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Evaluating the usefulness of paratransgenesis for malaria control

Bhushan Kotnis*, Joy Kuri

Department of Electronic Systems Engineering, Indian Institute of Science, Bangalore, India

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ABSTRACT

Malaria is a serious global health problem which is especially devastating to the developing world. Most malaria control programs use insecticides for controlling mosquito populations. Large scale usage of these insecticides exerts massive selection pressure on mosquitoes resulting in insecticide resistant mosquito breeds. Thus, developing alternative strategies are crucial for sustainable malaria control. Here, we explore the usefulness of an alternative strategy, paratransgenesis: the introduction of genetically engineered plasmodium killing bacteria inside the mosquito gut. The genetically modified bacterial culture is housed in cotton balls dipped in a sugar solution (sugar bait) and they enter a mosquito's midgut when it drinks from a sugar bait. We study scenarios where vectors and hosts mix homogeneously as well as heterogeneously and calculate the amount of baits required to prevent a malaria outbreak. Given the baits are attractive, we show that the basic reproductive number drops rapidly with the increase in bait density. Furthermore, we propose a targeted bait distribution strategy for minimizing the reproductive number for the heterogeneous case. Our results can prove to be useful for designing future experiments and field trials of alternative malaria control mechanisms and they also have implications on the development of malaria control programs.

1. Introduction

The spread of malaria is a serious health concern worldwide. Malaria alone is responsible for about six hundred thousand to one million deaths per year [1], and for infecting 300–500 million people every year. Malaria is particularly devastating for developing countries, resulting in a 1.3% loss of annual G.D.P growth [2]. The primary causative agent of malaria is the parasite *Plasmodium* which depends on the vector, the female *Anopheles* mosquito, for completing its life cycle. The parasite houses itself inside the salivary glands of the mosquito for gaining entry inside the human host's blood stream when the mosquito takes a blood meal. Conversely, hosts infected by *Plasmodium* can transfer the parasite to a mosquito when the latter takes a blood meal. Malaria cannot spread without mosquitoes; hence controlling the vector population, mosquito bites, or interfering in the ability of mosquitoes to house *Plasmodium* can limit the spread of malaria. Currently, no vaccine exists to prevent malaria, and hence efforts to control malaria are primarily based on vector control [3].

Insecticides have been very useful for controlling mosquitoes [3,4], and therefore control measures heavily depend on selective indoor residual spraying (IRS) and insecticide treated nets (ITN). The industrial scale usage of insecticides for controlling mosquito populations exerts massive selection pressure on mosquitoes. This evolutionary stress has resulted in insecticide resistant mosquito breeds [4,5]. Although development of new insecticides can address these problems, it is just a matter of time before mosquitoes develop resistance to these new insecticides. Another important problem with vector control is its continual administration [6]. An interruption in insecticide treatment will cause the mosquito population to rebound to pre-treatment levels. There is a great need to develop novel approaches for long term sustainable control of malaria. The malERA consulting group, in a recent report, has stressed that developing innovative strategies is crucial for sustainable vector control on a global scale [7]. To fill this need, we explore one such innovative mechanism.

The introduction of genetically modified viruses or bacteria, which can thrive in the mosquito's midgut and kill the parasite is termed as paratransgenesis [8]. This is different than *transgenesis*, i.e., modifying the mosquito genetically to impair their malaria parasite carrying capacity and releasing them in the wild to replace the wild type mosquitoes. Mosquito genes can be modified in the lab so that the mosquito produces proteins that either inhibit parasite reproduction, or kill the parasite. A variety of lab experiments [9,10] have shown that such genetic modification can reduce *Plasmodium* transmission. However, simply modifying the mosquitoes and releasing them in the wild may not be enough to prevent the

* Corresponding author. Tel.: +91 9448237187.
E-mail address: bkotnis@dese.iisc.ernet.in, bhushan.kotnis@gmail.com (B. Kotnis).

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spread of malaria [6]. To this end a variety of gene drive mechanisms using viruses (*Anopheles.gambiae densonucleosis virus* [11]), and bacteria (*Wolbachia* [12]) have been proposed to modify genes of wild type mosquitoes. Here, we focus on an alternative strategy - instead of modifying mosquito genes, genetically modifying bacteria are introduced inside the mosquito midgut to kill the parasite.

In a recent study [8], researchers introduced a genetically modified common mosquito symbiotic bacterium *Pantoea agglomerans* inside the mosquito's midgut. The genetically modified *P. agglomerans* produced a variety of anti-plasmodium molecules which resulted in up to 98% reduction in the *Plasmodium falciparum* population inside the midgut. Cotton balls dipped in a sugar solution containing the bacterial culture acted as baits. Thus, bacteria were introduced inside the mosquitoes when they took a sugar meal from the bait.

The implementation of such novel techniques is crucial for sustainable control and eradication of malaria. A quantitative study of the effectiveness of these novel strategies is needed before a full scale implementation. Here, we use mathematical models to do the same. The classical Ross-McDonald model proposed in the late 1950s has exerted a large influence in modeling malaria as most models proposed from 1970 to 2010 are not very different from the Ross–McDonald model [13–15]. Mathematical and data driven models have been used extensively for estimating the basic reproductive number [16], which is the key quantity that determines the chance of an outbreak. Through the insights gained by analyzing various mathematical and computational models (see [16] and [14] for a recent review), researchers have formulated and evaluated various control strategies which use: insecticides [17–19], insecticide treated nets [20,21], larval control [22], odor baited traps [23], entomopathogenic fungi [24], *wolbachia* [25] and genetic modification of mosquitoes [26,27]. However, to the best of our knowledge, no mathematical model has been formulated to evaluate the usefulness of paratransgenesis in malaria control.

Here we aim to study the usefulness of introducing genetically modified *P. agglomerans* inside mosquitoes through sugar baits for controlling malaria, with a focus on quantifying the amount of baits required to prevent an outbreak. Although, like insecticide spraying, sugar baits need to be replenished at regular intervals, replenishing sugar-baits is more economical and environmentally friendly than the continual usage of insecticides. Furthermore, since this strategy does not involve the killing of mosquitoes, its usage would not put evolutionary pressure on mosquitoes. An objection may be raised that the usage of anti-plasmodium molecules may result in plasmodium which are resistant to these molecules. This problem can be avoided by using a variety of anti-plasmodium molecules [6].

In the past, most studies have assumed homogeneous mixing between mosquitoes and hosts [14]. However, in reality vectors and hosts may not be well mixed [28,29]. In this paper, we not only study the homogeneous mixing case, but also the *heterogeneous* case. Studies [30–32] suggest that heterogeneous mixing between the vectors and hosts may increase the basic reproductive number. Therefore, for the heterogeneous mixing scenario we propose an optimal targeted bait allocation strategy for reducing the reproductive number. We use the *Susceptible Infected Susceptible* (SIS) model for human hosts and *Susceptible Infectious Removed Susceptible* (SEIRS) model with delay for vectors. This is one of the first models which incorporates a removed compartment for mosquitoes motivated by paratransgenesis.

Our contributions are summarized as follows:

- The reproductive number is calculated and a stability analysis is performed for the homogeneous mixing case.
- The conditions required for a malaria outbreak is calculated for the heterogeneous mixing case.
- An optimal targeted bait allocation strategy is proposed for the heterogeneous mixing case.
- We analytically show that the reproductive number is inversely proportional to the square of effective baits for high bait attractiveness. We also discover that improving the attractiveness of sugar baits is more fruitful than increasing the efficacy of paratransgenesis.

The article is organized as follows: the model is introduced in Section 2, rigorously analyzed in Section 3, results detailed in Section 4, and the implications and interpretations of the results are discussed in Section 5.

2. Model

We use a compartmental SIS model for human hosts and SIERS model with delay for mosquitoes. Human hosts can either be in the susceptible state, or the infected state. A susceptible human host can be infected by the disease, when a mosquito carrying the parasite bites the host. We assume that due to the availability of effective malarial medications, infected individuals recover at a constant rate and can be re-infected, but they do not die from the disease. After contracting the infection, mosquitoes become infectious after a fixed time duration (incubation time) which depends on the parasite.

When a wild type mosquito takes a blood meal from a host infected with the *plasmodium* parasite, the parasite enters the mosquito's midgut in the form of *gametocytes*, which reproduce, eventually producing *sporozoites*, which then invade the mosquito's salivary glands. If the mosquito's midgut contains the genetically modified bacteria then the parasite will be killed by the bacteria. However, if the sporozoites have already invaded the salivary gland then the bacteria are unable to kill them. This is because the bacteria are housed in the midgut and the anti-*plasmodium* molecules secreted by them cannot enter the salivary glands. There is a time lag (in days) between the introduction of gametocytes inside the mosquito's midgut and sporozoite invasion of its salivary glands. Based on these observations [8,33], we divide the mosquito population into four classes: susceptible, exposed, infectious, recovered. We incorporate the time lag (exposed class) using a fixed time delay τ. Mosquitoes who do not have both: malaria parasites in their body and the genetically modified bacteria in their midgut belong to the *susceptible* class. Mosquitoes with gametocytes in midgut but no sporozoites in salivary glands and no bacteria in the midgut belong to the *exposed* class. Mosquitoes whose salivary glands are invaded by the parasites belong to the *infectious* class.

The effect of paratransgenesis is studied by explicitly including the *removed* compartment in the model. Genetically modified *P. Aggloromerans* culture is mixed with a sugar solution to act as sugar baits. Such baits are positioned in places well within the range of mosquitoes. If a susceptible mosquito ingests the genetically engineered bacteria then it can no longer carry the parasite in its gut and enters the removed state. Although authors in [8] do not carry out experiments wherein the bacteria is introduced *after* the mosquitoes take a blood meal, we believe it is reasonable to assume a similar effect if such an experiment was carried out. This is because, as the authors report, that the population of *Pantoea agglomerans* increases rapidly and peaks just after 2 days. A mosquito that has ingested a blood meal, and ingests the bacteria during the incubation period, would stop carrying the parasite, because the bacteria would proliferate rapidly and release anti-plasmodium molecules that kill the oocysts in the midgut (which is also the place where the bacteria reside). Hence we assume than a mosquito in exposed state that ingests the bacteria enters the removed state.