

AN AGENT-BASED MODEL FOR THE CONTROL OF MALARIA USING GENETICALLY MODIFIED VECTORS

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KEYWORDS

Malaria, Agent Based Model, Population Dynamics, Epidemic Vectors, Transgenic Population, Fitness.

ABSTRACT

An agent-based model was developed to assess the use of Genetically Modified Mosquitoes (GMMs) as a control strategy for the Malaria epidemic. Mosquitoes responsible for the transmission of Malaria (vectors) have been modified genetically so that the probability of transmitting the parasite causing the disease when biting a human being is reduced with respect to wild type vectors. Our model represents the population dynamics of the introduction of a transgenic strain of malaria vectors of the species *Anopheles Gambiae*. In the model three different types of agents were included: wild type, homozygous and heterozygous transgenic mosquitoes. Each agent is characterized by a fitness parameter that represents a reproduction rate, relative to the wild type population. The model considers specific biological processes such as: gonotrophic cycle (the average interval between successive blood meals), egg maturation time and life cycle of the vector. Additionally, some spatial aspects such as: biting zones (human settlements) and water zones (breeding places) were included in the model to consider the influence of environmental conditions. Through simulations it was observed that the model represents adequately the dynamics of Malaria vectors. These results may be used to evaluate different control strategies considering spatial and environmental features.

INTRODUCTION

Malaria is one of the tropical diseases that have greater impact in terms of mortality and morbidity in the world. Annually, over a million people die due to this disease and almost 3200 million people in 107 countries and territories are in risk of developing it (WHO 2010). Currently, it is estimated that more than half of humanity is exposed to infection and unless new control measures are considered, the toll will be doubled in the next 20 years due to the effect of phenomena associated with climate change (Bremner, 2001).

The disease is transmitted to humans by a mosquito of the genus *Anopheles*, when an infected female takes a

blood meal. Traditional control measures for Malaria such as drug treatments, elimination or reduction of the vector's nesting places and the use of insecticides combined with bed nets, are not enough to control the spread of the disease. An effective vaccine is still far into the future (Ruiz et al. 2006).

In order to find more effective measures that can halt Malaria transmission, alternative strategies have been oriented to reduce or modify the vector population. In recent years, researchers have successfully developed genetically modified mosquitoes that are impaired for transmission of *Plasmodium berghei*. That seemed to reduce in an important level the transmission of the disease in controlled conditions (Ito et al., 2002). Later, it was established that GMMs had some fitness advantage over the wild type that could make them prevail (Gould et al., 2006). Therefore, a control strategy based on introducing GMMs into the wild mosquito population could be proposed.

On the other hand, literature on modeling of vector-borne disease spread, particularly Malaria, is abundant. There are many mathematical models that use ODEs (Ordinary Differential Equations) to represent interactions between humans and vectors as a function of time. Some of these models include environmental factors. Statistical models have also been proposed to predict the spatial distribution of vectors based on environmental variables. These models have showed the importance of combining spatial and temporal aspects of the spread of vector-borne diseases (Muller et al., 2004).

Boëte and Koella (2002) obtained a remarkable result from their stochastic model to study the spread of the refractory allele in the vector population. Their results show that if the refractoriness of transgenic vectors is not perfect (infectiousness equal to zero) then its effect on the epidemic will be totally insignificant.

Smith et al. (2006) developed an integrated dynamic mathematical model for predicting the economic and epidemiologic impact of a Malaria vaccine. This model is comprised of sub-models that were validated with data obtained from studies performed in Africa. One of the strengths of this modeling approach, is the possibility of consider many biological aspects in order to get a more realistic representation of the complex Malaria life cycle.

A mathematical model was used to analyze conditions for sweeping the wild type by GMMs (Lambrechts et al. 2007). Results showed that the fitness advantage of Malaria refractoriness might be reduced by the cost associated with two copies of the allele in the homozygous population. Consequently, the epidemic cannot substantially be reduced unless the transgenic vectors sweep the wild type.

Diaz et al. (2011) implemented a differential equation-based model that represents mosquito population dynamics when genetically modified individuals are introduced into a wild type population. The model describes the dynamics of gene selection under sexual reproduction in a closed vector population, showing that the determinant parameter for a complete invasion is the fitness of the resulting heterozygous population. In order to determine how feasible would be to control a Malaria epidemic, they combined the vector population model with an epidemiological model.

As an alternative to mathematical models, Agent-Based Models (ABM) have been proposed to represent the determinant factors in disease transmitting and their interactions in a specific spatial environment. ABMs are stochastic models that are used to describe interactions among agents of a population. The behavior of these agents is established by a simple set of rules (Bousquet et al. 2004). Linard et al. (2008) developed multi-agent simulations to evaluate the risk of Malaria reemergence in the south of France. This model represents different agents (mosquitoes, people, animals and environment) that can influence the disease transmission. The model simulates temporal and spatial variations in the biting rate of mosquitoes. These variations depend on the distribution of humans and vectors, their behavior and interactions.

In this paper we present an agent based model that takes into account vector population dynamics and the introduction of a relatively small invading population of transgenic mosquitoes that are partially refractory to Malaria. GMMs reproduce sexually with the existing wild type and fitness conditions are analyzed by massive simulations. The model allowed establishing conditions for an invasion to be successful.

THE MODEL

In this section, the model is described following the standard ODD protocol (Overview, Design concepts, and Details) for individual-based and agent-based models (Grimm et al., 2006). The Unified Modeling Language (UML) is used for this description, including a class diagram (Booch et al., 2004).

Overview

The main phenomenon modeled in this ABM is the vector feeding cycle that involves mobile agents of the model (mosquitoes); this process is represented in

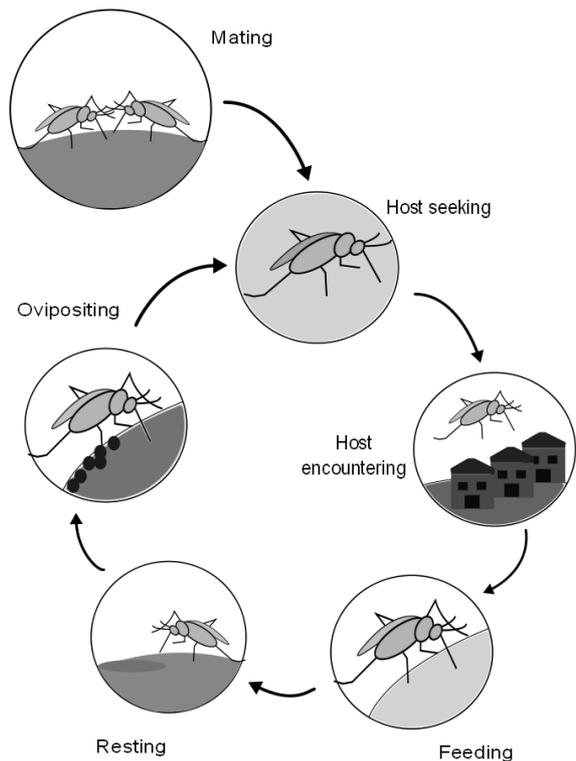


Figure 1: Mosquito feeding cycle.

figure 1. When new mosquitoes emerge from breeding sites, they mate and females search for a blood meal to complete the egg development. After the mosquito has found a host and has bitten it, it looks for a resting place where it can digest the blood. This process takes between two and three days in tropical areas. Then, the mosquito flies looking for a breeding site to lay the eggs. Finally, the mosquito lays the eggs and starts over again the feeding cycle seeking a host (Chitnis et al., 2010).

Purpose

The purpose of the model is to simulate spatial and temporal variations of Malaria vectors including the transgenic population. The main objective is to understand the factors that control these variations and evaluate the possibility of using GMMs as a control strategy.

State Variables and Scales

The model focuses on *Anopheles Gambiae*, which is represented in the model by mobile agents. These agents have some attributes that lead them to interact with the environment, with other agents and that determine the dynamics of the entire population. The mosquito fitness is one of these attributes. In our model this condition is represented by a variation in the average number of eggs that a mosquito of a specific genotype can lay. In this way, a mosquito with a higher

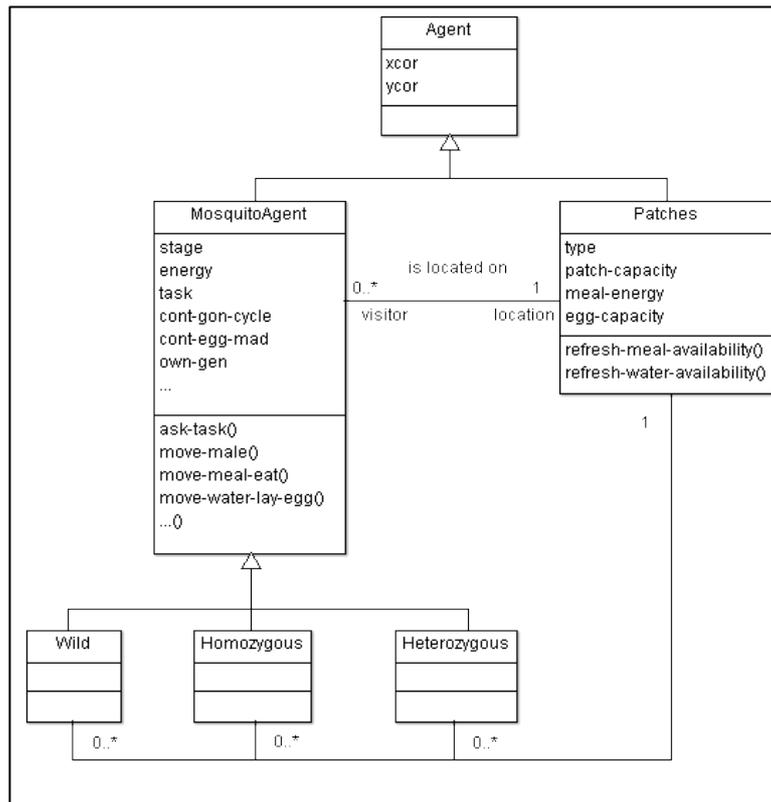


Figure 2: UML Class Diagram of the ABM.

fitness in relation with the wild type lays more eggs, whereas a mosquito with a lower fitness decreases the production of eggs. Fitness is an essential characteristic in the competition among populations of mosquitoes and a key factor for establishing conditions in which it is possible to use genetically modified vectors as a strategy to control the Malaria.

In the model, the landscape is represented by a grid that is formed by a group of cells (patches), which works as a spatial support for the movements and interactions among mosquitoes. In addition, patches have a set of attributes that can be sensed by the mosquitoes.

Figure 2 presents the UML class diagram of agents that compose the model. Rectangles in this diagram represent a set of objects (agents) that share the same attributes, operations, relationships and semantics. Each agent has a coordinate (xcor, ycor) that defines its location on the grid. Each patch of the grid is characterized mainly by four attributes: type, patch-capacity, meal-energy and egg-capacity.

The load capacity or patch capacity is related to the population of mosquitoes that each cell can support. The meal availability or meal-energy reflects the presence or absence of humans on each cell. This cell's attribute can be sensed by a mosquito and determine places where a mosquito can have a blood meal. A cell with nonzero meal availability implies that human

settlements are located there and, therefore, a mosquito could have a blood meal on that cell. Finally, each cell belongs to one of three types of land: water-type, meal-type and land-type. This is an important attribute that determines cells where the mosquitoes are able to develop different activities such as laying eggs or biting a human.

Mobile agents have also a set of attributes that characterize them. Wild, homozygous and heterozygous mosquitoes are mobile agents that have the same attributes and operations described for mobile agents in Figure 2. Some of these attributes are: stage, energy, fitness, a counter of gonotrophic cycle and a counter of egg maturation. The stage is related with the level of maturation of the mosquito. Immature stage includes the egg, pupae and larvae stage, and the mature stage represents the adult mosquito. The energy is an important attribute that determines the capacity of the mosquito to perform an activity. This parameter decreases when the mosquito flies, lay eggs and mate, and increases when the mosquito gets a blood meal. The gonotrophic cycle counter establishes the time necessary to complete the cycle. The egg maturation counter determines the time elapsed before the mosquito can lay its eggs after a blood meal.

In addition, each type of agent (mosquitoes and patches) can perform a set of operations that determine its behavior and the way they react to external factors. Mosquitoes can develop the following activities: seek a

mate, move to a meal and eat, move to water and lay eggs. Patches have some other operations like refresh meal or water availability.

Time is modeled as discrete time steps. Each time step represents a time period of six hours.

Process Overview and Scheduling

At each time step, the same sequence of procedures is activated and always in the same order. Similarly, each procedure is either applied by an agent or by the scheduler level.

After updating global variables and setting up the model, each mosquito, at each time step, can perform one out of three possible activities: find a mate and reproduce (activity that is carried out by the mosquito only once in the model), find a concentration of humans and have a blood meal or find a breeding site and lay eggs. At the scheduler level in each time step, the availability of water and blood-meal sites is updated.

Changes in blood-meal availability depend on the time of the day. Since mosquitoes bite mostly from dusk to midnight, the attribute of each patch reflecting the presence of humans is only activated once every four time periods. Finally, population density is saved at the scheduler level.

Design Concepts

Observation

The user interface of the model displays spatial and temporal variations of the abundance of mosquitoes. It also shows the proportion of each genotype and the total number of mosquitoes in the immature and mature stage.

Sensing

Mosquitoes react to external environmental factors such as: temperature (affects biological aspects of the mosquitoes like the gonotrophic cycle and the development rate of the egg), blood-meal sites (presence of humans) and breeding sites (water reservoirs).

Interactions

The dynamics of the system is driven by interactions between mosquitoes and land. Mosquitoes seek other mosquitoes to reproduce, and then they search blood-meal sites to bite a human host and mature their eggs. Finally, once the egg is mature and mosquitoes are ready to oviposit, they look for a breeding site to lay their eggs.

The type of land defines the cells in which the mosquitoes can bite a human host or lay their eggs. Additionally, the number of breeding sites changes seasonally due to variations in rainfall. These changes in land influence the time required for the development of immature mosquitoes and also the gonotrophic

cycle. Thus the vector population dynamics becomes affected.

Details

The model was implemented using NetLogo, a free programmable environment for the modeling of complex phenomena (Wilensky, 1999).

Initialization

Initial conditions of the model are mainly defined by the user or programmer. Parameters such as the initial number of wild, homozygous and heterozygous mosquitoes are established by the user, as well as the fitness of each type of mosquito. Initial number of patches associated with human concentrations and temperature value can also be defined for each simulation run. Finally, the location of mosquitoes, water patches and meal patches can be randomly established.

SIMULATION

This stage allows observing the behavior of the model. Then, a set of different setup conditions was tested to observe model's predictions. Simulations performed with the model were mainly done to determine conditions under which it is possible to use genetically modified vectors as a strategy to control the Malaria.

Given the stochastic elements in the model, we performed 100 simulations for each condition we analyzed. We tested the model in three different setup conditions mostly related with variations in the mosquito's fitness. One condition referred to the case where the heterozygous and homozygous are better adapted. Another one, where only the homozygous are the better adapted while the heterozygous are less adapted than the wild type. Finally, a third condition was studied, in which the heterozygous are much better adapted and the homozygous are less adapted. In all simulations, we consider the introduction of only 1% of GMMs on the total population of mosquitoes. A population of 5000 mosquitoes and a grid size that represents a landscape of one square kilometer was utilized in all simulations.

SIMULATION RESULTS

Results from simulations of the model in different setup conditions showed that fitness is the determinant parameter to establish strategy success. For all simulation cases, the dynamics of the population of mature mosquitoes were studied for ten years, the temperature value was 35 degrees Celsius, locations associated with human settlements corresponded to 1% of the environment simulated and the extension of water reservoirs varied seasonally between 0.5% and 1% of the number of patches.

As an example, simulation results of just one of the scenarios related with a particular setup condition are

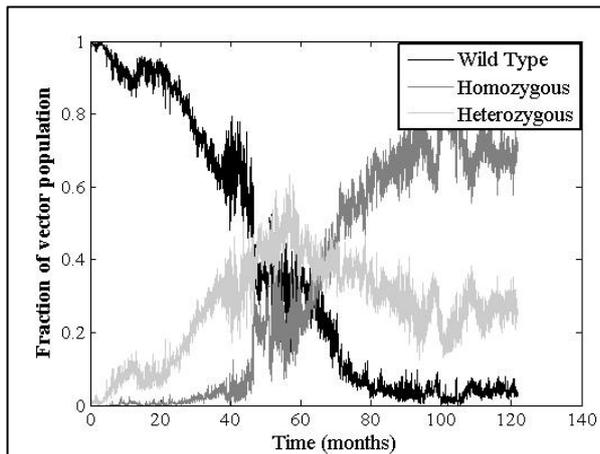


Figure 3: Time evolution of vector populations.
 Heterozygous Fitness = 1.05.
 Homozygous Fitness = 1.1.
 Wild Fitness = 1.

presented. Figure 3 shows the time evolution of vector populations, when the heterozygous and homozygous are better adapted (heterozygous fitness = 1.05, homozygous fitness = 1.1, wild type = 1).

In this case, at the beginning most of the population corresponds to the wild type and the proportion of heterozygous and homozygous vectors is very low. After five years, the density of different populations of vectors is practically the same and thenceforth the proportion of homozygous and heterozygous mosquitoes increases. Finally, nine years after the invading process started, the wild type has been practically swept by the population of transgenic heterozygous and homozygous mosquitoes. Therefore, this could be a good scenario for Malaria control, since most of the vectors are less capable of transmitting the parasite. Results from the simulation experiment are consistent with the results reported with the Malaria vectors dynamic obtained by Díaz et al. (2011).

CONCLUSIONS

An agent-based model of the population effect of introducing transgenic mosquitoes into a wild type population was presented. The model was developed to simulate spatial-temporal variations in the populations of Malaria vectors. Using this model, different conditions can be analyzed to establish conditions when a small invasion of genetically modified mosquitoes has any chance of controlling a Malaria epidemic.

As a future work, other conditions will be assessed including not only the GMMs, but also environmental factors such as temperature and rainfall variations. Additionally, the model will be complemented by including a human population in order to represent the dynamics of a Malaria epidemic. Finally, we will use the model to evaluate different strategies for the Malaria control taking into account spatial aspects.

REFERENCES

- Boete, C., Koella, J.C., 2002. A theoretical approach to predicting the success of genetic manipulation of malaria mosquitoes in malaria control. *Malaria J.* 1, 3.
- Booch, G., Rumbaugh, J., Jacobson, I., 2004. *The Unified Modeling Language User Guide*. Addison-Wesley, Boston, USA, 482 pp.
- Breman J., 2001. The ears of the hippopotamus: manifestations, determinants, and estimates of the malaria burden. *The American Journal of Tropical Medicine and Hygiene*, 64:1–11.
- Bousquet F. and Le Page C., 2004. Multi-agent simulations and ecosystem management: a review. *Ecological Modeling*, 176:313–332.
- Chitnis N., Schapira A., Smith T., Steketee R., 2010. Comparing the effectiveness of Malaria vector-control interventions through a mathematical model. *Am. J. Trop. Med. Hyg.*, 83(2), 2010, pp. 230–240.
- Depinay, J.M., Mbogo, C., Killen, G., Knols, B., Beier, J., Carlson, J., Dushoff, J., Bilingsley, P., Mwambi, H., Githure, J., Toure, A., McKenzie, E., 2004. A simulation model of African Anopheles ecology and population dynamics for the analysis of malaria transmission. *Biomed Central*. 3-29.
- Diaz, H., Olarte, A., Ramirez, A., Clavijo, C., 2011. A model for the control of malaria using genetically modified vectors. *Journal of Theoretical Biology* 276 (2011) 57–66.
- Gould, F., Magori, K., Huang, Y., 2006. Genetic strategies for controlling mosquito-borne diseases. *Amer. Scien* 94, 238.
- Grimm, V., Berger, U., Bastiansen, F., Eliassen, S., Ginot, V., Giske, J., Goss-Custard, J., Grand, T., Heinz, S.K., Huse, G., Huth, A., Jepsen, J.U., Jorgensen, C., Mooij, W.M., Muller, B., Pe'er, G., Piou, C., Railsback, S.F., Robbins, A.M., Robbins, M.M., Rossmannith, E., Ruger, N., Strand, E., Souissi, S., Stillman, R.A., Vabo, R., Visser, U., DeAngelis, D.L., 2006. A standard protocol for describing individual-based and agent-based models. *Ecol. Model.* 198 (1–2), 115–126.
- Harris, A., Matias-Arnéz, A., Hill, N., 2005. Biting time of *Anopheles darlingi* in the Bolivian Amazon and implications for control of malaria. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 100, 45–47.
- Ito, J., Ghosh, A., Moreira, L.A., Wimmer, E.A., Jacobs-Lorena, M., 2002. Transgenic anophelin mosquitoes impaired in transmission of a malaria parasite. *Nature* 417, 452.
- Lambrechts, L., Koella, J.C., Boete, C., 2007. Can transgenic mosquitoes afford the fitness cost?. *Trends Parasitol.* 24, 4.
- Linard C., Poncon N., Fontenille D., Lambin E., 2008. A multi-agent simulation to assess the risk of malaria re-emergence in southern France. *Ecological Modeling*, 220:160–174.
- Muller, G., Grébaud, P., Gouteux, J., 2004. An agent-based model of sleeping sickness: simulation trials of a forest focus in southern Cameroon. *C. R. Biol.* 327, 1–11.
- Ruiz D., Poveda G., Velez I., Quiñones M., Rua G., Velasquez L., Zuluaga J., 2006. Modeling entomological-climatic interactions of *Plasmodium falciparum* malaria transmission in two Colombian endemic-regions: contributions to a National Malaria Early Warning System. *Malaria Journal* 2006, 5:66.
- Smith T., Killen G., Maire N., Ross A., Molineaux L., Tediosi F., Hutton G., Utzinger J., Dietz K., Tanner M.,

2006. Mathematical Modeling of the Impact of Malaria Vaccines on the Clinical Epidemiology and Natural History of Plasmodium Falciparum Malaria: Overview. *Am. J. Trop. Med. Hyg.*, 75(Suppl 2), pp. 1–10.

Twonson, H., 2009. SIT for african malaria vectors: Epilogue. *Malaria J.* 8, S10.

WHO (World Health Organization), 2010. Report on Malaria in the world. Available in: www.who.int/es/index.html.

Wilensky, U., 1999. NetLogo. Available in: <http://ccl.northwestern.edu/netlogo/>.

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