1-8-2022

Analysis of a Generalized Discrete Periodic Model for the Spread of Wolbachia in a Mosquito Population

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Analysis of a Generalized Discrete Periodic Model for the Spread of *Wolbachia* in a Mosquito Population

by

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An Honors Capstone
submitted in partial fulfillment of the requirements
for the Honors Diploma
to

The Honors College

of

The University of Alabama in Huntsville

August 2021

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Date

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Dedication

This work is dedicated to Ms. Jenna Winn, Ms. Joan VanDyke, Mr. Travis Kuiper, Mr. Mark Warners, Mr. Tim VanDyke, and Ms. Eve Ricketts: the teachers who taught me to love mathematics and who continue to inspire their students.

Abstract

Mosquito-borne illnesses have posed an ongoing threat to humans, causing thousands of fatalities each year. *Wolbachia* bacteria have proven to be an effective way of limiting the ability of mosquitoes to transmit these diseases to humans, as well as to control the population by sterilizing male mosquitoes. For these reasons, researchers have performed field releases of *Wolbachia*-infected mosquitoes. To increase the likelihood that these releases will succeed, mathematical models have been developed to predict the spread of *Wolbachia* in mosquito populations following a field release. In a recently published article, a generalized model was proposed, with the intention of being applicable to a wide variety of release scenarios. Here, an analysis is performed of that model to find the periodic solutions of it, which determine the global dynamics of the system.

Introduction

Mosquito-borne illnesses such as dengue fever, Zika virus, and malaria have presented an ongoing public health issue. Historically, methods to reduce the impact of mosquito borne illnesses through vaccination or spraying insecticides have proven impractical on a large scale, and ideas to release large numbers of sterile mosquitoes in the wild raise concerns over unforeseen consequences in the ecosystem. A strategy that has gained popularity in recent years is the release of *Wolbachia*-infected mosquitoes. The *Wolbachia* bacteria prevents mosquitoes from carrying certain diseases that are harmful to humans, such as dengue fever. When an infected male mosquito mates with an uninfected female, the eggs will not hatch. This is called cytoplasmic incompatibility. When an infected female mates, *Wolbachia* is transmitted to the eggs; the percentage of eggs from an infected female that do not have *Wolbachia* is known as the maternal leakage rate. Thus, there are two beneficial impacts of a field release. One of these is controlling the mosquito population through cytoplasmic incompatibility. Additionally, *Wolbachia* is spread throughout the mosquito population, by maternal transmission. This reduces the population's ability to spread disease to humans.

As researchers seek to maximize the effect of *Wolbachia*-infected mosquito releases, a number of mathematical models have been developed. These usually seek to handle special release cases, where assumptions are made with regards to male-to-female release ratios, cytoplasmic incompatibility and maternal leakage rates, or the number of releases needed for effective disease control. In a recent paper by Zheng et al. (2021), published in *Science China Mathematics,* a more generalized model was presented, which allows for varying release ratios and number of subsequent releases.

Zheng et al. (2021) demonstrated the effectiveness of this model by showing its equivalency to previous models for the relevant specific cases. Their paper concluded with open questions regarding the periodic release ratios in their model. A periodic solution is a repeating solution, in this case, a solution that repeats every T number of generations of mosquitoes. In order to effectively use the model, it is important to know the number and stability of the periodic solutions, hence the current questions regarding them. This paper attempts to answer those questions. Finding the T-periodic solutions for this model allows us to predict the infection frequency, and the behavior of that frequency, of *Wolbachia* in subsequent generations of the mosquito population.

The focus of this paper is to present conditions that guarantee the maximum number of periodic solutions for useful cases of the aforementioned model.

Literature Review

Most models that deal with the spread of *Wolbachia* bacteria among mosquitoes are simplified by assumption. In regards to assumptions about male-to-female release ratios, assumptions are typically made that either there is equal sex distribution (Shi and Yu), (Hu et al.), and (Li et al.), or that exclusively male mosquitoes are released (Li et al.). Another common set of assumptions are simplified values for certain population variables, including maternal leakage rate and cytoplasmic incompatibility (Hu et al.). It is also often convenient to assume the number of releases preformed (Zheng et al. 2019). While these assumptions make models simpler, and therefore easier to analyze and use, the assumptions may not be accurate or relevant for a given release scenario. When this occurs, it is desirable to use a model that is not reliant upon these assumptions, in order to obtain the most accurate and applicable results. The model examined here, presented by Zheng et. al. (2021), allows for varied sex distribution, release periods, and population variables, making it a generalized model, and thus more versatile.

The model in question is given by $x_{n+1} = F(x_n)$, where:

$$F(x_n) = \frac{(1-\mu)(1-s_f)(1+m_n)(x_n+f_n)}{s_h x_n^2 - \left(s_f + s_h + m_n(s_f - s_h)\right)x_n + 1 + (1-s_f)f_n + (1-s_h)m_n + (1-s_f)f_n m_n}$$

$F(x_n)$, then, describes the *Wolbachia* infection frequency in one generation of mosquitoes. This is an index of the relevant variables:

m_n: Ratio of released males to total males

f_n: Ratio of released females to total females

s_f: Relative fitness cost of infected females

s_h: Cytoplasmic incompatibility intensity (s_h percent of eggs from an infected male will not hatch)

μ: Maternal leakage rate (μ percent of offspring from infected females are uninfected)

There is one additional piece of notation that is important. Let Q(x) denote $F(x_n)$ when $m_n = f_n = 0$, meaning that there are no releases in the generations described by Q. $P_n(x)$, n = 1,2,3, denotes generations where *Wolbachia* infected mosquitoes are released. In the case of $P_1(x), f_n \neq 0, m_n \neq 0$. For $P_2(x)$, $f_n \neq 0, m_n = 0$, and for $P_3(x)$: $f_n = 0, m_n \neq 0$. The model to be solved is a composition of Q(x) and $P_n(x)$. As an illustrative example of what this means, for T = 5 (a period of five generations), a periodic solution is x^* such that $h(x^*) = (Q \circ Q \circ Q \circ P_n \circ P_n)(x^*) = x^*$.

The first open question about this model covers the case where $m_n = f_n = \alpha$; the second, when $f_n = \alpha \neq 0$, $m_n = 0$; the third, when $f_n = 0$, $m_n = \alpha \neq 0$. For each of these cases, the model is examined for instances where $\mu = 0$ and $\mu \in (0, \mu^*), \mu^* \leq \frac{(s_f - s_h)^2}{4 s_h (1 - s_f)}$. Conditions were sought to guarantee the number of periodic solutions for each of these six cases.

Methods

Throughout this work, results were found by working with the equation in a fully abstract form and were verified numerically using a graphing software.

At Least One Solution

The first goal of this research was finding conditions to guarantee that there is at least one solution to the model. It can be shown that for $x \in [0,1]$, Q(x) and $P_n(x)$, n = 1,2,3 are monotonically increasing. Additionally, it can be shown that there is an interval $I = [a_n, b_n]$, such that $Q: I \to I, P_n: I \to I, n = 1,2,3$. If $Q(\alpha_q) = \alpha_q, Q(\beta_q) = \beta_q, \alpha_q < \beta_q$, then $I \subseteq [\alpha_q, \beta_q]$. Similarly, if $Pn(\alpha_p) = \alpha_p, P_n(\beta_p) = \beta_p, \alpha_p < \beta_p$, then $I \subseteq [\alpha_p, \beta_p]$. When these conditions are met, the Intermediate Value Theorem (IVT) guarantees that there will be at least one solution to the model.

The Maximum Possible Number of Solutions

Next, the case was examined where the maximum possible number of solutions was present. The nth solution x_n^* is found $a_k < x_n^* < b_k$, where a_k, b_k are some zeros of Q(x)-x, $P_n(x)$-x. Then there is a solution in (a_k, b_k) when, either, $h(a_k) < a_k$ and $b_k < h(b_k)$, or $a_k < h(a_k)$ and $h(b_k) < b_k$. Additionally, as mentioned above, Q and P_n are increasing at a_k, b_k. When these conditions are met, the IVT can be used to guarantee the existence of a solution between a_k and b_k. The given conditions are simple to check by a computer program.

Results

The IVT was used to prove that a solution lies on the intervals given below. This is ensured by the fact that the functions Q(x) and $P_n(x)$, n = 1,2,3 are monotonically increasing on $x \in [0,1]$. For $x \in [0,1]$ and s_f, s_h, μ, α ∈ (0,1), all of the derivatives of Q(x), $P_1(x)$, $P_2(x)$, $P_3(x)$ are positive.

It can be shown that for all $x \in (0,1), s_f < s_h, P_n(x) > Q(x), n = 1,2,3$. For $x = 0, x = 1, s_f < s_h, P_n(x) \geq Q(x), n = 1,2,3$. Coupled with this, and the fact that Q and P are monotonically increasing on our interval of interest, the following ideas can be observed from Q and P.

For all $P_n(x)$, with $x \in (0,1)$, $P_n(x) > Q(x)$. When there are a maximum of three solutions, the following can be shown.

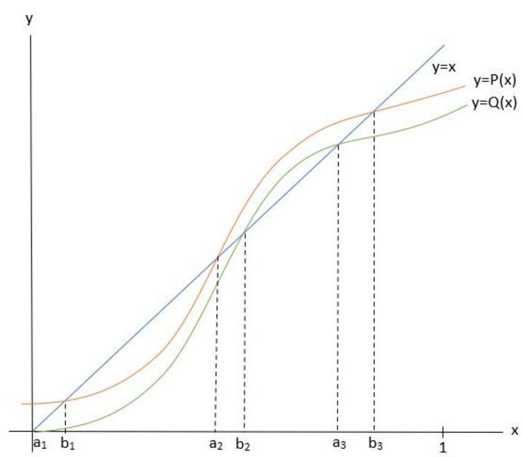

Figure 1: A representative graph for a case with three solutions

Consider Figure 1 above. For the first solution x_1^*, it is found that

$$a_1 = Q(a_1) < Q(x_1^*) < Q(b_1) < b_1$$

$$a_1 < P_n(a_1) < P_n(x_1^*) < P_n(b_1) = b_1$$

It is similarly true for the third solution x_3^*,

$$a_3 = Q(a_3) < Q(x_3^*) < Q(b_3) < b_3$$

$$a_3 < P_n(a_3) < P_n(x_3^*) < P_n(b_3) = b_3$$

The same does not hold when the middle periodic solution, x_2^*, is considered. Rather, it is seen that

$$a_1 = Q(a_1) < Q(x_2^*) < Q(b_3) < b_3$$

$$a_1 < P_n(a_1) < P_n(x_2^*) < P_n(b_3) = b_3$$

This is the case when n = 1, and n = 2, for $\mu \in (0, \mu^*)$.

When there are a maximum of two solutions, the following may represent Q and P:

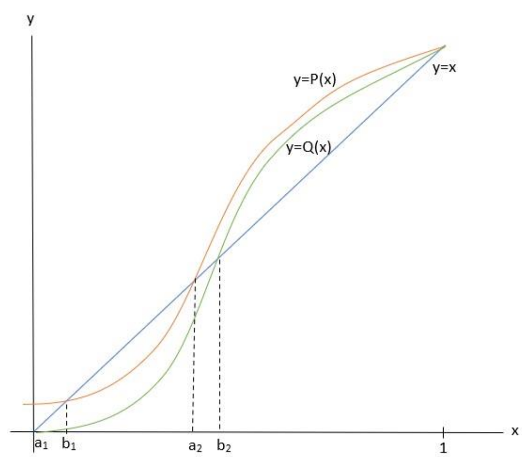

Figure 2: A representative graph for a case with two solutions

When the functions appear as in Figure 2, it is seen that

$$a_1 = Q(a_1) < Q(x_1^*) < Q(b_1) < b_1$$

$$a_1 < P_n(a_1) < P_n(x_1^*) < P_n(b_1) = b_1$$

which describe the interval that the first solution exists on. For the second solution,

$$a_1 = Q(a_1) < Q(x_2^*) < Q(1) = 1$$

$$a_1 < P_n(a_1) < P_n(x_2^*) < P_n(1) = 1$$

This is the case when n = 1, and n = 2, for $\mu = 0$.

Alternatively, when there are a maximum of two solutions, it may be that Q and P are represented in the following way:

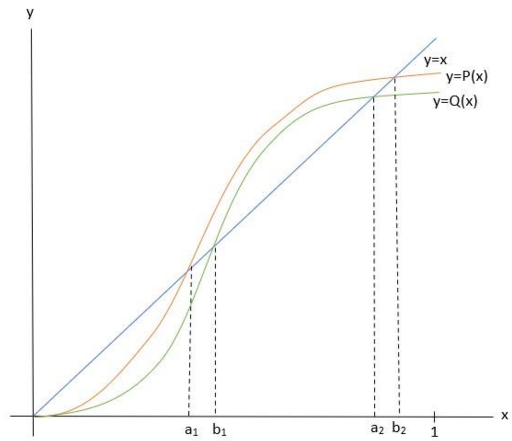

Figure 3: A representative graph for a different case with two solutions

In this case, it can be seen that, for the first solution,

$$0 = Q(0) < Q(x_1^*) < Q(b_2) < b_2$$

$$0 < P_n(0) < P_n(x_1^*) < P_n(b_2) = b_2$$

The interval for the second solution may be given more precisely:

$$a_2 = Q(a_2) < Q(x_2^*) < Q(b_2) < b_2$$

$$a_2 < P_n(a_2) < P_n(x_2^*) < P_n(b_2) = b_2$$

This is the case for n = 3, $\mu \in (0, \mu^*)$.

For the case where n=3, $\mu = 0$. there is a maximum of one solution. The following is observed:

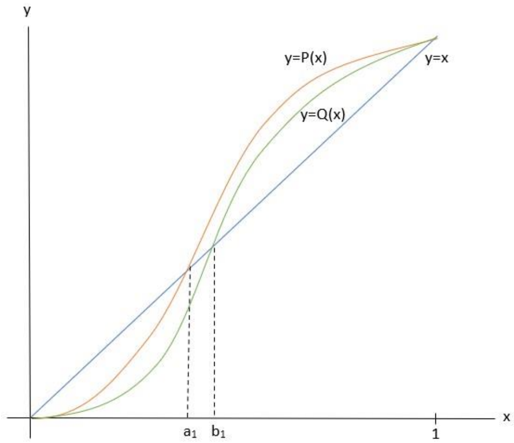

Figure 4: A representative graph for a case with one solution

For this solution,

$$0 = Q(0) < Q(x_1^*) < Q(1) = 1$$

$$0 = P_n(0) < P_n(x_1^*) < P_n(1) = 1$$

These pairs of expressions provide the interval $I = [a_n, b_n]$ described above. Since $Q: I \to I, P: I \to I$, there is a solution on I.

Solution Intervals

Here the intervals are provided on which the solutions exist, given that the corresponding conditions hold.

For the case $P_1(x)$: $f_n \neq 0, m_n \neq 0$, when $\mu = 0$, there are a maximum of two solutions. Those solutions are found to be:

$$x_1^* \in \left(0, \frac{s_f + \alpha(s_f - s_h) - \sqrt{s_f^2(1+2\alpha) + \alpha^2(s_f - s_h)^2 + 2\alpha s_f s_h(1+2\alpha) - 4\alpha s_h(1+\alpha)}}{2s_h}\right)$$

$$x_2^* \in (0,1)$$

When

$$\frac{\alpha}{1+\alpha} \leq -\left(\frac{s_f}{s_h}\right)^2 \left(\frac{1+\alpha}{\alpha}\right) + \frac{4-2s_f}{s_h}$$

Additionally, when $\mu \in (0, \mu^*)$, there are a maximum of three solutions. Let

$$\delta = -2\left(s_f + s_h + \alpha\left(s_f - s_h\right)\right)^3 + 9s_h\left(s_f + s_h + \alpha\left(s_f - s_h\right)\right)\left[(1-s_h)\alpha + \left(1-s_f\right)\alpha^2 + s_f + \left(1-s_f\right)(1+\alpha)\mu\right] - 27s_h^2\alpha(1-\mu)\left(1-s_f\right)(1+\alpha)$$

$$\xi = \sqrt[3]{\frac{\delta + \sqrt{\delta^2 - 4\left[\left(s_f + s_h + \alpha(s_f - s_h)\right)^2 - 3s_h[(1-s_h)\alpha + (1-s_f)\alpha^2 + s_f + (1-s_f)(1+\alpha)\mu]\right]^3}}{2}}$$

$$\sigma = \frac{-1+\sqrt{-3}}{2}$$

Then

$$x_1^* \in \left(0, \frac{1}{3s_h}\left[-\left(s_f + s_h + \alpha(s_f - s_h)\right) + \xi + \frac{\left(s_f + s_h + \alpha(s_f - s_h)\right)^2 - 3s_h[(1-s_h)\alpha + (1-s_f)\alpha^2 + s_f + (1-s_f)(1+\alpha)\mu]}{\xi}\right]\right)$$

$$x_2^* \in \left(0, \frac{1}{3s_h}\left[-\left(s_f + s_h + \alpha\left(s_f - s_h\right)\right) + \sigma\xi + \frac{\left(s_f + s_h + \alpha(s_f - s_h)\right)^2 - 3s_h[(1-s_h)\alpha + (1-s_f)\alpha^2 + s_f + (1-s_f)(1+\alpha)\mu]}{\sigma\xi}\right]\right)$$

$$x_3^* \in \left(\frac{s_f + s_h + \sqrt{(s_f - s_h)^2 - 4s_h\mu(1 - s_f)}}{2s_h}, \frac{1}{3s_h}\left[-\left(s_f + s_h + \alpha(s_f - s_h)\right) + \sigma\xi + \frac{\left(s_f + s_h + \alpha(s_f - s_h)\right)^2 - 3s_h[(1 - s_h)\alpha + (1 - s_f)\alpha^2 + s_f + (1 - s_f)(1 + \alpha)\mu]}{\sigma\xi}\right]\right)$$

When

$$18s_h\left[s_f + s_h + \alpha\left(s_f - s_h\right)\right]\left[(1 - s_h)\alpha + \left(1 - s_f\right)\alpha^2 + s_f + \left(1 - s_f\right)(1 + \alpha)\mu\right]\alpha(1 - \mu)\left(1 - s_f\right)(1 + \alpha) - 4\left[s_f + s_h + \alpha\left(s_f - s_h\right)\right]^3\alpha(1 - \mu)\left(1 - s_f\right)(1 + \alpha) + \left[s_f + s_h + \alpha\left(s_f - s_h\right)\right]^2\left[(1 - s_h)\alpha + \left(1 - s_f\right)\alpha^2 + s_f + \left(1 - s_f\right)(1 + \alpha)\mu\right]^2 - 4s_h\left[(1 - s_h)\alpha + \left(1 - s_f\right)\alpha^2 + s_f + \left(1 - s_f\right)(1 + \alpha)\mu\right]^3 - 27\left[s_h\alpha(1 - \mu)\left(1 - s_f\right)(1 + \alpha)\right]^2 > 0$$

In the second case, where P2(x): $f_n \neq 0, m_n = 0$, when $\mu = 0$, there are a maximum of two solutions. These are found

$$x_1^* \in \left(0, \frac{s_f - \sqrt{s_f^2 - 4s_h\left(1 - s_f\right)\alpha}}{2s_h}\right)$$

$$x_2^* \in (0,1)$$

When $\mu \in (0, \mu^*)$, and there are a maximum of three solutions, let

$$\delta = -2\left(s_f + s_h\right)^3 + 9s_h\left(s_f + s_h\right)\left[(\alpha + \mu)\left(1 - s_f\right) + s_f\right] - 27s_h^2(1 - \mu)\left(1 - s_f\right)\alpha$$

$$\xi = \sqrt[3]{\frac{\delta + \sqrt{\delta^2 - 4\left(\left(s_f + s_h\right)^2 - 3s_h\left[(\alpha + \mu)\left(1 - s_f\right) + s_f\right]\right)^3}}{2}}$$

$$\sigma = \frac{-1+\sqrt{-3}}{2}$$

Then

$$x_1^* \in \left(0, \frac{-1}{3s_h}\left[-\left(s_f+s_h\right)+\xi+\frac{\left(s_f+s_h\right)^2-3s_h\left[(\alpha+\mu)\left(1-s_f\right)+s_f\right]}{\xi}\right]\right)$$

$$x_2^* \in \left(0, \frac{-1}{3s_h}\left[-\left(s_f+s_h\right)+\sigma\xi+\frac{\left(s_f+s_h\right)^2-3s_h\left[(\alpha+\mu)\left(1-s_f\right)+s_f\right]}{\sigma\xi}\right]\right)$$

$$x_3^* \in \left(\frac{s_f+s_h+\sqrt{\left(s_f-s_h\right)^2-4s_h\mu\left(1-s_f\right)}}{2s_h}, \frac{-1}{3s_h}\left[-\left(s_f+s_h\right)+\sigma\xi\right.\right.$$

$$\left.\left.+\frac{\left(s_f+s_h\right)^2-3s_h\left[(\alpha+\mu)\left(1-s_f\right)+s_f\right]}{\sigma\xi}\right]\right)$$

When

$$18s_h(s_f+s_h)[(\alpha+\mu)(1-s_f)+s_f](1-\mu)(1-s_f)\alpha-4(s_f+s_h)^3(1-\mu)(1-s_f)\alpha$$

$$+(s_f+s_h)^2\,[(\alpha+\mu)(1-s_f)+s_f]^2-4s_h[(\alpha+\mu)(1-s_f)+s_f)]^3$$

$$-27[{s_h}^2(1-\mu)(1-s_f)\alpha]^2>0$$

For the final case, where $P_3(x)$: $f_n=0, m_n\neq 0$, the case where $\mu=0$ has a maximum of one solution in the interval

$$x_1^* \in (0,1)$$

When $\mu \in (0,\mu^*)$, there are a maximum of two solutions, which are found

$$x_1^* \in \left(0, \frac{s_f+s_h+\alpha\left(s_f-s_h\right)+\sqrt{\left(s_f-s_h\right)^2(1+\alpha)^2-4s_h\mu\left(1-s_f\right)(1+\alpha)}}{2s_h}\right)$$

$$x_2^* \in \left(\frac{s_f + s_h + \sqrt{\left(s_f - s_h\right)^2 - 4s_h\mu\left(1 - s_f\right)}}{2s_h}, \frac{s_f + s_h + \alpha\left(s_f - s_h\right) + \sqrt{\left(s_f - s_h\right)^2 (1+\alpha)^2 - 4s_h\mu\left(1 - s_f\right)(1+\alpha)}}{2s_h} \right)$$

When

$$\alpha \leq \frac{4s_h\mu\left(1 - s_f\right)}{\left(s_f - s_h\right)^2} - 1.$$

Discussion

The conditions provided above allow someone using the model to determine whether the given number of periodic solutions exist for the proposed variable values. These periodic solutions determine the global dynamics of the model. If the conditions are met, an interval can be found on which the periodic solutions exist. While these conditions and intervals are time-consuming to determine and check by hand, it would be quite simple to write a computer program to perform the checks and computations, and the conditions and intervals described are general so as to be applicable for any situation in which the studied model is being used.

While conditions were provided for the maximum number of periodic solutions, analysis should be done of the stability of the periodic solutions. This would allow researchers to fully understand the global dynamics of the system, and thereby make our results as useful as possible.

Conclusion

Field releases of *Wolbachia*-infected mosquitoes provide a viable solution to the long-standing problem of mosquito-borne diseases. However, these releases require many resources of time and money to prepare. This has given rise to a good deal of modeling work surrounding such releases. These models help to ensure the success of proposed release plans, but are often too specialized to be broadly useful. Here, an analysis has been presented of a generalized model for *Wolbachia* field releases. Given that the corresponding conditions are met, the intervals that solutions appear in when the maximum number of solutions exist can be shown. This allows researchers to more clearly use the studied model to determine the success of planned field releases in advance of their execution and to prepare accordingly.

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