

Global Asymptotic Stability in the Jia Li Model for Genetically Altered mosquitoes

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1 Introduction

Malaria remains a major killer with more than 1 million deaths each year in sub-Saharan Africa alone while yellow fever, dengue fever, West Nile virus, encephalitis and filariasis continue to have an impact on populations worldwide. The *Anopheles* strains of mosquitoes are largely responsible for the transmission of *Plasmodium* or malaria, the *Culex tarsalis* accounts largely for West Nile virus, encephalitis and filariasis and the *Aedes aegypti* is associated with yellow fever and dengue.

Much work has been done to genetically modify mosquitoes in the laboratory to hinder or block parasite transmission thus making the mosquitoes refractory. This is done by insertion of genes at appropriate sites to create a stable germline. The progress in this area is fairly recent. In 2000 Catteruccia, et al. [4] report: "Success has only been achieved in the last five years, with the transformation of the Mediterranean fruitfly *Ceratitis capitata*, the yellow fever mosquito *Aedes aegypti* and the flour beetle *Tribolium castaneum*."

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One of the many problems faced by researchers is a reduction of fitness caused by the mutations resulting from the gene insertions and the inbreeding while transformed lines are established, [4, 3]. More recent significant results were obtained by Moreira, Wang, Collins and Jacobs-Lorena, [15]. They produced transgenic *Anopheles stephensi* expressing either of two effector genes, a tetramer of the SM1 dodecapeptide or the phospholipase A2 gene (PLA2) from honey bee venom. Both were effective in impairing the transmission of *Plasmodium berghei* [14, 10, 9, 11]. However by measuring mosquito survival, fecundity and fertility they found that mosquitos transformed with the SM1 showed *no significant reduction* in these fitness parameters relative to the nontransgenic controls. On the other hand, the PLA2 transgenics had reduced fitness that seemed to be independent of the gene insertion site. This reduced fitness was also observed in the *Culex tarsalis* mosquito, [1] where they also report on a stable germline transformation of the *Culex quinquefasciatus* mosquito using a *Hermes* transposable element containing an enhanced green fluorescent protein marker. Similar results were also obtained by Jasinskiene, et al. [12] using *Hermes* to modify *Aedes aegypti*. Coates, et al. [5] show that the *mariner* transposable element functions as a heritable, stable and efficient mediator of gene insertion into *Aedes aegypti*.

Another factor affecting the mosquito's survival probability when attacking a defensive host is that sporozoite-infected mosquitoes probe more often and spend more time probing for a blood meal than their uninfected counterparts due to impaired salivary gland function, see Anderson, et al. [2] and references therein.

In this paper we consider the discrete-time mathematical model for populations consisting of wild and genetically altered mosquitoes proposed by Jia Li [13]. In that paper a two species model having a hybrid Ricatti/Ricker type nonlinearity and equal survival probabilities is developed and sufficient conditions are given guaranteeing the existence of a *locally* asymptotically stable fixed point. It is shown below that under less restrictive conditions the fixed point is actually *globally* asymptotically stable with respect to initial populations in which both species are present. We then investigate the cases in which the survival probabilities (fixed as well as density dependent) are different for the two species, and show that the model becomes sensitive to small changes in the survival parameters. In particular it is *very* sensitive to changes in the density-dependent survival parameters. For related results see Jim Cushing [6] where he presents linear and nonlinear matrix population models for structured species and for the interaction of

several structured species and provides stability results for certain types of nonlinear models in which the nonlinearities appear as a common factor of each equation of the system.

2 Model for population of mosquitoes

The following description closely follows [13]. Let x_n be the number of wild mosquitoes present at generation n . The population dynamics of the wild mosquitoes is described by the difference equation

$$x_{n+1} = f(x_n)s(x_n)x_n, \quad (2.1)$$

where f is the birth function (per-capita rate of offspring production) and s is the survival probability (fraction of the off-spring that survive). The survival probability is assumed to have a Ricker-type nonlinearity $s(x_n) = e^{-d-kx_n}$.

Let y_n be the number of genetically altered mosquitoes present at generation n , and assume that before the wild and altered mosquitoes interact, the dynamics of the altered mosquito population is similar to that of the wild type. Once the altered mosquitoes are released into the wild mosquito habitat, the populations are governed by the system of difference equations

$$\begin{aligned} x_{n+1} &= f_1(x_n, y_n)x_n e^{-d-k(x_n+y_n)}, \\ y_{n+1} &= f_2(x_n, y_n)y_n e^{-d-k(x_n+y_n)}. \end{aligned} \quad (2.2)$$

It is assumed that both wild and altered mosquitoes have the same survival probability $e^{-d-k(x_n+y_n)}$. For $x_n > 0$, $y_n > 0$ the birth rate functions f_1 and f_2 are given by

$$\begin{aligned} f_1(x_n, y_n) &= c(N_n) \frac{\alpha_1 x_n + \beta_1 y_n}{x_n + y_n}, \\ f_2(x_n, y_n) &= c(N_n) \frac{\alpha_2 x_n + \beta_2 y_n}{x_n + y_n}, \end{aligned} \quad (2.3)$$

where $c(N_n)$ is the number of matings per individual, per unit time with $N_n = x_n + y_n$. At generation n the number of matings, per individual, with wild mosquitoes is $c(N_n)x_n/(x_n + y_n)$ and with altered mosquitoes, $c(N_n)y_n/(x_n + y_n)$. Let α_1 be the number of wild offspring that a wild

mosquito produces through mating with a wild mosquito, and β_1 be the number of wild mosquitoes produced through mating with an altered mosquito. Similarly, α_2 and β_2 are the number of altered mosquitoes produced by the mating of altered mosquitoes with wild and altered mosquitoes respectively.

Combining (2.2) and (2.3) gives the following set of difference equations that govern the interacting populations of wild and altered mosquitoes

$$\begin{aligned} x_{n+1} &= c(N_n) \frac{\alpha_1 x_n + \beta_1 y_n}{x_n + y_n} x_n e^{-d-k(x_n+y_n)} \\ y_{n+1} &= c(N_n) \frac{\alpha_2 x_n + \beta_2 y_n}{x_n + y_n} y_n e^{-d-k(x_n+y_n)}. \end{aligned} \quad (2.4)$$

The mating rate depends on the population density. When the population is relatively small the mating rate will be assumed to be proportional to the total population, N_n , that is, $c(N_n) = c_0 N_n$. Once the population size exceeds a certain level, we expect the number of matings to saturate, and we assume the mating rate is constant, that is, $c(N_n) = c$.

In this paper we will focus on the constant mating rate case. Thus letting $a_i = c\alpha_i$ and $b_i = c\beta_i$, for $i = 1, 2$, (2.4) becomes

$$\begin{aligned} x_{n+1} &= \frac{a_1 x_n + b_1 y_n}{x_n + y_n} x_n e^{-d-k(x_n+y_n)} \\ y_{n+1} &= \frac{a_2 x_n + b_2 y_n}{x_n + y_n} y_n e^{-d-k(x_n+y_n)}. \end{aligned} \quad (2.5)$$

In (2.5) we assume that $x_n > 0$, $y_n > 0$, $n \geq 0$.

3 Global asymptotic stability

In this section we will study the ratio $z_n = x_n/y_n$ and we will show that under certain conditions the positive fixed point of (2.5) is globally asymptotically stable (GAS). In fact, we will show that this takes place under less stringent conditions than those imposed in [13] to obtain *local* asymptotic stability.

Lemma 3.1 *Suppose $a, b, c, d > 0$, $z \geq 0$ and consider the difference equation*

$$\begin{aligned} z_{n+1} &= f(z_n), \quad \text{with} \\ f(z) &= z \frac{az + b}{cz + d}. \end{aligned} \tag{3.1}$$

If $b/d > 1$ and $c/a > 1$, then (3.1) has a unique positive, GAS fixed point.

Proof. From the hypothesis we have that $bc/ad > 1$ and so $bc - ad > 0$. Through direct computation we have that

$$f'(z) = \frac{acz^2 + 2adz + bd}{(cz + d)^2} > 0 \text{ for } z \geq 0. \tag{3.2}$$

We have that $f'(0) = b/d > 1$ and

$$f'' = \frac{2d(ad - bc)}{(cz + d)^3}$$

Therefore $f''(z) < 0$ for all $z > 0$, and (3.1) has the unique positive fixed point $z^* = (d - b)/(a - c)$. It is easily seen from the increasing and concave properties of f that the positive fixed point is unique and GAS (for $z > 0$). See [8] for more details. ■

Considering the ratio $z_n = x_n/y_n$ and using (2.5) we get

$$z_{n+1} = \frac{a_1 z_n + b_1}{a_2 z_n + b_2} z_n. \tag{3.3}$$

Due to the decay survival probability term in (2.5) the populations can not grow indefinitely ($x_n + y_n \rightarrow \infty$ is not possible).

The nonzero fixed point of (3.3) is

$$\hat{z} = \frac{b_2 - b_1}{a_1 - a_2}. \tag{3.4}$$

With $a = a_1$, $b = b_1$, $c = a_2$, and $d = b_2$ (3.3) is just (3.1). If $b_1/b_2 > 1$ and $a_2/a_1 > 1$ then the conditions of Lemma 3.1 apply and the positive fixed point of (3.3) given in (3.4) is GAS (for $z > 0$).

Note that a fixed *point* for (3.3) represents a fixed or invariant line in the (x, y) plane, i.e. the line $S = \{(x, y) : y/x = r\}$ is invariant where $r = \frac{a_2 - a_1}{b_1 - b_2}$. From the GAS of this fixed point we then have that $\frac{y_n}{x_n} \rightarrow \frac{1}{\hat{z}} = r$,

i.e. the ω -limit set of any point (x, y) with $x > 0$, $y > 0$ lies in the line S . Then to study the solutions in S we can set $y_n = rx_n$ in the first equation of (2.5), and in the second equation we can set $x_n = (1/r)y_n$. Using these substitutions we get the following two uncoupled Ricker's equations (on S).

$$\begin{aligned} x_{n+1} &= \frac{a_1 + b_1 r}{1 + r} x_n e^{-d - k(1+r)x_n}, \\ y_{n+1} &= \frac{a_2 + b_2 r}{1 + r} y_n e^{-d - k(1+1/r)y_n}. \end{aligned} \quad (3.5)$$

The above two equations are of the general form of the Ricker's equation

$$w_{n+1} = R(w_n), \text{ where } R(w) \doteq \rho w e^{p - \alpha w}. \quad (3.6)$$

The nonzero fixed point of (3.6) is $w^* = (p + \ln(\rho))/\alpha$, and w^* is GAS for $0 < p + \ln(\rho) < 2$, or $e^{-p} < \rho < e^{2-p}$, [7] with

$$\rho = \frac{a_1 + b_1 r}{1 + r} = \frac{a_2 + b_2 r}{1 + r} = \frac{a_1 b_2 - b_1 a_2}{a_1 - a_2 + b_2 - b_1}. \quad (3.7)$$

The fixed points of the decoupled system (3.5) are

$$\begin{aligned} \hat{x} &= (-d + \ln(\rho))/(k(1+r)), \\ \hat{y} &= r(-d + \ln(\rho))/(k(1+r)), \end{aligned} \quad (3.8)$$

and these fixed points are stable provided $0 < -d + \ln(\rho) < 2$.

This shows the following result.

Theorem 3.2 *The positive fixed point of (2.5) (given in (3.8)) is globally asymptotically stable in the first open quadrant provided that $b_1/b_2 > 1$, $a_2/a_1 > 1$ and $0 < -d + \ln(\rho) < 2$.*

Let

$$N = \frac{(a_1 - a_2)(b_2 - b_1)}{a_1 b_2 - b_1 a_2}, \quad \text{and} \quad P = -d + \ln(\rho). \quad (3.9)$$

Thus if $b_1/b_2 > 1$, $a_2/a_1 > 1$ and $0 < P < 2$, then (2.5) has a positive fixed point and it is GAS. In terms of N and P , Li's result (Theorem 3.2, [13]) requires $b_1/b_2 > 1$, $a_2/a_1 > 1$, $0 < P$, and

$$N(P - 1) < P < 2 + (N/2)(P - 2) \quad (3.10)$$

for *local* asymptotic stability of the positive fixed point. The right portion ($P < 2 + (N/2)(P - 2)$) of the inequality in (3.10) is equivalent to $P < 2$. Note that $N < 0$, and thus if $P < 1$ then $N(P - 1)$ is a finite positive quantity so that the left inequality in (3.10) is more restrictive than just $P > 0$ as the following example illustrates.

4 Numerical examples

Here we construct an example in which Theorem 3.2 applies but condition (3.10) is violated.

Example: Consider a system (2.5) with the following set of parameter values: $a_1 = 2$, $a_2 = 3$, $b_1 = 7$, $b_2 = 6.9$, $k = 0.2$, and $d = 1.87$. The parameter values satisfy $b_1/b_2 > 1$ and $a_2/a_1 > 1$. Using (3.4) the fixed point for the ratio system is $\hat{z} = 0.1$. Using (3.6) the fixed point of the decoupled system is $\hat{x} \approx 0.00398674828$ and $\hat{y} \approx 0.03986748281$. The condition $0 < -d + \ln(\rho) < 2$ is satisfied with $P = -d + \ln(\rho) = 0.008770846$, and thus by (Theorem 3.2) the point (\hat{x}, \hat{y}) of the coupled system (2.5) is GAS within the open first quadrant.

Using an initial condition of $(x_0, y_0) = (0.03, 0.07)$ direct simulations confirm the expected behavior of the system. Figure 1 shows the population level of the wild and altered mosquitos for the first 4000 generations. As expected, the population of the wild and altered mosquitos approach the fixed level (\hat{x}, \hat{y}) given above. The ratio dynamics for $z_n = x_n/y_n$ is shown in Figure 2 and as guaranteed by Theorem 3.2 the iterates approach the computed fixed value of $\hat{z} = 0.1$. The parameter values of this example do not satisfy condition (3.10). In fact $N(P - 1) \approx 0.01376707158$.

5 The model is not robust

In the previous sections it was assumed that the survival probabilities of the wild and the altered mosquitoes are identical. In this section we will show that in spite of the global asymptotic stability exhibited by the system, only a slight deviation from identical survival probabilities yields dynamics which

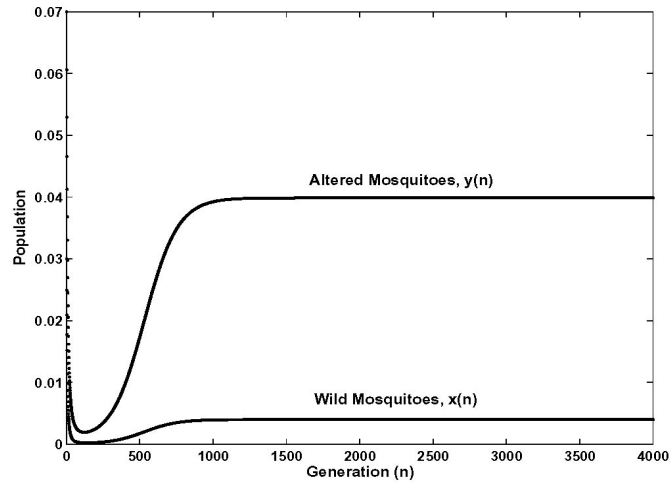


Figure 1: Wild and altered mosquitoes–4000 generations

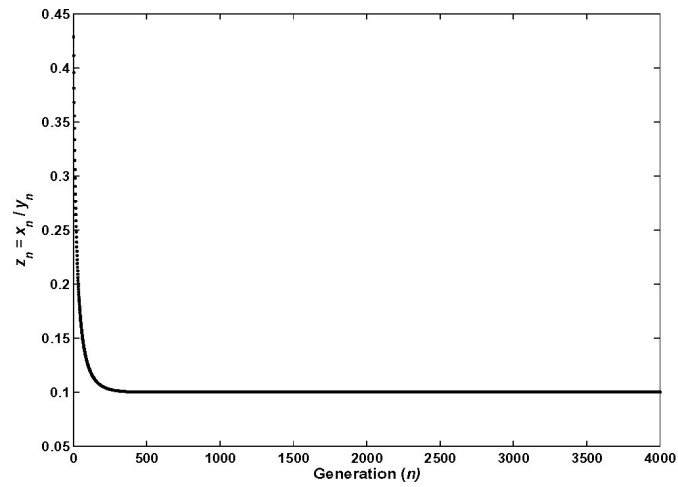


Figure 2: Ratio dynamics $z_n = x_n / y_n$ for 4000 generations

are quite different. In particular the frequency of the altered mosquitoes can decrease radically due to a small decrease in the survival probabilities, especially the density dependent survival probability k_y (below).

In this section we will focus on the case when the survival probability of the wild and altered mosquitoes are not equal. In this case (2.5) becomes

$$\begin{aligned} x_{n+1} &= \frac{a_1 x_n + b_1 y_n}{x_n + y_n} x_n e^{-d_x - k_x(x_n + y_n)} \\ y_{n+1} &= \frac{a_2 x_n + b_2 y_n}{x_n + y_n} y_n e^{-d_y - k_y(x_n + y_n)}. \end{aligned} \quad (5.1)$$

Two cases will be considered. In the first case $k_x = k_y$, and in the second case $k_x \neq k_y$. Consider the case when $k_x = k_y = k$. For this special case we have the advantage that we can easily follow the process given in section (3) to show global asymptotic stability of the positive fixed point of (5.1). Let $\Delta d = d_x - d_y$, then the ratio $z_n = x_n/y_n$ becomes

$$z_{n+1} = \frac{a_1 z_n + b_1}{a_2 z_n + b_2} z_n e^{-\Delta d}. \quad (5.2)$$

The ratio given in (5.2) is very similar to the one presented in (3.3) for the identical survival probability case. The only difference is that (5.2) contains the constant exponential term $e^{-\Delta d}$, and due to this term the stability of (5.2) requires that $b_1 e^{-\Delta d}/b_2 > 1$ and $a_2/(a_1 e^{-\Delta d}) > 1$. Comparing with the case $\Delta d = 0$, $\Delta d > 0$ increases the region of stability in the (a_1, a_2) plane and reduces the region of stability in the (b_1, b_2) plane. In contrast, $\Delta d < 0$ reduces the region of stability in the (a_1, a_2) plane and increases the region of stability in the (b_1, b_2) plane.

The nonzero fixed point of (5.2) is

$$\hat{z} = \frac{b_2 - b_1 e^{-\Delta d}}{a_1 e^{-\Delta d} - a_2}. \quad (5.3)$$

Similar to (3.5), the uncoupled equations of (5.1) become

$$\begin{aligned} x_{n+1} &= \frac{a_1 + b_1 r}{1 + r} x_n e^{-d_x - k(1+r)x_n}, \\ y_{n+1} &= \frac{a_2 + b_2 r}{1 + r} y_n e^{-d_y - k(1+r/r)y_n}, \end{aligned} \quad (5.4)$$

with now $r = \frac{a_2 - a_1 e^{-\Delta d}}{b_1 e^{-\Delta d} - b_2}$. The following conditions are required for the stability of the uncoupled Ricker's equations (5.4)

$$\begin{aligned}
0 < -d_x + \ln\left(\frac{a_1 + b_1 r}{1 + r}\right) < 2, \\
0 < -d_y + \ln\left(\frac{a_2 + b_2 r}{1 + r}\right) < 2.
\end{aligned}
\tag{5.5}$$

Note that the two above inequalities are equivalent, i.e.

$$-d_x + \ln\left(\frac{a_1 + b_1 r}{1 + r}\right) = -d_y + \ln\left(\frac{a_2 + b_2 r}{1 + r}\right).$$

Thus (5.5) imposes only one set of inequalities.

The fixed points of the decoupled system (5.4) are

$$\begin{aligned}
\hat{x} &= \frac{-d_x + \ln\left(\frac{a_1 + b_1 r}{1 + r}\right)}{k(1 + r)}, \\
\hat{y} &= r\left(\frac{-d_y + \ln\left(\frac{a_2 + b_2 r}{1 + r}\right)}{k(1 + r)}\right).
\end{aligned}
\tag{5.6}$$

Similarly to Theorem 3.2, the positive fixed point of (5.1) (given in (5.6)) is GAS in the first open quadrant provided that $b_1 e^{-\Delta d}/b_2 > 1$, $a_2/a_1 e^{-\Delta d} > 1$ and (5.5) holds.

One way to measure which type of mosquito is the dominant mosquito in the population at generation m is to determine the ratio (frequency) $R_m = y_m/(x_m + y_m)$. Here, as before, x_m and y_m are the number of wild and genetically altered mosquitoes present at generation m respectively. If $R_m > 0.5$, then the genetically altered mosquitoes are the dominant type of mosquito in the population.

The following example illustrates the sensitivity of the model to changes in the survival probability, specifically sensitivity to changes in d_x and d_y . Consider a system (5.1) with the following set of parameter values: $a_1 = 2$, $a_2 = 3$, $b_1 = 7$, $b_2 = 6.9$, $k_x = k_y = k = 0.2$, and d_x and d_y vary. In Figure 3 the values of R_m are shown as a function of d_x and d_y . The values of R_m were numerically computed by using (5.1) and $m = 5000$. It is clear that that by simply changing d_y or d_x there can be a switch in the dominant type of mosquito.

In the general case with $k_x \neq k_y$ the equation for the ratio dynamics can not be reduced to an equation in terms of z only, and thus we can not follow the above process. The following example illustrates the sensitivity

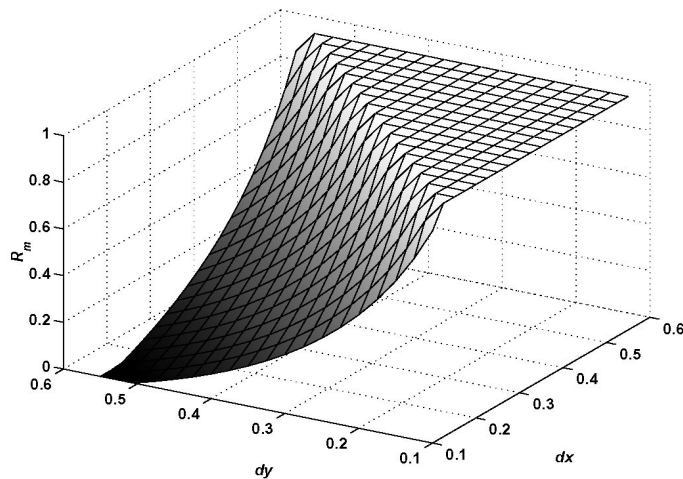


Figure 3: Ratio R_m as a function of d_x and d_y

of the model to changes in k_x and k_y . Consider a system (5.1) with the following set of parameter values: $a_1 = 2$, $a_2 = 3$, $b_1 = 7$, $b_2 = 6.9$, $d_x = d_y = d = 0.25$, and k_x and k_y vary.

In Figure 4 the values of R_m are shown for the cases when either k_x or k_y was kept fixed and either k_y or k_x was allowed to vary for two different values of a_1 . The values of R_m were numerically computed by using (5.1) and $m = 5000$. This example show a very small change in k_y or k_x can induce a very large change in R_m and thereby induce a switch in the dominant type of mosquito. This effect is even stronger for the parameter value of $a_1 = 2.5$.

6 Conclusions

In this paper we explored some aspects of a discrete-time mathematical model for populations consisting of wild and genetically altered mosquitoes proposed by Jia Li [13]. We show that under certain conditions the fixed point of the system studied is globally asymptotically stable. The global

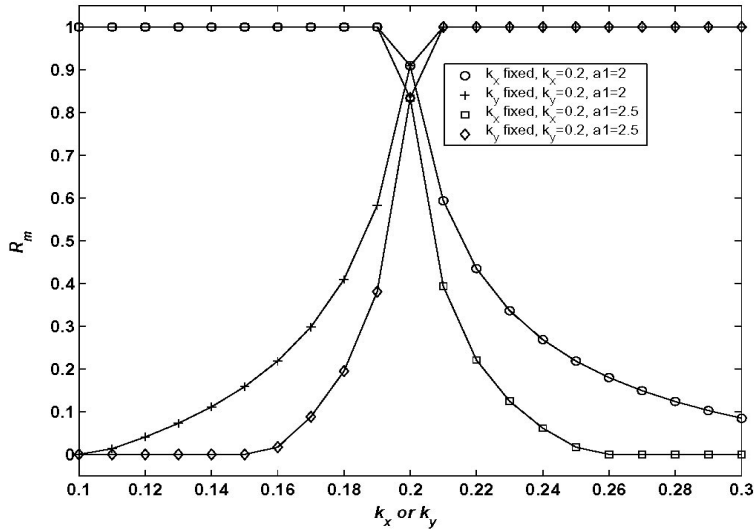


Figure 4: Ratio R_m as a function of k_x and k_y keeping one of k_x or k_y constant

stability is achieved under less stringent conditions than those imposed by [13] to obtain *local* asymptotic stability. A numerical example is presented to illustrate the result.

The model proposed by [13] assumes that the survival probabilities of the wild and the altered mosquitoes are identical. In this paper we show that with only a slight deviation from identical survival probabilities the model can yield dynamics which are quite different. We provide several examples where it is possible to change which population is the dominant one by just slightly changing the survival probability of one of the populations.

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