Modeling spreading and interaction between wild and transgenic mosquitoes with randomic diffusion

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Abstract. *Due to recent advances in genetic manipulation, transgenic mosquitoes may be a viable alternative to reduce some diseases. Feasibility conditions are obtained by simulating and analyzing mathematical models that describe the behavior of wild and transgenic populations living in the same geographic area. In this work, we present a reaction–diffusion model where the reaction term is a nonlinear function that describes the interaction between wild and transgenic mosquitoes taking into account the zygosity. The system of partial differential equations obtained is solved numerically by combining Runge-Kutta's method and finite element method through the sequential operator splitting technique. This scheme is numerically implemented considering uncertainty in the diffusion parameters of the model. Simulations indicate that the best release strategy for transgenic mosquitoes is not punctual, but covering the region where there are wild mosquitoes.*

Keywords: *Mathematical model, transgenic mosquitoes, reaction-diffusion systems, operator splitting, uncertainty.*

Introduction

Vector-borne diseases have always been of great concern to populations and government authorities in countries with tropical climate, especially those with low human development. The combination of favorable climate with precarious conditions of basic sanitation provides ideal environmental conditions for the proliferation of many vectors causing various types of diseases that affect populations of these regions. Besides the acceleration of global warming, especially in the last decade, has been extended to regions beyond the tropics, making many of these diseases a focus of worldwide attention.

According to the World Health Organization, about 17% of the global population suffers from mosquito-borne infectious diseases, with malaria being the most deadly, resulting in 395,000 deaths in 2015. However, among the vector-borne diseases, the incidence of dengue is the fastest growing in the world, with a 30-fold increase over the past 50 years WHO (2015). In addition to malaria and dengue, yellow fever, chikungunya, zika and others are also prominent.

Vector control is the primary way to prevent and reduce transmission of these diseases. Combined strategies are strongly designed to achieve the greatest benefit of controlling the proliferation of diseases, minimizing impacts to the ecosystem as well as adverse effects on public health. It is then necessary to understand the local vector ecology and the local patterns of disease transmission so that we can choose the appropriate vector control tools from the wide range of available options.

Within recent advances in genetic manipulation of mosquitoes, in particular, *Aedes spp.* and *Anopheles spp.*, there has been considerable enthusiasm in the search for novel vector control approaches to prevent a range of diseases. In this way, the use of genetically modified mosquitoes can be a promising alternative to control mosquito–borne infections besides the traditional prophylaxis, vaccines, medication, and insecticides.

The conception of control diseases by genetic manipulation is not new, its concept arises in the 1930s-40s for control of arthropod vectors by three independent research pioneers: Serebrovskii (1940), Vanderplank (1947) and Knipling (1955). Considerable researches about genetic strategies to control mosquitoes were conducted during the 1970s (Curtis et al., 1976) on mosquitoes populations with sterile males. A review of applications of genetics to vector control can be seen in Amaku et al. (2014), Bowman et al. (2005) and Dyck et al. (2005).

The notion of increasing a gene frequency, in a vector population, that interferes with a pathogen has made substantial progress, Collins and James (1996), whose hypothesis result in the reduction or elimination of transmission of that pathogen. Laboratory-based discovery research is now underway on a variety of genetic engineering strategies for controlling arthropod vectors of disease, producing mosquitoes that, when released, reproduce with wild mosquitoes and cause their offspring to be refractory to diseases (Ito et al., 2002), (Moreira et al., 2002), unable to detect CO_2 (McMeniman et al., 2014), carrying a lethal gene (Thomas et al., 2000) or sterile (Dyck et al., 2005).

Genetically modified mosquitoes refractory to malaria, for example, were first obtained in 2002 using a technique developed in Catteruccia et al. (2000). To obtain them, scientists have developed two different types of transgenic mosquitoes of species *Anopheles stephensi* using the CP (carboxypeptidase) promoter: one of them expressed the synthetic peptide SM1 (salivary gland and midgut binding peptide 1) (Ito et al., 2002), while other expressed the enzyme PLA2

(phospholipase A2) present in bee venom (Moreira et al., 2002).

Assuming these ideas and linking them with mathematics models, the dynamics governing the interaction between wild and transgenic mosquitoes has been studied ever since. For example, Li (2004) presented a discrete system model that considered the interaction between two varieties of mosquitoes: wild and transgenic, without distinction of zygosity; a continuous version was obtained from Li (2007) and the impact of transgenic mosquitoes on malaria transmission in Li (2011). In another way, a discrete time model, without distinction of zygosity and taking into account only the horizontal and vertical transmission of a genetically modified bacterium was proposed by Li (2012); in this case, horizontal transmission depends on mating between wild mosquitoes and those that have mutated due to contact with the bacteria. Continuous modeling with the distinction of zygosity was proposed by Wyse et al. (2016) and Wyse et al. (2017), based on the initial sketch for the interaction between three varieties of mosquitoes: wild, heterozygous and homozygous transgenic shown in Wyse (2007). A version in dimensionless form was considered in the model of Diaz et al. (2011), where the fitness of wild and transgenic mosquitoes was considered to be different.

Strategies for delivering malaria-resistant and sterile genetically modified mosquitoes are in Rafikov et al. (2009), Rafikov et al. (2010) and Li and Yuan (2015), respectively, using techniques of optimal and inundative control. Studies like these allow the achievement of sustainable genetic control programs, helping public health agencies in making decisions, indicating the amount of transgenics required, which genetic composition is most appropriate, the ideal and local timing for release, as well as cost implications. The goal of this paper is to propose a mathematical model so that these new transgenic insects must interact with the wild mosquitoes by mating, and spreading the transgene that determines the interruption of an epidemiological process, setting in the population. Thus, the applicability of the model may be, for example, to disease refractoriness and/or inability to find blood by CO_2 detection. In this text, we propose a continuous model that takes into account the zygosity of transgenic mosquitoes, for which, the total population was considered composed of three subpopulations of mosquitoes: wild, heterozygous and homozygous transgenics. The interaction between mosquitoes is a nonlinear dynamics, so that mating and competition occur, describing a density-dependency for vital rates and imposing a maximum limit of population growth that occurs according to the carrying capacity. An important aspect to be considered for this purpose, besides taking into account the zygosity of the population of transgenic mosquitoes, all populations are in absolute numbers, preserving parameters that can describe effects such as seasonality, stochasticity, etc. The spreading is governed by Fick's law, with randomic diffusion coefficient. Thus, the mathematical model obtained is a nonlinear reaction-diffusion system with uniformly distributed parameters.

In the following sections, we introduce a model of mosquito dispersal, with uncertainty parameters and nonlinear dynamics obtained by interaction between wild and transgenic populations. The parabolic partial differential equations resulting is epitomized by the nonlinear reaction-diffusion systems with uniformly distributed parameters, which represents two distinct, but simultaneously occurring processes. This distinction between processes, represented by reaction and diffusion operators, motivated the use of operator splitting techniques, also known as split-step methods. Operator splitting methods are well known in problems solving that result in large systems of partial differential equations as well as in problems involving nonlinear chemical reactions (Couto and Malta, 2008), mosquito dispersal (Dufourd and Du-

mont, 2013), the nonlinear Schrdinger applications (Taha and Xu, 2005) and others. Sequential and iterative splitting for nonlinear problems with locally Lipschitz-continuous operators, which generates lowest splitting error and convergence of first order, was presented and verified in Ladics (2016). Besides being physically meaningful, operator splitting simplifies the solution method in several ways. After splitting the system into two parts, we solve each one separately with the specialized numerical techniques, in this case, combining the fourth order Runge-Kutta method for the nonlinear dynamic problem and space-time finite element method with distributed parameters for the diffusion problem. The numerical solution obtained from different initial conditions show some of the possible scenarios, which will be discussed in order to investigate the propagation of transgenic mosquitoes on a domain, analyze their behavior on uncertainty parameter and some guidelines for future investigations.

Mathematical model of mosquito population dynamics

This section describes the population dynamics resulting from the introduction of genetically modified mosquito into a wild-type population. The proposed mathematical model is based on strategies aimed at the development of genetically modified mosquitoes that are engineered to have a reduced capacity to transmit a particular pathogen, fertile and able of propagating and perpetuate the inheritable trait of reduced pathogen transmission within the wild mosquito vector population. For this, let us consider transgenic mosquitoes expressing SM1 (Ito et al., 2002), so that no significant effect on fitness was observed for mosquitoes expressing this peptide (Moreira et al., 2004).

Mathematical modelling of mosquito dispersal

Let u_i, $i = 1, 2, 3$ denote populations of wild, heterozygous and homozygous transgenic mosquitoes, respectively. If we assume that the movement of individual mosquitoes is similar to Brownian motion, in a non-uniform field, then we can define the rate of change of mosquito density at time $t > 0$ as

$$\frac{\partial u_i(x,t)}{\partial t} = \kappa_i \frac{\partial^2 u_i(x,t)}{\partial x^2}, \tag{1}$$

where $x \in \overline{I}_d = [0, L] \subset I\!R$, the spatial domain, with $L > 0$, κ_i denoting the random diffusion coefficients rate of both wild and transgenic mosquito. These coefficients aim to evolve a probabilistic response, creating a random heterogeneous medium. We also assume that the boundary of region $\overline{I}_d$ does not permit mosquito transport and thus we have zero flux boundary conditions

$$\frac{\partial u_i}{\partial x}(0,t) = \frac{\partial u_i}{\partial x}(L,t) = 0. \tag{2}$$

This environment affecting mosquitoes dispersal behavior was considered by Lutambi et al. (2013) and the change of mosquitoes density was described by discrete-space continuous-time mathematical model, also Dufourd and Dumont (2013) showed that environmental parameters, like vegetation, may have an intrinsic influence on mosquito distribution and efficiency of vector control tools. Taking into account the relationship between environmental variability and dispersal of mosquitoes, it is feasible to consider diffusion coefficients are not deterministic parameters.

Table 1: Genotypic offspring frequencies obtained from all expected mating combinations between wild and transgenic heterozygous and homozygous mosquitoes

Matting / Genotype	$u_1 \times u_1$	$u_1 \times u_2$	$u_1 \times u_3$	$u_2 \times u_2$	$u_2 \times u_3$	$u_3 \times u_3$
(w, w)	a_{11}	a_{12}	0	a_{22}	0	0
(w, g)	0	b_{12}	b_{13}	b_{22}	b_{23}	0
(g, g)	0	0	0	c_{22}	c_{23}	c_{33}

The populations u_i have same fitness, ensuring equal reproductive success and reflecting how well transgenic mosquitoes are adapted to the wild environment, with the ability to compete and mate. Each individual progresses and emerges into adulthood at a rate ϵ and leaves due to mortality. Assuming a stable environment, competition for resources may occur leading to density-dependent mortality $\dfrac{\gamma \sum u_i}{C}$, being γ the intrinsic rate of growth, C the carrying capacity and $\sum u_i = u_1 + u_2 + u_3$, or natural death δ. These processes account for the dynamics of each subgroup over time.

Since allele combinations are equally likely to occur, the matings are random and a Punnett Square can be a tool to predict the probability of a mating producing each genotype (Hartl and Jones, 1998). Being mosquitoes diploid organisms, it is proper to establish wild mosquitoes genotype as (w, w) and homozygous transgenic genotype as (g, g), after crossing, we established homozygous populations (w, w) and (g, g) and heterozygous population (w, g), as can be seen in Table 1. The dominance of w or g will define the phenotype of heterozygous and depends on genetic manipulation, but it is out of the scope of this paper.

Let a_{ij}, b_{ij} and c_{ij} denote genotypic frequencies for u_1, u_2 and u_3 obtained from mating $u_i \times u_j$, $i, j = 1, 2, 3$, respectively. Table 1 shows that wild mosquitoes u_1 are generated from mating $u_1 \times u_1$ in the frequency of $a_{11} = 1$ while $u_1 \times u_2$ in the frequency of $a_{12} = 1/2$ and $u_2 \times u_2$ in the frequency of $a_{22} = 1/4$; heterozygous transgenic u_2 are generated from the mating $u_1 \times u_2$ in the frequency of $b_{12} = 1/2$, $u_2 \times u_2$ in the frequency of $b_{22} = 1/2$, $u_2 \times u_3$ in the frequency of $b_{23} = 1/2$ and $u_1 \times u_3$ in frequency of $b_{13} = 1$; homozygous transgenic u_3 are generated from mating $u_2 \times u_2$ in the frequency of $c_{22} = 1/4$, $u_2 \times u_3$ in the frequency of $c_{23} = 1/2$, and $u_3 \times u_3$ in the frequency of $c_{33} = 1$.

From assumptions above, the dynamics of interaction between wild and transgenic mosquitoes with spreading can be established as follows:

Spatio-temporal model: Denote $\overline{I}_d \equiv [0, L]$ the spatial domain and $\overline{I}_t \equiv [t_0, T]$ the time interval, with $t_0 \geq 0$ representing the initial time and $T > 0$ the final time. Let $(\Omega; \mathscr{F}; P)$ be a probability space in which the variations of the random inputs exhibit, where Ω is the set of outcomes, $\mathscr{F} \subset 2^{\Omega}$ is the σ-algebra of events and $P : \mathscr{F} \to [0, 1]$ is a probability measure. Given $\{a_{ij}, b_{ij}, c_{ij}, \gamma, C, \delta\} \in I\!R$, the model problem is to find the population of mosquitoes $u_i(x, t, \omega) \in I\!R$ for all $x \in \overline{I}_d$, $t \in \overline{I}_t$ and $\omega \in \Omega$ such that satisfying the following system of

nonlinear boundary value problem with random diffusion coefficient

$$\begin{cases} \dfrac{\partial u_1}{\partial t} = \kappa_1(\omega)\dfrac{\partial^2 u_1}{\partial x^2} + \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(a_{11}u_1^2 + 2a_{12}u_1u_2 + a_{22}u_2^2\right) - \delta u_1, \\ \dfrac{\partial u_2}{\partial t} = \kappa_2(\omega)\dfrac{\partial^2 u_2}{\partial x^2} + \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(2b_{12}u_1u_2 + b_{22}u_2^2 + 2b_{23}u_2u_3 + \right. \\ \qquad\qquad\qquad\qquad \left. + 2b_{13}u_1u_3\right) - \delta u_2, \\ \dfrac{\partial u_3}{\partial t} = \kappa_3(\omega)\dfrac{\partial^2 u_3}{\partial x^2} + \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(c_{22}u_2^2 + 2c_{23}u_2u_3 + c_{33}u_3^2\right) - \delta u_3, \end{cases} \tag{3}$$

with Neumann boundary conditions given by

$$\frac{\partial u_i}{\partial x}(0,t) = \frac{\partial u_i}{\partial x}(L,t) = 0, \tag{4}$$

and initial conditions

$$u_i(x,t_0) = \overline{u}_i(x), \tag{5}$$

Here the diffusion coefficients κ_i are uniformly distributed random fields in the range $[\kappa_{min}, \kappa_{max}] \subset I\!R$, written as $\kappa_i \sim U(\kappa_{min}, \kappa_{max})$. These coefficients will be useful to improve the computational model and calibrate a known parameter in order to build a regularized solution u_i.

Adding up the three Eq. (3), the total mosquitoes population is described by Verhulst–Pearl logistic equation with harvesting

$$\frac{dN}{dt} = \gamma N\left(1 - \frac{N}{C}\right) - \delta_2 N, \tag{6}$$

where $N = \sum u_i$ is the total population of mosquitoes and $\gamma = \varepsilon - \delta_1$, being ε the rate of emergence of mosquitoes into adulthood and δ_1 the mortality rate due to natural causes. The capture effect represented by density-independent mortality rate δ_2, ensure stabilization of the population below of the carrying capacity C, more precisely at non-null equilibrium point

$$N^* = C\left(1 - \frac{\delta_2}{\gamma}\right).$$

Mosquitoes population dynamics described by Eq. (6) was fitted to field data for some regions in Wyse (2007) and Wyse et al. (2007), with accurate results. Mathematical models considering variable mosquito population were used in Ngwa (2000), Ngwa (2004) and Wyse et al. (2007), suggesting the logistic form to intraspecific competition.

Numerical Formulation

In this section, we focus on the development of discrete formulations and applications of computational techniques to numerically solve the proposed model. For this, we present an operator splitting method (Geiser, 2009) used to solve the nonlinear reaction-diffusion system (3). The idea is to decouple the original system into another equivalent, generating a combination

of two distinct physical subsystems formed by problems of less complexity. Taking advantage of favorable structure of the reaction-diffusion system, which allows a natural decomposition into independent problems of different mathematical nature, we were motivated to construct the resolution algorithm based on operator splitting method. The advantage of adopting this type of strategy is that we can prevent systems that require costly operations and have the possibility to choose the most optimized algorithms for each operator.

Now we will consider here the sequential operator-splitting method, which solves two subproblems sequentially on each time subinterval and connects them via initial conditions. To describe the developed algorithm, we proceed with a natural decomposition of the system (3) into two coupled new problems: a system of partial differential equations with the purely diffusive term, and a system of nonlinear differential equations, associated with the purely reactive term. To solve the diffusive problem, we will use the semi-discrete finite element method with an implicit finite difference scheme of the type Crank-Nicolson. The second system, that is nonlinear, will be solved using the fourth-order Runge-Kutta method due to its better accuracy. The uncertainty on diffusion parameter was quantified using Monte Carlo method.

Introducing temporal discretization $\overline{I}_t = [t_0, T] = \bigcup_{n=0}^{N} I_{t_n}$, such that $I_{t_n} = [t_n, t_{n+1}]$ is a partition of I_t,, $N = T/\Delta t$ number of partitions of I_t, and $\Delta t = t_{n+1} - t_n$ the time step, assumed to be uniform, we follow the procedure below:

***Step 1*:** For the initial time, $t = t_0$, initialize the variables $u_i(x, t_0) = \overline{u}_i(x)$, for each $i = 1, 2, 3$.

***Step 2*:** For some fixed $n \geqslant 0$, considering known the initial conditions $u_i(x, t_n)$ and defining $\breve{u}_i(t_n) = u_i(x, t_n)$, we calculate $\widetilde{u}_i(x, t)$ in the time step t_{n+1} through the following problem:

Problem A: Given $\kappa_i : \Omega \to (0, \infty)$, to find $\widetilde{u}_i(x, t, \omega) \in I\!R$, with $x \in \overline{I}_d$, $t \in I_{t_n}$ and $\omega \in \Omega$, satisfying the following subsystem:

$$\frac{\partial \widetilde{u}_i(x,t,\omega)}{\partial t} = \kappa_i(\omega) \frac{\partial^2 \widetilde{u}_i(x,t,\omega)}{\partial x^2}, \tag{7}$$

with boundary conditions

$$(\widetilde{u}_x)_i(0,t) = (\widetilde{u}_x)_i(L,t) = 0, \tag{8}$$

and initial conditions

$$\widetilde{u}_i(x, t_n) = \breve{u}_i(t_n). \tag{9}$$

***Step 3*:** In the same time interval I_{t_n}, we use the solution of Problem A, given by the previous step, as the initial condition for calculating the solution of the system of coupled nonlinear ordinary differential equations, associated with the model reaction term (3), expressed by the following problem:

Problem B: Given $\{a_{ij}, b_{ij}, c_{ij}, \gamma, C, \varepsilon\} \in I\!R$, find $u_i(t) \in I\!R$, $t \in I_{t_n}$ satisfying the following

subsystem:

$$\begin{cases} \dfrac{du_1}{dt} = \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(a_{11}u_1^2 + 2a_{12}u_1u_2 + a_{22}u_2^2\right) - \delta u_1, \\ \dfrac{du_2}{dt} = \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(2b_{12}u_1u_2 + b_{22}u_2^2 + 2b_{23}u_2u_3 + 2b_{13}u_1u_3\right) - \delta u_2 \\ \dfrac{du_3}{dt} = \left(\dfrac{\epsilon}{\sum u_i} - \dfrac{\gamma}{C}\right)\left(c_{22}u_2^2 + 2c_{23}u_2u_3 + c_{33}u_3^2\right) - \delta u_3, \end{cases} \tag{10}$$

with initial condition

$$u_i(t_n) = \widetilde{u}_i(x, t_{n+1}), \tag{11}$$

being $\widetilde{u}_i(x, t_{n+1})$ the solutions obtained from Problem A. In the vector form, the Eqs. (10) - (11) reduces to

$$\frac{d\mathbf{u}}{dt} = \mathbf{F}(t, \mathbf{u}), \quad \mathbf{u}(t_n) = \widetilde{\mathbf{u}}(t_{n+1}). \tag{12}$$

***Step 4*:** The solution of Problem B is given by approximate solution of the model at $t_{n+1} \in I_{t_n} \subset I_t$. If $t_{n+1} < T$, increments n, returns to step 2 and repeat the process until equality occurs.

Solution of the Problem A

In order to solve Problem A, we propose a primary variational formulation and introduce its approximation using a semi-discrete Galerkin finite element method with uniformly distributed parameters, using the Monte Carlo scheme to obtain the first and second moment of the solution. Let $V = \{v_i(x,t) \in H^1(I_d) \mid v_i(0,t) = v_i(L,t) = 0\}$ be the space of weight functions, the spatial domain is discretized using an uniform finite element partition consisting in n_e elements I_e, such that $\overline{I}_d = \bigcup_{e=1}^{n_e} I_e$ and $\bigcap_{e=1}^{n_e} I_e = \emptyset$. Let $V_h = \{v^h(x,t) \in C^0(I_d) \mid v^h(0) = v^h(L) = 0, \forall\, v^h(I_e) \in \hat{P}_l(I_e)\} \subset V$ be the Lagrangian finite element space of class $C^0(I_d)$ and degree l. Thus, the problem to be approximated is given by:

Problem (A_h): For each realization on the diffusion parameter $\{\kappa_i(\xi^{(k)}) \in [\kappa_{min}, \kappa_{max}]\}$ $(k = 1, \ldots, N_r)$ (N_r is the sample size), find $\widetilde{u}_i^h(x, t, \xi^{(k)}) \in V_h$, with $t \in I_{t_n}$ and $\xi^{(k)}$ uniformly distributed on interval $[0, 1]$, such that

$$\int_0^L \frac{\partial \widetilde{u}_i^h v^h}{\partial t} dx + \int_0^L \kappa_i(\xi^{(k)}) \frac{\partial \widetilde{u}_i^h}{\partial x} \frac{\partial v^h}{\partial x} dx = 0, \quad \forall v^h \in V_h, \tag{13}$$

and initial conditions

$$\widetilde{u}_i^h(x, t_n) = \breve{u}_i(t_n). \tag{14}$$

In order to solve this problem, we will use a semi-discrete finite element method. For this, take the time approximation t of the form

$$\widetilde{u}_i^h(x,t) = \sum_{j=1}^{n_p} \widetilde{u}_{ij}(t)\varphi_j(x)$$

and $v^h(x,t) = \sum_{m=1}^{n_p} \varphi_m(x)$ to construct the interpolation and test functions of the finite element method, respectively. Here n_p is the total number of degrees of freedom and $\varphi_j(x)$ are global form functions. Then, the discrete form of the problem leads to the following system of ordinary differential equations:

$$\begin{aligned} \sum_{j=1}^{3n_p} \left[M_{mj} \frac{d(\widetilde{u}_i)_j}{dt} + K_{mj}^{(k)} \widetilde{u}_i \right] &= 0, \qquad 1 \leqslant m \leqslant 3n_p, \\ \widetilde{u}_i(0) &= \breve{u}_i(x), \end{aligned} \tag{15}$$

where

$$M_{mj} = \int_{I_e} \varphi_m(x)\varphi_j(x)dx, \tag{16}$$

$$K_{mj}^{(k)} = \int_{I_e} \kappa_i(\xi^{(k)})\varphi'_m(x)\varphi'_j(x)dx, \tag{17}$$

which can be written in the following matrix form:

$$\begin{aligned} \mathbf{M}\frac{d(\widetilde{\mathbf{u}}(t))}{dt} + \mathbf{K}^{(k)}\widetilde{\mathbf{u}}(t) &= \mathbf{0}, \\ \widetilde{\mathbf{u}}(t_n) &= \breve{\mathbf{u}}(t_n), \end{aligned} \tag{18}$$

By definition, the mass matrix $\mathbf{M}$ and stiffness $\mathbf{K}^{(k)}$ are defined positively and symmetrically for each index k. Since the matrix $\mathbf{M}$ is invertible, the system of ordinary differential equations has a unique solution $\widetilde{\mathbf{u}}(t)$ to $t \in I_t$. Thus, to solve numerically the system (18), we will use the transient algorithm to obtain the vector $\widetilde{\mathbf{u}}^n = (\widetilde{u}_1^n, \widetilde{u}_2^n, \widetilde{u}_3^n), \forall\, n \in \mathbb{N}$. For this, we consider a semi-discrete formulation

$$\begin{aligned} \mathbf{M}\boldsymbol{\nu}^{n+1} + \mathbf{K}^{(k)}\widetilde{\mathbf{u}}^{n+1} &= \mathbf{0}, \\ \widetilde{\mathbf{u}}^{n+1} &= \widetilde{\mathbf{u}}^n + \Delta t \boldsymbol{\nu}^{n+\alpha}, \\ \boldsymbol{\nu}^{n+1} &= (1-\alpha)\boldsymbol{\nu}^n + \alpha\boldsymbol{\nu}^{n+1}, \end{aligned} \tag{19}$$

where $\alpha = 1/2$. Consequently, the equation derived from expression (19) in function of $\mathbf{u}$ has the mathematical form:

$$(\mathbf{M} + \alpha\Delta t\mathbf{K}^{(k)})\widetilde{\mathbf{u}}^{n+1} = (\mathbf{M} - (1-\alpha)\Delta t\mathbf{K}^{(k)})\widetilde{\mathbf{u}}^n. \tag{20}$$

Solution of the Problem B

In order to solve the system of ODE defined by Eq. (10), we employ the equations of fourth order Runge-Kutta method given by

$$\widetilde{\mathbf{u}}^{n+1} = \widetilde{\mathbf{u}}^n + \frac{h}{6}(\mathbf{k}_1 + 2\mathbf{k}_2 + 2\mathbf{k}_3 + \mathbf{k}_4) \tag{21}$$

where,

$$\begin{aligned} \mathbf{k}_1 &= h\mathbf{F}(t_n, \widetilde{\mathbf{u}}^n), \\ \mathbf{k}_2 &= h\mathbf{F}(t_n + \frac{h}{2}, \widetilde{\mathbf{u}}^n + \frac{k_1}{2}), \\ \mathbf{k}_3 &= h\mathbf{F}(t_n + \frac{h}{2}, \widetilde{\mathbf{u}}^n + \frac{k_2}{2}), \\ \mathbf{k}_4 &= h\mathbf{F}(t_n + h, \widetilde{\mathbf{u}}^n + k_3), \end{aligned}$$

and $\widetilde{\mathbf{u}}$, $\mathbf{f}$ are terms associated with system reaction (10).

Finally, the statistical moments of the discrete variables are computed by generating a population of N_s samples $\{\widetilde{u}_i^n(\cdot,\xi^{(k)}),\ k=1,\ldots,N_s; i=1,2,3\}$ corresponding to the problems A and B. The mean and variance are computed using the approximation

$$\mu(\widetilde{u}_i) = \frac{1}{N_s}\sum_{k=1}^{N_s}\widetilde{u}_i(\cdot,\xi^{(k)}), \tag{22}$$

$$\sigma^2(\widetilde{u}_i) = \frac{1}{N_s}\sum_{k=1}^{N_s}(\widehat{u}_i(\cdot,\xi^{(k)}))^2, \tag{23}$$

respectively, where $\widehat{u}_i = \widetilde{u}_i - \mu(\widetilde{u}_i)$ is the fluctuation around the mean.

Numerical experiments

In this section we report results of numerical experiments performed to illustrate the behavior of computational techniques to numerically solve the proposed diffusion-reaction model problem.

The numerical simulations presented in a transient media were obtained using the Crank-Nicolson method with a step-time $\Delta t = 0.01$ month, on a time domain $\overline{I}_t = [0,4]$ which corresponds to four months, while the spatial domain $\overline{I}_d = [0,30]$ was uniformly discretized into 460 elements on a mesh defined in km.

We also used the coefficients estimated in Wyse et al. (2007) and those estimated in Section 2 and summarized in Table 2. The solution of the model was computed by the Monte Carlo method. For this, we employ 500 unconditional realizations generated from a uniform distribution in the interval $[0.35, 0.5]$, and studied the regularity of the solution, considering the diffusion coefficient κ_i, $i = 1,2,3$ on this interval. The quality of these realizations are examined for each experiment proposed in the model by comparing their sample statistics (mean, variance) of these realizations.

This assumption assures us that, there are not evidence about differences in flight ability for wild and transgenic mosquitoes, and consequently all mosquitoes have the same probability to dispersal. Furthermore, these experiments put the uncertainty in a scenario where the diffusion of wild mosquitoes and transgenic mosquitoes varies randomly in the same range.

The scenarios in the following section represent the population dynamics of each specie on different initial conditions. We assume that all mosquito population is zero at the boundaries and no flux occurs, being completely unsuitable for species mosquitoes no breeding grounds and blood meals. Given a starting mosquito population, the wild and transgenics populations gradually grows or decreases, according to the dynamics imposed by the reaction term, and progressively propagates to the neighborhoods in the natural habitat.

For the numerical simulations, no homozygous transgenic individual was released but arises naturally from the mating process. In laboratory experiments is common to work with heterozygous lines, obtaining homozygous lines by crossing for some generations, because heterozygous are not subject to the inbreeding, leading to a reduction in fitness, and also there are situations in which mutations are usually recessive (see Catteruccia et al. (2003), Marrelli et al. (2006)).

Parameter	Description	Value
I_d	Spatial domain (km)	[0,10]
κ_i	Diffusion coefficients(km^2/month)	$[0.3, 0.5]$
ϵ	Recruitment rate to the adult stage (month^{-1})	8.114
δ_1	Death rate (month^{-1})	4
δ_2	Death rate (month^{-1})	2.545
C	Carrying capacity	85
a_{ij}	Genotypic frequency of u_1	$a_{11} = 1.0$, $a_{12} = 0.5$, $a_{22} = 0.25$
b_{ij}	Genotypic frequency of u_2	$b_{12} = b_{22} = b_{23} = 0.5$, $b_{13} = 1.0$
c_{ij}	Genotypic frequency of u_3	$c_{22} = 0.25$, $c_{23} = 0.5$, $c_{33} = 1.0$

Table 2: Parameters of model, with ϵ, δ_1 , δ_2 and C estimated in Wyse et al. (2007) and a_{ij}, b_{ij}, c_{ij} obtained in Section 2.

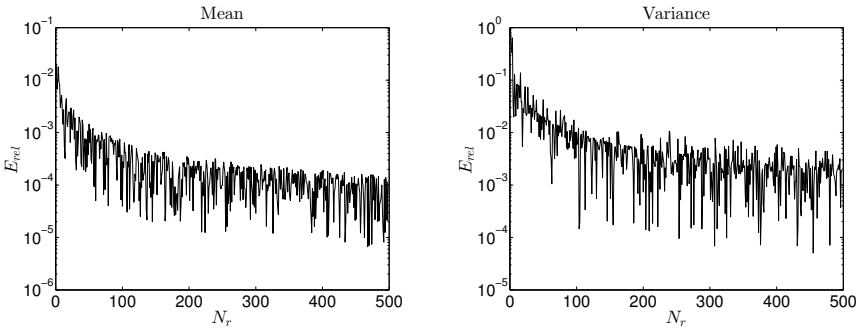
We will present an experiment whose initial conditions are equivalent to laboratory experiment conducted by Moreira et al. (2004). This experiment started by crossing heterozygous transgenic mosquitoes expressing SM1 in the gut and GFP (Green Fluorescent Protein) as a marker in the eyes, resulting in a frequency of 44% GFP positive and 56% GFP negative for the subsequent generations (Hardy-Weinberg equilibrium) that imply no fitness load. In our simulation we consider 200 wild and 200 heterozygous transgenic mosquitoes homogeneously distributed over a $4\ km$ stretch and simulate their behavior during 4 months. This start situation is represented by the following initial conditions:

$$u_1(x,0) = u_2(x,0) = \begin{cases} 50 \quad if \quad 13 \leq x \leq 17, \\ 0 \quad if \quad 0 \leq x < 13 \quad and \quad 17 < x \leq 30 \end{cases} \tag{24}$$
$$u_3(x,0) = 0.$$

In order to check the quality of the realizations, we compute the solution of various samples in the last step of time and calculate the relative error of the mean and variance of wild mosquitoes defined as

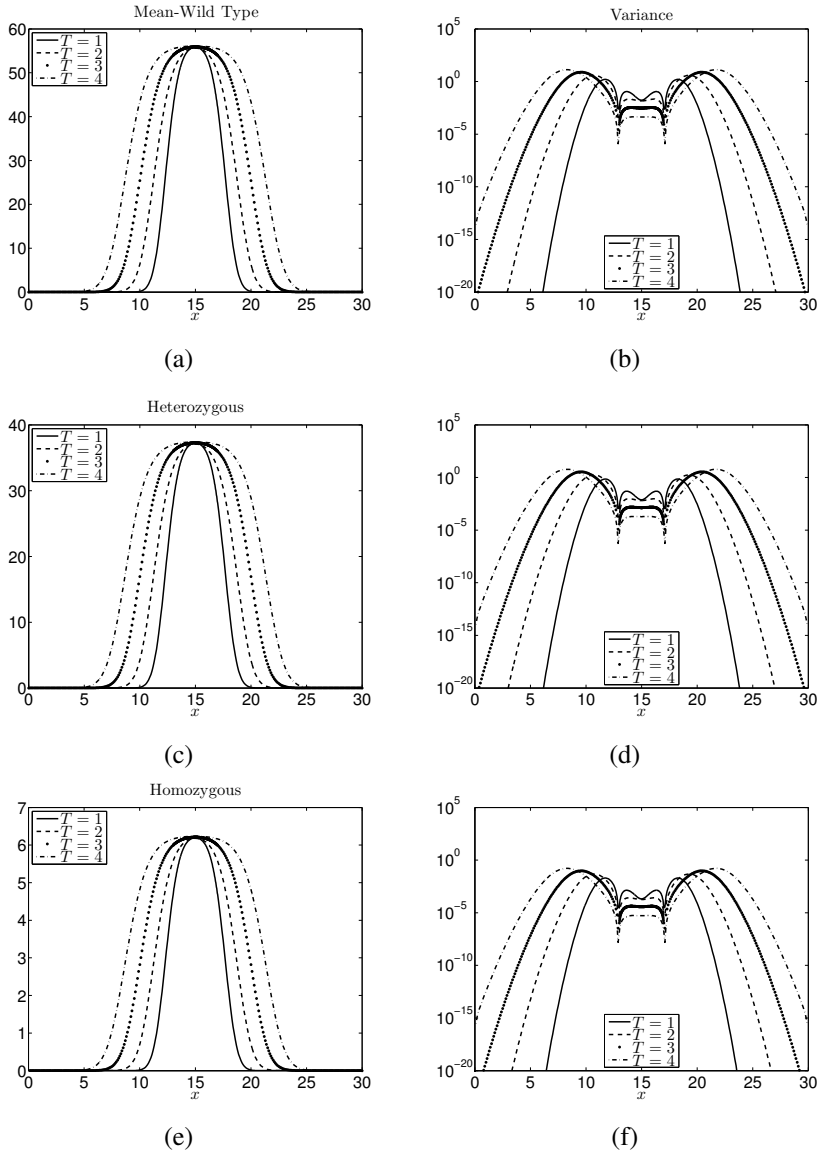
$$E_{rel}(N_r) = \frac{\|m_{u_1}(N_r) - m_{u_1}(N_r+1)\|}{\|m_{u_1}(N_r+1)\|}. \tag{25}$$

Here $m_{u_1}(N_r)$ denotes the mean or variance of N_r samples generated by the target solution which was computed on L^2-norm. Once computed the relative error of the mean and variance for the N_r realizations, was chosen the target solution with 500 realizations since the fluctuation of the relative error in both moments is converging to values close or below 10^{-3} (see Figs. 1). Similar results were obtained for the transgenic populations, and therefore they were omitted from the text in all other experiments.



(a) (b)

Figure 1: Statistical convergence of first and second moment of the wild mosquito population. Relative error: (a) Mean and (b) Variance.

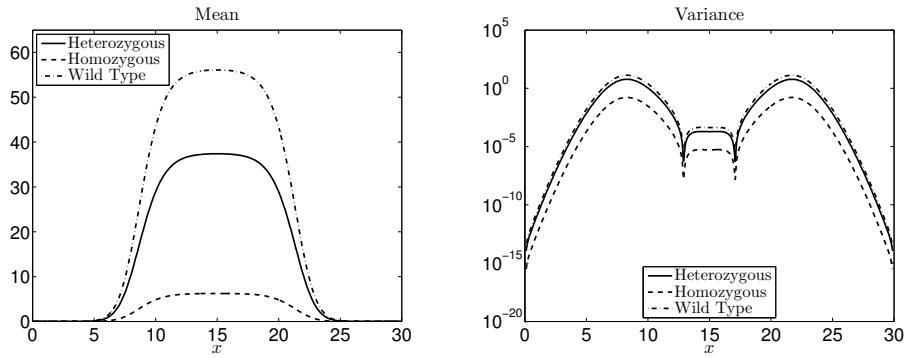


(a) (b)

(c) (d)

(e) (f)

Figure 2: Level curves at times $t = 1, 2, 3, 4$ months of (a)-(c)-(e) Mean and (b)-(d)-(f) Variance (semi-log scale) of population of wild, heterozygous and homozygous transgenic mosquitoes on initial conditions (24)**.**



(a) (b)

Figure 3: Level curves considering the last step of time of (a): Mean and (b) Variance (semi-log scale) of population of wild mosquitoes, heterozygous and homozygous transgenic on initial conditions (24)**.**

In this first experiment, whose moments are presented in Figures 2 – 3 show the behavior of the mean and variance of three varieties starting with 200 wild, 200 heterozygous and none homozygous, distributed homogeneously over the central $4\ km$ from $30\ km$ available, according to initial conditions (24). In this scenario, none homozygous transgenic individual has been released, but it will arise naturally from the mating process. The average amount of mosquitoes obtained at the end of each month, represented by mean $\mu^T(\cdot)$ and its respective variance by $\sigma^{2T}(\cdot)$, $i = 1, 2, 3$, resulting from the integration of the obtained solution into the $\overline{I}_d$ domain is presented in Table 3. Here we compute the total population on a fixed diffusion and another randomly varying. In second moment we use the semi-log scale in order to better visualize the discrepancy between the average amount of mosquitoes for each variety obtained from fixed and randomic difusion parameter. The value of this integral is obtained by the trapezoidal rule correspond to approximately 56% of wild mosquitoes and 44% of transgenic (heterozygous and homozygous) mosquitoes, in accordance with the experiment described in Moreira et al. (2004) to initial conditions (24). In addition, the variance begins very small due to the strong influence of the deterministic initial data. As time evolutes, the profile grows with higher uncertainty in the half-range and decreases again in the center of the domain. These results also include an approximate variation of 5% on the population of wild mosquitoes and 2% of transgenic mosquitoes indicating a low variability of the samples associated with initial condition of this experiment. Besides, the coverage was increased from $4\ km$ to $22\ km$, being distributed at the end of 4 months from $x = 4$ until $x = 26$.

In the next experiment, we will consider an initial population composed by 200 wild, 100 heterozygous and none homozygous, distributed over $30\ km$ in different ways, in order to obtain clues as to how best to release transgenic mosquitoes.

Initial conditions for the second experiment describe an initial population starting from the

	$t=1$	$t=2$	$t=3$	$t=4$
$\mu^T(u_1)$	291.7848	399.9036	532.8329	680.6816
$\sigma^{2T}(u_1)$	3.9993	13.1030	31.0411	59.5581
$\mu^T(u_2)$	194.6214	266.6026	355.2220	453.7877
$\sigma^{2T}(u_2)$	1.7789	5.8236	13.7960	26.4703
$\mu^T(u_3)$	32.3878	44.4337	59.2037	75.6313
$\sigma^{2T}(u_3)$	0.0493	0.1618	0.3832	0.7353

Table 3: Total populations of the corresponding estimated values of the mean and variance at $t = 1, 2, 3, 4$, using Monte Carlo simulations, both on initial conditions (24)**.**

following distribution:

$$u_1(x,0) = \begin{cases} 50 & if \quad 13 \leq x \leq 17, \\ 0 & if \quad 0 \leq x < 13 \quad and \quad 17 < x \leq 30 \end{cases}$$

$$u_2(x,0) = \begin{cases} 25 & if \quad 13 \leq x \leq 17, \\ 0 & if \quad 0 \leq x < 13 \quad and \quad 17 < x \leq 30 \end{cases} \tag{26}$$

$$u_3(x,0) = 0.$$

It means that, in a $4\ km$ range centered in $[0, 30]$ containing 200 wild-type mosquitoes homogeneously distributed, 100 heterozygous transgenic mosquitoes will be inserted, according to (26). Numerical simulations presented in Figures 4–5 illustrate mean and variance of wild, heterozygous and homozygous transgenic mosquitoes.

Comparing Tables 3 and 4, this reduction of 50% of initial conditions of heterozygous transgenic in relation to initial conditions (24) implies a final lost of 31% heterozygous and 58.56% homozygous transgenics. On another hand, wild mosquitoes are increasing in 13.11%. At the end of 4 months of simulation, there are 69.44% wild, 27.78% heterozygous and 2.78% homozygous transgenic mosquitoes to initial conditions (26). This consequently contributed to the growth of wild mosquito variance to 7.6% and a decrease of trangenic mosquitoes corresponding to 1.2% both on its total population. Similar influence of the initial conditions on the first experiment is also observed in this experiment.

Conclusions

In this paper we present the development of the first mathematical model to describe the interaction and spreading of wild and transgenic mosquitoes taking into account the zygosity, considering all populations in absolute numbers and admitting randomic diffusion coefficients.

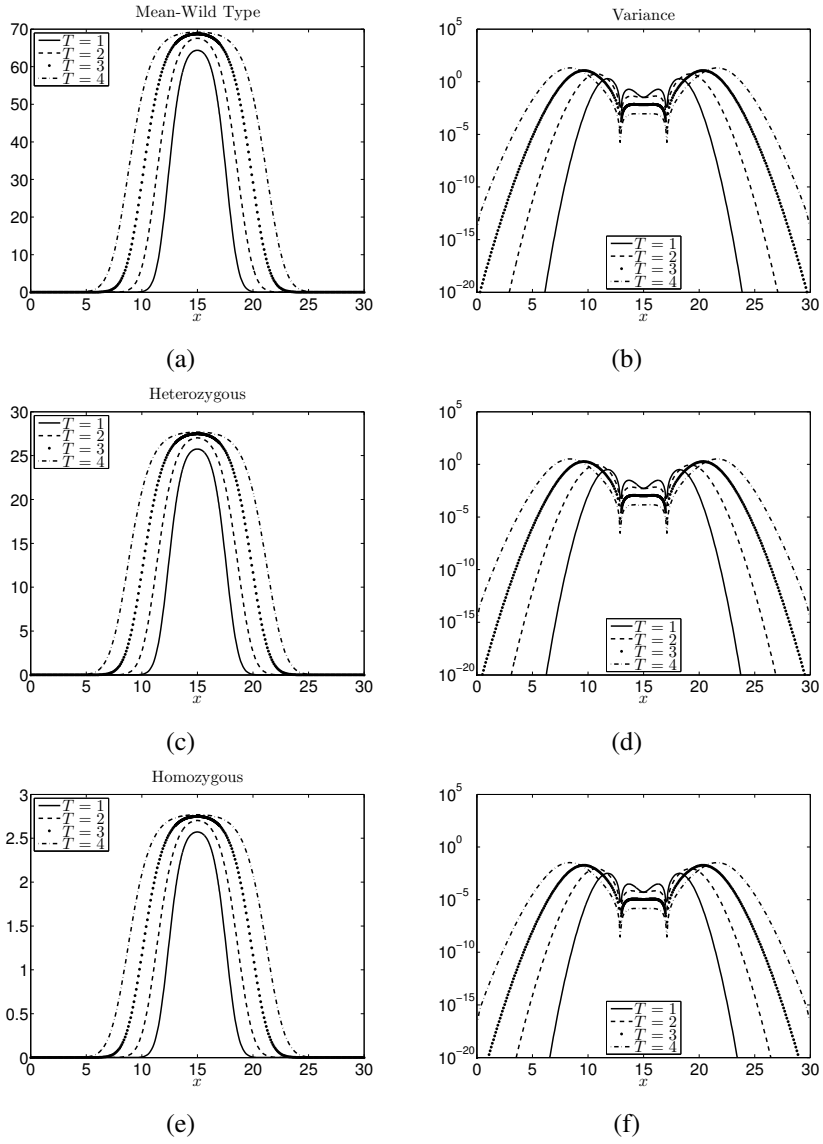


Figure 4: Level curves at times $t = 1, 2, 3, 4$ months of (a)-(c)-(e) Mean and (b)-(d)-(f) Variance (semi-log scale) of population of wild, heterozygous and homozygous transgenic mosquitoes on initial conditions (26)**.**

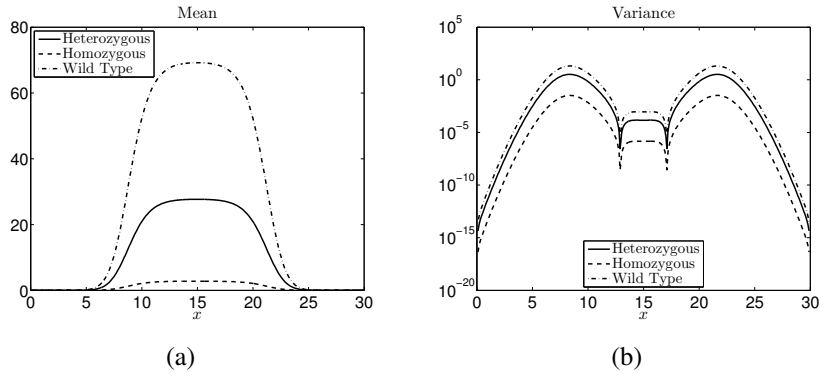


Figure 5: Level curves considering the last step of time of (a): Mean and (b) Variance (semi-log scale) of population of wild mosquitoes, heterozygous and homozygous transgenic on initial conditions (26)**.**

	$t=1$	$t=2$	$t=3$	$t=4$
$\mu^T(u_1)$	328.2072	473.5665	641.8788	825.8599
$\sigma^{2T}(u_1)$	5.0587	18.5888	46.4850	91.4454
$\mu^T(u_2)$	131.3123	189.4266	256.7515	330.3439
$\sigma^{2T}(u_2)$	0.8097	2.9742	7.4376	14.6313
$\mu^T(u_3)$	13.1165	18.9426	25.6752	33.0344
$\sigma^{2T}(u_3)$	0.0081	0.0297	0.0744	0.1463

Table 4: Total populations of the corresponding estimated values of the mean and variance at $t = 1, 2, 3, 4$, using Monte Carlo simulations, both on initial conditions (26)**.**

These characteristics become the description more realistic, ensuring the existence of all possible phenotypes, the preservation of parameters that there not exist in the dimensionless form and allowing the mosquitoes a non-uniform displacement.

The dynamic system was developed in order to preserve the peculiarities of the species and avoid an overlap of individuals when the transgenics are inserted, respecting the environmental support capacity. The terms describing mating and competition implied the nonlinearities of this system, which are characteristic of the great majority of population dynamics models and, the diffusion term, based on Fick's law, describes a symmetrical spread of the mosquito population with randomic dispersal.

The solution of the proposed problem was obtained using operator decomposition method to decouple the diffusion-reaction system in two subproblems, where the diffusive problem was solved using the finite element method and the reactive problem using the fourth order Runge-Kutta method. The low computational cost, ease of implementation and the history of good results already obtained in the modeling of chemical reactions encouraged us to adopt this procedure.

The results shown are consistent with the expected behavior, indicating a constant presence of transgenic mosquitoes since the first release, reducing the costs of inserting them periodically, as is the case of sterile mosquitoes. Numerical simulations give guidelines, indicating more efficiency when the release of transgenics is done in a broader coverage, regardless of whether wild mosquitoes are clustered or scattered over a subregion of the domain. For another hand, the worst strategy is release transgenic mosquitoes concentrated in a unique small region, allowing wild-type to mate with one another and to breed while contact with transgenics is still not done.

This is an initial proposal that opens possibilities for future investigations. Initial conditions most appropriate to reality, need to be tested in order to obtain a strategy for the release of transgenic insects into the environment. Factors such as seasonality, temperature, winds, rainfall, and superiority of transgenics can be introduced into the model, making it more realistic.

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