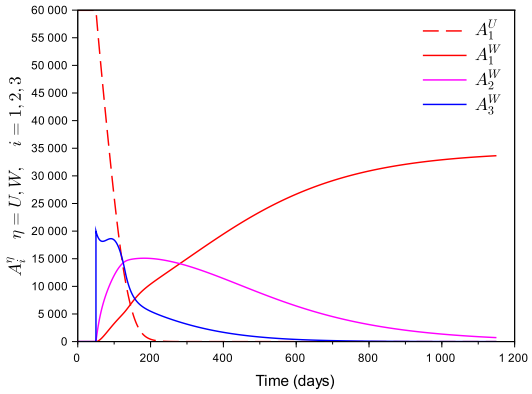
Simulations 4 and 5 illustrate the effect of use larvicide or adulticide respectively have in a control campaign (see Figures 5.4 and 5.5, respectively). The comparison between the results illustrated in Figures 5.1b, 5.4b and 5.5b shows that an insecticide with larvicide and adulticide effect will require more effort than one with only the adulticide. Meanwhile, the control method that requires the least effort is the one that only has the adulticide (Table 5.3). Given the set of parameters and the initial condition of these simulations, as can be seen in Figures 5.1e, 5.4e and 5.5e, the fixation time of totally infected population is similar when the larvicide or adulticida is applied.

Indeed, these simulations indicate that the use of adulticide agents will be favorable in the release campaigns of mosquitoes infected by *Wolbachia*.

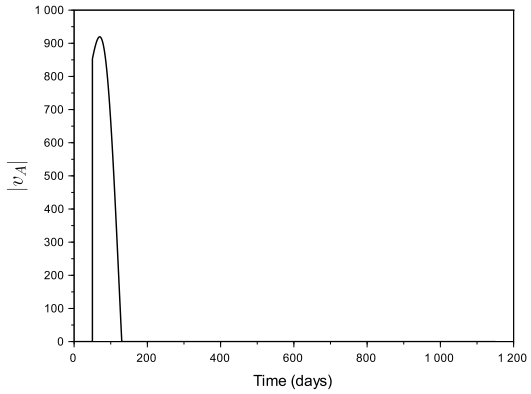
5.7.3.3 Influence by allelic dominance level

As mentioned in Chapter 4, the phenotypes presented during the use of an insecticide depend on the allelic dominance, which can be altered by the lethal dose and the type of insecticide used. In that sense, simulations 6 and 7 illustrate the allelic dominance level effect during a campaign to release mosquitoes infected with *Wolbachia* (see Figures 5.6 and 5.7).

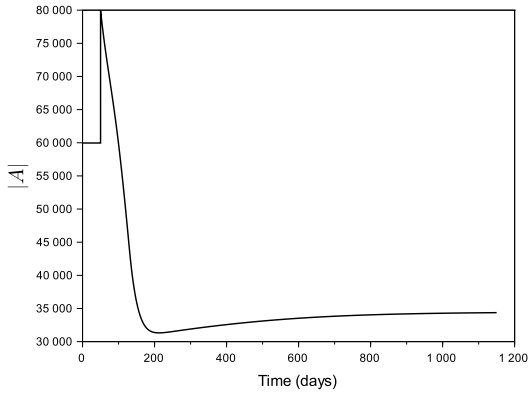
A comparison between simulations 4, 6 and 7 evidences that the level of dominance alters the required control effort —see Table 5.3. As we can see, a greater effort is needed when the resistance is recessive (heterozygous with phenotype equal to the homozygous susceptible). Moreover, in the case of incomplete dominance, the needed control effort is smaller than the resistance dominance case (heterozygous with phenotype equal to the homozygous resistant). In fact, given the parameters setting and



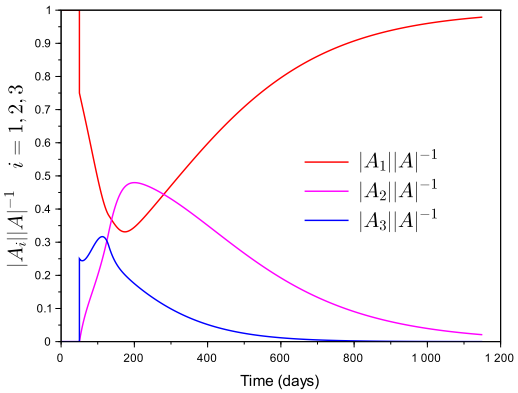
(a) Numerical solution for the control system



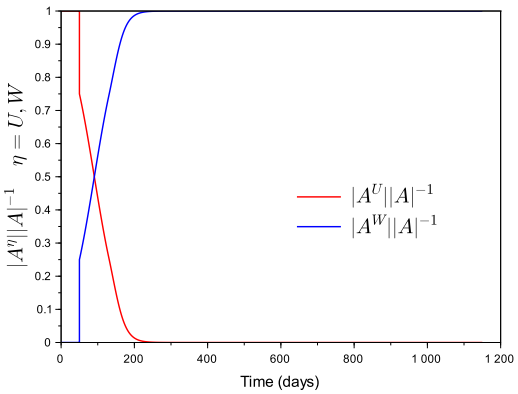
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\, dt$



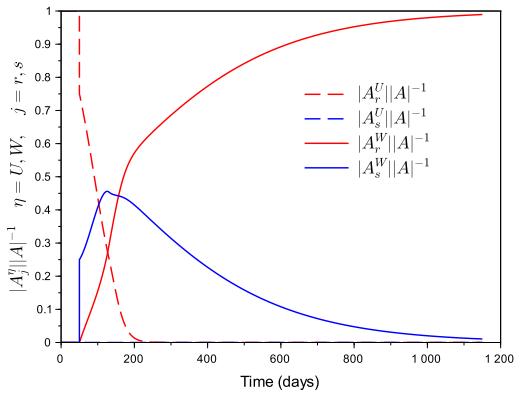
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

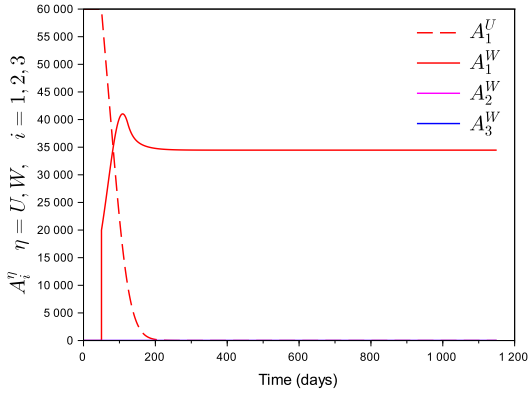


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

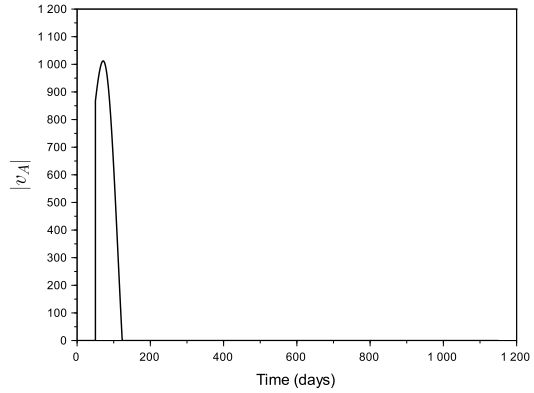


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

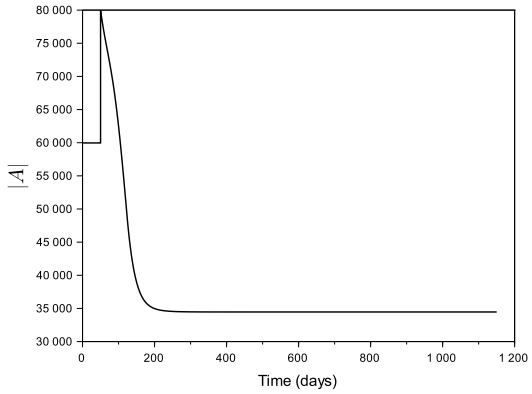
Figure 5.1: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* is illustrated. The setting for simulation 1 is given in Tables 5.2 and 5.1. Notice that, as foreseen by Theorem 5.6, point 3, no other non-infected genotype appears. See further explanations in Section 5.7.3.1.



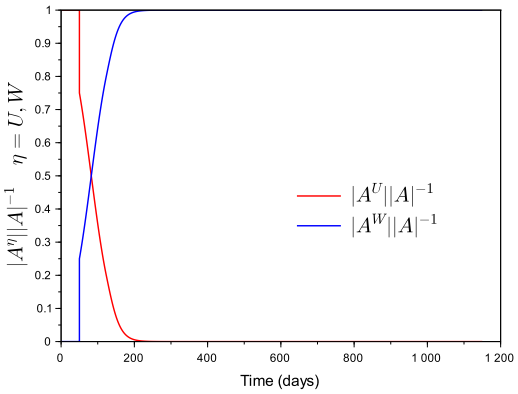
(a) Numerical solution for the control system



(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$

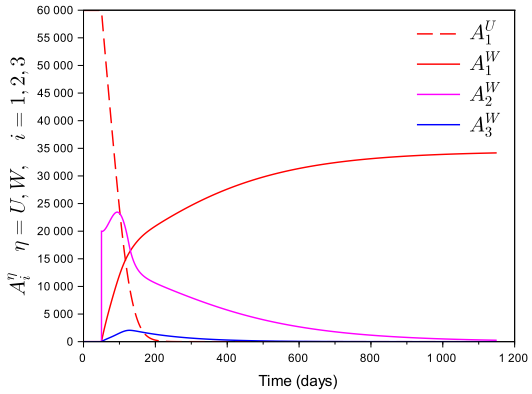


(c) Total population $|A(t)|$

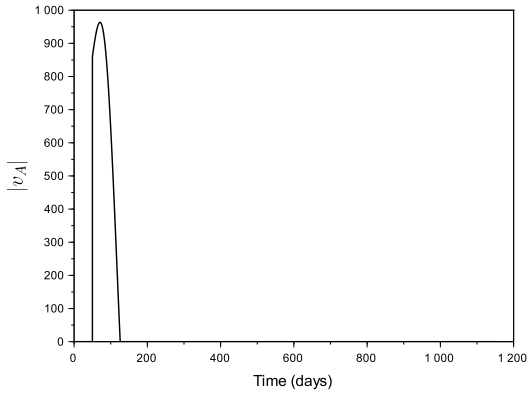


(d) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

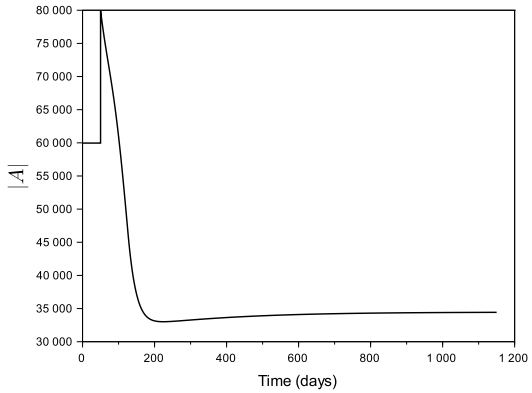
Figure 5.2: The expected scenario during the release of insecticide-resistance mosquitoes infected by *Wolbachia* is illustrated. The setting for simulation 1 is given in Tables 5.2 and 5.1. Notice that no other genotypes than the resistant ones appear. See further explanations in Section 5.7.3.1.



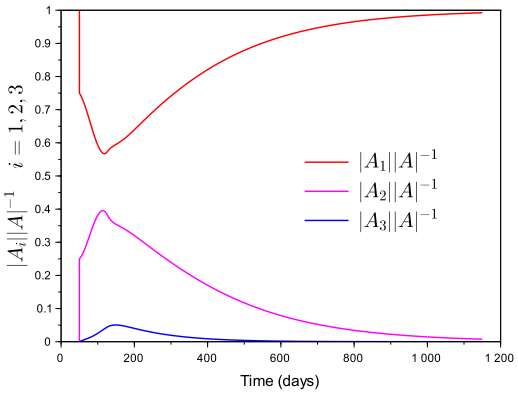
(a) Numerical solution for the control system



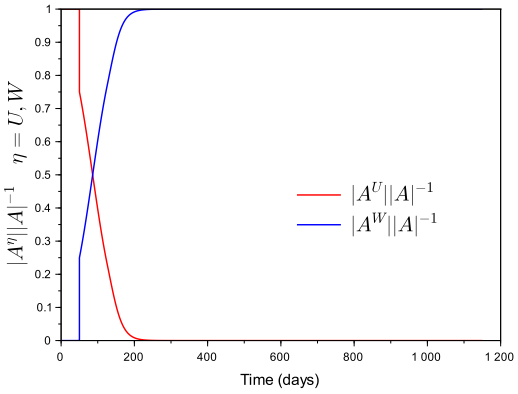
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



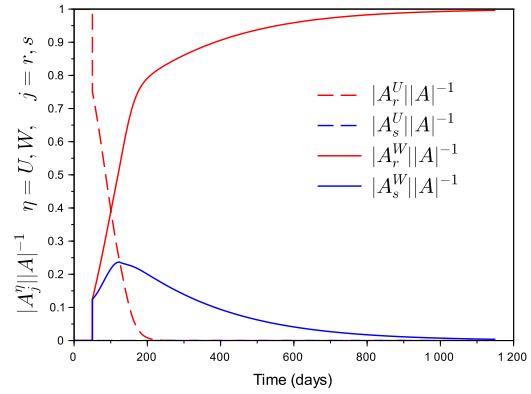
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

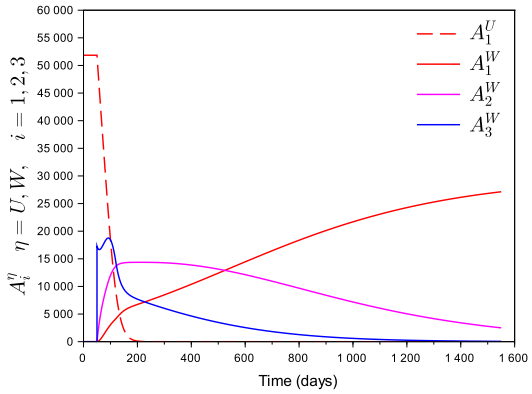


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

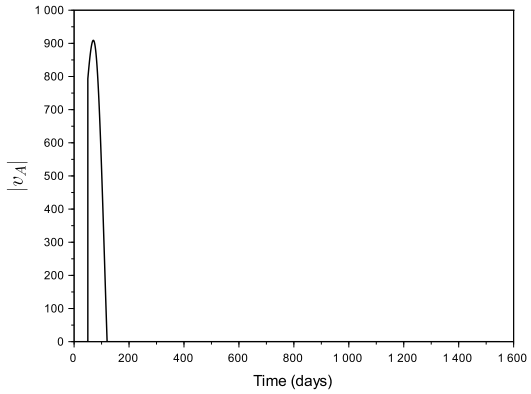


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

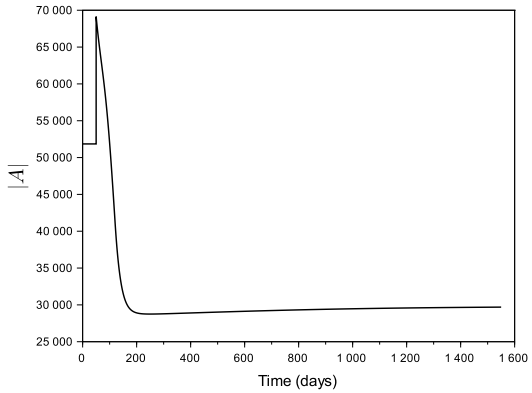
Figure 5.3: The expected scenario during the release of heterozygous mosquitoes infected by *Wolbachia* is illustrated. The setting for simulation 3 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.1.



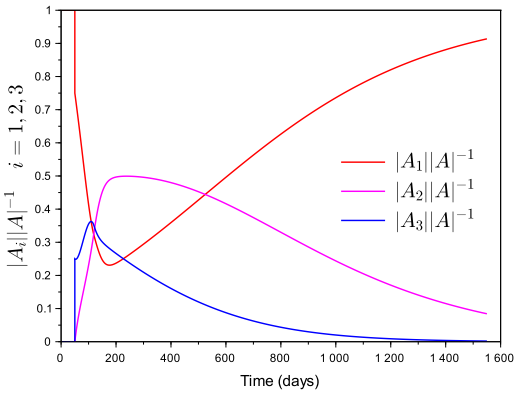
(a) Numerical solution for the control system



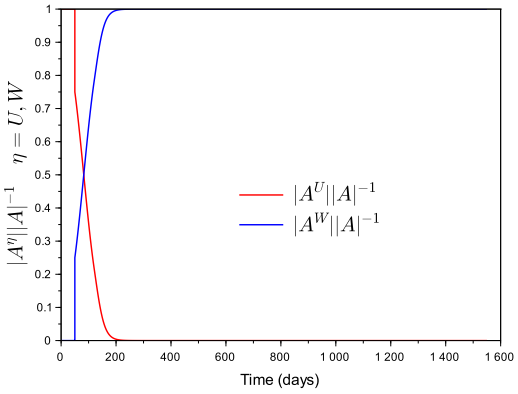
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



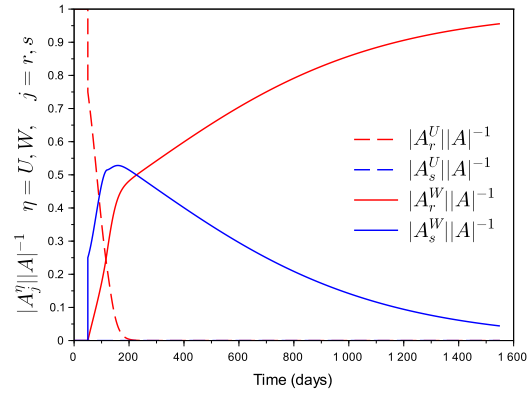
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

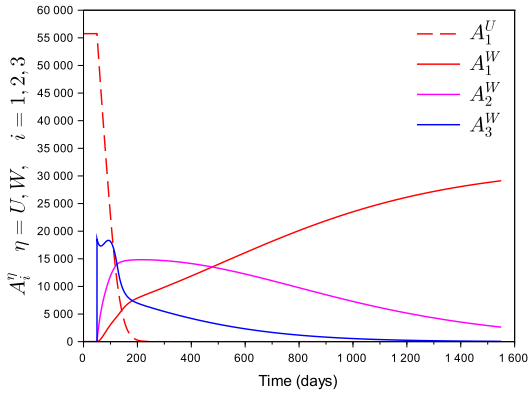


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

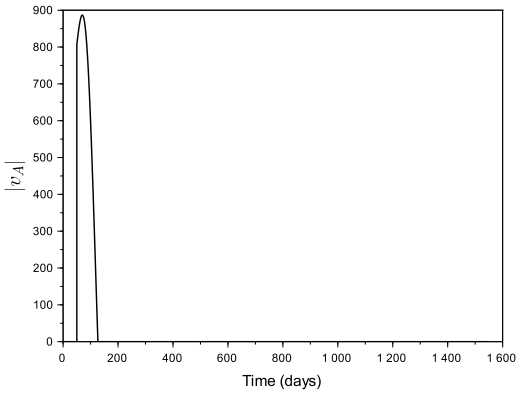


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

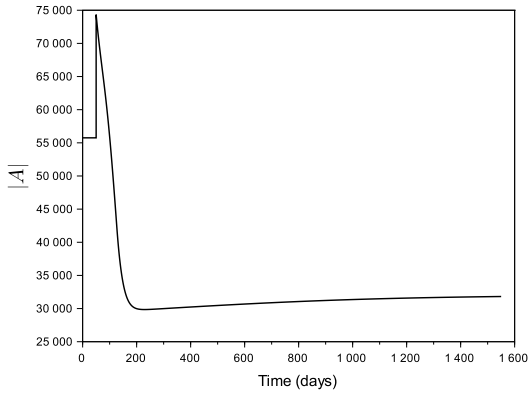
Figure 5.4: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* when only adulticide is used is illustrated. The setting for simulation 4 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.2.



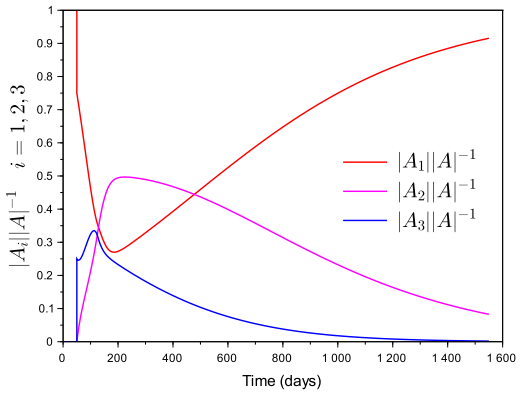
(a) Numerical solution for the control system



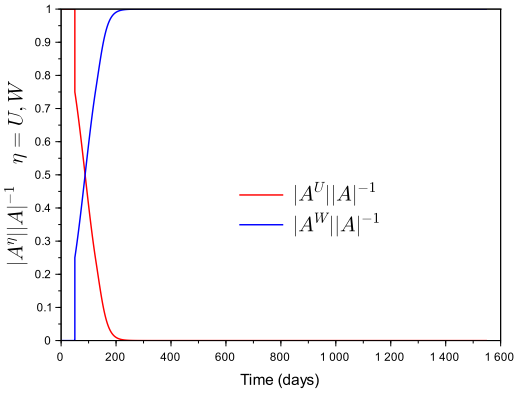
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



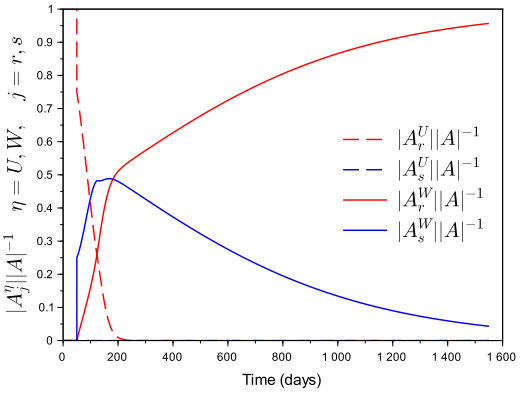
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$



(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$



(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

Figure 5.5: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* when only larvicide is used is illustrated. The setting for simulation 5 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.2.

initial conditions in the simulations, note that among the compared cases (Figures 5.4e, 5.5e and 5.6e) there are no notable differences between the times required for the fixation of a population totally infected by *Wolbachia*.

5.7.3.4 Influence by increase in scramble competition in larvae phase

Simulation 8 illustrates the effect that an increase in density dependent mortality by scramble competition among larvae have, for example by the reduction in breeding sites number (Figure 5.8). As previously mentioned —see equation (5.95) and its biological interpretation, this phenomenon is represented by an increase in the constant $\hat{\mu}$. Note that in comparison to the cases presented above, the increase in scramble competition can facilitate the replacement of an uninfected population with a completely infected by *Wolbachia*, even reducing the time required (Figures 5.3 and 5.8e). Similarly, any factor that leads to an increase in the number of breeding sites is expected to require greater effort to release *Wolbachia*-infected mosquitoes.

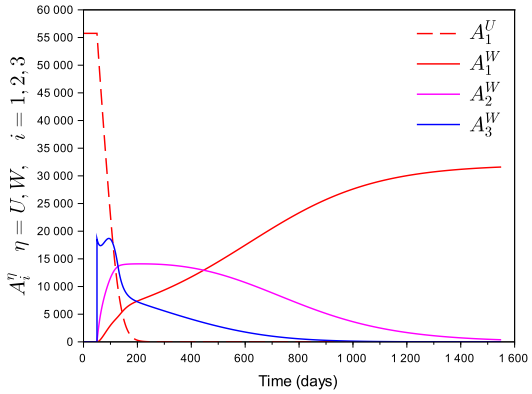
5.7.3.5 When the control law fails?

Influence by incomplete cytoplasmic incompatibility

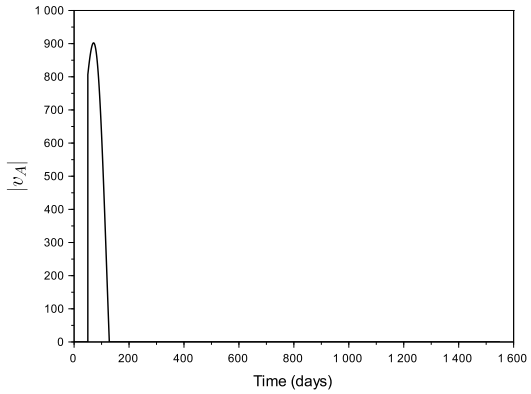
Simulations 9 and 10 illustrate the effect of the use of *Wolbachia* strains with different level of incomplete cytoplasmic incompatibility (Figures 5.9 and 5.10). The results illustrated in Figure 5.9 show that the proposed control law is robust at 0.8 level of incomplete cytoplasmic incompatibility. However, as shown in Figure 5.10 if the cytoplasmic incompatibility is 0.5 or lower, the replacement of a uninfected population by an infected one is not achieved, even with a sustained release of infected mosquitoes a equilibrium of coexistence is achieved. To sum up, we can not guarantee on this algorithm efficiency in presence of incomplete cytoplasmic incompatibility (recall that Theorems 5.11 and 5.12 assume that $\sigma = 1$). However, it is important to note that has been reported that the σ presents values in $[0.9, 1]$ (Walker et al., 2011a; Koiller et al., 2014a; Bliman et al., 2018a; Adekunle et al., 2019).

Also, these results show that when the cytoplasmic incompatibility is incomplete, the flow of alleles occurs bidirectionally, reaching a polymorphic and heterogeneous trajectory. Note that in this case, as in all previous cases, the release of *Wolbachia*-infected mosquitoes leads to a decrease in the total population size at the equilibrium point.

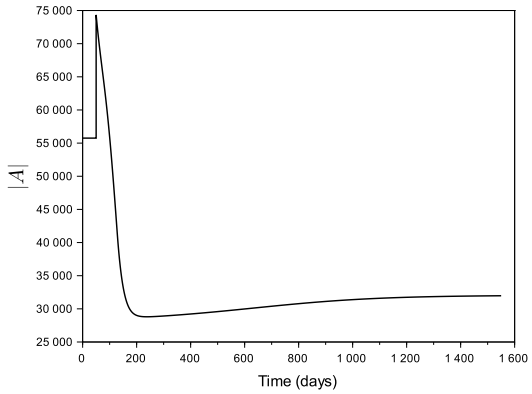
Influence by insufficient initial infected mosquitoes release



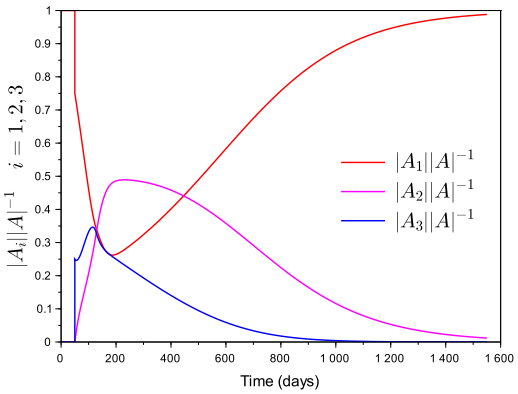
(a) Numerical solution for the control system



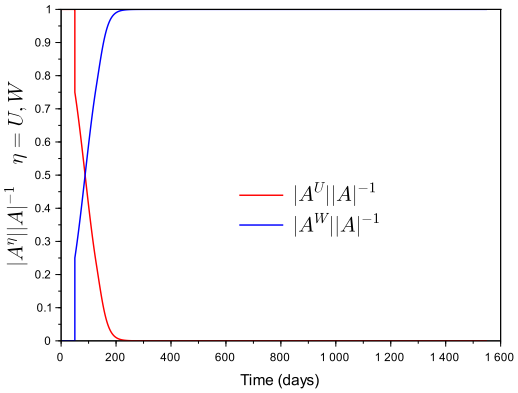
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



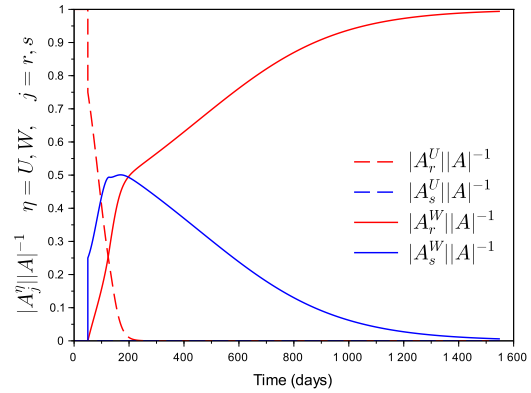
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

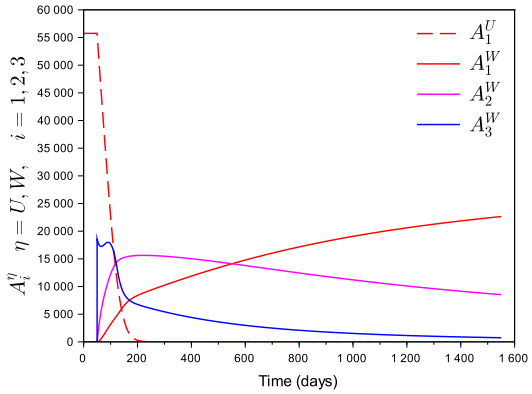


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

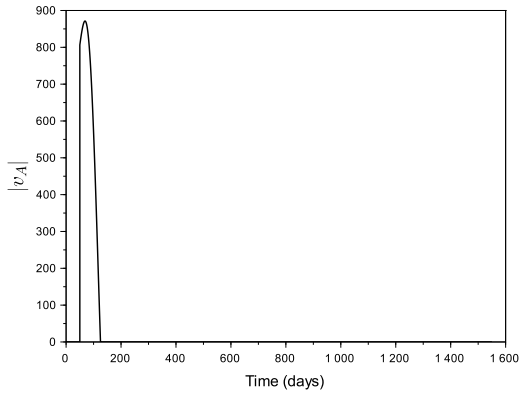


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

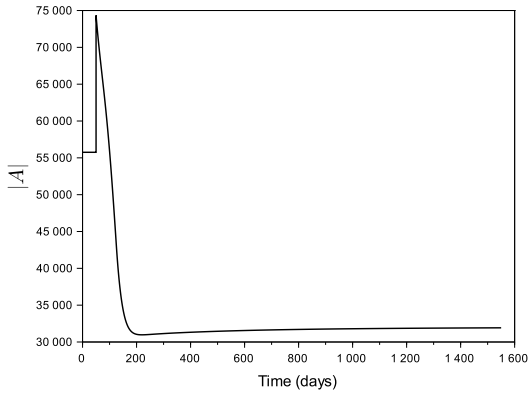
Figure 5.6: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* when only adulticide is used and assuming recessiveness for resistance is illustrated. The setting for simulation 6 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.3.



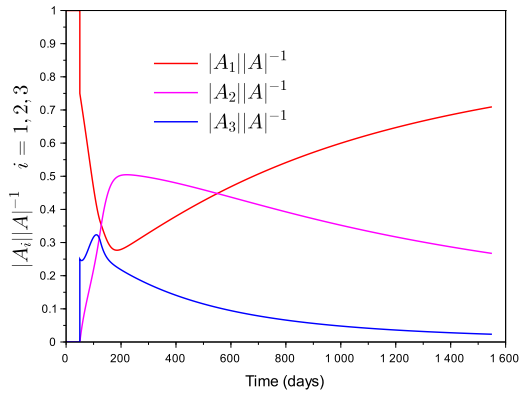
(a) Numerical solution for the control system



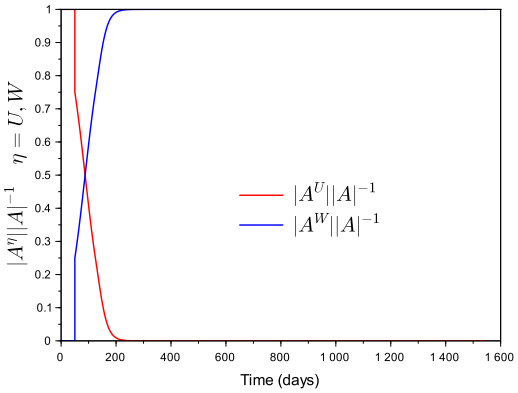
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



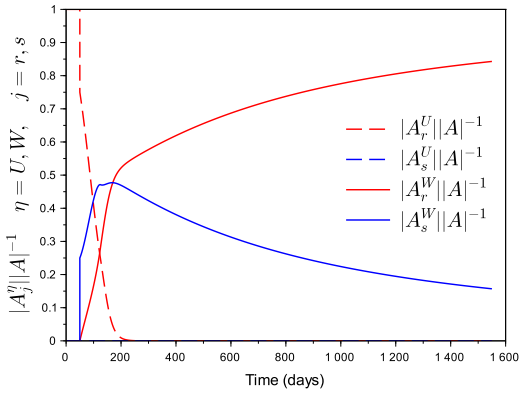
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

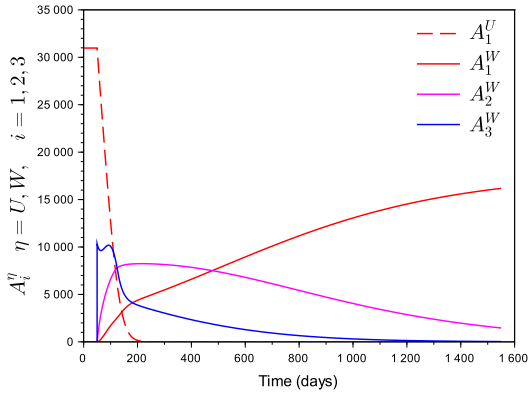


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

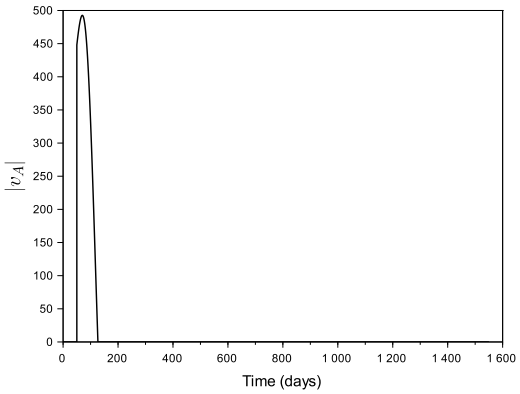


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

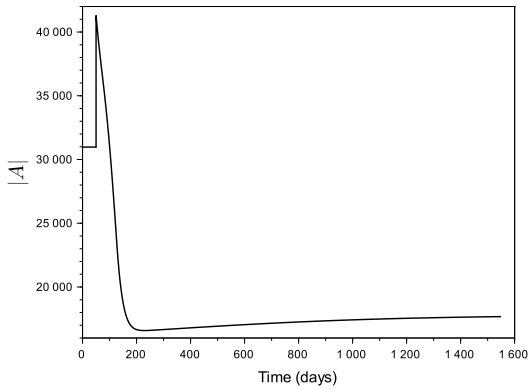
Figure 5.7: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* when only adulticide is used and assuming dominance for resistance is illustrated. The setting for simulation 7 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.3.



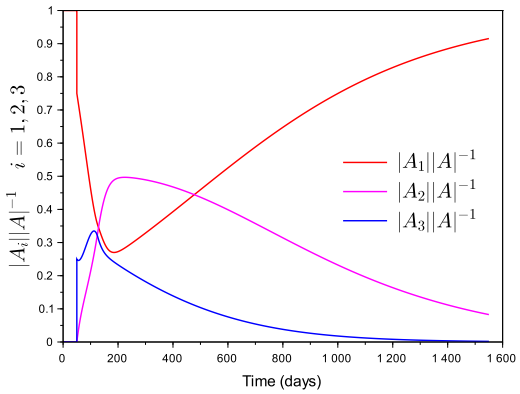
(a) Numerical solution for the control system



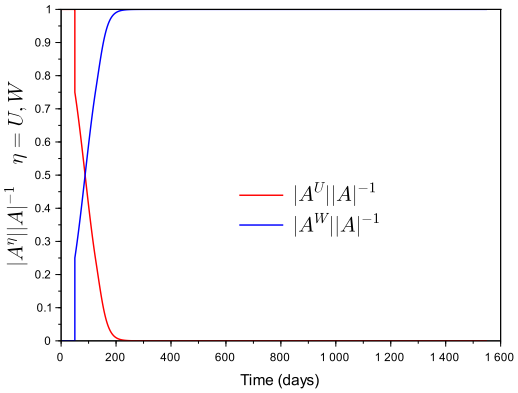
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



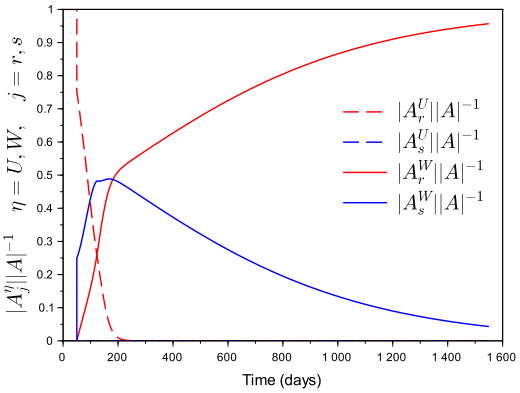
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

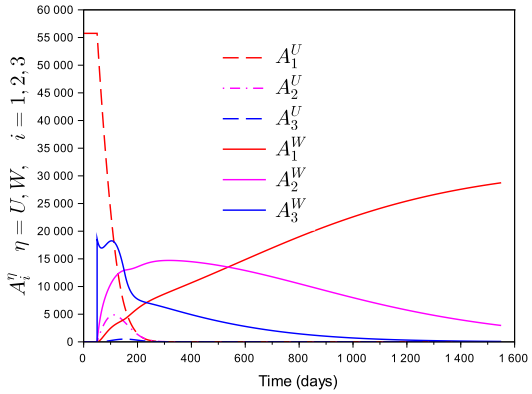


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

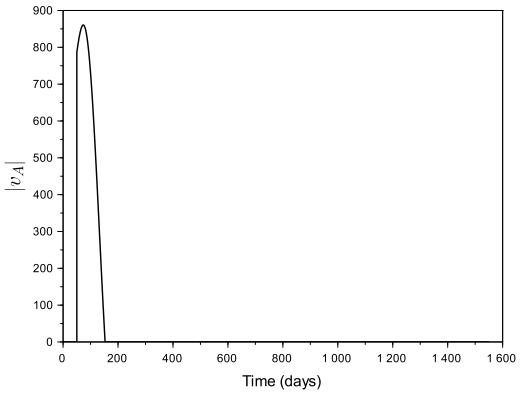


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

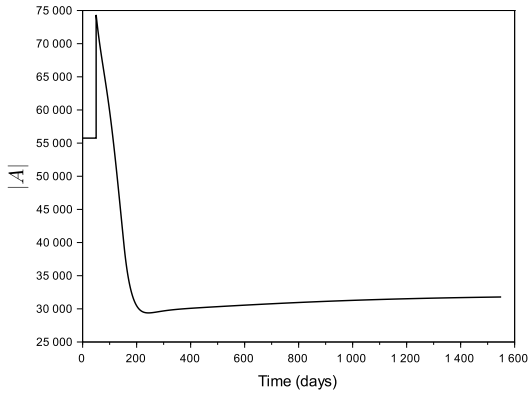
Figure 5.8: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* when scramble competition is increased and only adulticide is used is illustrated. The setting for simulation 8 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.4.



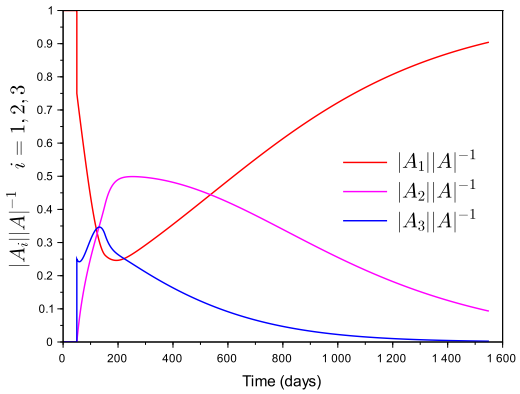
(a) Numerical solution for the control system



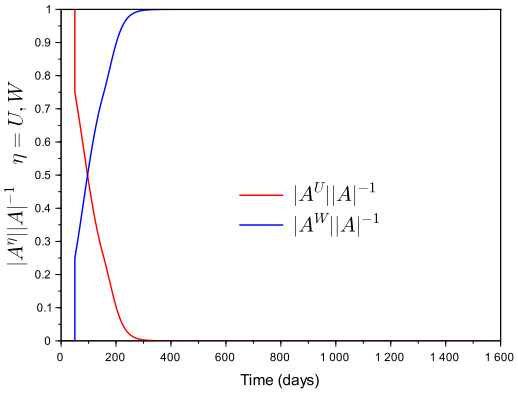
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



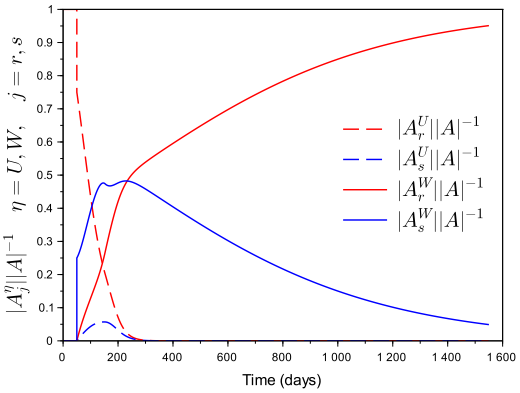
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$

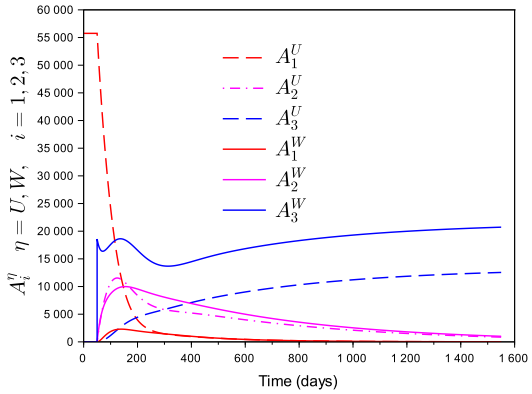


(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$

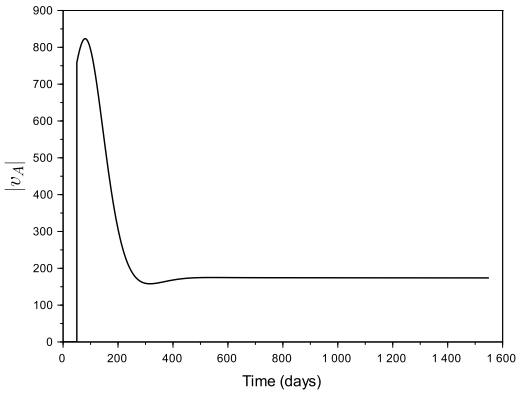


(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

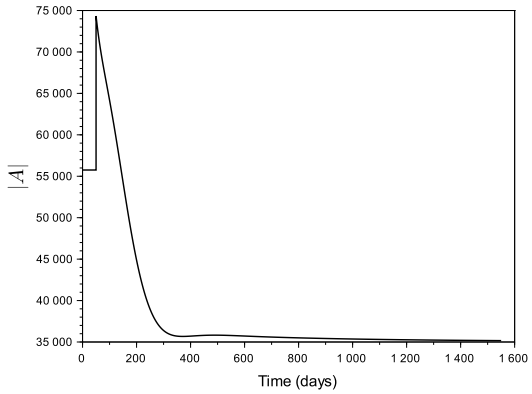
Figure 5.9: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* with slight incomplete cytoplasmic incompatibility ($\sigma = 0.8$) and only adulticide is used is illustrated. The setting for simulation 9 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.5.



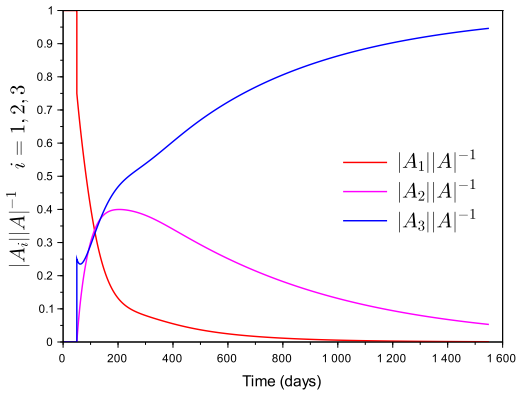
(a) Numerical solution for the control system



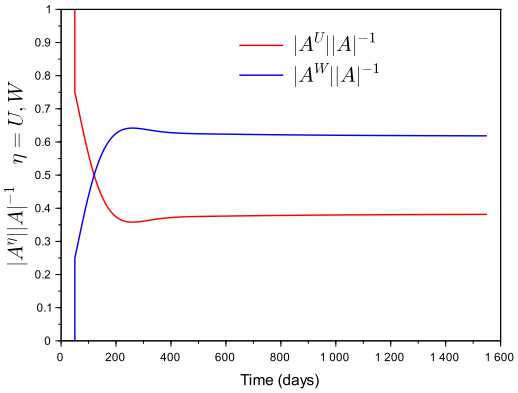
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\, dt$



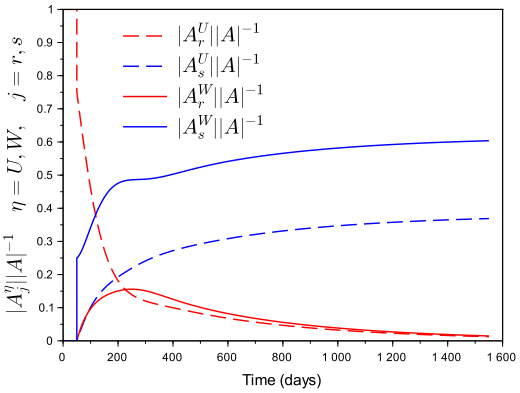
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$



(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$



(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

Figure 5.10: The expected scenario during the release of insecticide-susceptible mosquitoes infected by *Wolbachia* with $\sigma = 0.5$ incomplete cytoplasmic incompatibility and only adulticide is used is illustrated. The setting for simulation 10 is given in Tables 5.2 and 5.1. See further explanations in Section 5.7.3.5.

Figure 5.11 illustrates a scenario in which the initial proportion of infected mosquitoes released is not sufficient. Unlike all the previous illustrated cases in which twice as many infected mosquitoes have been released than the initial uninfected population, in this simulation infected mosquitoes are released at the same density as the initial uninfected mosquito population. As can be seen, this amount turns out to be insufficient to guarantee the replacement of non-infected mosquitoes by infected mosquitoes by the proposed control law.

5.8 Conclusions

- In this work we contribute a class of models that allows us to consider several mechanisms of inheritance together in the sexual reproduction, in particular, maternal inheritance for *Wolbachia* and Mendelian inheritance for resistance to insecticides.

- Analytical results are provided for a strategy that ensures a fully *Wolbachia*-infected population. For this, a control law is proposed for the release of laboratory mosquitoes of any genotype, also susceptible to insecticides in environments with insecticide-resistant mosquitoes.

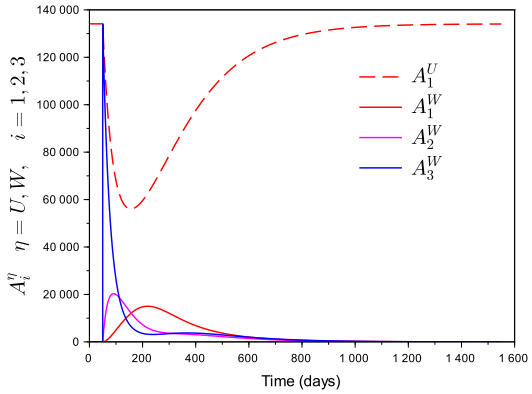
- Numerical simulations have been provided to illustrate the analytical results. In addition, different mosquito release scenarios were illustrated.

5.9 Future issues

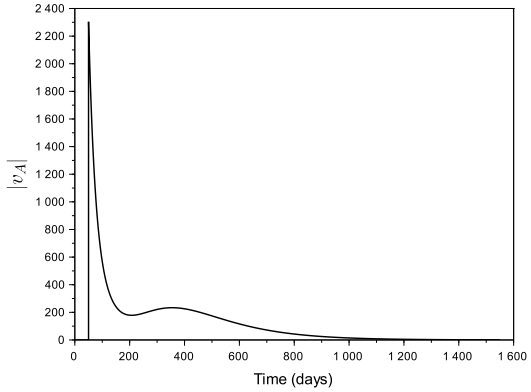
Next, we emphasize the future issues that can be covered by the class of the proposed models. Namely, as for the evolution of resistance, cases of multiple loci; multiple infections and superinfection with *Wolbachia*, selective sweep in mitochondrial genes induced by *Wolbachia*, effect of bidirectional complete incompatibility between different *Wolbachia* strains, and *Wolbachia* interaction with other population genetic attributes and how it can affect the control strategy.

On the other hand, the formulation of the births using a bilinear form would allow to obtain a diecious model (model of two sexes). A model with these characteristics can help to better understand the release of infected males or females. Including asymmetric releases.

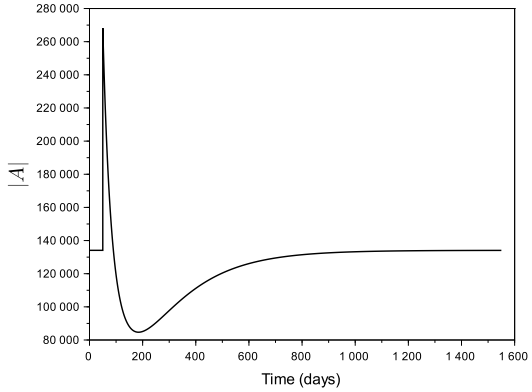
In this work, continuous releases and perfect knowledge of the state at each time have been considered. As illustrated in this Chapter, this can be quite useful for



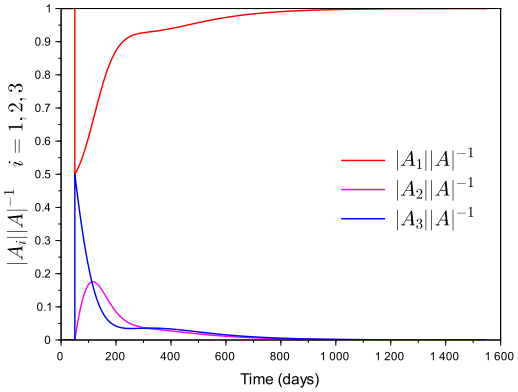
(a) Numerical solution for the control system



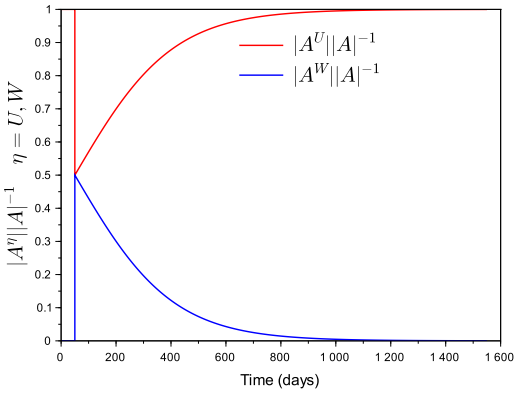
(b) Control effort $\int_{t_0}^{t_{max}} |v_A(t)|\ dt$



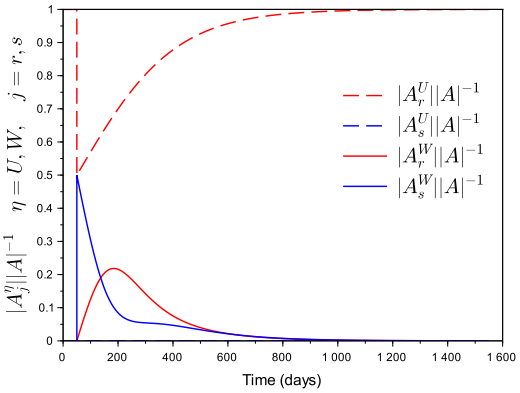
(c) Total population $|A(t)|$



(d) Observed genotype frequency $|A_i(t)|$, $i = 1, 2, 3$



(e) Frequency of infected and uninfected $|A^\eta(t)|$, $\eta = U, W$



(f) Allelic frequency in infected and uninfected $u_j^\intercal A^\eta(t)$, $\eta = U, W$, $j = r, s$

Figure 5.11: The expected scenario during the initial release insufficient insecticide-susceptible mosquitoes infected by *Wolbachia* in an environment subjected to a strong effect of adulticide is illustrated. The setting for simulation 11 is given in Tables 5.2 and 5.1 (such that assumption (5.76) in Theorem 5.11 is not satisfied). See further explanations in Section 5.7.3.5.

simulating different alternative release scenarios. However, in practice, step function strategies can be given and discrete measurements, these are topics that we want to study in future works.

5.10 Appendix – Technical results

5.10.1 Some algebraic relations

Lemma 5.13.

$$\alpha(e^\eta \otimes e_i) = (e^\eta \otimes e_i), \qquad \eta = U, W,\ i = 1, 2, 3 \tag{5.1}$$

Proof. For any $\eta' = U, W$, $i' = 1, 2, 3$, one has —see (5.3)

$$\alpha_{i'}^{\eta'}(e^\eta \otimes e_i) = (e^\eta \otimes e_i)^\intercal (G^{\eta'} \otimes G_{i'})(e^\eta \otimes e_i) = (e^{\eta\intercal} G^{\eta'} e^\eta) \otimes (e_i^\intercal G_{i'} e_i)$$

The proof is obtained from the fact that $(e^{\eta\intercal} G^{\eta'} e^\eta) = 1$ if $\eta = \eta'$, and is 0 otherwise; and that $(e_i^\intercal G_{i'} e_i) = 1$ if $i = i'$, and is 0 otherwise. □

Lemma 5.14. *For any $A \in \mathbb{R}^6_+$,*

$$\alpha_i^W(A) + \frac{1}{2}\alpha_2^W(A) = \frac{1}{2}A_j^W + \frac{1}{2}\frac{|A_j||A^W|}{|A|}, \qquad j = r, s, \tag{5.2a}$$

$$\alpha_i^U(A) + \frac{1}{2}\alpha_2^U(A) = \frac{1}{2}\left(1 - \sigma\frac{|A^W|}{|A|}\right)A_j^U + \frac{1}{2}\frac{|A_j| - \sigma A_j^W}{|A|}|A^U|, \qquad j = r, s, \tag{5.2b}$$

where by convention in (5.2b), and (5.2c) and (5.2e) below, $i = 1$ (resp. $i = 3$) when $j = r$ (resp. $j = s$). *Moreover,*

$$\sum_{i=1}^3 \alpha_i^W(A) = |A^W|, \qquad \sum_{i=1}^3 \alpha_i^U(A) = |A^U|\left(1 - \sigma\frac{|A^W|}{|A|}\right), \tag{5.2c}$$

$$|\alpha(A)| = \sum_{\eta=U,W}\sum_{i=1}^3 \alpha_i^\eta(A) = |A| - \frac{\sigma}{|A|}|A^U||A^W|, \tag{5.2d}$$

$$\sum_{\eta=U,W} \alpha_i^\eta(A) = \frac{1}{|A|}\left(|A_j|^2 - \sigma A_j^W A_j^U\right), \qquad i = 1, 3, \tag{5.2e}$$

$$\sum_{\eta=U,W} \alpha_2^\eta(A) = \frac{1}{|A|}\left(2|A_r||A_s| - \sigma A_r^W A_s^U - \sigma A_s^W A_r^U\right). \tag{5.2f}$$

Proof. Notice first that (5.2) implies

$$G_1 + \frac{1}{2}G_2 = \frac{1}{2}\left(u_r \mathbf{1}_3^\intercal + \mathbf{1}_3 u_r^\intercal\right), \qquad G_3 + \frac{1}{2}G_2 = \frac{1}{2}\left(u_s \mathbf{1}_3^\intercal + \mathbf{1}_3 u_s^\intercal\right), \qquad \sum_{i=1}^{3} G_i = \mathbf{1}_3\mathbf{1}_3^\intercal, \tag{5.3a}$$

$$\sum_{\eta=U,W} G^\eta = \mathbf{1}_2\mathbf{1}_2^\intercal - \sigma\, e^W e^{U\intercal} \tag{5.3b}$$

On the other hand, for any $\eta = U, W$,

$$\alpha_i^\eta(A) + \frac{1}{2}\alpha_2^\eta(A) = \frac{1}{|A|}A^\intercal\left((G^\eta \otimes G_i) + \frac{1}{2}(G^\eta \otimes G_2)\right)A\ .$$

Consider first the case $\eta = W$. Using the convention in the statement, one has, for any $A \in \mathbb{R}^6_+ \setminus \{0_6\}$,

$$\begin{aligned}
\alpha_i^W(A) + \frac{1}{2}\alpha_2^W(A) &= \frac{1}{|A|}A^\intercal\left(G^W \otimes \left(G_i + \frac{1}{2}G_2\right)\right)A \\
&= \frac{1}{2|A|}A^\intercal\left(G^W \otimes \left(u_j \mathbf{1}_3^\intercal + \mathbf{1}_3 u_j^\intercal\right)\right)A \\
&= \frac{1}{2|A|}A^\intercal\left((\mathbf{1}_2 e^{W\intercal}) \otimes \left(u_j \mathbf{1}_3^\intercal + \mathbf{1}_3 u_j^\intercal\right)\right)A \qquad \text{(due to (5.1))} \\
&= \frac{1}{2|A|}A^\intercal\left[(\mathbf{1}_2 \otimes u_j)(e^W \otimes \mathbf{1}_3)^\intercal + (\mathbf{1}_2 \otimes \mathbf{1}_3)(e^W \otimes u_j)^\intercal\right]A \\
&= \frac{1}{2|A|}\left(|A_j||A^W| + |A|A_j^W\right)
\end{aligned}$$

which is (5.2a).

Similarly,

$$\alpha_i^U(A) + \frac{1}{2}\alpha_2^U(A) = \frac{1}{2|A|}A^\intercal\left((\mathbf{1}_2 e^{U\intercal} - \sigma e^W e^{U\intercal}) \otimes \left(u_j \mathbf{1}_3^\intercal + \mathbf{1}_3 u_j^\intercal\right)\right)A.$$

This expression is linear with respect to σ. In the same way than for $\eta = W$, one obtains that for $\sigma = 0$ the previous formula is equal to

$$\frac{1}{2|A|}\left(|A_j||A^U| + |A|A_j^U\right),$$

while the coefficient of σ is

$$-\frac{1}{2|A|}A^{\intercal}\left((e^W e^{U\intercal})\otimes\left(u_j\mathbf{1}_3^{\intercal}+\mathbf{1}_3u_j^{\intercal}\right)\right)A \tag{5.4}$$

$$=-\frac{1}{2|A|}A^{\intercal}\left[(e^W\otimes u_j)(e^U\otimes\mathbf{1}_3)^{\intercal}+(e^W\otimes\mathbf{1}_3)(e^U\otimes u_j)^{\intercal}\right]A$$

$$=-\frac{1}{2|A|}\left(A_j^W|A^U|+|A^W|A_j^U\right)$$

This demonstrates (5.2b).

The two formulas in (5.2c) are then obtained by summation, for the values $j=r$ and $j=s$, of the identity in (5.2a), and then in (5.2b). Formula (5.2d) comes when summing up the expressions in (5.2c) for the indices $\eta=U,W$.

Finally, (5.3b) yields

$$\sum_{\eta=U,W}\alpha_i^{\eta}(A)=\frac{1}{|A|}A^{\intercal}((\mathbf{1}_2\mathbf{1}_2^{\intercal}-\sigma\, e^W e^{U\intercal})\otimes G_i)A$$

For $i=1$ or 3, let $j=r$ or s, according to the convention in the statement. Then,

$$\begin{aligned}\sum_{\eta=U,W}\alpha_i^{\eta}(A) &= \frac{1}{|A|}A^{\intercal}((\mathbf{1}_2\mathbf{1}_2^{\intercal}-\sigma\, e^W e^{U\intercal})\otimes(u_ju_j^{\intercal}))A\\ &= \frac{1}{|A|}\left[((\mathbf{1}_2\otimes u_j)^{\intercal}A)^2-\sigma((e^W\otimes u_j)^{\intercal}A)((e^U\otimes u_j)^{\intercal}A)\right]\\ &= \frac{1}{|A|}\left(|A_j|^2-\sigma A_j^W A_j^U\right)\end{aligned}$$

that is (5.2e).

On the other hand, for $i=2$, one has

$$\begin{aligned}\sum_{\eta=U,W}\alpha_i^{\eta}(A) &= \frac{1}{|A|}A^{\intercal}((\mathbf{1}_2\mathbf{1}_2^{\intercal}-\sigma\, e^W e^{U\intercal})\otimes(u_ru_s^{\intercal}+u_su_r^{\intercal}))A\\ &= \frac{1}{|A|}\Big[2((\mathbf{1}_2\otimes u_r)^{\intercal}A)((\mathbf{1}_2\otimes u_s)^{\intercal}A)-\sigma((e^W\otimes u_r)^{\intercal}A)((e^U\otimes u_s)^{\intercal}A)\\ &\qquad -\sigma((e^W\otimes u_s)^{\intercal}A)((e^U\otimes u_r)^{\intercal}A)\Big]\\ &= \frac{1}{|A|}\left(2|A_r||A_s|-\sigma A_r^W A_s^U-\sigma A_s^W A_r^U\right)\end{aligned}$$

which is identical to (5.2f). Notice that summing up (5.2e) for $j=r$ and $j=s$, together with (5.2f), gives a variant demonstration of (5.2d). The proof of Lemma 5.14 is completed. □

Lemma 5.15. *Let $A\in\mathbb{R}^6_+$.*

1. *For any* $j = r, s$,

$$A_j = 0_2 \quad \Rightarrow \quad \alpha_i^\eta(A) = \alpha_2^\eta(A) = 0,\ \eta = U, W \tag{5.5}$$

where by convention, $i = 1$ (resp. $i = 3$) when $j = r$ (resp. $j = s$).

2. *For any* $\eta = U, W$,

$$A^\eta = 0_3 \quad \Rightarrow \quad \alpha_i^\eta(A) = 0,\ i = 1, 2, 3 \tag{5.6}$$

3. *For any* $\eta = U, W$, *for any* $i, i' = 1, 2, 3$ *such that* $\{i, i'\} = \{1, 3\}$ *or* $2 \in \{i, i'\}$,

$$A_i^\eta > 0, A_{i'}^\eta > 0 \quad \Rightarrow \quad \alpha_{i''}^\eta(A) > 0,\ i'' = 1, 2, 3 \tag{5.7}$$

4. *For any* $i, i' = 1, 2, 3$ *such that* $\{i, i'\} = \{1, 3\}$ *or* $2 \in \{i, i'\}$,

$$A_i^U > 0, A_{i'}^W > 0 \quad \Rightarrow \quad \alpha_{i''}^W(A) > 0 \ \ or \ \ \alpha_{i''}^W(\alpha(A)) > 0,\ i'' = 1, 2, 3 \tag{5.8}$$

5. *If* $\sigma = 1$, *for any* $j = r, s$,

$$A_j^U = 0 \quad \Rightarrow \quad \alpha_i^U(A) = \alpha_2^U(A) = 0, \tag{5.9}$$

where $i = 1$ *(resp.* $i = 3$*) when* $j = r$ *(resp.* $j = s$*).*

The first two points of Lemma 5.15 indicate that in a monomorphic state, all offsprings have the same identical homozygous genotype; and that in a homogeneous non-infected (resp. infected) state, all offsprings are non-infected (resp. infected).

The last three points describe the result of mixing. Point 3 states that if two different non-infected (resp. infected) genotypes are present in some state, or if heterozygous are present, then the birth rate of every non-infected (resp. infected) genotype is positive: as a matter of fact, if two genotypes are present or if the heterozygous genotype is present, then the two alleles are present, and consequently all genotypes are present in the offspring. Point 4 is more intricate. It states that if two different genotypes are present, one in non-infected mosquitoes and the other in infected mosquitoes, or if an heterozygous is present in a heterogeneous state, then the birth rate of every *infected* genotype is positive. Contrary to point 3, where the appearance of the missing genotypes occurs "directly", through the first mating ($\alpha_{i''}^\eta(A) > 0$), here this may happen "indirectly", after the second mating: $\alpha_{i''}^\eta(\alpha(A)) > 0$. This is for example the case when mixing non-infected of genotype (r, r) with infected of genotype (s, s): infected

of genotypes (s,s) and (r,s) arise from the first mating, and infected of genotype (r,r) only after the second mating. In the case of complete cytoplasmic incompatibility ($\sigma = 1$), the symmetric property is *not* true for the birth rate of non-infected, as *e.g.* the mixing of non-infected mosquitoes bearing genotype (r,r), with infected of any genotype may only produce non-infected of the same genotype. This is the sense of point 5.

Proof of Lemma 5.15.
• Let $A \in \mathbb{R}^6_+$ with $A_j = 0_2$ for given $j \in \{r,s\}$, and let $i \in \{1,3\}$ be chosen according to the depicted convention. Let also $i' \in \{1,3\}$ be such that $i' \neq i$. Using the first decomposition formula in (5.3e), one has $A = A_{i'} \otimes e_{i'}$. Therefore, for any $\eta = U, W$,

$$\alpha_i^\eta(A) = \frac{1}{|A|} A^\intercal (G^\eta \otimes G_i) A = \frac{1}{|A|} (A_{i'} \otimes e_{i'})^\intercal (G^\eta \otimes G_i)(A_{i'} \otimes e_{i'}) = \frac{1}{|A|} (A_{i'}^\intercal G^\eta A_{i'}) \otimes (e_{i'}^\intercal G_i e_{i'})$$

From (5.2) one sees that $e_{i'}^\intercal G_i e_{i'} = 0$, due to the fact that $i' \neq i$. Therefore, $\alpha_i^\eta(A) = 0$ for $\eta = U, W$, and the same argument yields $\alpha_2^\eta(A) = 0$. This proves (5.5).
• Let $A \in \mathbb{R}^6_+$ with $A^\eta = 0_3$, for given $\eta \in \{U, W\}$. Let also $\eta' \in \{U, W\}$ be such that $\eta' \neq \eta$. Using the second decomposition formula in (5.3e), one has $A = e^{\eta'} \otimes A^{\eta'}$. Therefore, for any $i = 1, 2, 3$,

$$\alpha_i^\eta(A) = \frac{1}{|A|} A^\intercal (G^\eta \otimes G_i) A = \frac{1}{|A|} (e^{\eta'} \otimes A^{\eta'})^\intercal (G^\eta \otimes G_i)(e^{\eta'} \otimes A^{\eta'}) = \frac{1}{|A|} (e^{\eta' \intercal} G^\eta e^{\eta'}) \otimes (A^{\eta' \intercal} G_i A^{\eta'})$$

Yet, (5.1) shows that $e^{\eta' \intercal} G^\eta e^{\eta'} = 0$, as a consequence of the fact that $\eta' \neq \eta$. Therefore, $\alpha_i^\eta(A) = 0$ for $i = 1, 2, 3$. This establishes (5.6).
• Observe that, for any $\eta = U, W$,

$$G_1 \geq \frac{1}{4} e_2 e_2^\intercal, \quad G_2 \geq \frac{1}{2} e_2 e_2^\intercal, \quad G_3 \geq \frac{1}{4} e_2 e_2^\intercal, \tag{5.10}$$

(taking here and below in the present demonstration the order relation in the sense of positive semi-definiteness of symmetric matrices), in such a way that

$$\alpha_1^\eta(A) = \frac{1}{|A|} A^\intercal (G^\eta \otimes G_1) A \geq \frac{1}{4|A|} (A_2^\eta)^2 > 0,$$

$$\alpha_2^\eta(A) \geq \frac{1}{2|A|} (A_2^\eta)^2 > 0,$$

$$\alpha_3^\eta(A) \geq \frac{1}{4|A|} (A_2^\eta)^2 > 0$$

if $i = 2$ or $i' = 2$ in the statement of the Point 3.

On the other hand,

$$G_1 \geq e_1 e_1^\intercal, \quad G_2 \geq e_1 e_3^\intercal + e_3 e_1^\intercal, \quad G_3 \geq e_3 e_3^\intercal, \tag{5.11}$$

so if $\{i, i'\} = \{1, 3\}$, then

$$\alpha_1^\eta(A) \geq \frac{1}{|A|}(A_1^\eta)^2 > 0, \qquad \alpha_2^\eta(A) \geq \frac{2}{|A|} A_1^\eta A_3^\eta > 0, \qquad \alpha_3^\eta(A) \geq \frac{1}{|A|}(A_3^\eta)^2 > 0.$$

This provides the proof of (5.7).

• The argument to obtain (5.8) is similar. In fact, for any $i = 1, 2, 3$,

$$(G^W \otimes G_i) = \left(\left(\mathbf{1}_2 e^{W\intercal}\right) \otimes G_i\right) = \left(\left(e^U e^{W\intercal}\right) \otimes G_i\right) + \left(\left(e^W e^{W\intercal}\right) \otimes G_i\right),$$

and using inequalities similar to (5.10) and (5.11), one deduces that

$$\alpha_1^W(A) = \frac{1}{|A|} A^\intercal (G^W \otimes\ G_1) A \geq \frac{1}{4|A|}(A_2^W)^2 > 0,$$

$$\alpha_2^W(A) \geq \frac{1}{2|A|}(A_2^W)^2 > 0,$$

$$\alpha_3^W(A) \geq \frac{1}{4|A|}(A_2^W)^2 > 0$$

if $i' = 2$ in (5.8); and

$$\alpha_1^W(A) \geq \frac{1}{2|A|} A_2^U A_{i'}^W > 0, \quad \alpha_2^W(A) \geq \frac{1}{2|A|} A_2^U A_{i'}^W > 0, \quad \alpha_3^W(A) \geq \frac{1}{2|A|} A_2^U A_{i'}^W > 0$$

if $i = 2$.

If now *e.g.* $i = 1$ and $i' = 3$

$$\alpha_2^W(A) \geq \frac{1}{2|A|} A_1^U A_3^W > 0,$$

but $\alpha_1^W(A)$ or $\alpha_3^W(A)$ may be zero. However, applying to $\alpha(A)$ the property previously proven in the Point 3, one shows that all the components of $\alpha^W(\alpha(A))$ are then positive. This proves the Point 4 if $i = 1$ and $i' = 3$, and the proof is similar if $i = 3$ and $i' = 1$.

• Last, assume that $\sigma = 1$. Then $G^U = e^U e^{U\intercal}$. Let *e.g.* $A_1^U > 0 = A_2^U = A_3^U$.

$$\begin{aligned}
\alpha_3^U(A) + \frac{1}{2}\alpha_2^U(A) &= \frac{1}{|A|}A^\intercal\left(G^U \otimes \left(G_3 + \frac{1}{2}G_2\right)\right)A \\
&= \frac{1}{2|A|}A^\intercal\left(e^U e^{U\intercal} \otimes (u_s \mathbf{1}_3^\intercal + \mathbf{1}_3 u_s^\intercal)\right)A \\
&= \frac{1}{2|A|}A^\intercal\left((e^U \otimes u_s)(e^U \otimes \mathbf{1}_3)^\intercal + (e^U \otimes \mathbf{1}_3)(e^U \otimes u_s)^\intercal\right)A \\
&= 0 \qquad \text{(because } (e^U \otimes u_s)^\intercal A = 0\text{)}
\end{aligned}$$

This shows the Point 5 in this case. The argument is identical when $A_1^U = A_2^U = 0 < A_3^U$. This achieves the proof of Lemma 5.15. □

5.10.2 Differentiation of the map α

Lemma 5.16. *For any $i, i' \in \{1,2,3\}$, for any $\eta, \eta' \in \{U, W\}$, for any $A \in \mathbb{R}^6_+ \setminus \{0\}$,*

$$\frac{\partial \alpha_i^\eta(A)}{\partial A_{i'}^{\eta'}} = -\frac{1}{|A|^2}A^\intercal(G^\eta \otimes G_i)A + \frac{1}{|A|}A^\intercal\left((G^\eta + G^{\eta\intercal}) \otimes G_i\right)(e^{\eta'} \otimes e_{i'}) \tag{5.12}$$

and the Jacobian matrix of the map α defined in (5.9) *is therefore given by the 6×6-matrix:*

$$\begin{aligned}
J_\alpha(A) &= -\frac{1}{|A|}\alpha(A)\mathbf{1}_6^\intercal + \frac{1}{|A|}\beta(A), \\
\beta(A) &:= \sum_{\eta,\eta'=U,W}\ \sum_{i,i'=i,2,3} A^\intercal\left((G^\eta + G^{\eta\intercal})e^{\eta'} \otimes G_i e_{i'}\right)\ (e^\eta \otimes e_i)(e^{\eta'} \otimes e_{i'})^\intercal
\end{aligned} \tag{5.13}$$

Understanding the second formula in (5.13) is easier when considering that the components are indexed in $\mathbb{R}^2 \times \mathbb{R}^3$ rather than in $\mathbb{R}^6$: it expresses exactly that the scalar quantity $A^\intercal((G^\eta + G^{\eta\intercal})(e^{\eta'} \otimes G_i e_{i'})$ is the "$(\eta, i) \times (\eta', i')$-component" $(e^\eta \otimes e_i)^\intercal \beta(A)(e^{\eta'} \otimes e_{i'})$ of the matrix $\beta(A)$.

Proof of Lemma 5.16. Recall that, for any component of $\alpha(A)$, one has by definition (see (5.8))

$$\alpha_i^\eta(A) = \frac{1}{|A|}A^\intercal(G^\eta \otimes G_i)A$$

Deriving this product with respect to the component $A_{i'}^{\eta'}$ with index (η', i') yields the scalar quantity in the right-hand side of (5.12), using the fact that $G_i = G_i^\intercal$. This

expression may be identified to the expression

$$(e^{\eta} \otimes e_i)^{\intercal} \left[-\frac{1}{|A|}\alpha(A)\mathbf{1}_6^{\intercal} + \frac{1}{|A|}\beta(A) \right] (e^{\eta'} \otimes e_{i'}) \ .$$

This demonstrates formula (5.13), and achieves the proof of Lemma 5.16. □

5.10.3 Differentiation of the map b^*

Lemma 5.17. *The gradient of the map b^* defined in* (5.14) *is given, at any point $A \in \mathbb{R}^6_+ \setminus \{0_6\}$, by the formula:*

$$\begin{aligned} &\nabla b^*(A) \\ &= \sum_{\eta=U,W} \sum_{i=1,2,3} \left[\left(1 + \sum_{\eta'=U,W} \sum_{i'=1,2,3} \frac{r^{\eta'} A_{i'}^{\eta'}}{(\hat{\mu}_{i'}^{\eta'}(b^*(A)) + \nu)^2} \frac{d\hat{\mu}_{i'}^{\eta'}}{db}(b^*(A)) \right)^{-1} \frac{r^{\eta}}{\hat{\mu}_i^{\eta}(b^*(A)) + \nu} \right] (e^{\eta} \otimes e_i) \end{aligned} \tag{5.14}$$

For any $\eta = U, W$, any $i = 1, 2, 3$, the expression between brackets in (5.14) thus represents the component of the gradient in the direction of the vector $(e^{\eta} \otimes e_i)$. Notice that the fact that the maps $\hat{\mu}_i^{\eta}$ are increasing implies that the scalar expression between parenthesis is positive, and thus invertible.

Proof of Lemma 5.17. Differentiating (5.14) with respect to A_i^{η} yields

$$\frac{\partial b^*(A)}{\partial A_i^{\eta}} = \frac{r^{\eta}}{\hat{\mu}_i^{\eta}(b^*(A)) + \nu} - \sum_{\eta'=U,W} \sum_{i'=1,2,3} \frac{r^{\eta'} A_{i'}^{\eta'}}{(\hat{\mu}_{i'}^{\eta'}(b^*(A)) + \nu)^2} \frac{d\hat{\mu}_{i'}^{\eta'}}{db}(b^*(A)) \frac{\partial b^*(A)}{\partial A_i^{\eta}}$$

from which is deduced (5.14). □

From Lemmas 5.16 and 5.17, one may deduce the value of the gradient of the map $b^*(\alpha(A))$ which appears in the system under study, through the identity

$$\frac{\partial b^*(\alpha(A))}{\partial A_i^{\eta}} = \nabla b^*(\alpha(A)) \cdot \left(J_{\alpha}(A)(e^{\eta} \otimes e_i) \right), \qquad \eta = U, W, \ i = 1, 2, 3 \tag{5.15}$$

Appendix A

Computational implementation

The implementation for numerical simulations was done with Scilab https://www.scilab.org/. Each software was developed based on the Yann Debray (2016) tutorial https://news.scilab.io/news11/, the work procedure used will facilitate future cloud deployment (running in Scilab Cloud with rendering through the web browser) https://www.scilab.org/cloud/web-application.

Below is a list of repositories[1] that allow access to codes:

- Two life phases Mendelian model
- One life phase Mendelian Model
- Singular and regular perturbation for two life phases Mendelian model
- Wolbachia∩Resistance control model
- Visualization R code

Each version provided in this annex is a beta version that, while fulfilling the purposes of the thesis are still under construction.

[1] https://drive.google.com/drive/folders/1UFnQo8QG-pOccAx9CiCsuphrIAxYdj-n?usp=sharing

Appendix B

Resumen extendido en español

B.1 Introducción

B.1.1 Mosquitos y arbovirosis

La dinámica de los arbovirus depende de una circulación entre artrópodos hematófagos y vertebrados hospederos. Estos virus necesitan de los artrópodos para su replicación, su propagación y subsistencia. Controlar las poblaciones de vectores es una forma eficiente de mitigar los problemas de salud por arbovirosis.

Cerca de 700 millones de personas contraen enfermedades transmitidas por mosquitos todos los años (Caraballo and King, 2014). De los más de 500 arbovirus, se sabe que 150 causan enfermedades en humanos (Roehrig and Lanciotti, 2009). Los arbovirus con morbilidad grave y mortalidad transmitidos por mosquitos a humanos pertenecen a las familias *Flaviviridae*, *Togaviridae* y *Bunyaviridae* (Blair et al., 2000). Estos virus se clasifican según sus características epidemiológicas en causantes de complicaciones hemorrágicas o predominio de daño neurológico (Zuckerman, 2009). Con excepción del virus O'nyong-nyong, trasmitido por mosquitos *Anopheles*, todos los demás virus son transmitidos por *Culicidae*, en especial por *Aedes* y *Culex* (Franz et al., 2015). El dengue en particular, propagado por *Ae. aegypti*, es la enfermedad viral más importante transmitida por mosquitos por su potencial epidémico global (Bhatt et al., 2013; Organization et al., 2014; Shepard et al., 2016). Además, *Ae. aegypti* es el principal vector para la fiebre amarilla (Tomori, 2004), Chikungunya (Halstead, 2015) y el Zika (Bharucha and Breuer, 2016).

Las características que hacen de un insecto como Ae. aegypti un factor de riesgo global de epidemias son: (a) su distribución generalizada en regiones tropicales y subtropicales (Kraemer et al., 2015); (b) está en asociación estrecha con poblaciones hu-

manas (Powell and Tabachnick, 2013); y (c) tiene competencia vectorial para diversos virus (Nene and *et al.*, 2007). El riesgo de que insectos como Ae. aegypti diseminen enfermedades graves quedo en evidencia con el Zika (Gulland, 2016). En el 2007 el Zika había reportado solo 14 casos confirmados en humanos con distribución geográfica en África tropical y el sudeste asiático (Duffy et al., 2009; Faye et al., 2014). Sin embargo, en mayo de 2015 se identificó un tercer brote de Zika en Brasil, el cual se extendió rápidamente por Sudamérica y luego por 62 países (Kindhauser et al., 2016).

B.1.2 Control en poblaciones de mosquitos

Las estrategias más eficientes de mitigación de las arbovirosis se basan en el control de la población de vectores (Beaty et al., 2010). Debido a esto, es fundamental comprender la dinámica de las poblaciones de insectos para conseguir un control artificial efectivo. De forma natural dos tipos de mecanismos pueden actuar sobre la dinámica de estas poblaciones (ver (Turchin, 2003)): a) Controladores intrínsecos (endógenos) que operan a través de mecanismos de retroalimentación negativa dependientes de la densidad, de modo que la supervivencia y la fertilidad se reducen cuando la densidad de la población aumenta. b) Controladores extrínsecos (exógenos), que incluyen variables ambientales y acciones de control humano que afectan la densidad de la población, pero que no se ven afectadas por ella. Como ejemplo de factores exógenos naturales que son apropiados para el aumento de la densidad de mosquitos están la lluvia y la temperatura. La lluvia afecta directamente a la disponibilidad de sitios de reproducción (Yang et al., 2008), mientras que la temperatura afecta el tiempo de desarrollo y la mortalidad de las larvas (Lahondère and Lazzari, 2012; Ewing et al., 2016). En general, las poblaciones de mosquitos muestran una fuerte regulación intrínseca natural en dependencia de la densidad (Yang et al., 2008).

En la práctica, la estrategia de control de insectos más utilizada se basa en métodos químicos (Levick et al., 2017), *i.g.*, el uso de larvicidas y/o adulticidas. Sin embargo, se ha advertido de que el uso de insecticidas afecta la biodiversidad (Oosthoek, 2013). Además, su uso prolongado genera resistencia a los insecticidas (Brown, 1986; Hemingway and Ranson, 2000,?; Schechtman and Souza, 2015) lo cual reduce la eficiencia de las campañas de control químico y limita su tiempo de vida útil (Koella et al., 2009a; Gourley et al., 2011).

Debido a los problemas asociados al uso de insecticidas, en los últimos 15 años se ha avanzado en el desarrollo de estrategias alternativas que van desde los métodos de control biológico hasta la modificación genética de las poblaciones de insectos (McGraw and O'Neill, 2013). Entre estas se destacan las innovaciones conocidas como

control genético, las cuales se definen como métodos de control biológico que dependen de la difusión de factores hereditarios que reducen el daño de plagas (Alphey, 2014). Estos controles pueden tener como finalidad suprimir una población como los insecticidas o remplazarla por mosquitos con competencia vectorial reducida o nula (Walker et al., 2011b; Alphey, 2014). Sin embargo, antes de la aplicación extendida de estos métodos, existen cuestiones teóricas y experimentales relacionadas al uso simultáneo de estrategias que deben ser respondidas –ver (Hoffmann and Turelli, 2013a; Alphey, 2014; Hoffmann et al., 2015).

B.1.3 La resistencia a los insecticidas y el uso de *Wolbachia* como estrategia de control

Los factores que originan y propagan la resistencia son de importancia académica y aplicada (Daborn et al., 2004). El problema de la resistencia a los insecticidas en mosquitos proporciona un modelo biológico ilustrativo para comprender cómo evolucionan las nuevas adaptaciones por selección natural. Como en un gran número de casos:

- el agente de selección es conocido, *e.g.*, un determinado insecticida (Vontas et al., 2012a);
- la evolución es reciente y rápida, pocos años después del uso del insecticida (Koella et al., 2009a);
- los mecanismos biológicos y genéticos para la resistencia a menudo se conocen (Labbé et al., 2011).

En tal sentido, debido al costo, el riesgo y las dificultades logísticas de estudios de campo prospectivos de la evolución de la resistencia, los modelos matemáticos útiles para la simulación numérica por computadora pueden ayudar a mejorar las estrategias de manejo de los insecticidas.

Por otra parte, el abanico de posibilidades de control de mosquitos ha aumentado de forma notable en la última década (Kean et al., 2015). Por ello, comprender las limitaciones y potencialidades del uso simultáneo de algunas de estas estrategias representa un desafío muy reciente. Un ejemplo de esto se observó cuando se realizó un control utilizando mosquitos cultivados con *Wolbachia*—una bacteria heredada por vía materna al igual que las mitocondrias capaz de reducir la competencia vectorial. Los resultados muestran que el éxito del uso de *Wolbachia* está influenciado por el control químico en una población local resistente de mosquitos (Hoffmann and Turelli, 2013a).

En efecto, no se puede comprender ni precisar los alcances del uso de *Wolbachia* y su interacción con otros rasgos genéticos como la resistencia a insecticidas sin la utilización de modelos matemáticos que representen la herencia.

B.1.4 Estado del conocimiento de modelos de resistencia y *Wolbachia*

No podemos hablar de resistencia a insecticidas o control genético sin referirnos a la evolución biológica. La literatura sobre modelos de evolución por selección, así como modelos de evolución de resistencia en poblaciones diploides es bastante extensa. No es nuestra intención proporcionar aquí un inventario riguroso al respecto. Si no más bien, posicionar la contribución de la tesis con respecto al estado del conocimiento actual. La aproximación típica en la literatura para modelos de evolución incluye procesos estocásticos de tiempo-discreto con un locus genético simple con un número dado de alelos (Huillet and Martinez, 2011). Respecto a modelos de evolución por selección, para una visión general y didáctica del estado del conocimiento se tienen las obras de Warren J. Ewens (Ewens, 2011), Peter Schuster (Schuster, 2011a,b) y Reinhard Bürger (Bürger, 2011). Con respecto a la evolución de la resistencia en poblaciones diploides, el enfoque y los supuestos subyacentes que se hacen a menudo son pautas utilizadas para construir modelos de genética de poblaciones (ver (Levick et al., 2017) y textos clásicos citados). A continuación se proporciona algunos comentarios sobre los modelos clásicos.

En los modelos clásicos de genética de poblaciones, para omitir el efecto de la deriva genética, en un marco probabilístico, es común apelar a la ley de grandes números y asumir un tamaño de población invariante infinita. Luego, es posible enfocar el análisis matemático en un *símplex* que represente frecuencias alélicas o genotípicas, de igual modo que en teoría de juegos evolutivos. Ciertamente, se sabe que la reproducción y la selección tienen efectos estocásticos inherentes, la incorporación de estos efectos produce modelos que se formulan en términos de procesos estocásticos, generalmente Markovianos, y agregan una complejidad matemática considerable (Bürger, 2011). Estos fenómenos no representan el enfoque de esta Tesis.

En contraste, en las estrategias de supresión por control químico y cuando se mantiene la evolución de la resistencia, uno desea estudiar, además de los cambios en las frecuencias alélicas, la eficiencia en la supresión del tamaño de la población, si se puede provocar una extinción o un umbral de tamaño de población deseado. El estudio de la supresión de una población de mosquitos no es compatible con la consideración teórica de poblaciones con tamaños infinitos.

Por otras parte, el fitness es un concepto central en los modelos de selección (Orr, 2009; Wu et al., 2013), este es una medida relacionada con la tasa reproductiva neta y depende de la viabilidad relativa (*e.g.* tasa de mortalidad después del contacto con el insecticida), y/o la disminución de la fertilidad. En el enfoque tradicional de la genética de poblaciones, el fitness de un genotipo se define con referencia al de otros individuos mediante el cálculo de sus cocientes (Wilson and Bossert, 1971). Por simplicidad, es común en genética de poblaciones, que los mecanismos por los cuales se reduce el fitness no están especificados (Barbosa and Hastings, 2012; Levick et al., 2017), *i.e.*, no se aclara si la medida del fitness está relacionada con la fertilidad, la viabilidad o ambos.

No obstante, considerando la complejidad de la historia de vida en mosquitos y los principios de herencia para la reproducción sexual, algunos escenarios realistas pueden requerir un tratamiento más general de los mecanismos que afectan el fitness. Por supuesto, idealmente con un equilibrio entre simplicidad y generalidad. Por ejemplo, el uso de larvicidas y/o adulticidas para el control de mosquitos afecta de manera diferente la viabilidad en la fase prereproductiva y reproductiva, respectivamente. Además, la viabilidad puede disminuir en una población en crecimiento debido a la limitación de algunos recursos por la competencia, y puede depender de la densidad. A su vez, esto puede afectar de forma diferente a los individuos en la población.

Un enfoque no tradicional para modelos de resistencia se presenta en Langemann *et al.* (Langemann et al., 2013). Estos autores proponen un modelo determinístico que combina el crecimiento logístico en una población con el rearreglo de alelos en los genotipos dados por la herencia. Además, muestran de que manera su modelo se puede aplicar para casos de loci múltiple, extenderlo para poliploides y otros números de alelos.

Por otra parte, se han propuesto varios modelos matemáticos para infecciones por *Wolbachia* en una población de mosquitos. Por ejemplo, Turelli (Turelli, 2010) describe un modelo simple con una sola ecuación diferencial, suficiente para revelar la naturaleza biestable de la dinámica de *Wolbachia*. Koiller *et al.* (Koiller et al., 2014b) describen un modelo basado en datos para estimar con precisión algunos parámetros biológicos al ajustar del modelo con datos de campo y laboratorio. Mas recientemente, Bliman *et al.* (Bliman et al., 2018a) presentaron una versión simple del modelo anterior, con cuatro dimensiones de variables de estado (pre-adulta y adulta, infectada y no infectada), enfocando su esfuerzo principal en el análisis del control.

Un artículo cercano al propósito principal de esta tesis fue publicado por Hoffmann y Turelli (Hoffmann and Turelli, 2013a). Estos autores proponen un modelo para el uso

simultaneo de la resistencia a insecticidas y la infección por *Wolbachia*. El modelo que proponen asume generaciones discretas y se enfoca en el estudio de las frecuencias de los biotipos de la población. Este enfoque se asemeja al de la genética de poblaciones clásica.

B.2 Formulación del problema y objetivos de la tesis

Una cuestión fundamental con relación a la introducción de *Wolbachia* en poblaciones silvestres de mosquitos es de qué manera se puede garantizar el éxito incluso en una población con adaptaciones locales tales como la resistencia a insecticidas. En tal sentido en esta tesis queremos responder a la siguiente pregunta:

¿Es posible introducir *Wolbachia* en una población de mosquitos silvestres no infectados resistentes a los insecticidas utilizando mosquitos de laboratorio infectados con *Wolbachia* y susceptibles a los insecticidas?

A los efectos se utilizará modelado matemático. De este modo, los objetivos de esta tesis se dan a conocer a continuación.

Objetivo general

Determinar una estrategia de control para mosquitos resistentes a insecticidas usando *Wolbachia*.

Objetivos específicos

1. Modelar un sistema de herencia mendeliana para la resistencia a insecticidas en mosquitos.
2. Analizar el modelo de herencia mendeliana propuesto para la resistencia a insecticidas en mosquitos.
3. Modelar un sistema de herencia materna para *Wolbachia* en mosquitos.
4. Analizar el modelo de herencia materna propuesto para em Wolbachia en mosquitos.
5. Proponer un modelo unificado de herencia materna y autosómica para el análisis de una estrategia de control con *Wolbachia* de mosquitos resistentes a los insecticidas .

B.3 Sumario de resultados

Tal como se ha mencionado antes, los mosquitos son vectores de enfermedades virales con potencial epidémico en muchas regiones. El control poblacional de mosquitos es la principal alternativa debido a las dificultades en el uso de vacunas contra estas enfermedades. En este sentido, el control químico a través de insecticidas ha sido una de las estrategias convencionales. Sin embargo, con el tiempo las poblaciones de mosquitos desarrollan resistencia a los insecticidas, codificada a nivel genético. Además, los productos químicos utilizados como insecticidas pueden afectar a otros grupos de insectos y causar daños ecológicos. Por estas razones, se han propuesto nuevas alternativas de control. Uno de ellos es el control mediante la liberación de mosquitos infectados con *Wolbachia*. En este contexto, esta tesis aporta modelos matemáticos, análisis y simulaciones para comprender cómo la *Wolbachia* puede trabajar en la interacción con rasgos genéticos como la resistencia a los insecticidas.

Para dar cuenta de la aparición y propagación de fenómenos de resistencia por el efecto de la exposición a larvicidas y/o adulticidas, desarrollamos un modelo poblacional general de tiempo continuo con dos fases de vida, posteriormente simplificado a través de la "slow manifold theory". Los modelos derivados presentan tasas de reclutamiento y mortalidad dependientes de la densidad de una manera no convencional. Mostramos que, en ausencia de selección, evolucionan de acuerdo con el principio de Hardy-Weinberg; mientras que en presencia de selección, en los casos dominantes o de dominancia intermedia, se produce la convergencia al genotipo más apto. Luego, presentamos un enfoque de modelado explícito y simulaciones numéricas que ilustran los resultados analíticos en este contexto. Además de la selección direccional para la evolución de la resistencia a los insecticidas, a fin de ilustrar la cualidad descriptiva de la clase de modelos propuestos, se simulan otros escenarios de evolución no direccional, *i.e.*, sobredominancia y subdominancia. Del mismo modo, presentamos simulaciones que ilustran cómo el nivel de dominación y la inversión da la evolución de la resistencia pueden prolongar la efectividad del control químico.

Finalmente, con base a la clase de modelos presentados anteriormente, se deriva un modelo que unifica el control químico con el control biológico para las infecciones por *Wolbachia*. Se propone un modelo poblacional representado por la combinación de atributos de herencia autosómica para resistencia a insecticidas y herencia materna para *Wolbachia*. Se deduce una ley de control para la liberación de genotipos específicos de mosquitos infectados con *Wolbachia* para el control por remplazo. Se presentan resultados analíticos que describen el comportamiento cualitativo del sis-

tema. Se demuestra la validez de la ley de control propuesta. Finalmente, para ilustrar los resultados analíticos, se presentan simulaciones computacionales, que evidencian la influencia que algunos factores deben tener en las campañas de liberación de mosquitos de genotipo específico infectados con *Wolbachia*.

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