Agent-Based Modelling: An *In Silico* Study on the Effectiveness of *Wolbachia*-Infected Mosquitoes as Vector Control Agents

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Abstract—Dengue Fever (DF) is a mosquito-borne disease which is a major epidemic concern especially in the South East Asia region. Various control intervention have been implied to control the breeding of mosquito vectors including the application of *Wolbachia* infected mosquitoes to reduce the transmission of dengue fever in Malaysia. Using the available data on the life cycle and transmission pattern of *Aedes* mosquitoes, this study explore the probability of the interaction of releasing *Wolbachia*-infected mosquitoes with dengue-infected mosquitoes spatially, and how would this interaction be able to reduce the case of dengue fever. A simple model is designed based on epidemiological data available and introduced in agent-based modelling. The model operates at local scale with support of computational infected mosquito with *Wolbachia* and with dengue virus by using GAMA Modelling and simulation platform (http://gama-platform.org), scheduled using a time scale of 60 minutes over 6 months period. The model predicted that 96% of dengue-infected mosquito will be replaced by *Wolbachia*-infected mosquito over a period of 6 months. The result proposed that the release of *Wolbachia*-infected mosquito into dengue hotspot population may reduce the case of dengue fever. This model has been designed to be completely generic and applicable to any geographic setting at any spatial scale. More modification of parameters will be implemented and the length of the exposure *in silico* will be expanded for five and ten years period to increase the strength of the model.

Keywords—dengue fever, Wolbachia, agent-based modelling, GAMA platform

I. INTRODUCTION

DENGUE fever, which is especially common in the Southeast Asian region, is now endemic in more than 100 countries worldwide [12]. It is estimated that approximately 390 million people are infected with DF annually of which half a million are afflicted with dengue haemorrhagic fever (DHF) [14]. The two recognized species of the vector transmitting dengue are *Aedes aegypti* and *Aedes albopictus* [7]. Traditional control strategies, which focuses on reducing populations of the main transmission vector, the *Aedes* mosquito, is done by destroying, altering, or removing potential vector breeding spots, or even by just simply killing them in both their larvae or adult stage by using chemical control methods [15]. However, these have ultimately failed to slow the spread of the disease [10]. This has led to a search for novel technologies to break dengue transmission cycles.

One promising approach is provided by the intracellular insect bacterium, *Wolbachia pipientis*, which can spread rapidly into uninfected host populations by inducing cytoplasmic incompatibility [8]. Since *Wolbachia* are maternally inherited, this effect provides a transmission advantage for the symbiont, resulting in the insect host populations to be rapidly invaded [6].

With the usage of agent-based modelling and simulation, the effectiveness of this approach can be tested before releasing *Wolbachia* infected mosquitoes into populations. Agent-based modelling and simulation is generally applied in computational laboratories, whereby researchers may test different hypotheses in a systematic way related to attributes of the agents, their behavioural rules, and the types of interactions, and their effect on macro level stylized facts of the system [5]. By using these parameters, it is possible to model and simulate the spread of diseases as well as ways to control them in realistic urban environment.

Agent-based models are now commonly used in numerous application domains such as ecology and social sciences [1,9] but their use is still impeded by the lack of generic yet ready-to-use tools supporting the design and the simulation of complex models integrating multiple level of agency and realistic environments. GAMA, short for GIS & Agent-based Modelling Architecture, modelling and simulation platform aims at addressing these flaws [11]. By using GAMA, the dengue virus outbreaks, as well as establishing *Wolbachia* in *Aedes* populations to suppress dengue transmission in urban areas can be observed by creating a realistic simulation in specific environment.

II. RESEARCH METHODS

A. Data Mining

Computerized searches were conducted on NCBI PubMed, Science Direct, and Google Scholar. The search time window was set between the years 2012 to 2017, as to make sure the studies retrieved were up to

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date and reliable, with no language limit. The reference lists of the retrieved articles were also manually searched to identify more qualified studies. Data retrieved were used to calculate the infection mean, as well as the birth and death mean of the mosquitoes in the simulation.

B. Construction of Sample Model

In order to examine the interaction between mosquitoes as agents for the study, to test out the birth and death rate of the mosquitoes in the simulation, as well as to determine how dengue and *Wolbachia* spreads among mosquito population in the simulation, a sample model was created for this purpose. The following modelling choice were made in the construction of this sample model:

- Simulation step = 1 minute
- Mosquitoes move at random within 15m range in the simulation
- All mosquitoes have the same spend and move at a constant speed
- Uninfected mosquitoes can be infected with either dengue or *Wolbachia*
- Dengue-infected mosquitoes can be infected with *Wolbachia*
- Dengue and *Wolbachia*-infected mosquitoes are never cured

C. Integration of GIS Data

One of the special features of GAMA is that it allows the implementation and integration of GIS data in the model, and it can automatically read GIS data that are formatted as shapefiles. This can be done by defining two agents, which are the building agents and the road agents. These agents will only be displayed as a map in the simulation and have no particular behaviour or actions upon them.

D. Managing and Manipulating Time

There are three crucial global variables that manages time in GAMA which are the cycle (the current simulation step), step (the duration of a simulation step), and time (the current time spent since the beginning of the simulation). As shown in the sample model constructed, the number of cycles are based on real time and follows each step is equivalent to 1 minute of the simulation. With this, the concept of time can be implemented into the simulation, and the creation of day and night cycles can be done.

E. Implementation of 'People' Species

Since the creation of vectors and implementation of GIS has been done, as well as adding the concept of time in the simulation, the next step would be to declare and implement a new species, which is the 'people' species. This species would follow the S-I-R model; susceptible, infected, and recovered. In this simulation, it is assumed that the people will not be born or die, and will be limited to 100 agents. However, this parameter is optional, and can be changed accordingly. The behaviour of the agent in the simulation is also defined, whereby the people will stay in buildings at a certain time in the simulation, and will move around to other buildings through the roads at a certain time as well. Other than that is that, when a dengue-infected mosquito is nearby, the people will have a probability of getting infected with dengue, and will stay infected for seven days.

F. Simulation on GAMA Platform

After the construction of the full model has been completed, the simulation is run for a period of six months in order to gather the necessary data for this research. There are two different simulations done, one is without the presence of *Wolbachia*, and the other is with the presence of *Wolbachia*. This is to determine the difference in how *Wolbachia*-based strategies can act as a method of control for dengue. Each simulation is run 10 times in order to get an average for a more accurate result.

III. RESULT AND DISCUSSION

A. Wolbachia as Effective Vector Control

There were two different simulations that were run during the course of this study, one of which is without the presence of *Wolbachia*, and the other is with the presence of *Wolbachia*. This is to determine whether or not *Wolbachia*-infected mosquitoes can actually reduce dengue incidence in the simulation by comparing the data retrieved from both the simulations. Two tables are drawn; Table 1 is the data gathered from the simulation without the presence of *Wolbachia*-infected mosquitoes, and Table 2 is the data gathered from the simulation with the presence of *Wolbachia*-infected mosquitoes.

Agents / Month	Initial	1st	2nd	3rd	4th	5th	6th
People							
Susceptible	100	94	85	77	69	60	53
Dengue cases	0	6	15	23	31	40	47
Mosquito							
Uninfected	18	8	3	1	0	0	0
Dengue-infected	2	13	19	22	23	24	25
Wolbachia-infected	0	0	0	0	0	0	0

Table 1 Data from simulation without *Wolbachia*-infected mosquitoes

Agents/Month	Initial	1st	2nd	3rd	4th	5th	6th
People							
Susceptible	100	97	91	87	81	79	79
Dengue cases	0	3	9	13	19	21	21
Mosquito							
Uninfected	17	10	4	1	0	0	0
Dengue-infected	2	9	10	9	6	3	1
Wolbachia-infected	1	3	7	12	17	20	24

Table 2 Data from simulation without *Wolbachia*-infected mosquitoes

A graph was also drawn to represent the data in a visual way. The graph shows that when there is an increase of dengue-infected mosquitoes, there is also an increase of dengue-infected people. Meanwhile, when *Wolbachia*-infected mosquitoes are implemented into the simulation, it can be seen that the number of

dengue-infected people slows down when the *Wolbachia*-infected mosquitoes take over the mosquito population. This is shown in both Fig. 1 and Fig. 2.
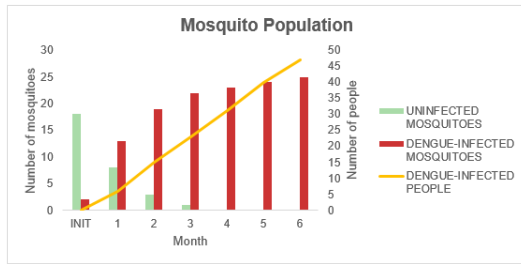

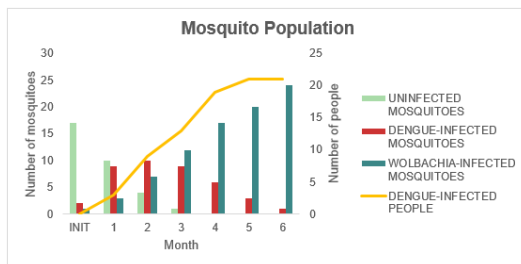Fig. 1 Data from simulation without *Wolbachia*-infected mosquitoes

Fig. 2 Data from simulation with *Wolbachia*-infected mosquitoes

Since there are no vaccines currently available to the public other than vaccine clinical trials done in five countries in the Asia-Pacific [3], as well as in Latin America [13] to name a few, the best way to reduce dengue virus transmission for now still relies on vector control, which ultimately aims to maintain *Aedes* mosquitoes below a certain threshold to avoid outbreaks [4].

In this study, it was found that the number of dengue cases will continue to increase when there is an abundance of dengue-infected mosquitoes. When *Wolbachia*-infected mosquitoes are introduced in the simulation, it can be seen that the number of dengue cases is reduced from 6% at the beginning of the simulation to 0% by the end of the simulation. The simulation was run in the span of 24 weeks to see what would be the effect of implementing *Wolbachia*-based strategies in real life. The simulation was also run 10 times to get an average in order to ensure the accuracy of data retrieved.

Based on the results gathered, it can be said that the parameters added or altered in the simulation greatly affects the results whereby if the parameters for the *Wolbachia*-infected mosquitoes are increased, the overall mosquito population would be infected with *Wolbachia*-infected mosquitoes in less than 24 weeks. Other than that, the alteration of parameters for the overall population of mosquito agents as well as the spatial size of the simulation would also affect the results gathered from the simulation.

B. Gama as a Disease Modelling Tool

In this study, the usage of GAMA as a new approach for disease modelling was explored, as well as the techniques used to create a convincing simulation. The steps and methods used to create a simulation to predict the effectiveness of introducing *Wolbachia* to wild mosquitoes in a certain area in order to reduce the incidences of dengue fever were described. To some degree, computer simulations such as GAMA can be seen as an experimental procedure for hypothesis testing and scenario analysis, as well as for the understanding of a complex system, which can be utilized in combination with experiments in real-life.

The usage of GAMA as a disease modelling tool helps in exploring the complex dynamics of diseases, in this case, the effect of using *Wolbachia* as an approach for vector control. The results gathered from this study is not 100% credible [2], however, the results is suggesting that the implementation of *Wolbachia*-based strategies can actually help in reducing dengue incidences, especially since the data used in this study is based on researches done on using *Wolbachia*-based strategies as a vector control approach.

IV. CONCLUSION

Wolbachia-based strategies has been proposed as a method to control the spread of the dengue, and acts as a vector control method. By using *in silico* approach, a simulation was created to test the effectiveness of using *Wolbachia*-infected mosquitoes as a vector control method to reduce the number of dengue incidence. A simple model was designed based on epidemiological data collected and introduced in agent-based modelling, specifically using GAMA platform. The model predicted that 96% of dengue-infected mosquitoes will be replaced by *Wolbachia*-infected mosquitoes over a period of 24 weeks, which is equivalent to six months. The result proposed that the release of *Wolbachia*-infected mosquitoes into dengue endemic population may reduce the number of dengue incidence in that area. The model used in this research is designed to be completely generic, and there are no environmental factors affecting the results of the simulation. Further work is needed in order to create a more solid model, in which the modification of parameters will be implemented, as well as the length of the simulation can be expanded to a five to ten-year period.

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