Genetically Modified Mosquito: Myth and Reality

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Abstract

Sterile Insect Technique (SIT) has been applied successfully in some agricultural pest control programs in the past, but in many cases, success has not been sustainable in the long run. Various attempts have been made to duplicate this limited success SIT application in agriculture to other areas of applications, particularly in vector control. For example, a recent mosquito control program has been initiated in Malaysia to eliminate dengue-mosquitoes *Aedes aegypti* by releasing large amount of genetically modified GM male mosquitoes into the field to outcompete the wild male mosquitoes. Field experimental data that has been made available in the literature is limited, rendering it difficult to make independent assessment on its short-term efficacy and long-term sustainability of this GM control strategy. This paper presents a preliminary assessment of the effectiveness of GM mosquito in controlling dengue mosquito population by means of model simulations via DEER (Dengue Encephalitis Eradication Routines). Preliminary results indicate negative conclusion regarding the effectiveness of GM mosquitoes in controlling wild *A. aegypti* population over the long-term. Essentially, significant reduction of wild mosquito population is possible only if large over-flooding ratios are applied. Further, repeated releases must be maintained over an infinite time horizon to continue to sustain low population of mosquitoes. Major difficulty remains to be resolved. In particular, in-depth cost-benefit analysis on this control program is essential to ensure long-term institutional and social support.

Keywords: DEER; genetically modified mosquito; simulation

1. INTRODUCTION

Dengue virus is transmitted to human and female mosquitoes through the bites of female *Aedes aegypti* mosquitoes. Dengue has been endemic in Malaysia since 1902. In year 2010, around 43,500 dengue fever cases have been reported with 128 fatalities in Malaysia. Effective prevention strategies could reverse these trends, and vector control aimed at vector reduction and interrupting transmission is seen as a key component of such strategies in the absence of effective vaccine for dengue fever. One such vector control method is the Sterile Insect Technique (SIT). SIT is a species-specific and environmentally nonpolluting method of insect control that relies on the release of large numbers of sterile insects [1,2]. Mating of released sterile males with wild females leads to a decrease in the female's reproductive potential. This eventually would lead to the local elimination or suppression of the pest population if sterile males are released in sufficient numbers over a sufficient period of time. Highly successful, area-wide SIT programs have eliminated or suppressed a range of major veterinary and agricultural pests around the world.

Large rearing facility can produce around 2 billion sterile male Mediterranean fruit flies per week (~20 tons/week). For these agricultural pests, SIT is a proven cost-effective strategy for eradication or suppression of target populations, or to protect areas against invasion or re-invasion. For mosquitoes, the situation is less clear. Field trials in the 1970s and 1980s demonstrated that SIT could also be made to work against mosquitoes, even with the technology then available [3,4]. Recent advances suggest several potential improvements over the methods available in the past. Most current SIT programs use radiation to sterilize the insects. However, it has proven difficult to irradiate mosquitoes to near-complete sterility without significantly weakening them. The field release of a genetically modified (GM) mosquito version of the sterile insect technique (SIT) for *Aedes aegypti* to eliminate the dengue-mosquitoes is recently experimented in Malaysia. The GM mosquitoes being used in these field experiments are *Aedes aegypti* OX513A produced by Oxitec.

The male mosquitoes are genetically modified in such a way that when they breed with wild females, their offspring will die early, leading to reduced wild mosquito population. These field experiments have aroused considerable anxiety among NGOs and concerned scientists, primarily due to the lack of transparency, the absence of meaningful and effective public participation, and the seeming haste in the approval process [5,6,7]. This paper investigates by model simulations the efficacy of controlling natural *Aedes aegypti* mosquito population by the release of GM mosquitoes into the natural habitat.

2.   DEER MODEL

The in-house simulation model DEER for mosquitoes is developed based upon adaptation of the concepts contained in the mathematical model (1) – (6) for SIT proposed by Esteva and Yang [8]. The mosquito population is divided into six compartments A, F_s, F_f, F_u, M and M_T (Figure 1). The compartment A consists of immature aquatic form of the mosquito. The adult wing female mosquitoes are divided into three compartments, while the males are divided into two compartments, as required by the concept of SIT. One compartment consists of unmated single females, which is denoted by F_s. Some of these single unmated females remain unmated and therefore remain in F_s, while the remaining singles are mated. The mated females are further divided into two compartments. Those that are fertilized are moved into compartment denoted by F_f, while the unfertilized females are moved to the compartment F_u.

$$\frac{dA}{dt} = \phi\left(1 - \frac{A}{C}\right)F_f - (\gamma + \mu_A)A \tag{1}$$

$$\frac{dF_s}{dt} = r\gamma A - \frac{\beta M F_s}{M + M_T} - \frac{\beta_T M_T F_s}{M + M_T} - \mu_s F_s \tag{2}$$

$$\frac{dF_f}{dt} = \frac{\beta M F_s}{M + M_T} - \mu_f F_f \tag{3}$$

$$\frac{dF_u}{dt} = \frac{\beta_T M_T F_s}{M + M_T} - \mu_u F_u \tag{4}$$

$$\frac{dM}{dt} = (1 - r)\gamma A - \mu_M M \tag{5}$$

$$\frac{dM_T}{dt} = \alpha - \mu_T M_T \tag{6}$$

The male mosquitoes are divided into two compartments in order to facilitate modeling the competition between the wild and GM male mosquitoes. Natural male mosquitoes form members of the compartment denoted by M. Finally, the GM male mosquito is grouped into compartment denoted by M_T. This set of compartment notations will be used in this paper. For example, the per capita mortality rates of the immature aquatic form, unmated single females, mated fertilized females, mated unfertilized females, natural male and GM male mosquitoes are denoted by μ_A, μ_s, μ_f, μ_u, μ_M and μ_T, respectively. Other rate constants in this model include the development rate of aquatic forms γ, the mating rate of natural mosquito β, the number of winged GM males released per day α, the oviposition rate of winged fertilized females ϕ, the carrying capacity of aquatic forms C, the proportion of aquatic forms that becomes winged females r, the proportion of winged GM males that are released in adequate places p and the proportion of effective mating rate of winged GM males q. The parameter $\beta_T = pq\beta$ represents the mating rate of winged

GM males. The parameter p is related to the proportion of GM males that are released in suitably selected locations and q is related to the proportion of effective mating rate of GM males. The male to female ratio of the adult mosquitoes hatched from eggs is assumed to be 1:1 ($r = 0.5$). The parameter values used in the simulations are summarized in Table 1. Details of the model can be referred to Esteva and Yang [8] and Koh et al. [6].
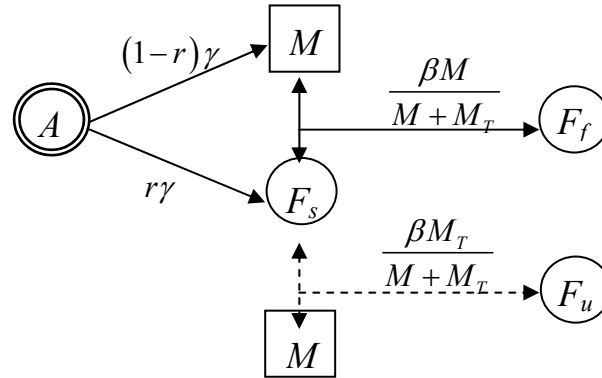
$(1-r)\gamma$ M $\dfrac{\beta M}{M + M_T}$ F_f

A

$r\gamma$ F_s

$\dfrac{\beta M_T}{M + M_T}$ F_u

M

Figure 1: Compartments in DEER model for GM mosquitoes

Table 1: Parameter values used for simulation study [8]

μ_A	μ_s	μ_f	μ_u	μ_M	μ_T
0.05	0.05	0.05	0.05	0.1	0.1
ϕ	γ	r	β	C	pq
5.0	0.075	0.5	1.0	600	0.7

3.   RESULTS AND DISCUSSION

3.1   Isolated Release Site

We first consider the case in which the release site is assumed to be completely isolated from its neighbors, with no possibility of wild mosquito recruits coming from neighborhood regions. This scenario is unlikely to prevail. This model scenario represents the most optimal situation for the local success of GM experiments. We consider a one-off release of GM male mosquitoes at simulation time with peak mosquito population. Various one-off release proportions (M_T/F) in increasing order of 1, 10, 100 and 1000 are considered to facilitate the assessment of impact of larger amount of GM release. The proportion M_T/F represents the ratio of the GM male mosquito population to the present total population of female mosquitoes in the simulation site. For example, the proportion $M_T/F = 1$ indicates that the population of GM males released is equal to the present total population of female mosquitoes; while $M_T/F = 10$ indicates that the population of GM males released is ten times the

present total population of female mosquitoes. We use the number of aquatic forms scaled to the carrying capacity as a measure of mosquito population.

Figure 2 shows the simulated proportion of aquatic form to its carrying capacity (denoted by A/C). Simulation results indicate that a large one-off release of GM male mosquitoes (of the order of hundreds times the present female mosquito population) will quickly decrease the number of aquatic forms. This is so because most of the aquatic offspring come from female mosquitoes that have mated with GM male mosquitoes, and these will die during the aquatic phase before they can develop into mature form. Hence, the adult form will be decimated. However, without continuous release of GM male mosquitoes after the one-off release, the GM male mosquitoes released into the wild will eventually die. The residual wild mosquito population in the enclosed site will then recover to their normal population levels in the absence of GM males. Of course the time taken to recover to the natural wild population level varies with the one-off release rates. The higher the one-off release rates, the longer will be the time taken to recover to the wild natural state, as higher one-off release rates would decimate the wild population further.

On the other hand, if the GM male mosquitoes are released continuously, the natural mosquitoes will be wiped out eventually as shown in Figure 3 when sufficiently large continuous release rate of GM males is maintained. A continuous release of GM males at a large rate over a long period may not be economically sustainable, however. Cost-benefit analysis must therefore be carefully performed. It should be noted that these simulation results are obtained based upon estimation of the parameter values such as p and q as well as estimated total population of wild mosquitoes at the release site. Under normal field conditions, these parameter values may not be accurately known. Hence controlled field experiments must include these set of parameters to allow reliable assessment of the benefits of GM release.
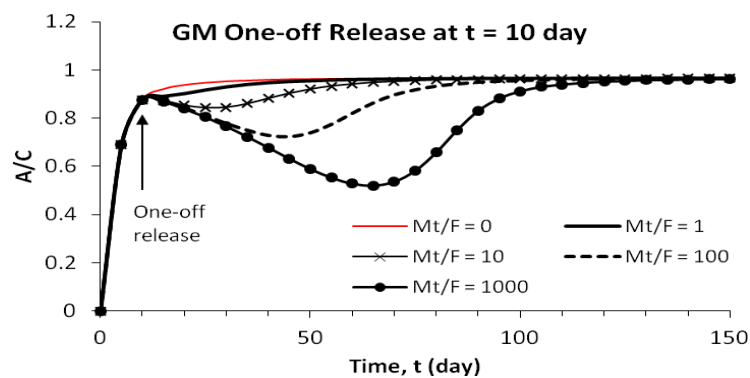

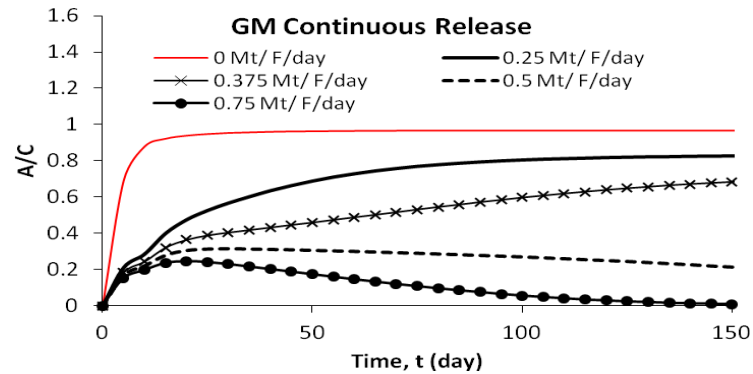**Figure 2**: Proportion A/C subject to various one-off release at time t = 10 days

Figure 3: Proportion *A/C* subject to various continuous release rate

3.2   Natural Release Site

A completely isolated release site is unlikely to prevail as mosquitoes tend to spread over the neighborhoods. Physically connected to neighborhoods, a natural release site is neither completely enclosed nor completely isolated from its neighbors. Hence, spatially-explicit models are needed in order to allow mosquitoes to spread. We enhance the model formulation contained in Equations (1) to (6) into the spatially-explicit framework of DEER to simulate the spatial-temporal distribution of mosquito population subject to GM release [9]. The mosquito population is initiated by a small starting population at location X = 5 km in a natural habitat covering a distance of ten kilometers. We assume that the wild mosquito population is zero at the two boundaries, being completely unsuitable for *A. aegypti* mosquitoes (for example, no breeding grounds and blood meals). Given a small starting mosquito population at location X = 5 km, the natural mosquito population gradually grows and progressively propagates to the neighborhoods in the natural habitat, in the absence of GM release.

Figure 4 demonstrates the scaled female mosquito population distributed over the distance of 10 km, at five increasing time steps t_1 to t_5. At each location, the population increases with time, until it reaches the steady state at t_5. Further, at steady state, the female population gradually decreases near to the computational boundaries, where the conditions are not favorable to mosquitoes. To eradicate the wild mosquito population in this habitat, GM male mosquitoes are released continuously at the location X = 5 km at the rate of 0.75 M_T/F/day. Figure 5 depicts the spatial distribution of GM male mosquitoes at steady state condition, indicating rapid decrease of GM male population away from the release site.
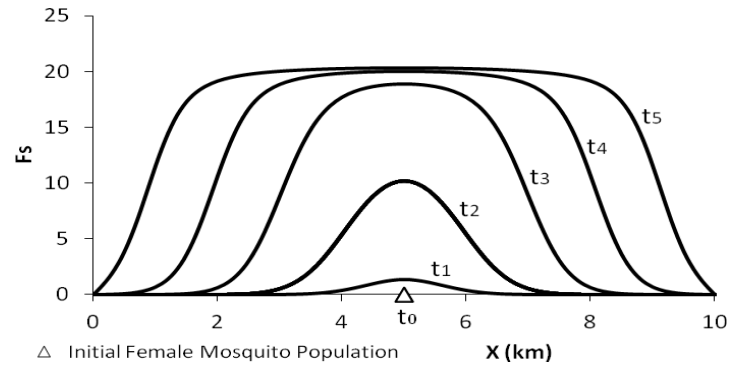
Figure 4: Spatial distribution over time of female mosquitoes in the absence of GM males
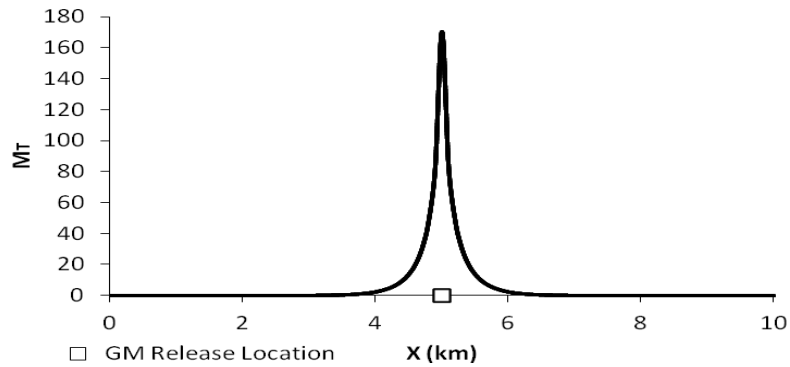

Figure 5: Spatial distribution of GM males with a continuous release (0.75 M_T/F/day) at X = 5 km

Figure 6 shows the simulated spatial distribution (over increasing time steps) of females subject to a continuous release of GM males at location X = 5 km. Near to the release site, the GM males help to maintain the wild population at low levels as desired. However, wild mosquitoes from adjacent areas gradually invade the GM release site and its neighborhoods. At steady state, female population near to the GM release site has grown significantly. Further, at location barely a few km away from the release site, the wild populations are hardly affected. The population levels would depend on several key parameters involved in the population dynamics. Yet these key parameters are not accurately known. These simulation results would indicate that the strategy of GM male release to control natural mosquito population is not sustainable in the long run.
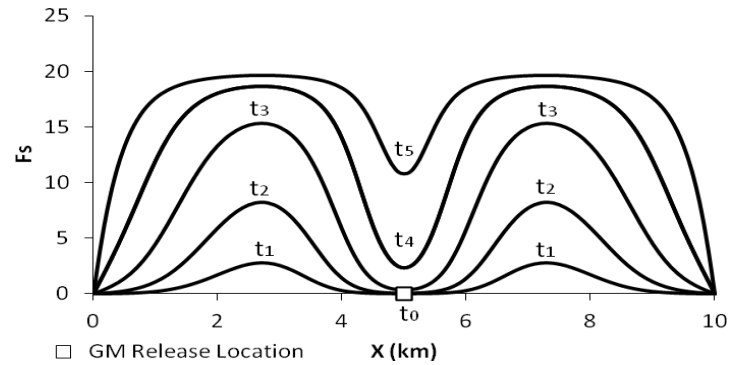
Figure 6: Spatial distribution over time of female mosquitoes subject to continuous release of GM males (0.75 M_T/F/day) at X = 5 km

4.   CONCLUSION

In summary, the proposed GM mosquito release program is not a viable strategy to eradicate natural *A. aegypti* mosquitoes. Significant reduction of wild mosquito population is possible only if large over-flooding ratios are applied. Further, repeated releases must be maintained over an infinite time horizon to continue to sustain low wild mosquito population. Major difficulty remains to be resolved. In particular, in-depth cost-benefit analysis on this control program is essential to ensure long-term institutional support.

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