Modelling the Spatial Spread of *Wolbachia* Bacteria in Mosquitoes

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Abstract

Modelling the Spatial Spread of *Wolbachia* Bacteria in Mosquitoes

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Wolbachia is a maternally inherited, intracellular bacteria that causes a number of abnormalities in their host's reproductive system. Recent studies show that infecting mosquito populations with *Wolbachia* is a promising new strategy for controlling diseases such as dengue fever and yellow fever. *Wolbachia* infection can spread rapidly through mosquito populations following its introduction, and infected mosquitos have been shown to have a much reduced capacity to transmit disease. The success of this strategy depends on how easily and rapidly the *Wolbachia* spreads. This report is focused on the dynamics of *Wolbachia* infection in spatially heterogenous environments. We extend the single-patch model of mosquito population to the two-patch model as the simplest spatially heterogenous system. The two-patch model describes the interaction between mosquito population dynamics and *Wolbachia* infection frequency for an age-structured insect population regulated by larval density dependence. We show that spatial subdivision and migration between patches can affect to the dynamics of mosquitoes and spreads of *Wolbachia*. The results help to design a proper *Wolbachia*-releasing strategy to the heterogenous distribution of mosquito habitats.

KeyWords: *Wolbachia* bacteria, mosquito vectors of human disease, population dynamics, epidemiology, network theory, modelling of complex systems

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Chapter 1

Introduction

Wolbachia are a common and widespread group of bacteria found in reproductive tissues of insects or worms. *Wolbachia* have attracted great interest for a number of reasons. Firstly, they can dramatically alter reproductive biology of the host insect, for example by inducing parthenogenesis [1, 2]. Secondly they can protect the host insect from infection by pathogens [3]. Recently, *Wolbachia* have been recognized as a potential means of controlling vector-borne diseases. For example, in the mosquito *Aedes aegypti*, *Wolbachia* infection can prevent the mosquito from transmitting important human diseases such as the dengue and yellow fever viruses [4]. In this work, the spatial spread of *Wolbachia* in a heterogeneous environment will be discussed as a potential biological control method to prevent vector-bone diseases. In order to focus on the spread of *Wolbachia*, we first discuss the biology of cytoplasmic incompatibility.

Cytoplasmic incompatibility (CI)

Wolbachia spreads through the host population by inducing cytoplasmic incompatibility (CI). CI is a reproductive incompatibility between the sperm and the egg. The bacteria are transmitted in eggs but are not transmitted through sperm. Incompatibility occurs when the sperm from a *Wolbachia*-infected male fertilizes an uninfected egg. In Figure 1.1, the schematic diagrams of CI of *Wolbachia* are given for two cases, perfect maternal transmission (left) and imperfect maternal transmission (right). Perfect transmission of *Wolbachia* means that all offspring inherit the infection from the mother, where as some offspring of infected mothers are uninfected in the case of imperfect maternal transmission. In this diagram, while the fertility of infected females is unaffected by *Wolbachia* regardless of males, matings between infected males and uninfected females are infertile, which is denoted as "CI" in the figure. When infected females fail to transmit *Wolbachia* to an offspring in the case of imperfect maternal transmission, the bacteria from the infected sperm still cause incompatibility. This mechanism of CI can increase the frequency of *Wolbachia* infection in subsequent generations of the host population. Usually,
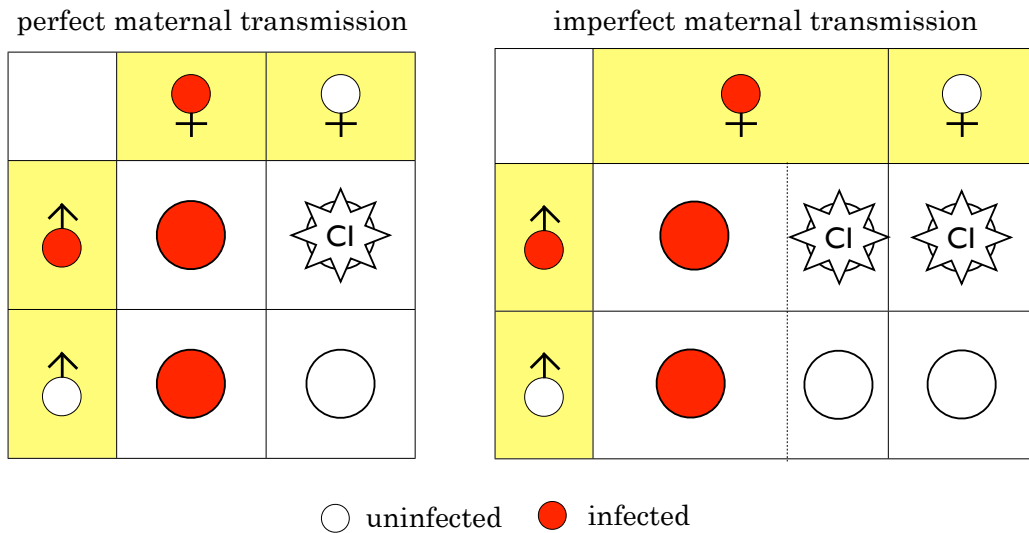
Figure 1.1: *Wolbachia* induced Cytoplasmic Incompatibility (CI) when maternal transmission of *Wolbachia* is perfect (left) and imperfect (right) in absence of paternal transmission.

the *Wolbachia* spread rapidly the population because the probability of failure of maternal transmission is relatively low(around 1%) and the probability of infertility due to CI is relatively high(around 99%) [5].

Biological control implication

Using *Wolbachia* in biological control is a considerably interesting issue because *Wolbachia* influences the ability of insects to transmit pathogens. This can be achieved indirectly by reducing insect life span or directly by reducing the ability of viruses and other pathogens to proliferate within the insect [6, 7]. In particular, from recent studies in recent 2-3 years, infecting mosquito populations with *Wolbachia* has been recognized as a promising new strategy to prevent transmission of diseases such as dengue fever and yellow fever. The observation is that *Wolbachia* provide greater disruption to dengue transmission and successful invasion for dengue control [8]. Furthermore, these bacteria confer greater fitness costs to the mosquito host as well. From this aspect, biological control aimed at suppressing mosquito populations or reducing their capacity to transmit disease may be a useful and important addition to traditional vector control strategies, especially if the mosquito populations' resistance to chemical insecticides continues to increase.

Spread of *Wolbachia* infection can be accelerated through mosquito populations following introduction of infected mosquitoes. The success of this strategy depends on how easily and rapidly the *Wolbachia* spreads. This report is focused on the dynamics of *Wolbachia* infection in spatially heterogenous environments. As understanding of the effects of host population heterogeneity on the spread of *Wolbachia* is crucial to predicting how this disease control strategy will perform in the real world. Here, we will develop the spatial dynamics of *Wolbachia* infection in a mosquito population from a two-patch model to a network model [5, 9].

Chapter 2

Single-patch Model

One of the simplest mathematical models of *Wolbachia* dynamics are derived by Turelli [9]. This model describes the dynamics of *Wolbachia* infection frequency with several assumptions : (1) maternal transmission is imperfect, (2) paternal transmission is absent, (3) mating is random, (4) the infection affects female fecundity but no other fitness component, (5) only vertical transmission can occur, (6) the host population mixes homogeneously, and (7) generations are discretized. Turelli's *Wolbachia* dynamics show that spread occur if the infection frequency exceeds a threshold that is higher for the bacteria that cause stronger reductions in host fitness. However, the Turelli model considers changes in infection frequency but not changes in host population abundance, and assumes that host population dynamics do not affect the dynamics of *Wolbachia* infection.

There has been limited consideration of the role of host life history and demography in *Wolbachia* infection dynamics, and host populations are typically assumed to have discrete, non-overlapping generations like Turelli's. The changes of hosts' demographic rates have to be considered for understanding more realistic model such as immigration of infected individuals, dependence on the population density, and seasonal variations in abundance.

In this section, a continuous-time demographic model of *Wolbachia* spread through a host population will be given in a homogenous, single-patch system. In this model, some assumptions from Turelli's model will be used(1,2,3 and 5). The overlapping generations will be considered and the dynamics are regulated by density-dependent processes. Furthermore, host age structure and adult age-specific mortality is also included. The model that will be given in the following sections is obtained from the paper of Hancock et al.[5].

2.1 Mosquito population without *Wolbachia*

The model divides the mosquito population into larvae and adults. Let $L(t, l)$ and $S(t, a)$ be the numbers of larvae and adults at time t that have survived until ages l and a in two different stages, respectively. The probability that a larva survives until time l is defined as $\theta_L(t, l)$. This probability is a function of time because larval mortality is density dependent. Defining the total number of larvae at time t as $\tilde{L}(t)$, the larval survival, $\theta_L(t, l)$ can be written as

$$\theta_L(t, l) = \exp\left(-\int_{t-l}^{t} \mu_L(\tilde{L}(\tau))d\tau\right). \tag{2.1}$$

The mortality rate of larvae $\mu_L(\tilde{L}(t))$ can be modeled as

$$\mu_L(\tilde{L}(t)) = \mu + \alpha(\tilde{L}(t))^\beta \tag{2.2}$$

where μ, α, and β are constants. In this larval mortality function, there are two parts. The first part is a constant rate μ and the second one is the function of density that can represent with different forms [10, 11]. In this model, the power-law function is taken as density dependence. The values of α and β correspond to carrying capacity and strength of the dependence on density of the patch, respectively. Similarly, at the adult stage, let the probability an adult survives until age a be $\theta_S(a)$, which depends on age alone:

$$\theta_S(a) = \exp\left(-\int_0^a \mu_S(\tau)d\tau\right), \tag{2.3}$$

with mortality,

$$\mu_S(a) = c + \gamma r(ra)^{\gamma-1}. \tag{2.4}$$

where c is the constant rate and the age dependent mortality function has the Weibull shape with shape and scale (rate) parameters γ and r, respectively [12]. By using the survival probabilities (2.1,2.3), the population dynamics of the model is given as following:

$$L(t, l) = \frac{\lambda}{2}\tilde{S}(t-l)\theta_L(t, l), \quad l \leq T_L, \tag{2.5a}$$

$$S(t, a) = L(t-a, T)\theta_S(a) \tag{2.5b}$$

where $\tilde{S}(t)$ is the total number of adults at time t, $\tilde{S}(t) = \int_0^\infty S(t, a)da$ and λ is the female fecundity per unit time. The factor 2 means that the sex ratio is unity. In equations (2.5), the maximum length of the larval stage is assumed as T_L. From the equilibrium analysis (see Appendix A), one can get the total number of larvae at the equilibrium, $\tilde{L}^*$,

$$\tilde{L}^* = \left[\frac{1}{\alpha T_L} \ln\left(\frac{\lambda \Theta_S}{2} e^{-\mu T_L}\right)\right]^{1/\beta}, \tag{2.6}$$
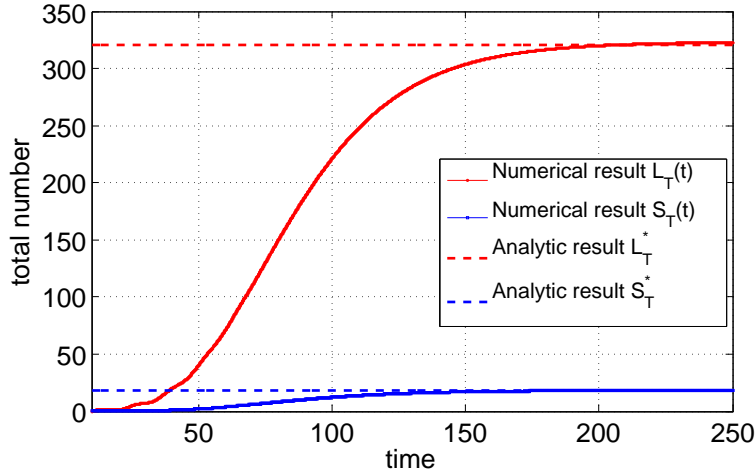
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Figure 2.1: Mosquito population dynamics without *Wolbachia*, from equation (2.5) with parameters, $\lambda_U = 15, T_L = 10, \mu = 0.1, \alpha = 0.1, \beta = 0.2, c = 0.1, \gamma = 1.5$, and $r = 0.025$. Good agreement with analytical results is obtained at equilibrium.

where $\Theta_S = \int_0^\infty \theta_S(a)da$, which is average adult lifetime. The total number of adults can be obtained from the total larval density from the relation,

$$\tilde{S}^* = \frac{2\tilde{L}^*}{\lambda \Theta_{LD}}, \tag{2.7}$$

where $\Theta_{LD} \equiv \int_0^{T_L} \theta_L^*(l)dl = \frac{1-e^{-(\mu+\alpha \tilde{L}^{*\beta})T_L}}{\mu+\alpha \tilde{L}^{*\beta}}$, which is average larval lifetime.

Computer simulation is conducted by using the model without *Wolbachia*, equations (2.5). In this project, MATLAB code was developed to perform the computer simulation. The result is illustrated in Figure 2.1. In this numerical calculation, the parameters are given as $\lambda_U = 15, T_L = 10, \mu = 0.1, \alpha = 0.1, \beta = 0.2, c = 0.1, \gamma = 1.5$, and $r = 0.025$. The analytical results are obtained from equations (2.6) and (2.7). The numerical results of total number of individuals agree with analytical results at equilibrium.

2.2 Mosquito population with *Wolbachia*

The population dynamics with *Wolbachia* will be presented in this section. Let the subscripts U and W represent uninfected and infected insects, respectively. $p(t)$ is the infection frequency, which can be obtained by $p(t) = \frac{S_W(t)}{S_W(t)+S_U(t)}$. A fraction s_h of the offspring of any uninfected female that mates with an infected male will fail to develop because of the cytoplasmic incompatibility (CI) by *Wolbachia* infection. Infected females fail to transmit *Wolbachia* to a fraction ω of their offspring. The changes in fecundity caused by *Wolbachia* carriage might be defined with s_f by $\lambda_W = (1-s_f)\lambda_U$. In this model, the potential

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effect on any life-history parameter from *Wolbachia* and random mating are assumed. The dynamics are given as following:

$$L_W(t,l) = \frac{\lambda_W}{2}(1-\omega)\tilde{S}_W(t-l)\theta_{L,W}(t,l), \quad l \leq T_W, \tag{2.8a}$$

$$\begin{aligned} L_U(t,l) = \ & [1 - s_h p(t-l)]\theta_{L,U}(t,l) \\ & \times \left[\frac{\lambda_U}{2}\tilde{S}_U(t-l) + \omega\frac{\lambda_W}{2}\tilde{S}_W(t-l)\right], \quad l \leq T_U, \end{aligned} \tag{2.8b}$$

$$S_W(t,a) = L_W(t-a,T_W)\theta_{S,W}(a), \tag{2.8c}$$

$$S_U(t,a) = L_U(t-a,T_U)\theta_{S,U}(a). \tag{2.8d}$$

The total number of infected and uninfected adults at time t are $\tilde{S}_W(t)$ and $\tilde{S}_U(t)$, respectively. Equation (2.8.a, b) can be obtained by modelling the mechanism of CI for the case of imperfect maternal transmission from Figure 1.1. The equilibria of the dynamics can be obtained as following (see Appendix B for the derivation):

$$p^*_{s/u} = \frac{s_h + A - B \pm \sqrt{(s_h + A - B)^2 - 4s_h A(1-B)}}{2s_h A}. \tag{2.9}$$

The constants are defined as $A = 1 - \omega(1-s_f)$ and $B = (1-\omega)(1-s_f)(1-s_d)(1-s_g)$, where $\frac{\Theta_W}{\Theta_U} = 1 - s_g$ and $\frac{\theta^*_{L,W}(T_W)}{\theta^*_{L,U}(T_U)} = 1 - s_d$. s_d and s_g indicate the amounts of reduction in average adult lifespan and equilibrium reduction in juvenile survival, respectively. These are the fitness costs caused by *Wolbachia* infection. When there is no *Wolbachia* infection-effect, the fitness costs on average life-time (i.e. $s_d = s_g = 0$), B becomes $(1-\omega)(1-s_f)$ and equation (2.9) has the same result with Turelli's model [9].

In equation (2.9), there are two possible fixed points. p^*_s with the sign $+$ gives the stable fixed point of the dynamics. If the bacteria could spread to the population, the infection frequency at the equilibrium becomes p^*_s. The unstable fixed point p^*_u gives the threshold value for spreads. If the infection frequency is larger than this threshold, the spreads of *Wolbachia* occurs. If the frequency is smaller that this threshold, the infected individuals will be extinct because $p^* = 0$ is another trivial equilibrium. This implies the spreads of *Wolbachia* fails.

The numerical results of the single-patch model with *Wolbachia* are given in Figure 2.2. In this figure, the cases of two different initial initial frequencies are examined with same parameters. In the figure, the threshold value is given in black dashed line, which is obtained from equation (2.9). When $p(0)$ is smaller than threshold value(blue line), the infection frequency goes to zero. In the other case, when $p(0)$ is larger than threshold, the spread of *Wolbachia* occurs.

The immigration or introduction of mosquitoes carrying *Wolbachia* affects infection frequency. The population model with introduction of *Wolbachia* carrying adults at a constant rate can be described
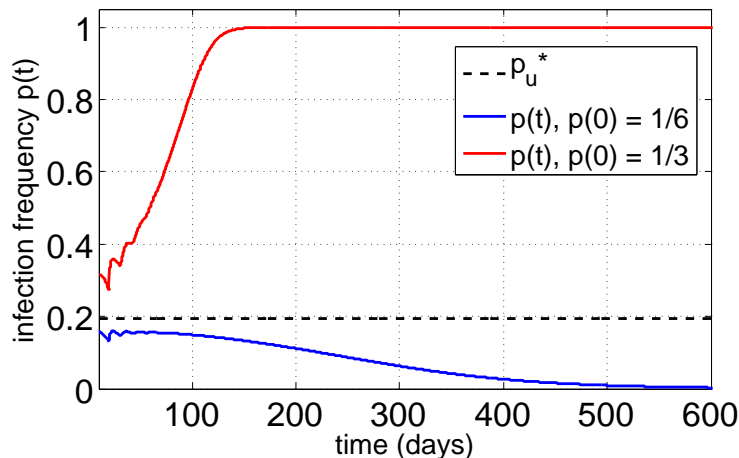
Figure 2.2: Population-*Wolbachia* model without Introduction, equation (2.8) with parameters, $\lambda_U = 15, T_U = T_W = 10, \mu = \mu_W = 0.1, \alpha = \alpha_W = 0.1, \beta = 1, \beta_W = 0.2, c = 0.24, \gamma = 1, r = 0.025, c_W = 0.1, \gamma_W = 1.5, r_W = 0.05$, and $s_f = 0.05$. The fitness cost of infection for the adults is considered as $s_g \approx 0.095$. The black dashed line indicates the threshold of infection frequency, p_u^*. The red solid line is for the case of successful spreads for *Wolbachia* with initial frequency $p(0) = 1/3 > p_u^*$, the blue line is for the case of failure of spreads with $p(0) = 1/6 < p_u^*$.

from simple extension of equation (2.8c) [5]. Introducing infected individuals to insect population can breach the threshold for *Wolbachia* to spread. This can be used for control of mosquito-borne diseases. In addition, since female mosquitoes bite people and they can potentially transmit disease, it is desirable that only a minimum number of female insects are released as part of a *Wolbachia* introduction. The theory for male-biased release strategies can be considered [13].

Until now, we have seen the model of mosquito population dynamics in the single-patch. For considering the spatial heterogeneity, we need to consider multi-patch system. In the following, we will discuss about the two-patch system as the most simplest heterogeneous system.

Chapter 3

Two-patch model without *Wolbachia*

Let's consider a model that subdivides the mosquito population into two patches connected by migration, assuming for now that *Wolbachia* is absent from the system. The two patches represent spatially discrete larval habitats. Adults may migrate between the two patches and oviposit in the patch in which they are currently present. From equations (2.5), the single-patch model can be extended to two-patch model with migration between patches as following:

$$L_i(t, l) = \frac{\lambda}{2} \tilde{S}_i(t - l) {\theta_L}^i(t, l), \quad l \leq T_L, \tag{3.1a}$$

$$S_i(t, a) = L_i(t - a, T_L) {\theta_S}^i(a) \theta_M^i(a) + I_{j \to i}(t, a), \tag{3.1b}$$

where $i \neq j$. The influx of population with age a from patch j to patch i at time t is denoted as $I_{j \to i}(t, a)$. The schematic representation of the two-patch system is illustrated in Figure 3.1. In equation (3.1b), $\theta_M^i(a)$ indicates the staying probability during time a at patch i. If the migration rate from patch i to j is constant, m_{ji}, the probability of remaining in patch i during time T can be obtained as

$$\theta_M^i(T) = e^{-\int_t^{t+T} m_{ji} d\tau} = e^{-m_{ji}T}. \tag{3.2}$$

Basically, the number of adults is the sum of the number of native mosquitoes who never left patch i, the first term in equation (3.1b), and the influx from the other patch. The survival probabilities can be obtained in the same manner as equation (2.1) and (2.3). The mortality rate of larvae is given as

$$\mu_L^i(\tilde{L}_i(t)) = \mu_i + \alpha_i(\tilde{L}_i(t))^{\beta_i}, \tag{3.3}$$

where μ_i, α_i, and β_i are constants. μ_i indicate a constant rate of mortality. One can assume that the constant mortality rates are the same for two different patches because this rate is a larval property of the specific species. The density dependence of the mortality is assumed to be a power-law function. The value of α_i is inversely proportional to carrying capacity of the patch i and the value of β_i represents the
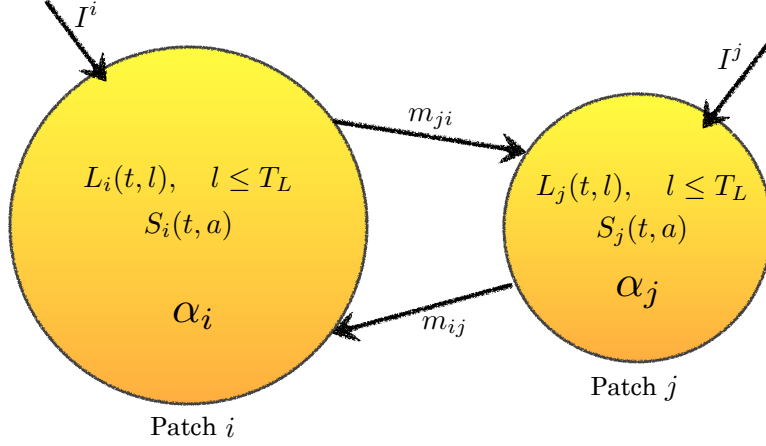
Figure 3.1: The schematic representation of two-patch model.

density-dependence of the larval mortality in the patch i. We assume that the form of density dependence, β, is the same across the patches but the carrying capacity of each patch, α, may be different. In addition, since the mortality function of adults depends on the species of mosquito, we assume the $\theta_S^i(a)$ are the same for different patches as well.

3.1 Migration in two-patch model

The influx of population with age a from patch j to i at time t is denoted as $I_{j \to i}(t, a)$. This is the integral over the entire influx of adult mosquitoes which have the age a during the given time interval. It can be written as

$$I_{j \to i}(t, a) = m_{ij} \int_0^a S_j(t - \xi, a - \xi)\theta_S^i(\xi)\theta_M^i(\xi)d\xi, \tag{3.4}$$

where the migration rate m_{ij} is constant. $m_{ij}S_j(t-\xi, a-\xi)$ represents the number of migrating mosquitoes with age $a - \xi$ from patch j to patch i at time $t - \xi$. For these migrating mosquitoes, after moving to patch i, they have remained with probability $\theta_S^i(\xi)\theta_M^i(\xi)$ untill time t. This means that mosquitoes can only leave from the patch because of death or migration. With this influx function, equation (3.1b) can be rewritten as following :

$$S_i(t, a) = L_i(t - a, T_L)\theta_S^i(a)\theta_M^i(a) + m_{ij} \int_0^a S_j(t - \xi, a - \xi)\theta_S^i(\xi)\theta_M^i(\xi)d\xi. \tag{3.5}$$

By putting $S_j(t - \xi, a - \xi)$ in the previous equation, one can get a new expression of age distribution of the adults.

$$
\begin{aligned}
S_i(t,a) = {} & L_i(t - a, T_L)\theta_S{}^i(a)\theta_M^i(a) && \text{(3.6a)} \\
& + m_{ij} \int_0^a L_j(t - a, T_L)\theta_S^j(a - \xi)\theta_M^j(a - \xi)\theta_S{}^i(\xi)\theta_M^i(\xi)d\xi && \text{(3.6b)} \\
& + m_{ij}m_{ji} \int_0^a \int_0^{a-\xi} S_i(t - \xi - \xi_1, a - \xi - \xi_1)\theta_S^j(\xi_1)\theta_M^j(\xi_1)\theta_S{}^i(\xi)\theta_M^i(\xi)d\xi_1 d\xi. && \text{(3.6c)}
\end{aligned}
$$

In equation (3.6), the first term (3.6a) indicates the 'native' mosquitoes in patch i who have never left their habitat since they were born. The second term (3.6b) is a part of the number of 'immigrants' with age a who left patch j when their age was $a - \xi$ and never returned to patch j. The last term (3.6c) could be called 'travellers'. They travelled between patch i and patch j several times and they are observed at patch i at that time. However, from this expression for travellers, we cannot identify, in which patch they were born. A traveller could be a native or an immigrant.

3.2   Subdivision of the system : Spatial heterogeneity

The dynamics of two-patch system can be reduced to two single-patch systems by assuming there is no migration. A proper comparison between spatially homogeneous system(i.e. single-patch) and spatially heterogeneous system could be attained by assuming the two-patch system is the subdivided system of one single-patch system.

Let's consider the concept of resource distribution. A patch in the model represents a mosquito's habitat where the insects can breed their offsprings. The larvae can survive with nutrients in the patch. When a comparison between the single-patch system and the two-patch system is needed, we should consider the carrying capacity or the amount of nutrients of each patch. In equation (2.6), the total number of larvae at equilibrium is given. From this, we interpret the total number of larvae as the proper size of the population that the patch can support. By assuming that the characteristics of mosquitoes are the same for different patches, the properties of patches are given from just two parameters α and β. When the reciprocal of carrying capacity for each patches are given as α_1 and α_2 and the density dependence is the same $\beta_1 = \beta_2 = \beta$, the single-patch system with the same amount of nutrients as the two-patch system is obtained as following (see Appendix C for the derivation):

$$
\alpha_s = \frac{\alpha_1\alpha_2}{\left(\alpha_1^\beta + \alpha_2^\beta\right)^{1/\beta}}, \tag{3.7}
$$

where α_s is the reciprocal carrying capacity of the single-patch. By using equation (3.7), one can set the comparable different systems with same amount of nutrients.

3.3 Two-patch model with constant mortality and migration

After setting the two-patch system with different carrying capacities, now we can consider the spatially heterogenous model analytically. Firstly, for simplicity, let's assume that adult mortality is constant and does not depend on adult age. In this case, the parameter r is zero in equation (2.3). Then, the survival probability, $\theta_S^i(a)$, becomes

$$\theta_S^i(a) = \theta_S^j(a) = e^{-ca}. \tag{3.8}$$

Here, we assume that $c = c_i = c_j$ since we are considering the same species of mosquito in similar generations. By assuming the migration rate between two patches is the same and constant (i.e. $m_{ij} = m_{ji} = m$), one can get the reduced form of the mosquito population dynamics, equations (3.1) and (3.6)

$$L_i(t,l) = \frac{\lambda}{2}\tilde{S}_i(t-l)\theta_L^i(t,l), \quad l \leq T_L, \tag{3.9a}$$

$$\begin{aligned} S_i(t,a) &= L_i(t-a,T_L)e^{-(c+m)a} + maL_j(t-a,T_L)e^{-(c+m)a} \\ &+ m^2 \int_0^a \int_0^{a-\xi} S_i(t-\xi-\xi_1, a-\xi-\xi_1)e^{-(c+m)(\xi+\xi_1)}d\xi_1 d\xi. \end{aligned} \tag{3.9b}$$

By successive substitutions of $S_i(t,a)$, age-distribution of the number of adults is obtained as (see Appendix D.1 for the derivation),

$$S_i(t,a) = \cosh{(ma)}L_i(t-a,T_L)e^{-(c+m)a} + \sinh{(ma)}L_j(t-a,T_L)e^{-(c+m)a}. \tag{3.10}$$

In equation (3.10), the first term indicates the number of "native" mosquitoes with age a at time t in the patch i, $S_i^n(t,a)$, and the second term indicates the number of "immigrant" mosquitoes from patch j, $S_i^{im}(t,a)$. Since the $L_i(t-a,T_L)$ term means the number of newborns in patch i at time $t-a$, one can interpret the factor $\cosh(ma)e^{-ma}$ as the probability of being present in the birth patch at age a, due to not emigrating or returning after emigration, and the factor $\sinh(ma)e^{-ma}$ as the probability of being an immigrant at age a. When $m = 0$, only the first term remains and there would be no immigrants because the probability of immigration becomes zero. As m increases, the probability of staying gets smaller and the probability of immigration gets bigger. When ma becomes very large, the probabilities of staying and immigration asymptotically tend to $\frac{1}{2}$. This implies that the migration rate is large enough, probabilities of staying and migrating become almost same.

In Figure 3.2, numerical results of time evolution of total adults populations for each patch are plotted with given parameters with $\alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2} \approx 0.0802$ and $\beta = 0.2$. These values give the proportion of populations at the equilibrium in two patches as $\tilde{S}_1^* = \tilde{S}_2^* = 1 : 3$, which is obtained from proportion of nutrients (see previous section and Appendix C). The solid lines are obtained from
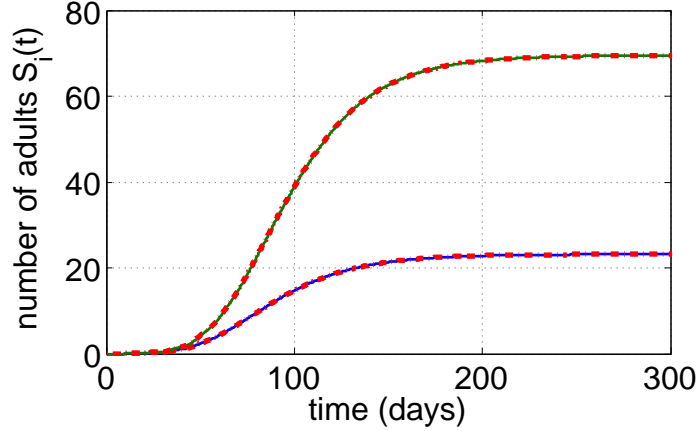
Figure 3.2: Time evolution of total adult populations, $\tilde{S}_i(t)$ for each patch, The parameters are assigned as $\lambda_U = 15, T_L = 10, \mu = 0.1, \alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2} = 0.0802 \cdots, \beta = 0.2, c = 0.1$, and the migration rate $m = 0.05$. The blue solid line is the time evolution of $\tilde{S}_1(t)$ and the green solid line is the one of $\tilde{S}_2(t)$. The red dot-dashed lines are obtained from equation (3.10). The results show good agreements between two different equations, (3.9b) and (3.10).

equations (3.9) and the red dot-dashed lines are obtained from equation (3.10). The results are agreed to each other very well. This implies that the equations are equivalent. Thus, the two-patch model with constant migration can be interpreted with probabilities of staying and emigrating between two patches. In addition, the proportion of adults population between two patches approaches $1 : 3$ as we expected from α, β values.

The numerical results of composition of adults population are given in Figure 3.3. In this figure, we made two different patches which have different carrying capacities, $\alpha_1 = 0.1$, $\alpha_2 = \frac{0.1}{3^{0.2}}$, and $\beta_{1,2} = 0.2$ like the previous figure. Other parameters are set to be the same. From the α values, one can say that the patch 1 as a small patch and patch 2 as a big patch. Red solid lines show the total number of adults $\tilde{S}_1^*$ (left) and $\tilde{S}_2^*$ (right). Green solid lines and blue solid lines are results of the total number of natives, $\tilde{S}_1^{n*}$, and the total number of immigrants, $\tilde{S}_1^{im*}$, respectively. The values are analytically tractable as following:

$$\tilde{S}_i^{n*} = \int_0^\infty \cosh(ma) L_i^*(T_L) e^{-(c+m)a} da = \frac{c+m}{c(c+2m)} L_i^*(T_L) \tag{3.11}$$

$$\tilde{S}_i^{im*} = \int_0^\infty \sinh(ma) L_j^*(T_L) e^{-(c+m)a} da = \frac{m}{c(c+2m)} L_j^*(T_L). \tag{3.12}$$

The numbers of natives and immigrants are dependent on the constant mortality rate c, migration rate m, and the number of larvae with stage T_L at equilibrium, $L_i^*(T_L)$. The numbers of larvae with stage T_L
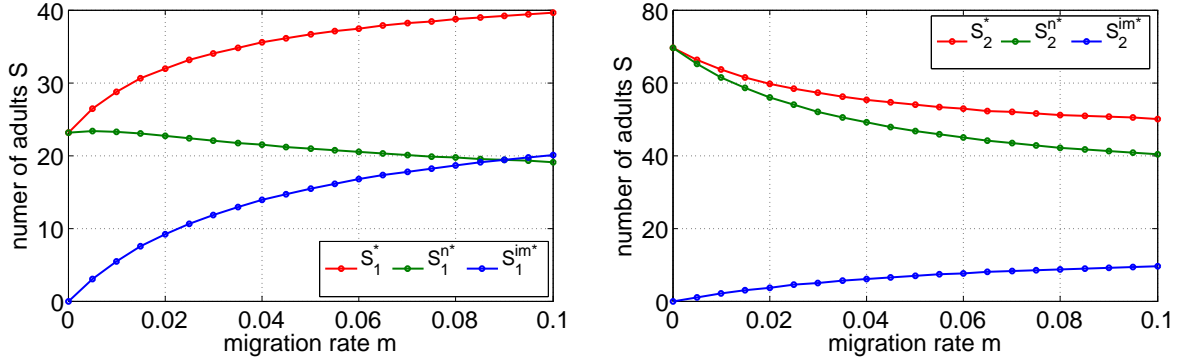
13

Figure 3.3: Composition of adults for different migration rates. Equation (3.10) is used with one possible set of parameters, $\lambda_U = 15, T_L = 10, \mu = 0.1, \alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2} \approx 0.0802, \beta_{1,2} = 0.2$, and $c = 0.1$. The left panel is for the result of patch 1, the small patch and the right one is for the large patch. Red solid lines are the total numbers of adults at equilibria, the green ones are the numbers of natives and the blue lines are the numbers of immigrants.

are not determined yet because of complex properties of density mortality function.

In Figure 3.3, as the migration rate m increases, the numbers of adults at the equilibria of each patch shows different behaviour. In the small patch (left panel), the total number of mosquitoes is increasing because of migration effect. As the number of immigrants $S_1^{\mathrm{im}*}$ increases, the number of natives decreases. This is because of the density dependent mortality function. The carrying capacity of the small patch is relatively small to support many larvae in the patch but their is always some influx from the big patch. On the other hand, for the big patch, many larvae can survive in the early stage from the density dependent mortality. Because of migration, the small patch can get more immigrants and the big patch can lose their natives. That results the increase of the total number of adults in the small patch and the decrease of the total number of adults in the big patch.

3.4 Density dependent mortality and migration

In the previous section, the density mortality function has an important role in the two-patch model with migration. However, since the migration rate and the density of each patch are coupled in the dynamics, it is hard to understand the relation between density dependent mortality and migration. In this section, the effects of migration to the larval density dependent mortality will be discussed.

The numerical results of the total number of adults at equilibria for different migration rate are given in Figure 3.4. As we mentioned in the chapter 2, the density dependent mortality is chosen as power-law function. The value β corresponds to strength of the dependence on density of the patch. For higher
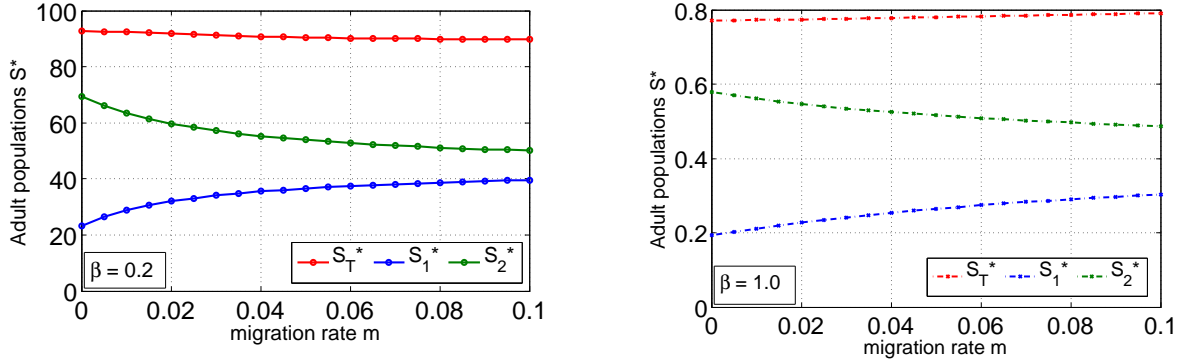
14

Figure 3.4: Number of adults for different migration rates. Equation (3.9) is used with parameters, $\lambda_U = 15, T_L = 10, \mu = 0.1$, and $c = 0.1$. The sizes of patches are given with proportion $1 : 3$ for patches. The parameters are $\alpha_1 = 0.1, \alpha_2 = 0.1/3^\beta$ The left panel is for the case $\beta = 0.2$ (solid line with circles) and the right panel is for $\beta = 1.0$ (dashed line with $\times$). Red solid lines are the total numbers of adults at equilibria, the green ones are the numbers of adults in patch 1 (small) and the blue lines are numbers of adults in patch 2 (big).

values of β, larval mortality responds more strongly to changes in larval density. Here, we examine for two different values of β. The left panel shows the case when $\beta = 0.2$ and the right one shows the case when $\beta = 1.0$. The carrying capacities are chosen as $\alpha_1 = 0.1$ and $\alpha_2 = 0.1/(0.3)^\beta$, which gives the proportion between the numbers of adults in each patch as $1 : 3$.

In Figure 3.4, the overall behaviours of two cases seem similar regardless of density dependency. As migration rate m increases, the population in small patch, which is shown as blue line, increases and the population in big patch, green line, decreases. The total population of entire system seems unchanging. Since the migration rate m is given as constant, the big patch lose its population constantly but the influx from small patch is always smaller than its efflux. For the small patch, vice versa.

However, there is very important difference between two cases. The total number adults in the system is slightly changed because of migration. For the case $\beta = 0.2$, the total number of adults (red line) shows a slight decrease as migration rate increases. This indicates that the influx from big patch is too large to support for the small patch. The larvae from immigrants make the density in the small patch higher. This causes the strong competition between larvae. As an overall effect to two-patch system, the total number of adults decreases even though the adult population in small patch increases. On the other hand, for the case $\beta = 1.0$, the observed is a slight increase of total number of adults in the system. This is a counter effect of the density dependence. In this case, the mortality function is linearly depend on the larval density. Larval mortality responds to the change of density too strong. This enables the system

has a low population so that each patch can support. The pressure experienced in the small patch due to immigration from the big patch is demonstrated by sharp reduction in the larval survival in the small patch as the migration rate increases (See Appendix E.). However, the larval survival in the big patch increases due to lower population pressure. This counteracts the loss of offspring in the small patch with the overall result that the meta-population size is not greatly affected by increased migration.

The density dependence mortality becomes more important when we consider the migration in the heterogenous environment. As we have seen previous results, when the density dependence is too strong, the effect of the migration cannot have a critical role to change entire system's behaviour. In real ecosystem, the density dependence cannot be too high to be independent from migration. In the case of $\beta = 1.0$, the mortality function increases linearly. This cannot be a proper description for the real ecosystem. From the previous study, the proper value of β is required.

Chapter 4

Two-patch model with *Wolbachia*

In this chapter, we explore the effect of spatial subdivision of the mosquito population on the dynamics of *Wolbachia* infection. This analysis involves extending the two-patch model to include *Wolbachia* infection. We assume in this analysis that *Wolbachia* infection is introduced into the mosquito population via immigration of *Wolbachia* infected adults from an external source. The population dynamics are given as following:

$$L_W^i(t,l) = \frac{\lambda_w}{2}(1-\omega)\tilde{S}_W^i(t-l)\theta_{L,W}^i(t,l), \quad l \leq T_W, \tag{4.1a}$$

$$L_U^i(t,l) = [1 - s_h p_i(t-l)]\left[\frac{\lambda_u}{2}\tilde{S}_U^i(t-l) + \omega\frac{\lambda_w}{2}\tilde{S}_W^i(t-l)\right]\theta_{L,U}^i(t,l), \quad l \leq T_U, \tag{4.1b}$$

$$S_W^i(t,a) = \left(L_W^i(t-a,T_W) + I_W^i\right)\theta_{S,W}^i(a)\theta_M^i(a) + m_{ij}\int_0^a S_W^j(t-\xi,a-\xi)\theta_S^i(\xi)\theta_M^i(\xi)d\xi, \tag{4.1c}$$

$$S_U^i(t,a) = L_U^i(t-a,T_U)\theta_{S,U}^i(a)\theta_M^i(a) + m_{ij}\int_0^a S_U^j(t-\xi,a-\xi)\theta_S^i(\xi)\theta_M^i(\xi)d\xi, \tag{4.1d}$$

where each superscript(i.e. i, j) indicates the index of each patch. In equation (4.1.c), the term of *Wolbachia* introduction is included for considering the biological control strategies. In the equation, the *Wolbachia* infected adults are introduced onto each other patch at a constant rate $I_W^{i/j}$. In the aspects of strategies, introduction of infected mosquitoes could be different for each patch.

Two-patch model of *Wolbachia* with constant adult-mortality and migration

For simplicity, we assume age-independent adults mortality and the constant rate of migration between two patches as the previous chapter. With the exponentially decaying probability of survival, equations (4.1.c,d) becomes simpler.

$$S_W^i(t,a) = \left(L_W^i(t-a,T_W) + I_W^i\right)e^{-(c+m)a} + m\int_0^a S_W^j(t-\xi,a-\xi)e^{-(c+m)\xi}d\xi, \tag{4.2a}$$

$$S_U^i(t,a) = L_U^i(t-a,T_U)e^{-(c+m)a} + m\int_0^a S_U^j(t-\xi,a-\xi)e^{-(c+m)\xi}d\xi. \tag{4.2b}$$

From equation (4.2), the age-distribution of each class of adults can be obtained by conducting the same analytical method as in previous section.

$$S_W^i(t,a) = \left[\cosh(ma)\left(L_W^i(t-a,T_L)+I_W^i\right)+\sinh(ma)\left(L_W^j(t-a,T_L)+I_W^j\right)\right]e^{-(c+m)a} \quad (4.3)$$

$$S_U^i(t,a) = \left[\cosh(ma)L_U^i(t-a,T_L)+\sinh(ma)L_U^j(t-a,T_L)\right]e^{-(c+m)a}. \quad (4.4)$$

Despite understanding the effects of migration, there are 8 different equations with 8 variables. Because of the complexity of the coupled equations, it is not analytically tractable. For these equations, we present the numerical results of the model.

The most important measure in the dynamics of the two-patch model with *Wolbachia* could be the meta-infection frequency. The meta-infection frequency is defined as,

$$p_M(t) \equiv \frac{\tilde{S}_W^T(t)}{\tilde{S}_U^T(t)+\tilde{S}_W^T(t)} = \frac{\tilde{S}_W^i(t)+\tilde{S}_W^j(t)}{\tilde{S}_U^i(t)+\tilde{S}_U^j(t)+\tilde{S}_W^i(t)+\tilde{S}_W^j(t)}. \quad (4.5)$$

This meta-infection frequency gives information about how quickly the *Wolbachia* spreads through the host population in a heterogeneous environment. The infection frequency of each patch is denoted as $p_{i/j}(t) = \frac{\tilde{S}_W^{i/j}(t)}{\tilde{S}_U^{i/j}(t)+\tilde{S}_W^{i/j}(t)}$. From these infection frequencies, we can see the dynamics of *Wolbachia* instead of mosquito populations.

In Figure 4.1, the numerical results of meta-frequencies are given for different migration rates. In this figure, two different cases are plotted. (1)The case that two identical patches (top) with sizes $\alpha_1 = \alpha_2 = 0.1/2^{0.2}$. (2) Two patches with different sizes, $1:3$ nutrient system (i.e. $\alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2}$). These α values are chosen as same amount of nutrients for entire system and equally and unequally distributed for each case. The rest of parameters are equivalent for two patches. For the introduction rate, $I_W^{i/j} = 0.05$ is used and the releasing started at $t = 400$ after stabilizing the uninfected mosquito population. This value of introduction rate I_W is chosen to be enough to spread to the host population(i.e. $I_W^{i/j} > I_{Wc}$ where I_{Wc} is the minimum rate of introduction required for *Wolbachia* to invade the uninfected population.).

In the top figure, we show the meta-infection frequencies when the two patches are identical. The conditions are the same for each patch. The meta-infection frequencies show almost same behaviour regardless of migration. In the bottom figure, the case of the system with different patches shows different results to the identical case. The red line in the figure shows the case of the absence of migration. The isolation of the two patches implies the bacteria are spreading in each patch independently. The red curve of $p_M(t)$ is not smooth and there is a hump near $t \approx 700$ because of an effect of isolation. This shows the *Wolbachia* quickly spread in the small patch first and then, spread to the second patch. This
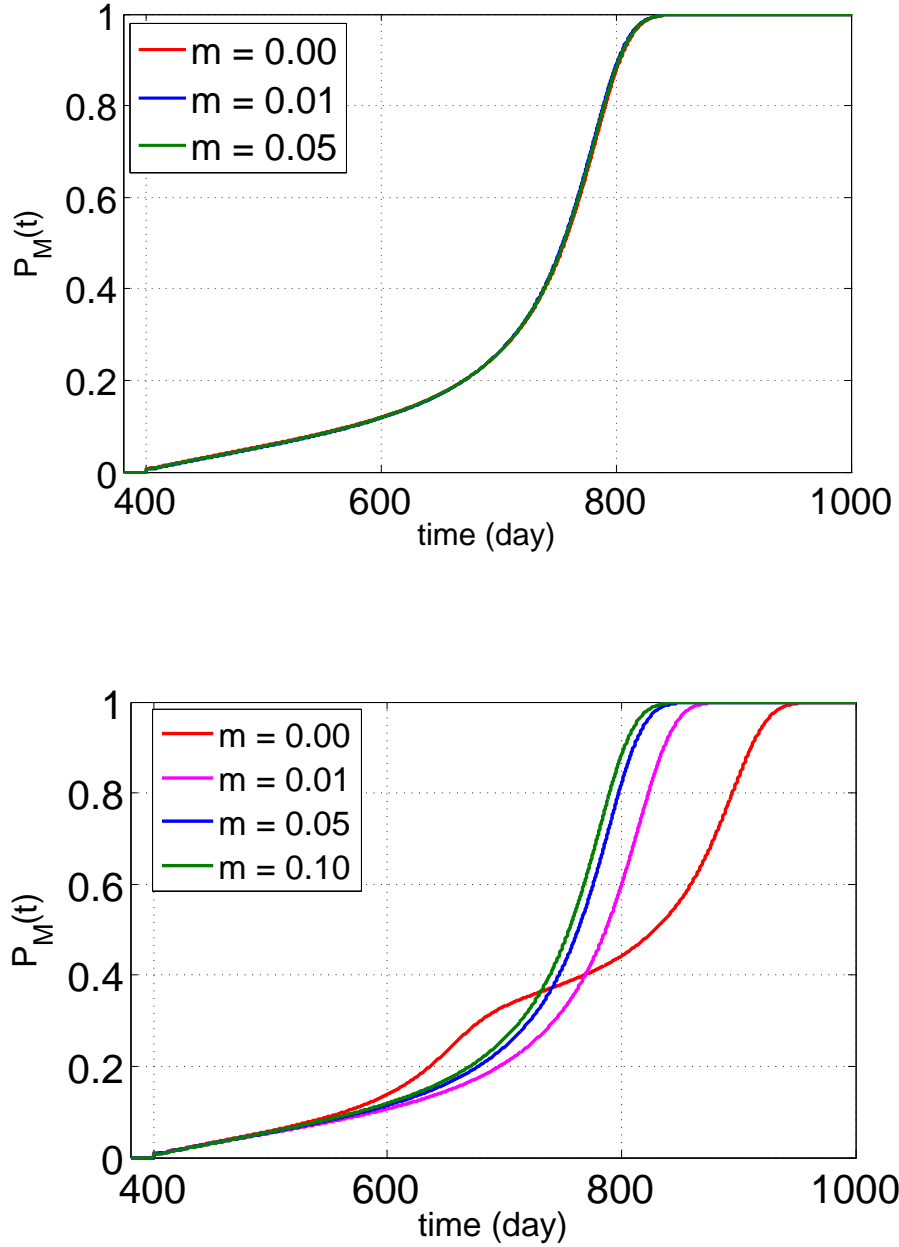
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Figure 4.1: Time evolution of the meta-infection frequencies $p_M(t)$ for the two different cases with different migration rate. Used parameters are $\lambda_U = 15, T_L = 10, \mu = 0.1, \beta_{1/2} = 0.2, c = 0.1, s_f = 0.05, s_h = 0.99$, and $\omega = 0.01$. Infected mosquitoes starts being released at $t = 400$ with the constant introduction rate $I_W = 0.05$ to each patch. (1) The case that two identical patches (top) with sizes $\alpha_1 = \alpha_2 = 0.1/2^{0.2}$. (2) The case that patches with nutrient proportion 1:3 (bottom) with sizes $\alpha_1 = 0.1$ and $\alpha_2 = 0.1/3^{0.2}$.
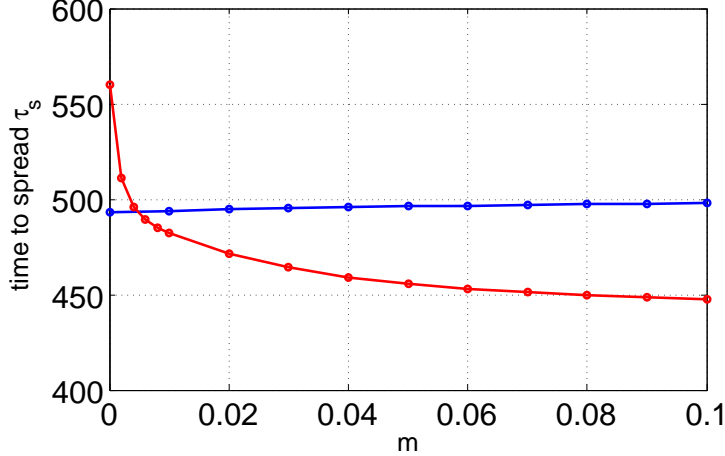
Figure 4.2: Time to spread τ_s(bottom) for different migration rate with parameters, $\lambda_U = 15, T_L = 10, \mu = 0.1, \beta_{1/2} = 0.2, c = 0.1, s_f = 0.05, s_h = 0.99$, and $\omega = 0.01$. Infected mosquitoes starts being released at $t = 400$ with the constant introduction rate $I_W = 0.05$ to each patch. The case that two identical patches (blue line) with sizes $\alpha_1 = \alpha_2 = 0.1/2^{0.2}$. The case that patches with nutrient proportion 1:3 (red line) with sizes $\alpha_1 = 0.1$ and $\alpha_2 = 0.1/3^{0.2}$. The threshold of frequency p_{th} is defined as 0.999.

is because the carrying capacity of the patch and the rate of introduction are fixed. However, if the migration factor is considered, the *Wolbachia* infection frequency in meta level becomes smooth function and the spread becomes more faster.

In order to quantify the speed of spread of *Wolbachia*, another interesting measure could be the time to spread through the entire system. We define the time to spread τ_s as

$$\tau_s \equiv \min\{\, t \mid p_M(t) > p_{th}\} \tag{4.6}$$

where p_{th} is the threshold value that we can vary. τ_s indicates the time to spread of *Wolbachia* to the entire system after releasing infected adults to uninfected patches. In Figure 4.2, the changes of the time to spread for different migration rates are plotted. In this simulation, we use the threshold of frequency as $p_{th} = 0.999$. When the patches are identical, the time to spread slightly increases but there is not remarkable change. On the other hand, when the patches are different, the time to spread shows rapid decrease as soon as migration added to each patch. When the migration is high enough, heterogenous system shows more faster spreads than identical patch because the small patch acts as an extra source of *Wolbachia* introduction into the big patch once spread occurs in the small patch.

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Chapter 5

Discussion and Conclusions

In previous chapters, we have seen the two-patch model, which includes the heterogenous of the sub-division, the form of density-dependent regulation, and rates of migration between the patches. From this model, we obtain the results that spatial subdivision and migration affect the mosquito population dynamics and the dynamics of *Wolbachia*. Because of subdivision, the population dynamics with no *Wolbachia* shows that the number of adult population goes down. This effect depends on the nature of the density dependent competition operating in the larval stage. Effects of subdivision on *Wolbachia* dynamics are increases of the rate of *Wolbachia* spread. In a heterogenous system with different size of patches, greater migration between patches can lead to faster spread. This analysis will be important to predicting the dynamics of *Wolbachia* when used as a strategy for controlling mosquito-bone diseases.

The strategy for introducing *Wolbachia* infected mosquitoes to the patch is aimed at attaining fast spreads of the bacteria in the target population system. From the perspective of the experiment, we compare three strategies of releasing infected mosquitoes. (1) Introducing *Wolbachia* with same rate to each patch (i.e. $I_W^1 = I_W^2$). In this strategy, we do not need to consider about properties of patches for releasing, such as carrying capacity. (2) Introducing the bacteria only in the big patch (i.e. $I_W^1 = 0, I_W^2 > 0$, when $\alpha 1 > \alpha_2$.). This strategy is considered because the big patch can affect to the small patch easily through migration. (3) Introducing the bacteria to the small patch (i.e. $I_W^1 > 0, I_W^2 = 0$, when $\alpha 1 > \alpha_2$.). This strategy can be helpful to attain an infected patch as soon as possible. The small patch can easily get the threshold of infection frequency because of relatively small population in the patch. The second and the third strategies require information about patches. This means that, in order to release *Wolbachia*, we need to find out which patch is smaller or bigger.

In Figure 5.1, the schematics of three different model systems are given. According to the subdivision method (see Appendix C), three representative systems are chosen. a) A single patch with the amount of nutrients N_s and the carrying capacity α_s. b) An identical two-patch system that each patch has the half
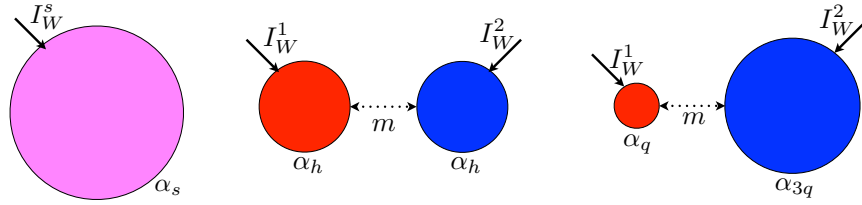
Figure 5.1: The schematics of three different cases.
From left to right, (a) A single system, (b) A half-system, (c) A quarter-system.

of nutrients for single system, $\frac{N_s}{2}$ (i.e $\alpha_1 = \alpha_2 = \alpha_h$ or $\frac{N_s}{2} = N_1 = N_2$, which we call a half-system). c) A heterogeneous two-patch system(i.e. $\alpha_1 \neq \alpha_2$) that the nutrients are divided to $1:3$ for each. We set $\frac{N_s}{4} = N_1 = \frac{N_2}{3}$, which we call a quarter-system. In the numerical calculation, we set $\alpha_s = \frac{0.1}{4^{0.2}}$, $\alpha_h = \frac{0.1}{2^{0.2}}$, $\alpha_q = 0.1$ and $\alpha_{3q} = \frac{0.1}{3^{0.2}}$ and $\beta = 0.2$.

The numerical results for the comparison of meta-infection frequencies for different strategies are given in Figure 5.2. The results show the most effective strategy when we are using the same amount of infected mosquitoes to release. The top figure illustrates the meta-infection frequencies of the half-system for different strategies and the below figure is the results of the quarter-system. In both results, we allow the migration between patches with migration rate $m = 0.05$.

In Figure 5.2, the black dot-dashed lines show the $p_M(t)$ of single-patch system with $I_W^s = 0.1$. These lines are added as a reference in the homogenous system. The green, blue, red lines indicates the different strategies, (1) the two-patch system with same introduction rate, $I_W^1 = I_W^2 = 0.05$, (2) the two-patch system with big patch introducing, $I_W^1 = 0$ and $I_W^2 = 0.1$, (3)the two-patch system introduction to the small patch, $I_W^1 = 0.1$ and $I_W^2 = 0$, respectively.

In the top figure, the half-system case, the spreads of *Wolbachia* are almost the same as a single-patch system even though the patches are subdivided and strategies are different. If the two patches are identical, migration is no longer important to the mosquitoes because the conditions in the patch, such as mortality rates, the amount of nutrients are the same in each patch. From this, we can expect that many identical patches can be interpreted as a homogenous system if the patches are connected to each other with constant migration rate.

In the bottom figure, the results of quarter-system case are given. The meta-infection frequencies show the different behaviour for the different strategies. For the strategy (1) (green), the spread of *Wolbachia* is not as fast as in single-patch system. Even though the nutrients are separated, the small patch is too small to support introduced mosquitoes. The density-dependent mortality kills the larvae from introduced mosquitoes. If there is no migration between patches, the spread time would be the longest
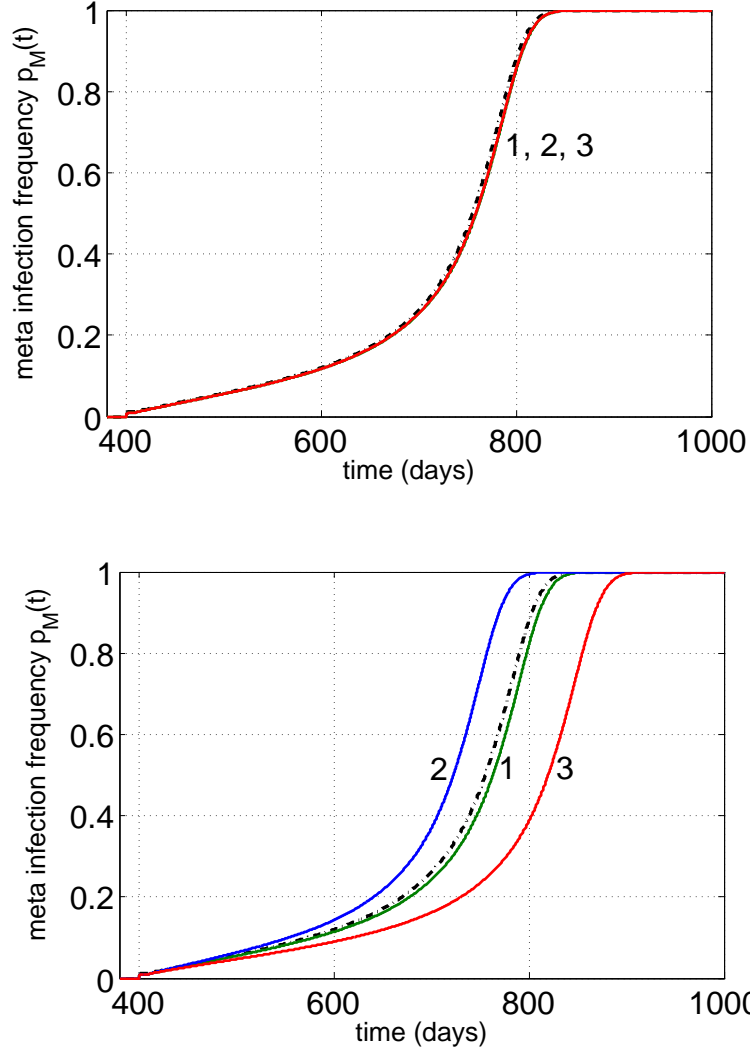
Figure 5.2: Meta infection frequencies $p_M(t)$ for different strategies. On the top, the result of the half-system is given with patch sizes, $\alpha_1 = \alpha_2 = 0.1/2^{0.2}$. On the bottom, the result of the quarter-system is given with $\alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2}$. Other parameters are chosen as $\lambda_U = 15, T_L = 10, \mu = 0.1, \beta = 0.2, c = 0.1, s_f = 0.05, s_h = 0.99$, and $\omega = 0.01$. Migration between patches are allowed with the constant rate $m = 0.05$. Infected mosquitoes start being released at $t = 400$ with the different introduction rate for each strategies. The black dot-dashed lines show the $p_M(t)$ of single-patch system with size $\alpha_s = 0.1/4^{0.2}$. This inverse carrying capacity gives the same amount of nutrients as other two systems. The introduction rate to the single patch is $I_W^s = 0.1$. The green lines do the two-patch system with same introduction rate, $I_W^1 = I_W^2 = 0.05$ (i.e. Strategy (1)), the blue lines do the two-patch system with big patch introducing, $I_W^1 = 0$ and $I_W^2 = 0.1$ (i.e. Strategy (2)), and the red lines do the two-patch system with small patch introducing, $I_W^1 = 0.1$ and $I_W^2 = 0$ (i.e. Strategy (3)).

because many mosquitoes that introduced as strategies to small patch would be killed in larval stage. For the strategy (2) (blue), the spread of *Wolbachia* occurs relatively fast compared other strategies. The patch, which is referred as a big patch, has the size of 3/4 of the single patch. For the bacteria, this implies that this system is more easier to conquer than single-patch system and the spread to the small patch can be attained easily because of migration. Lastly, for the strategy (3), this shows slow spreads to the meta system. As we mentioned before, since the density dependent mortality regulates the population size, the introduced mosquitoes cannot make many larvae in the small patch. Not like strategy (2), larvae of introduced mosquitoes will be killed in the small patch. For the *Wolbachia*, avoiding density dependent mortality and conquering the big patch could be the best strategy to be spread for entire system. As a strategy for spreading *Wolbachia* to the mosquito population, introducing the infected mosquitoes to the biggest patch can be the best strategy when we are able to access the information of the patches, for example, carrying capacity or amount of nutrients.

In conclusion, we have shown that the spatially heterogeneous environment can affect to the population dynamics of mosquitoes and the dynamics of *Wolbachia* spread. The migration between different patches and the density dependent mortality are highly connected to each other. Because of migration, the mosquitoes can moved to another better patch to survive. Furthermore, because of migration, the larvae from the emigrating mosquitoes can cause the increase of larval density in the patch and the high larval density induces the high mortality to the larvae. An understanding of these factors from the two-patch model is critical to analyze the real ecosystem. To approach to the real ecosystem, the modelling on the multi-patch system is required. Analysis of multi-patch systems will be complicated and the dynamics will be influenced by the processes that we have identified as important in this two patch analysis. These include the heterogenous of the subdivision, the form of density-dependent regulation, and rates of migration between the patches. From this two-patch model, we can expect the mechanisms that this study has identified to be amplified in a multi-patch network model. In the multi-patch model, heterogeneity and inter-patch migration will be even more important because there will be feedback effects in a multi-patch system.

Appendix A

Single-patch model without *Wolbachia*

Here I derive the equilibrium of the numbers of larvae and adults in single-patch model without *Wolbachia*.

At the equilibrium, the dynamic equations (2.5) have to be satisfied

$$L^*(l) = \frac{\lambda}{2}\tilde{S}^*\theta_L^*(l), \tag{A.1a}$$

$$S^*(a) = L^*(T_L)\theta_S(a). \tag{A.1b}$$

Taking the integration over all the ages(i.e $\int_0^\infty da$) of equation (A.1b), one can obtain an expression of $\tilde{S}^*$,

$$\tilde{S}^* = L^*(T_L)\Theta_S \tag{A.2}$$

where $\Theta_S = \int_0^\infty \theta_S(a)da$, which is average adult lifetime. At the last stage of larvae $l = T_L$, the probability of larval survival at the equilibrium can be given by using equation (A.1a).

$$\theta_L^*(T_L) = \frac{2L^*(T_L)}{\lambda\tilde{S}^*} = \frac{2}{\lambda\Theta_S}. \tag{A.3}$$

This implies the probability of larval survival at equilibrium is the reciprocal of expected lifetime production of adult female. On the other hand, this larval survival probability can be obtained analytically as following[14].

$$\begin{aligned}
\theta_L^*(T_L) &= \exp\left(-\int_{t-T_L}^t \mu_L(\tilde{L}^*)d\tau\right) \\
&= \exp\left(-\int_{t-T_L}^t \mu + \alpha\tilde{L}^{*\beta}d\tau\right) \\
&= \exp\left(-(\mu + \alpha\tilde{L}^{*\beta})T_L\right) \tag{A.4}
\end{aligned}$$

From the equivalence between equation (A.3) and (A.4), total number of larvae at the equilibrium is obtained as

$$\tilde{L}^* = \left[\frac{1}{\alpha T_L}\ln\left(\frac{\lambda\Theta_S}{2}e^{-\mu T_L}\right)\right]^{1/\beta}. \tag{A.5}$$

L^* also can be obtained from the integration over all stage l of the $L^*(l)$.

$$
\begin{aligned}
\tilde{L}^* = \int_0^{T_L} L^*(l)dl &= \frac{\lambda \tilde{S}^*}{2} \int_0^{T_L} \theta_L^*(l)dl \\
&= \frac{\lambda \tilde{S}^*}{2} \int_0^{T_L} e^{-\int_{t-l}^t \mu + \alpha \tilde{L}^{*\beta} d\tau} dl \\
&= \frac{\lambda \tilde{S}^*}{2} \int_0^{T_L} e^{-l(\mu + \alpha \tilde{L}^{*\beta})} dl \\
&= \frac{\lambda \tilde{S}^*}{2} \left(\frac{1 - e^{-(\mu + \alpha \tilde{L}^{*\beta})T_L}}{\mu + \alpha \tilde{L}^{*\beta}} \right).
\end{aligned}
\tag{A.6}
$$

From equation (A.6), the relation between total number of larvae and adults is given.

$$
\tilde{S}^* = \frac{2\tilde{L}^*}{\lambda \Theta_{LD}}
\tag{A.7}
$$

where $\Theta_{LD} \equiv \int_0^{T_L} \theta_L^*(l)dl = \frac{1 - e^{-(\mu + \alpha \tilde{L}^{*\beta})T_L}}{\mu + \alpha \tilde{L}^{*\beta}}$, which is average larval lifetime.

Appendix B

Single-patch model with *Wolbachia*

Here I derive the equilibrium of the numbers of larvae and adults in single-patch model with *Wolbachia*.

At the equilibrium, the dynamic equations (2.8) can be written as

$$L_W^*(l) = \frac{\lambda_W}{2}(1-\omega)\tilde{S}_W^*\theta_{L,W}^*(l), \quad l \leq T_W, \tag{B.1a}$$

$$L_U^*(l) = [1 - s_h p^*]\left[\frac{\lambda_U}{2}\tilde{S}_U^* + \omega\frac{\lambda_W}{2}\tilde{S}_W^*\right]\theta_{L,U}^*(l) \quad l \leq T_U, \tag{B.1b}$$

$$\tilde{S}_W^* = L_W^*(T_W)\int_0^\infty \theta_{S,W}(a)da = L_W^*(T_W)\Theta_W, \tag{B.1c}$$

$$\tilde{S}_U^* = L_U^*(T_U)\int_0^\infty \theta_{S,U}(a)da = L_U^*(T_U)\Theta_U. \tag{B.1d}$$

By substituting equation (B.1a) to (B.1c), the expression of $\theta_{L,W}^*(T_W)$ is given.

$$S_W^* = \frac{\lambda_W}{2}(1-\omega)\tilde{S}_W^*\theta_{L,W}^*(T_W)\Theta_W, \tag{B.2}$$

$$\theta_{L,W}^*(T_W) = \frac{2}{\lambda_W(1-\omega)\Theta_W} \quad \text{iff} \quad S_W^* \neq 0. \tag{B.3}$$

Next, substitute equation (B.1b) to (B.1d) to give

$$S_U^* = (1 - s_h p^*)\left[\frac{\lambda_U}{2}\tilde{S}_U^* + \omega\frac{\lambda_W}{2}\tilde{S}_W^*\right]\theta_{L,U}^*(T_U)\Theta_U. \tag{B.4}$$

The relative decrease of parameters, which is caused by *Wolbachia* infection can be expressed with relative constants.

$$\lambda_W = (1 - s_f)\lambda_U \tag{B.5}$$

$$\Theta_W = (1 - s_g)\Theta_U \tag{B.6}$$

$$\theta_{L,W}^*(T_W) = (1 - s_d)\theta_{L,U}^*(T_U) \tag{B.7}$$

Substitute equation (B.3) to (B.4)

$$\tilde{S}_U^* = \frac{2(1 - s_h p^*)}{(1 - \omega)(1 - s_d)(1 - s_f)(1 - s_g)} \left[\frac{1}{2} \tilde{S}_U^* + \omega \frac{1}{2}(1 - s_f)\tilde{S}_W^* \right]. \tag{B.8}$$

From dividing by the total number of adults at equilibrium, $\tilde{S}_U^* + \tilde{S}_W^*$, one can get simple quadratic equation of p^*

$$1 - p^* = \frac{(1 - s_h p^*)\left[1 - p^* + \omega(1 - s_f)p^*\right]}{(1 - \omega)(1 - s_d)(1 - s_f)(1 - s_g)} \tag{B.9}$$

Solving equation (B.9) gives fixed points of infection frequency p^*,

$$p^* = \frac{s_h + A - B \pm \sqrt{(s_h + A - B)^2 - 4s_h A(1 - B)}}{2s_h A} \tag{B.10}$$

where $A = 1 - \omega(1 - s_f)$ and $B = (1 - \omega)(1 - s_d)(1 - s_f)(1 - s_g)$. When there is no *Wolbachia* infection-effect on average life-time (i.e. $s_d = 0$ and $s_g = 0$), B becomes $(1 - \omega)(1 - s_f)$ and equation (B.10) has the same result with Turelli model[9] . At equilibrium, one can obtain the total number of infected and uninfected larvae and adults by integrating equations (B.1a,b) over entire stages(i.e. $\int_0^{T_{W/U}} dl$). For the larvae,

$$\tilde{L}_W^* = \frac{\lambda_W}{2}(1 - \omega)\tilde{S}_W^* \theta_{L,W}^*, \tag{B.11a}$$

$$\tilde{L}_U^* = (1 - s_h p^*)\left[\frac{\lambda_U}{2}\tilde{S}_U^* + \omega\frac{\lambda_W}{2}\tilde{S}_W^*\right]\theta_{L,U}^* \tag{B.11b}$$

Summation equations (B.11a,b) and substitution $\tilde{S}_U^* = \frac{1 - p^*}{p^*}\tilde{S}_W^*$ give

$$\tilde{S}_W^* = \frac{2p^* L_T^*}{(1 - s_h p^*)(\lambda_U(1 - p^*) + \omega\lambda_W p^*)\theta_{L,U}^* + \lambda_W(1 - \omega)p^*\theta_{L,W}^*} \tag{B.12}$$

where the total number of larvae, $\tilde{L}_T^* = \tilde{L}_W^* + \tilde{L}_U^*$. From equation (B.3), $\tilde{L}_T^*$ can be obtained. If the probability of infected larval survival is given as

$$\theta_{L,W}(t,l) = \exp\left(-\int_{t-l}^t \mu_W + \alpha_W(\tilde{L}_T(t))^{\beta_W} d\tau\right), \tag{B.13}$$

which has the same mortality function with parameters μ_W, α_W and β_W, at equilibrium, $\theta_{L,W}^*(T_W)$ is

$$\theta_{L,W}^*(T_W) = \frac{2}{\lambda_W(1 - \omega)\Theta_W} = e^{-(\mu_W + \alpha_W(\tilde{L}_T^*)^{\beta_W})T_W}. \tag{B.14}$$

Thus, the total number of larvae is

$$\tilde{L}_T^* = \left[\frac{1}{\alpha_W T_W}\ln\left(\frac{\lambda_W(1 - \omega)\Theta_W}{2}e^{-\mu_W T_W}\right)\right]^{1/\beta_W} \tag{B.15}$$

By substituting p^*, equation (B.10), and equation (B.15), the exact value of $\tilde{S}_W^*$ can be obtained.

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Appendix C

Subdivision of the system

If we assume that the characteristics of mosquitoes are the same for different patches, in other words, the expected life spans Θ_S, the fertility λ, the mortality μ, and the time of development of larvae T_L are given from the species, then the properties of patches are given from just two parameters α and β. From equation (2.6), the function of nutrients $N(\alpha, \beta)$ can be written as

$$N(\alpha, \beta) = n_0 \left[\frac{1}{\alpha} \right]^{1/\beta} \tag{C.1}$$

where n_0 is constant which indicates the characteristics of insects. In the two-patch model, without migration, the total amount of nutrients could be an extensive quantity, which means the amount of nutrients is additive.

$$
\begin{aligned}
N_{\text{tot}} &= N_1(\alpha_1, \beta_1) + N_2(\alpha_2, \beta_2) \\
&= n_0 \left[\frac{1}{\alpha_1} \right]^{1/\beta_1} + n_0 \left[\frac{1}{\alpha_2} \right]^{1/\beta_2} .
\end{aligned} \tag{C.2}
$$

By using the above equations, one can find a comparable two-patch model to a single-patch model. When the reciprocal of carrying capacity for each patches are given as α_1 and α_2 and the density dependence is the same $\beta_1 = \beta_2 = \beta$, the single-patch system with the same amount of nutrients as the two-patch system is obtained as

$$\alpha_s = \frac{\alpha_1 \alpha_2}{\left(\alpha_1^\beta + \alpha_2^\beta \right)^{1/\beta}} \tag{C.3}$$

where α_s is the reciprocal carrying capacity of the single-patch.

By using equation (C.3), we set the three different cases with same amount of nutrients: 1) A single patch, 2) An identical two-patch system (i.e $\alpha_1 = \alpha_2$ or $\frac{N_s}{2} = N_1 = N_2$, which we call a half-system) and 3) A heterogeneous two-patch system(i.e. $\alpha_1 \neq \alpha_2$). We set $\frac{N_s}{4} = N_1 = \frac{N_2}{3}$, which we call a quarter-system. In the numerical calculation, we set $\alpha_1 = 0.1$ and $\beta = 0.2$.
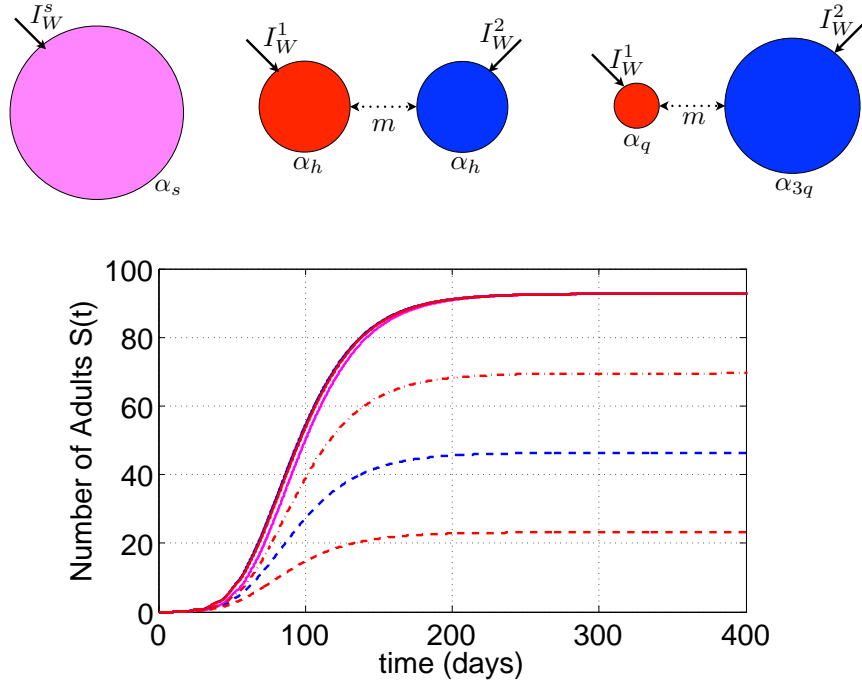
Figure C.1: Numerical results of the time evolution of the total number of adults in different patched system. The parameters are $\lambda_U = 15, T_L = 10, \mu = 0.1, \beta = 0.2, c = 0.1, I_W^i = 0$ and $m = 0.0$ (without migration). The pink solid line indicates the total(meta) population of adults in single-patch system, the blue one does the half-system, and the red one does the quarter-system. The dashed lines show the total number of adults for each patch.

In Figure C.1, the numerical result of time evolution of total number of adults are given. The pink solid line indicates the total number of adults in the single-patch model. For the half-system case, which is shown as blue lines, the population in each patch is exactly half of meta population, the blue dashed line. For the quarter system, the red lines, the proportion as the population between patches are given as $1:3$, which is the same proportion of the amount of nutrients. From these results, we can observe the several different and comparable cases of spatial heterogeneity.

Appendix D

Two-patch model without *Wolbachia*

D.1 The adult population for each patch

By putting the expression of $S_i(t - \xi - \xi_1, a - \xi - \xi_1)$,

$$S_i(t - \xi - \xi_1, a - \xi - \xi_1) = L_i(t - a, T_L)e^{-(c+m)(a-\xi-\xi_1)} + m(a - \xi - \xi_1)L_j(t - a, T_L)e^{-(c+m)(a-\xi-\xi_1)}$$
$$+ m^2 \int_0^{a-\xi-\xi_1} \int_0^{a-\xi-\xi_1-\xi_2} S_i(t - \xi - \xi_1 - \xi_2 - \xi_3, a - \xi - \xi_1 - \xi_2 - \xi_3)e^{-(c+m)(\xi_2+\xi_3)}d\xi_3 d\xi_2,$$

to equation (3.9), a new expression for the number of adults can be obtained because a change of integral variables gives always same form of integration. Keeping successive substitutions to the expression of $S_i(t, a)$ to itself gives the final expression of the age distribution of adults for each patch.

$$
\begin{aligned}
S_i(t, a) &= L_i(t - a, T_L)e^{-(c+m)a} \sum_{n=0}^{\infty} \frac{(ma)^{2n}}{(2n)!} + L_j(t - a, T_L)e^{-(c+m)a} \sum_{n=0}^{\infty} \frac{(ma)^{2n+1}}{(2n+1)!} && \text{(D.1)} \\
&= \cosh(ma)L_i(t - a, T_L)e^{-(c+m)a} + \sinh(ma)L_j(t - a, T_L)e^{-(c+m)a}. && \text{(D.2)}
\end{aligned}
$$

The time evolution of the number of adults with age a at given time is determined by the numbers of newborns for each patch at time $t - a$.

D.2 Equilibrium distribution for each patch

Here I derive the equilibrium of the numbers of larvae and adults in two-patch model without *Wolbachia*. At the equilibrium, the dynamic equations (3.9) have to be satisfied

$$
\begin{aligned}
L_i^*(l) &= \frac{\lambda}{2} \tilde{S}_i^* \theta_L^{i*}(l), \quad l \le T_L, && \text{(D.3a)} \\
S_i^*(a) &= L_i^*(T_L)e^{-(c+m)a} + maL_j^*(T_L)e^{-(c+m)a} \\
&\quad + m^2 \int_0^a \int_0^{a-\xi} S_i^*(a - \xi - \xi_1)e^{-(c+m)(\xi+\xi_1)}d\xi_1 d\xi. && \text{(D.3b)}
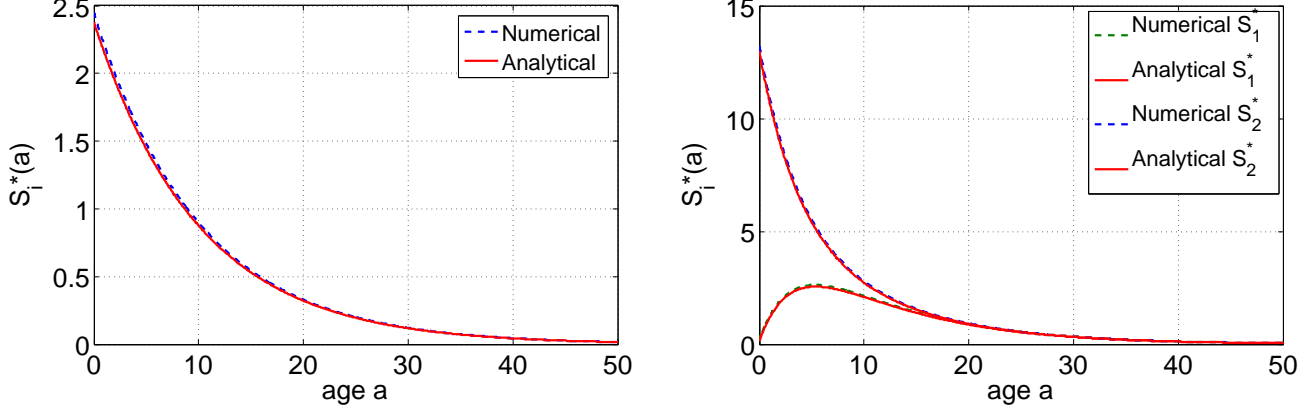\end{aligned}
$$

Figure D.1: The comparison between analytical results, equation (D.6), and numerical results for the age distribution of the number of adults for each patch. Above graph is the age distribution for equal size patches. Below graph is the age distribution for different size of patches. Green dashed line indicates the number of adults in small patch and blue dashed line is the number of adults in big patch.

By changing integration variable $x = a - \xi - \xi_1$ in equation (D.3b), one can get new expression of the number of adults at equilibrium.

$$
\begin{aligned}
S_i^*(a) &= L_i^*(T_L)e^{-(c+m)a} + maL_j^*(T_L)e^{-(c+m)a} \\
&\quad + m^2 e^{-(c+m)a} \int_0^a \int_0^{a-\xi} S_i^*(x)e^{(c+m)x} dx d\xi
\end{aligned}
\tag{D.4}
$$

$$
S_i^*(a)e^{(c+m)a} = L_i^*(T_L) + maL_j^*(T_L) + m^2 \int_0^a \int_0^{a-\xi} S_i^*(x)e^{(c+m)x} dx d\xi.
\tag{D.5}
$$

By solving the integral equation (D.5), one can get a solution of age-distribution function of the number of adults at equilibrium:

$$
\begin{aligned}
S_i^*(a)e^{(c+m)a} &= \frac{1}{2}\left[(L_i^*(T_L) + L_j^*(T_L))e^{ma} + (L_i^*(T_L) - L_j^*(T_L))e^{-ma}\right] \\
S_i^*(a) &= \left[\cosh(ma)L_i^*(T_L) + \sinh(ma)L_j^*(T_L)\right]e^{-(c+m)a}.
\end{aligned}
\tag{D.6}
$$

This equation agrees with equation (D.2), which is obtained from the condition of the age-distribution at time t. In equation (D.6), the numbers of larvae at the equilibrium, $L_{i/j}^*(T_L)$, are not analytically determined yet. In order to get a analytic result for the larvae, one should solve the coupled equation. However, because of complexity of coupled nonlinear equations, it is hart to obtain analytically.

Appendix E

The larval survival probability and the average lifetime of larvae

The larval survival probability $\theta_L^{i*}(T_L) = e^{-(\mu + \alpha_i \tilde{L}_i^{*\beta})T_L}$ and the average larval life time $\theta_{LD}^{i*} = \int_0^{T_L} \theta_L^{i*}(l)dl = \frac{1 - e^{-(\mu + \alpha_i \tilde{L}_i^{*\beta})T_L}}{\mu + \alpha_i \tilde{L}_i^{*\beta}}$ can be considered. In Figure E.1, the numerical results of larval survival probability $\theta_L^{i*}(T_L)$ (left) and the average larval life time θ_{LD}^{i*} (right) are given at equilibria for various migration rate m. Solid lines and dot-dashed lines are the case of $\beta = 0.2$ and $\beta = 1.0$, respectively. Green lines are the results of the big patch and blue lines are the results of the small patch. Red lines show the single-patch system (i.e. In the single patch system, the larval survival probability is fixed as $\theta_L^*(T_L) = \frac{2c}{\lambda}$, regardless of values of α and β (see Appendix A).). When $\beta = 0.2$, The larval survival probability in small patch rapidly decreases as migration rate increases. This is because of the influx from the big patch.
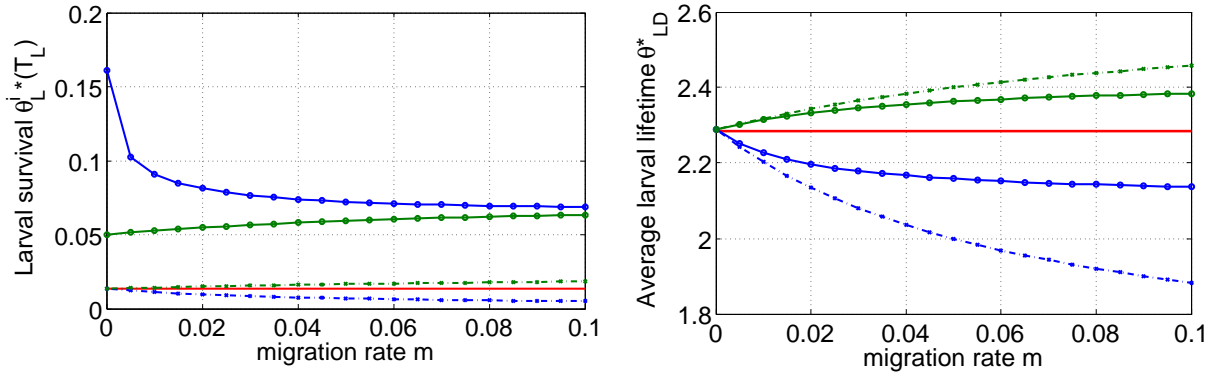

Figure E.1: The larval survival probability $\theta_L^{i*}(T_L)$ (left) and the average larval life time θ_{LD}^{i*} (right). Equation (3.9) is used with parameters, $\lambda_U = 15, T_L = 10, \mu = 0.1$, and $c = 0.1$. The solid lines with circles are the case of $\alpha_1 = 0.1, \alpha_2 = 0.1/3^{0.2} \approx 0.0802, \beta_{1,2} = 0.2$, and the dot-dashed lines are the case of $\alpha_1 = 0.1, \alpha_2 = 0.1/3, \beta_{1,2} = 1.0$. Green lines are the results of the big patch and blue lines are the results of the small patch. Red solid lines show a case of the corresponded single-patch system.

Bibliography

[1] Werren, J. Biology of wolbachia. *Annual Review of Entomology* **42**(1), 587–609 (1997).

[2] Werren, J., Baldo, L., and Clark, M. Wolbachia: master manipulators of invertebrate biology. *Nature Reviews Microbiology* **6**(10), 741–751 (2008).

[3] Hedges, L., Brownlie, J., O'Neill, S., and Johnson, K. Wolbachia and virus protection in insects. *Science* **322**(5902), 702–702 (2008).

[4] Moreira, L., Iturbe-Ormaetxe, I., Jeffery, J., Lu, G., Pyke, A., Hedges, L., Rocha, B., Hall-Mendelin, S., Day, A., Riegler, M., et al. A wolbachia symbiont in aedes aegypti limits infection with dengue, chikungunya, and plasmodium. *Cell* **139**(7), 1268–1278 (2009).

[5] Hancock, P., Sinkins, S., and Godfray, H. Population dynamic models of the spread of wolbachia. *American Naturalist* **177**, 323–333 (2011).

[6] Laven, H. Eradication of culex pipiens fatigans through cytoplasmic incompatibility. *Nature* **216**, 383–384 (1967).

[7] Dobson, S., Fox, C., and Jiggins, F. The effect of wolbachia-induced cytoplasmic incompatibility on host population size in natural and manipulated systems. *Proceedings of the Royal Society of London. Series B: Biological Sciences* **269**(1490), 437–445 (2002).

[8] Walker, T., Johnson, P. H., Moreira, L. A., Iturbe-Ormaetxe, I., Frentiu, F. D., McMeniman, C. J., Leong, Y. S., Dong, Y., Axford, J., Kriesner, P., Lloyd, A. L., Ritchie, S. A., O/'Neill, S. L., and Hoffmann, A. A. The wmel wolbachia strain blocks dengue and invades caged aedes aegypti populations. *Nature* **476**(7361), 450–453, 08 (2011).

[9] Turelli, M. Evolution of incompatibility-inducing microbes and their hosts. *Evolution* **48**(5), pp. 1500–1513 (1994).

[10] Bellows, T. The descriptive properties of some models for density dependence. *The Journal of Animal Ecology* **50**, 139–156 (1981).

[11] Legros, M., Lloyd, A., Huang, Y., and Gould, F. Density-dependent intraspecific competition in the larval stage of aedes aegypti (diptera: Culicidae): revisiting the current paradigm. *Journal of medical entomology* **46**(3), 409 (2009).

[12] Hancock, P., Thomas, M., and Godfray, H. An age-structured model to evaluate the potential of novel malaria-control interventions: a case study of fungal biopesticide sprays. *Proceedings of the Royal Society B: Biological Sciences* **276**(1654), 71 (2009).

[13] Hancock, P., Sinkins, S., and Godfray, H. Strategies for introducing wolbachia to reduce transmission of mosquito-borne diseases. *PLoS Neglected Tropical Diseases* **5**(4), e1024 (2011).

[14] Hancock, P. and Godfray, H. Application of the lumped age-class technique to studying the dynamics of malaria-mosquito-human interactions. *Malaria Journal* **6**(98) (2007).