Journal of Theoretical Biology 347 (2014) 33–43

Contents lists available at ScienceDirect

Journal of Theoretical Biology

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

# Impact of mating behaviour on the success of malaria control through a single inundative release of transgenic mosquitoes

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## HIGHLIGHTS

- We model the release of malaria-resistant mosquitoes on the success of malaria control.
- Both assortative and disassortative mating are able to favour the spread of refractoriness.
- Without a gene drive refractoriness can invade the population.
- Under certain conditions a significant reduction of human malaria prevalence can be reached.

## ARTICLE INFO

*Article history:*
Received 13 September 2013
Received in revised form
7 January 2014
Accepted 7 January 2014
Available online 15 January 2014

*Keywords:*
Malaria
Mosquito
Assortative mating
Transgenics
Vector-borne diseases

## ABSTRACT

Transgenic mosquitoes are a potential tool for the control or eradication of insect-vectored diseases. For malaria, one possible strategy relies on the introduction of malaria-refractory transgenes into wild *Anopheles* mosquito populations that would limit their capacity to transmit the disease. The success of such an approach obviously depends on a variety of factors. By developing a model that integrates both population genetics and epidemiology, we explore how mosquito mating preferences and the cost and efficacy of refractoriness affects the long-term prevalence of malaria in humans subsequent to a single generation inundative release of male transgenic mosquitoes. As may be intuitively expected, mating discrimination by wild-type individuals against transgenic ones generally reduces the probability that transgenes become stably established at a high frequency in mosquito populations. We also show that in circumstances where transgenic individuals exhibit some degree of discrimination against wild-type individuals, this can favour the spread of refractory alleles and lead to a significant reduction in malaria prevalence in the human population (if the efficacy of a dominant refractory mechanism exceeds at least 75%). The existence of such a non-intuitive outcome highlights the practical value of increasing the understanding of *Anopheles* mating preferences in the wild as a means to harness them in the implementation of population replacement approaches. Potential strategies by which previously described mating preferences of *Anopheles gambiae* populations could be exploited to manipulate the mate choice of transgenic release stocks are discussed.



## 1. Introduction

Mosquito-borne diseases such as malaria or dengue pose a major public health concern worldwide. To control and eradicate mosquito-borne diseases, there is a need to better use existing methods or to develop new ones. Over the last 15 years, the development of genetically modified (GM) mosquitoes is one of the most visible high-tech attempts to expand the range of available disease control techniques (Alphey et al., 2002; Harris et al., 2012; Marshall and Taylor, 2009; Scott et al., 2002). In using transgenic mosquitoes for the control of vector-borne diseases, two primary strategies are being considered. The first one involves the release of sterile or partially sterile genetically modified males into the wild to mate with wild-type females, resulting in unviable offspring (Alphey et al., 2002; Catteruccia et al., 2009). The goal behind this approach is the reduction in the mosquito population and consequently, a decrease or cessation in disease transmission. This strategy is currently undergoing large-scale trials in urban areas in Brazil using the mosquito species *Aedes aegypti*, which is the primary vector of dengue fever (Reis de Castro, 2013). The second strategy involves the replacement of a population of mosquito vectors by one engineered to be refractory to *Plasmodium*, resulting in a decrease in malaria transmission (Corby-Harris et al., 2010). It is generally assumed that refractory alleles will need to be genetically linked to a synthetic 'drive mechanism', engineered to favour its establishment at a high frequency (James, 2005; Sinkins and

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http://dx.doi.org/10.1016/j.jtbi.2014.01.010

Gould, 2006; Windbichler et al., 2011). Theoretical work has previously shown the importance of several parameters to ensure the spread of the transgenic allele of interest, including the costs and the benefits of refractoriness and its efficacy (Boëte and Koella, 2002, 2003; Koella and Zaghloul, 2008). However, information concerning the impact of the mating behaviour on the spread of an allele of interest in Anopheline populations is limited (Okanda et al., 2002; Cator et al., 2009; Agusto et al., 2012). This aspect is particularly important in *Anopheles* populations because these are well-known for their complexity and the existence of complexes with natural mating barriers that pose a challenge to any genetic approach (Deredec et al., 2011). To limit malaria transmission in many geographic areas of Africa, it may be necessary to control a number of assortatively mating forms and species. In the natural context, assortative mating between described molecular forms and species rely on cues that remain largely unknown in Anopheline mosquitoes (Dabiré et al., 2013; Pennetier et al., 2010; Ritchie and Immonen, 2010). However, mosquitoes of the genus *Aedes* have proven more tractable in identifying wing beat frequencies as a critical component of inter-sexual signalling (Cator et al., 2009), and a similar role for wing beat frequency has also been proposed in Anopheline mosquitoes (Sanford et al., 2011). The equilibrium frequency of any transgenic allele conferring refractoriness to malaria would inevitably be impacted by genetic linkage to traits affecting relative attractiveness.

At present, there is only one system that drives genes into populations of the *Anopheles gambiae* species complex (Windbichler et al., 2011) that are the primary global vectors of malaria. Consequently, there is interest in developing additional approaches (Rasgon, 2009), including exploring the potential of inundative releases to push genes into such populations (Benedict, 2011; Marsden et al., 2013).

Here, we present a model combining population genetics and epidemiology to measure the impact of sexual preference and mating behaviour on the spread of an allele conferring refractoriness against malaria parasites in a mosquito population. This work also provides information regarding the resulting impact on the prevalence of the parasite in the human population.

## 2. The model

The model presented here follows that of Boëte and Koella (2002), which describes the spread of an allele conferring refractoriness against *Plasmodium* in a mosquito population and its impact on the epidemiology of the disease in humans. In this model, refractoriness is determined by a single transgenic allele ($R$) and changes in its frequency are described by discrete generations. The model considers three different genotypes in the population, namely the homozygote ($RR$), the heterozygote ($Rr$) and the wild-type sensitive ($rr$) genotypes. We are interested in determining the impact of sexual attractiveness on the spread of the $R$ allele by exploring various scenarios using different levels of attractiveness between males and females of similar or different genotypes/ phenotypes. The model assumes that the transgenic allele is located on an autosome and linked to at least some alleles that modulate mate choice. Such genetic linkage could be achieved by inserting the transgene within a chromosomal inversion not present in the target wild-type population that encompasses appropriate mate choice alleles (see discussion section for additional details of how this can be achieved in practice).

Throughout the paper, the term 'genotype' is used to define one of the three types of mosquito individuals: transgenic homozygotes '*RR*', transgenic heterozygotes '*Rr*' and wild-type '*rr*'. Similarly, the refractory phenotype refers to individuals carrying at least one transgenic '*R*' allele, ('*RR*' or '*Rr*'), whereas the sensitive phenotype refers to wild-type individuals with the '*rr*' genotype. All the various scenarios modelled in this paper are based on the release of a single large number of homozygous ($RR$) males in a single generation.

### 2.1. Fitness

#### 2.1.1. Male mosquitoes

The model assumes that only male ($RR$) mosquitoes are released, as they do not blood feed and do not act as vectors of malaria. The release occurs at the $k^0$ generation. It is assumed that harbouring a resistance allele has a consistent detrimental effect on male mosquito fitness and this is independent of the prevalence of the *Plasmodium* parasite. Thus, the cost of harbouring the resistance allele is assumed fixed and is designated as $c_{res}$. If the fitness of a sensitive male is set to 1, then the fitness of a male harbouring a resistance allele is $(1-c_{res})$ for homozygotes and $(1-hc_{res})$ for heterozygotes, with $h$ being the level of dominance.

#### 2.1.2. Female mosquitoes

For female mosquitoes, the fitness cost of harbouring a resistance allele can be balanced by the benefit of resisting parasite infection, the probability of which is influenced by the frequency of people with malaria. This probability of female mosquito infection is proportional to the prevalence of malaria in the human population ($y$) and to the probability that a mosquito will become infected by a single infectious blood meal (we assume this value to be equal to 1, according to Boëte and Koella (2002)). If a mosquito bites a human, on an average $q$ times during its lifetime, the probability that it will become infected at least once during its lifetime is thus proportional to the nonzero-term of the Poisson distribution $[1-\exp(-yq)]$. The fitness of a susceptible female is then given as $1-[1-\exp(-yq)]\psi$, in which the parameter $\psi$ is the virulence of the parasite.

In our model, carrying the transgene is costly for both sexes, but for females, there is the potential that benefits can outweigh the cost due to resistance to Plasmodial infection. This leads to the following expression for the fitness of resistant homozygote female mosquitoes: $1-cres-[1-\exp(-yq(1-s)]\psi$. For the heterozygotes, the level of dominance for females ($h$) affects their fitness and this is given as $1-h^*cres-[1-\exp(-yq(1-hs))]\psi$.

### 2.2. Population genetics

The proportion of the $k$th generation that are male genotypes $rr$, $Rr$ and $RR$ are denoted as $u_{m,k}$, $v_{m,k}$ and $w_{m,k}$, respectively. The corresponding female proportions are given as $u_{f,k}$, $v_{f,k}$ and $w_{f,k}$. Following Marshall et al. (2011), the proportion of the $(k+1)$ generation embryos of the different genotypes are $u_{e,k+1}$, $v_{e,\,k+1}$ and $w_{e,\,k+1}$, in which:

in which the parameters $\alpha$ represent the level of attractiveness between the different combinations of male and female genotypes (see Table 1 legend for explanation of symbols and also Table 2).

$$u_{e,k+1} = u_{m,k}u_{f,k}(\alpha\,\square\bigcirc) + 0.5u_{m,k}v_{f,k}(\alpha\square\odot) + 0.25v_{m,k}v_{f,k}(\alpha\blacksquare\odot) + 0.5v_{m,k}u_{f,k}(\alpha\,\blacksquare\bigcirc)\,;$$

$$v_{e,k+1} = u_{m,k}w_{f,k}(\alpha\,\square\bullet) + 0.5u_{m,k}v_{f,k}(\alpha\,\square\odot) + 0.5v_{m,k}v_{f,k}(\alpha\blacksquare\odot) + 0.5v_{m,k}w_{f,k}(\alpha\,\blacksquare\bullet) +$$

$$0.5w_{m,k}v_{f,k}(\alpha\blacksquare\odot) + 0.5v_{m,k}u_{f,k}(\alpha\blacksquare\bigcirc) + w_{m,k}u_{f,k}(\alpha\,\blacksquare\bigcirc)$$

$$w_{e,k+1} = w_{m,k}w_{f,k}(\alpha\,\blacksquare\bullet) + 0.5w_{m,k}v_{f,k}(\alpha\blacksquare\odot) + 0.25v_{m,k}v_{f,k}(\alpha\blacksquare\odot) + 0.5v_{m,k}w_{f,k}(\alpha\blacksquare\bullet)\,;$$