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Preliminary Results: Simple Model of Evolutionary Dynamic on Insecticide Resistance in Mosquitoes

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Abstract. The information on insecticide resistance in mosquitoes as diseases vectors is a critical issue for the success of mosquito population control. This is because the resistance can reduce the effectiveness of insecticides. Based on the resistance level to insecticides, the mosquitoes are divided into susceptible and resistant groups. Genetically, the existence of susceptible and resistant mosquitoes are determined by the frequency of alleles. In this paper, a dynamical model is constructed based on the genetic information to observe the effect of selection by exposure to insecticides. The model is a two-dimensional nonlinear differential equation system. In the analysis of this mathematical model, we consider two important factors in the evolution of resistance, i.e., the fitness value and the effectiveness of the insecticide. The condition of coexistence and stability are obtained here. The simulations are performed to illustrate the effect of insecticide usage continuously on mosquito resistance. Based on analysis and simulation, the fitness value of intermediate mosquitoes plays an essential role in maintaining the coexistence of the mosquito population. Furthermore, the resistant mosquitoes increases significantly following the pattern of increasing the dose of exposure to insecticides.

1. Introduction

Mosquito population control is an important strategy to prevent the spread of vector-borne diseases such as dengue, zika, chikungunya and so on. In general, mosquito control in the tropics and subtropics is conducted by the use of insecticides. The effectiveness and relatively low toxicity are a consideration factor in choosing the type of insecticide [1]. Unfortunately, the insecticides usage continuously can lead to a new problem, i.e., insecticides resistance. It is defined as the ability to receive insecticide toxic substances that are usually lethal [2]. The study of the evolution of insecticide resistance becomes a significant part of mosquito control because the increasing of resistant mosquitoes can inhibit success in mosquito control.

One of the factors affecting the rate of resistance development is the level of selection pressure received by the mosquito population. Under the same environmental conditions, population that receive strong selection pressure can develop into resistant population faster than those receiving weak selection pressure. In addition, factors affecting the phenomenon of resistance are genetic, biological and operational factors. The genetic factors are a frequency, number and dominance of resistant alleles at a locus. Meanwhile, biological-ecological factors are insect behavior, number of generations per year, mobility, and migration. Whereas, the operational factors are the type of insecticide, number of applications, target site, dosage, frequency and method of application [3,4,5].

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According to Mendel in [6], the inheritable character is a character that is governed by a gene. The inheritance of parents' traits to the next generation is called heredity. Resistance is a character that governed by the R gene [7]. Consequently, if the parental generation of mosquitoes is resistance then the offspring is resistant mosquitoes. The facts that the resistance is governed by a gene R. For example, resistance to DDT in *A. Aegypti* is governed by the R^{DDT1} gene and the R^{DDT2} gene.

In previous works, the evolution of resistance received much attention from mathematicians with various approaches such as stochastic [8], discrete [9,10] as well as numerical [11]. The deterministic mathematical model approach [12] involves selection of under sexual reproduction. In [12] is concluded that the fitness value of the heterozygous mosquito population plays an essential role in the control of infectious vector diseases. In [11] a mathematical model was devised to study the comparison between the effectiveness of insecticide use in larvae and adult mosquitoes. The use of insecticide in the larvae is more recommended than in adult mosquitoes because it is faster to reduce the mosquito population and does not require higher doses [11]. Unfortunately, the fitness values and insecticide exposure effect are not discussed comprehensively in [9,10,11,12].

Here, we developed a mathematical model to illustrate the evolution of insecticide resistance in mosquito population. We consider two important factors in the evolution of resistance, i.e., the fitness value and the effectiveness of the insecticide. We find that the fitness value of intermediate mosquitoes plays an essential role in maintaining the coexistence of the mosquito population. Furthermore, the number of resistant mosquitoes increases significantly following the pattern of increasing the dose of exposure to insecticides. This paper is organized as follows. First, a mathematical model is constructed. In the next section, the equilibrium point and their stability analysis are discussed. In the third section, a numerical simulation to investigate the effect of insecticide exposure is performed. Finally, a conclusion and discussion are presented.

2. Mathematical Model

The fact that the insecticide-resistant property of the mosquito is governed by an R gene. Furthermore, another allele of the R gene is the S gene as the symbol of the recessive R gene. Since the mosquito is diploid, the chromosome will be paired. Consequently, from the R and S genes, there are three genotypes combinations, i.e., SS, SR, and RR. The mosquitoes with the SS gene will be affected by insecticide exposure because the R gene does not exist. Unlike SS-individual, the individual mosquito with RR genotype is not affected by exposure to insecticides. Meanwhile, when there is exposure to insecticides, the SR mosquito depends on the dominance of the S or R gene. If the R gene is dominant, then the SR mosquito will live together with the RR and the fitness value is not affected by the insecticide. However, if R genes are recessive then the mosquitoes with SR genotype will die together with the SS genotype and their fitness value will decrease as well as SS mosquitoes.

Furthermore, for the purposes of model construction, we assume some of the following, (a) The population is infinite, so the stochastic effect is neglected; (b) no gene flow factor (migration); (c) non-overlapping generations; (d) exposure to insecticides has an effect on reducing fitness value; (e) The fitness values are different from one another depending on the sensitivity of the mosquito to the insecticide; (f) The R gene is recessive, consequently the exposure to insecticide will affect the fitness value of the SR mosquito. Suppose x is the frequency of the S allele and y is the frequency of the R allele, such that $x + y = 1$. The number of SS genotype after selection is proportional to $\eta_1 x^2$, namely the frequency of SS before the selection is multiplied by the survival rate of the genetic SS, η_1 . To recover frequencies, we divide by the mean survival rate of the population $\bar{\eta}$ which serves as a normalization constant to ensure that post-selection genotype frequencies sum to one. The exposure to insecticides has an effect on survival rate, so the number of SS genotype is proportional to $\eta_1 (1 - u) x^2$ where u is the effectiveness of the insecticide exposure. The same procedure applies to other genotypes. Based on the assumptions and cross-breeding processes for the three genotypes SS, SR, and RR, as well

as the effect of insecticide exposure on each genotype, the change of genotype frequency in mosquitoes before and after insecticidal exposure is obtained as in table 1.

Table 1. The genotype frequency before and after insecticide exposure

Gametes uniting to form a zygote	Frequency before selection	Frequency after selection	Frequency after exposure to insecticides	Gamet produced	
				S	R
$S \times S$	x^2	$\frac{\eta_1}{\bar{\eta}} x^2$	$\frac{\eta_1(1-u)}{\bar{\eta}} x^2$	1	0
$S \times R$	$2xy$	$2\frac{\eta_2}{\bar{\eta}} xy$	$2\frac{\eta_2(1-u)}{\bar{\eta}} xy$	$\frac{1}{2}$	$\frac{1}{2}$
$R \times R$	y^2	$\frac{\eta_3}{\bar{\eta}} y^2$	$\frac{\eta_3}{\bar{\eta}} y^2$	0	1

where $\bar{\eta} = \eta_1(1-u)x^2 + 2\eta_2(1-u)xy + \eta_3y^2$

In constructing the model, we follow the formulations of Hofbauer and Sigmund or Nowark [13,14]. They are introduce dynamic formulations for subpopulation x_i under competition as follows

$$\frac{dx/dt}{x_i} = \text{fitness of } x_i - \text{average fitness} \quad (1)$$

In this case, we consider the allele frequency of each SS, SR, and RR genotype. Based on the definition, the correlation between allele and genotype frequency is $x = SS + (1/2)SR$ and $y = RR + (1/2)SR$ such that the fitness of each allele is given by

$$f_x = \frac{\eta_1(1-u)x^2 + \eta_2(1-u)xy}{x}, \quad f_y = \frac{\eta_2(1-u)xy + \eta_3y^2}{y} \quad (2)$$

Therefore, a mathematical model that describes the evolution of insecticide resistance in the mosquito population is a two-dimensional system of differential equations as follows,

$$\begin{aligned} \frac{dx}{dt} &= (\eta_1(1-u)x + \eta_2(1-u)y - \bar{\eta})x \\ \frac{dy}{dt} &= (\eta_2(1-u)x + \eta_3y - \bar{\eta})y \end{aligned} \quad (3)$$

due to $x + y = 1$, the equation (3) can be reduced to

$$\frac{dx}{dt} = (\eta_1(1-u)x + \eta_2(1-u)(1-x) - \bar{\eta})x \quad (4)$$

where

$$\bar{\eta} = \eta_1(1-u)x^2 + 2\eta_2(1-u)(1-x)x + \eta_3(1-x)^2 \quad (5)$$

with the initial condition $x(0) \geq 0$, and the domain is $\Omega = \{x \in \mathbb{R}_+ | 0 \leq x \leq 1\}$

3. Analysis Results

In this section, we will investigate the equilibrium points and their stability. Substitute of $\bar{\eta}$ to $\frac{dx}{dt} = 0$ in (4), such that we have a third order of polynomial equation below

$$x(x-1)((u-1)\eta_1 + 2(1-u)\eta_2 - \eta_3)x + (u-1)\eta_2 + \eta_3 = 0 \quad (6)$$

Immediately, we obtain the solution of (6) as follows

$$E_1 = 0, E_2 = \frac{(1-u)\eta_2 - \eta_3}{(1-u)(\eta_2 - \eta_1) + (1-u)\eta_2 - \eta_3}, \text{ and } E_3 = 1 \quad (7)$$

The equilibrium point E_1 and E_3 always exist not depend on parameters value. However, the equilibrium point E_2 exist if $\eta_3 < (1-u)\eta_2$ and $\eta_1 < \eta_2$. The Stability of these points is discussed in the theorem 1.

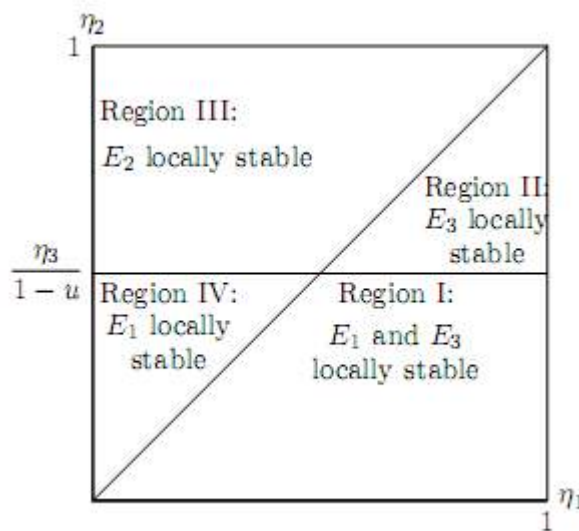


Figure 1. The region of stability in parameter space of η_1 and η_2

Theorem 1. If $\eta_3 < (1-u)\eta_2$ and $\eta_1 < \eta_2$, then E_1 and E_3 are unstable, whereas E_2 is locally asymptotically stable.

Proof. The first differential of the right-hand side of equation (4) is

$$J = \frac{df}{dx} = (3(1-u)(\eta_2 - \eta_1) + 3(1-u)\eta_2 - 3\eta_3)x^2 + (2(1-u)(\eta_1 - \eta_2) - 4((1-u)\eta_2 - \eta_3))x + (1-u)\eta_2 - \eta_3 \quad (8)$$

and its values at E_1, E_2 and E_3 are

$$\begin{aligned} J(E_1) &= (1-u)\eta_2 - \eta_3, \\ J(E_3) &= (1-u)(\eta_2 - \eta_1), \\ J(E_2) &= -\frac{(1-u)(\eta_2 - \eta_1)((1-u)\eta_2 - \eta_3)}{(1-u)(\eta_2 - \eta_1) + (1-u)\eta_2 - \eta_3} \end{aligned} \quad (9)$$

If $\eta_3 < (1-u)\eta_2$ and $\eta_1 < \eta_2$, then we have $J(E_1) > 0$, $J(E_3) > 0$ and $J(E_2) < 0$. Thus E_1 and E_3 are unstable and E_2 is locally asymptotically stable.

Remark. From equation (9), we can see that the stability condition for the equilibrium point E_1 and E_3 . If $\eta_1 > \eta_2$ then E_3 locally asymptotically stable and if $\eta_3 > (1-u)\eta_2$ then E_1 locally asymptotically stable. We summarize the stability region in figure 1.

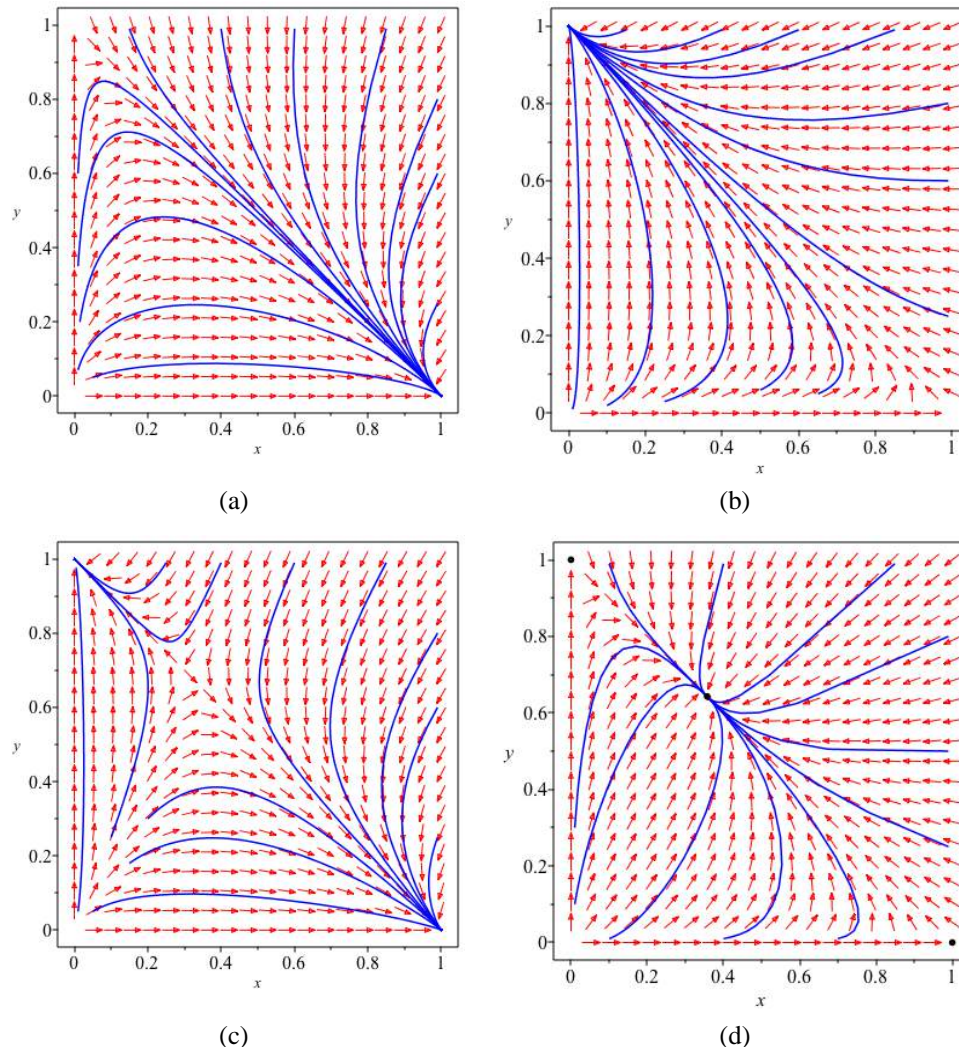


Figure 2. Phase portrait for the full system (3) with fixed parameter values $u = 0.10$; (a) $\eta_1 = 0.50, \eta_2 = 0.20, \eta_3 = 0.10$; E_1 locally asymptotically stable, (b) $\eta_1 = 0.10, \eta_2 = 0.20, \eta_3 = 0.50$; E_3 locally asymptotically stable, (c) $\eta_1 = 0.50, \eta_2 = 0.10, \eta_3 = 0.25$; E_1 and E_3 locally asymptotically stable, (d) $\eta_1 = 0.50, \eta_2 = 0.20, \eta_3 = 0.10$; E_2 locally asymptotically stable.

The figure 1 demonstrates the stability region for the equilibrium point in the parameter space of η_1 and η_2 . The Existence and stability of E_2 that represent coexistence of S and R allele are showed in Region III. Here, we find the extraordinary phenomena, i.e., the Region II is inversely proportional to Region IV and the Region I is inversely proportional to Region III. This relationship is determined by

the value of η_3 and u . Suppose the value η_3 is fixed. If the value of u is an increase, then Region II decreases but Region IV enlarges. This confirms to us that if the effectiveness of insecticide increases, then the mosquitoes with SS or RR genotype will exist indefinitely. This existence depends on the degree of domination of allele frequencies. If the S allele is more dominant than the R allele, then the mosquito with the SS genotype can exist indefinitely. However, as a result of enlarging Region I and narrowing Region III, the mosquito with RR genotype can exist indefinitely. Genotypically, That has occurred because the frequency of the R allele is more dominant than the S allele. Consequently, the mosquito population will be dominated by mosquitoes with RR genotype.

In order to support the analysis above, we perform some phase portraits in figure 2. In figure 2(a), we can see that the equilibrium point E_3 is locally asymptotically stable if $\eta_1 > \eta_2$. This shows that the mosquitoes with the SS genotype can exist indefinitely if the fitness value of the mosquitoes with the SS genotype bigger than the mosquitoes with the SR genotype. Consequently, the population will be dominated by susceptible mosquitoes. Figure 2(b) shows that the population is dominated by resistant mosquitoes. This condition is achieved when the fitness value of RR is higher than the SR fitness value such that the frequency of R allele will dominate. Furthermore, S and R alleles can exist indefinitely when the SR mosquito fitness value is higher than the SS and RR mosquito fitness. The SR genotype can dominate the mosquito population such that the mosquito populations with genotype SS and RR also can exist indefinitely (figure 2(d)). However, if any of the conditions are not met, for example, the SS or RR mosquito fitness value is higher than the SR mosquito fitness value then the mosquito population that can exist indefinitely is a mosquito with SS or RR genotype depending on the dominance level of the mosquito population (figure 2(c)).

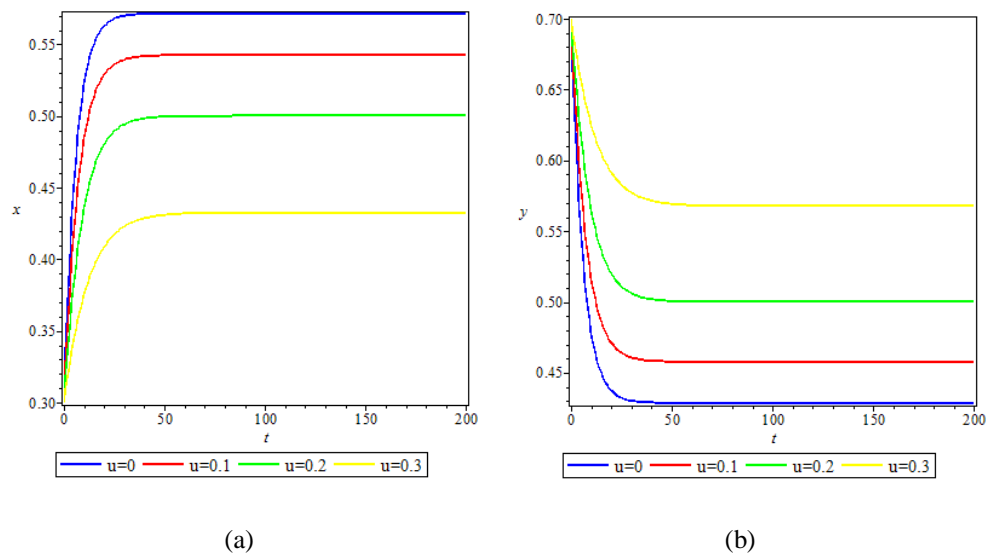


Figure 3. Trajectory of the solution with specific fitness parameter values and different effectiveness parameters (a) graph of solution trajectory x (b) graph of solution trajectory y

4. Numerical Exploration

In this section, we will investigate the effect of insecticide effectiveness on the frequency of S and R alleles. This investigation is performed when the coexistence equilibrium point is stable, i.e., when the fitness value of the mosquito with SR genotype is higher than the other. In this simulation is used the initial value $x = 0.3$ and $y = 0.7$ with the fitness value $\eta_1 = 0.5$, $\eta_2 = 0.8$ and $\eta_3 = 0.4$. The simulation results can be seen in figure 3.

Based on the simulation results, in figure 3(a), the frequency of S alleles can decrease as the value of effectiveness of insecticide exposure increases. Meanwhile, the frequency of resistant alleles

increases when the effectiveness of insecticide exposure rises also (see figure 3(b)). This indicates that too high doses can cause an increase in the frequency of the R allele. Consequently, the frequency of the RR genotype is increased such that the mosquito population in the next generation will be dominated by resistant mosquitoes. In addition, the constant and continuous properties of u illustrating the character of the insecticide application method. We can conclude that when one type of insecticide is used in continuous exposure to insecticide, the frequency of the R allele can increase. From these explanations can be seen that exposure to insecticides can accelerate the phenomenon of resistance in mosquitoes.

This simulation confirms preliminary findings that operational factors also influence the phenomenon of resistance [3,4,5]. Increased frequency of resistance in mosquitoes is caused by continuous exposure to insecticides with high doses. In addition, the type of single insecticide can also speed up the phenomenon of resistance.

5. Conclusion

Deterministic mathematical model to describe the evolution of insecticide resistance in mosquitoes population have been introduced in this paper. To explain the dynamic of insecticide resistance, we observe the frequency dynamic of R and S alleles in mosquitoes. The frequency of these alleles is strongly influenced by the effectiveness of insecticides and the fitness value of mosquitoes. The effectiveness of the insecticides and the individual fitness values of mosquitoes are involved in the model.

Based on analytical results, the fitness value of the genetic mosquito SR plays an essential role in maintaining the coexistence of the mosquito population. This is understandable, because the mosquitoes with SR genotypes can produce offspring of mosquitoes with complete genotype, i.e., SS, SR, and RR. Furthermore, the frequency of the R allele can predominate if the fitness value of the mosquitoes with the RR genotype is higher than the fitness value of the mosquito with the SR genotype. Similarly, the mosquitoes with the SS genotype can dominate when its fitness value is higher than SR fitness value. In addition, the effectiveness of exposure to insecticides is a factor that can affect the frequency of alleles. The insecticide effect on the allele S frequency is inversely proportional, i.e., when the value of insecticide exposure effectiveness increases, the frequency of the S allele will decrease. In contrast, the frequency of the R allele can be increased due to high-dose continuous exposure to insecticides. These results confirm that operational factors are also an essential factor that must be considered to inhibit the phenomenon of resistance. Overuse of insecticides and overly high doses of insecticides are responsible for the increase in the frequency of R alleles.

The results of this study can be exploited by the decision makers in mosquito control management. Some operational factors that must be considered in mosquito control are the frequency of exposure and the levels of insecticide doses. The type of insecticides is also a critical part of mosquito control because it is closely linked to the target site insecticide on the mosquito. The use of one type of insecticide can cause an increase in the frequency of the R allele quickly. However, there should be further studies on the effectiveness of two types of insecticides targeting different sites in mosquito control. In addition, the effect of insecticide exposure on individual mosquitoes should also be reviewed, since basically, insecticides can not only reduce the fitness value of mosquitoes but also kill individual mosquitoes directly.

6. Acknowledgments

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