Commun Nonlinear Sci Numer Simulat 31 (2016) 83–107

Contents lists available at ScienceDirect

Commun Nonlinear Sci Numer Simulat

journal homepage: www.elsevier.com/locate/cnsns

Periodic patterns and Pareto efficiency of state dependent impulsive controls regulating interactions between wild and transgenic mosquito populations

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ARTICLE INFO

Article history:
Received 1 November 2014
Revised 7 July 2015
Accepted 28 July 2015
Available online 4 August 2015

Keywords:
Transgenic mosquitoes
State-dependent impulsive perturbation
Order-1 periodic solution
orbital stability
Pareto efficiency
Pareto frontier

ABSTRACT

It is conceivable that genetically modified mosquitoes could stop the spread of malaria, by outcompeting the wild mosquitoes and interfering with their reproductive processes, and genetically inheriting and further transmitting a diminished potential to carry *Plasmodium*. To get insight into the possible outcomes, we formulate an ODE model for the interactions between wild and transgenic mosquito populations, which is subject to state-dependent impulsive perturbations. By first investigating the dynamics of the unperturbed system, we determine certain sufficient conditions for the existence and orbital stability of positive order-1 solution of the model system with state-dependent impulsive perturbations. Their feasibility is then illustrated by means of numerical simulations. In addition, to adequately control the wild mosquito population, we use a multi-target approach which, in addition to accounting for the total costs, keeps track of the total size of the wild mosquito population. To trade off these objectives, we consider the concept of Pareto efficiency to determine suitable control strategies which are near-optimal. Finally, we carry out numerical simulations to illustrate the Pareto frontier and then characterize the detailed Pareto efficient control regime.

1. Introduction

Anopheles maculipennis, the species of the genus *Anopheles* ("not of any benefit", from the Greek words *an*, "not" and *ophelos*, "benefit") was first described and classified by the German entomologist J. W. Meigen in 1818. Since R. Ross discovered in 1897 that *Anopheles* mosquitoes are able to transmit human malaria pathogen, *Plasmodium*, it has been observed that the transmission of malaria does not occur through human contact and that the mosquitoes in this genus are actually the sole malaria vectors [1]. Sickening over 200 million people and causing over 1 million deaths annually [2], malaria is, at the global scale, one of the most troublesome infectious diseases. Much efforts have been spent developing an effective vaccine over the past 30 years, as this would be an important step toward malaria prevention and control. However, this has been proved to be difficult, and only one candidate vaccine, RTS, S/AS01 has reached the stage of phase III clinical trials, with the prospect of being submitted for licensure in 2014 [3]. Unavailability of an effective vaccine has hampered so far the efforts to curtail the disease.

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http://dx.doi.org/10.1016/j.cnsns.2015.07.013
1007-5704/

Alternatively, efforts have been focused on both targeting the evolution of *Plasmodium* in humans and on interrupting the transmission of the disease by the vector [1,4,5]. The most powerful and widely used approach to vector control is the use of insecticides. Four classes of insecticides are used for public health purposes (pyrethroids, organochlorines, organophosphates and carbamates), usually by means of long-lasting insecticide-treated nets and indoor residual spraying. While insecticides have been proved very successful in reducing disease incidence, resistance to insecticides among malaria vectors has emerged more than 25 years ago in America, Africa and Europe [6], frequently due to gene mutations that help the mosquitoes' nerve cells withstand insecticide attack, the acetylcholinesterase enzyme losing sensitivity to organophosphates and carbamates. Other forms of resistance, depending on increased levels of mosquito enzymes that can destroy pyrethroids before they reach their target, are also possible [7].

Since mosquitoes are the sole vectors for malaria transmission, rendering them incapable of transmitting malaria parasites could limit the spread of the disease. *In vivo* studies have led to the identification of a peptide, called SM1 peptide, that binds to the two epithelia which should be traversed by the parasite and inhibits their crossing [8]. By injecting mosquito embryos with a synthetic gene containing four SM1 units, four separate lines of transgenic mosquitoes have been obtained, the transgene being strongly induced in the midgut of the transgenic mosquitoes by a blood meal. The expression of SM1 peptide in the mosquitoes midgut drastically reduced their vector capability by inhibiting *Plasmodium* development. In two of three experiments, no transmission has been detected, while in a third one the transmission rate has been reduced to less than one third of its initial value. Also, the SM1 peptide did not alter mosquito fitness traits such as longevity and egg production.

Inheritable genetic transformations have been achieved for the genome of *Anopheles stephensi* mosquitoes by means of the *Minos* transposable element from *Drosophila hydei*, with the expectation that this technique can be successfully extended to the most prominent malaria vector, *Anopheles gambiae* [9,10]. Recently, the establishment of a stable *Wolbachia* infection in a population of *Anopheles stephensi* has also been reported [11]. The *Wolbachia* strain wAlbB derived from *Aedes albopictus* was observed to form a stable symbiosis with *Anopheles stephensi* and to have perfect maternal transmission together with high levels of cytoplasmic incompatibility (enhancing its capability to spread), while conferring resistance to *Plasmodium*, possibly by stimulating a mosquito antiparasitic immune response. Further, the wAlbB infection has been able to reach 100% infection frequency in a naturally uninfected population, under certain release conditions, and to remain fixed in subsequent generations. This establishes the feasibility of producing transgenic mosquitoes that have diminished potential to carry the parasite and provides a new and effective weapon against malaria.

Once pathogen refractory transgenic mosquitoes are obtained, the next step is to release them into the environment, with the goal of replacing the pathogen susceptible wild mosquitoes. However, transgenic mosquitoes can experience reduced fitness, due to various circumstances: inbreeding depression, random integration of transposable elements altering important genes or toxicity of a foreign protein expressed in abundance [12]. Also, it is suggested in [13,14] that the released mosquitoes would need to be nearly 100% refractory in order to have a real impact on malaria transmission. Such a high refractory capability would need multiple refractory genes, which may come with greater fitness impairment. In practice, it is almost impossible to replace the wild mosquito population with transgenic mosquitoes in any particular environment. In this regard, the strategic policies emphasize implementing effective and economical control mechanisms to keep the size of the wild mosquito population as low as reasonably practicable. Actually, the celebrated work [15] states as early as 1928 that "... in order to counteract malaria anywhere we need not banish *Anopheles* there entirely ... we need only to reduce their numbers below a certain figure".

A question arises about how transgenic mosquitoes should be released in combination with pesticide release in order to effectively control the abundance of wild mosquitoes. To address this question, which is the aim of this paper, we formulate a model for the interaction between wild and transgenic mosquito populations based on a two-dimensional ODE system with state-dependent impulsive perturbations. State-dependent impulsive dynamical systems are a particular case of hybrid systems in which the impulsive perturbations of a given continuous dynamical system occur whenever a threshold trigger is initiated [16,17]. In recent years, state-dependent impulsive control strategies have proved their usefulness in the study of dynamics of prey–predator systems [18,19], management of fisheries [20], integrated pest management [21], pulse vaccination for human infectious diseases [22], and chemostat models [23,24].

From a practical viewpoint, it is feasible to take a first step toward implementing state-dependent impulsive control strategies and estimate the sizes of adult and larval mosquito populations via landing rate counts and, respectively, a dipper and then take data back to the laboratory for an analysis of the catch. However, before releasing transgenic mosquitoes, other particulars of the target wild mosquito population such as its genetic diversity, mating behavior and heterogeneous biting should be analyzed, together with locations where the releases should occur. Also, one should have in mind that in malaria transmission the environmental ecology is complex in most locations [12], due to the complex life cycle of the parasite and to the fact that breeding sites are very transient due to uncontrollable external factors such as drying or flooding. Another question that needs further investigation is how transgenic mosquitoes should be released as a part of a state-dependent control strategy which involves also pesticide release.

Motivated by the above-mentioned considerations and by the ideas of [25,26], we formulate a model for the interaction between wild and transgenic mosquito populations based on a two-dimensional ODE system which is subject to state-dependent impulsive perturbations. Since determining genotype distributions for the offsprings in a variable environment is not simple, we group all transgenic populations into a single population, without distinguishing for their zygosity [25]. Also, we consider generation overlapping for both types of mosquitoes.

The paper is structured as follows. We first study our model system without perturbations (Section 3) and then derive sufficient conditions for the existence and orbital stability of positive order-1 solutions of our system with state-dependent impulsive