GENERIC REACTION-DIFFUSION MODEL FOR TRANSMISSION OF MOSQUITO-BORNE DISEASES: RESULTS OF SIMULATION WITH ACTUAL CASES

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KEYWORDS
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ABSTRACT
Mosquitoes can cause a lot of suffering to humans by transferring diseases. Malaria is a mosquito-borne disease caused by the parasite Plasmodium. It is an acute public health issue in many countries and can be fatal. Considering the similarity in the transmission of mosquito-borne diseases, a generic spatial-temporal model for transmission of multiple mosquito-borne diseases was formulated. The main concern here is whether the numerical results produced by this reaction-diffusion generic model are comparable with actual cases. Here, the actual notified weekly cases for 36 weeks, which is from week 39 in 2012 to week 22 in 2013, for four districts in Sarawak, Malaysia, namely Kapit, Song, Belaga and Marudi are compared with simulations of the generic model. The random movement of human and mosquito populations are taken into account. It is discovered that the numerical results are in good agreement to the actual malaria cases in the four districts.

INTRODUCTION
Mosquito-borne diseases such as dengue, yellow fever, filariasis, Japanese Encephalitis, Zika fever and malaria are a few diseases which can be transmitted from human to human through mosquito bites. A mosquito will ingest a pathogen when it takes a blood meal on an infectious human. Next, when it bites a susceptible human, it injects saliva and anti-coagulants into the human’s blood. According to the World Health Organization, there were estimated 214 million malaria cases reported worldwide and 438000 deaths in 2015 (World Health Organization, 2015).

Disease models are essential in the armory of epidemiological devices as they can be utilized in spite of limitations in data. The mathematical models are based on the understanding of the dynamics of the host and pathogen and are used to provide forecast of the prevalence of an infection. The factors which contribute to the spread of the infection can be identified and to determine the best control measures to eradicate them. These models use mathematical equations to interpret the dynamics of diseases. Henceforth, experiments can be done without the necessity to carry it out in real life which might be unethical. By doing so, questions such as what-if can be answered. Deterministic models consist of ordinary differential equations, for example models by Ross (1910), Anderson and May (1979), Tumwiine et al. (2007), and Labadin et al. (2009). The compartmental mathematical models illustrate whether the disease will prevail or dies out in a population in time.

Researchers have been examining the impact of spatial heterogeneity and movements on the spread and persistence of diseases. Consequences of control measures such as vaccination in local region and its outcome can be analyzed. There are a few approaches to modeling spatial spread. Metapopulation models (Cliff, 1992, Ding et al. 2012) divide a population to multiple discrete groups. There are two ways these models are constructed, the mobility approach and the cross-coupled metapopulation approach. Most metapopulation models are the cross-coupled approach which consider transmission within and between groups. Spatially continuous models such as reaction-diffusion models assume the population is distributed continuously across the environment and not in discrete
populations. Spatially continuous models (Kon and Labadin, 2005, Ani and Capasso, 2012, Maidana and Yang, 2007) allow mathematical analysis of the general patterns of the spread of diseases. Lattice-based models group a particular grid site as a subpopulation and in cellular automata, interactions are assumed to occur only between neighbouring grids (Gibson, 1997). Geographic information systems (GIS) are used to secure, collect spatial data and when needed, regain and to depict the spatial facts. Hence, it can be utilized for data on populations, disease prevalence, environmental data and create a connection among them. Examples of application of GIS are carried out by Chapat et al. (2002) and Kitron (2000).

A reaction-diffusion generic model for mosquito-borne diseases was formulated (Kon and Labadin, 2015) based on the similarity in the manner of transmission of these infections. All mosquito-borne diseases are spread through vector mosquito; thus, this commonality is taken into account. A general model which incorporates both spatial and temporal factors as well as caters to the many different mosquito-borne diseases is profitable as most models constructed are for a specific disease. In this paper, the proposed new generic model will be discussed in the next section. After that, the reported weekly malaria cases in four districts in Sarawak are compared to simulations from the generic model for the spread of mosquito-borne infection. In the last section, conclusions and plans for future work are discussed.

**MODEL FORMULATION**

Mosquito-borne and vector-borne diseases compartmental models were deliberated and the similarities identified before formulating the generic model (Kon and Labadin, 2013). This is because the objective is to formulate a generic model which can be applied to different mosquito-borne diseases. The matching compartments used for vector-borne diseases are found to be susceptible and infectious for both human and vector population. Thus, the generic mosquito-borne diseases model consists of Susceptible-Infectious (SI) compartments for both human host and vector mosquito (Kon and Labadin, 2015). As we want to investigate the effect of spatial heterogeneity and movement of human and mosquito population on the spread of diseases, spatial factors are incorporated in the generic model. The common terms used for spatial spread were determined by studying the spatio-temporal disease models and they are found to be diffusion coefficients and location dependent parameters. Terms such as birth rate, death rate, force of infection and recovery rate were regularly included in vector-borne disease models. The focal point here is in the way these diseases are transmitted. The random movement of human and mosquito populations are included and they are depicted as random walks, where a group of dispersing humans and mosquitoes behave comparatively to a group of particles diffusing in Brownian motion at large spatial scale (Cantrell and Cosner, 2004).

Here, the human population is divided into two compartments namely susceptible $S_H$ and infectious $I_H$. The density of susceptible and infectious human populations are $S_H(t,x)$ and $I_H(t,x)$ where location $x$ is considered. It is assumed that dynamics of total human population obey

$$\frac{\partial N_H(t,x)}{\partial t} = D_H \frac{\partial^2 N_H(t,x)}{\partial x^2} + \gamma + d_H N_H(t,x)$$

where total human density is $N_H = S_H + I_H$. The diffusion coefficient $D_H$ portrays the change in the rate of change of human movement. It is assumed that diffusion coefficient for both susceptible and infectious is constant. The mosquito population is also divided into susceptible $S_M$ and infectious $I_M$. $S_M(t,x)$ and $I_M(t,x)$ are the spatial density of susceptible and infectious mosquito respectively. Moreover, total mosquito density is $N_M = S_M + I_M$, giving us the total human and mosquito density at any point $x$ and time $t$ are $N_H(t,x)$ and $N_M(t,x)$ respectively. An infectious mosquito transfers the infection if it takes blood meal on a susceptible human. The rate that susceptible human gets infected is $c \frac{gN_H(t,x)}{1 + g2N_H(t,x) N_H(t,x)}$ where $c$ is the probability of transmission per bite from an infectious mosquito to a susceptible human. The mean rate of bites per mosquito, and $\frac{I_M(t,x)}{N_H(t,x)}$ is the probability an infectious mosquito bites a human. The biting rate is density-dependent on the total human population as done by Wang and Zhao (2011). In addition, the number of new infectious cases is $c_H S_H(t - \tau_H,x) I_H(t - \tau_H,x) H(x)$ with the latent period for human given as $\tau_H$. Hence, the disease is considered to be transferred to an infectious human before the latent period. A susceptible mosquito gets infected when it takes a blood meal on an infectious human. The rate that susceptible mosquito gets infected is $b \frac{gN_H(t,x)}{1 + g2N_H(t,x) N_H(t,x)}$ where $b$ is transmission per bite from an infectious human to a susceptible mosquito and $\frac{I_H(t,x)}{N_H(t,x)}$ is the probability that a mosquito bites an infectious human, $I_H$. The number of new mosquito
infectious cases is \( b \beta \frac{S_M(t - \tau_M, x)}{H(x)} I_H(t - \tau_M, x) \), taking into account that contact occurred before the mosquito incubation period, \( \tau_M \).

The reaction-diffusion generic model for transmission of mosquito-borne infection is below:

\[
\frac{\partial S_H(t, x)}{\partial t} = D_H \frac{\partial^2 S_H(t, x)}{\partial x^2} + \gamma - c \frac{g N_H(t, x)}{1 + g N_H(t, x)} N_H(t, x) S_H(t, x) + r I_H - d_H S_H(t, x) \\
+ \Delta \frac{\partial S_M(t, x)}{\partial t} = D_M \frac{\partial^2 S_M(t, x)}{\partial x^2} + \Lambda - b \frac{g N_H(t, x)}{1 + g N_H(t, x)} N_H(t, x) S_M(t, x) - d_M S_M(t, x)
\]

(1)

\[
\frac{\partial I_H(t, x)}{\partial t} = D_H \frac{\partial^2 I_H(t, x)}{\partial x^2} + \frac{g N_H(t, x)}{1 + g N_H(t, x)} I_H(t, x) S_H(t, x) - (d_H + r) I_H(t, x) \\
+ \Delta \frac{\partial I_M(t, x)}{\partial t} = D_M \frac{\partial^2 I_M(t, x)}{\partial x^2} + \frac{g N_H(t - \tau_M, x)}{1 + g N_H(t - \tau_M, x)} I_M(t, x) S_M(t - \tau_M, x) - d_M I_M(t, x)
\]

(2)

\[
\frac{\partial I_H(t, x)}{\partial t} = D_H \frac{\partial^2 I_H(t, x)}{\partial x^2} + \frac{g N_H(t, x)}{1 + g N_H(t, x)} I_H(t, x) S_H(t, x) - (d_H + r) I_H(t, x) \\
+ \Delta \frac{\partial I_M(t, x)}{\partial t} = D_M \frac{\partial^2 I_M(t, x)}{\partial x^2} + \frac{g N_H(t - \tau_M, x)}{1 + g N_H(t - \tau_M, x)} I_M(t - \tau_M, x) S_M(t - \tau_M, x) - d_M I_M(t, x)
\]

(3)

\[
\frac{\partial I_H(t, x)}{\partial t} = D_H \frac{\partial^2 I_H(t, x)}{\partial x^2} + \frac{g N_H(t, x)}{1 + g N_H(t, x)} I_H(t, x) S_H(t, x) - (d_H + r) I_H(t, x) \\
+ \Delta \frac{\partial I_M(t, x)}{\partial t} = D_M \frac{\partial^2 I_M(t, x)}{\partial x^2} + \frac{g N_H(t - \tau_M, x)}{1 + g N_H(t - \tau_M, x)} I_M(t - \tau_M, x) S_M(t - \tau_M, x) - d_M I_M(t, x)
\]

(4)

Parameters used in the model above are as stated in Table 1. All parameters are assumed to be non-negative.

Table 1: Parameters used in the partial differential equations model

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_H )</td>
<td>diffusion rate for humans</td>
</tr>
<tr>
<td>( D_M )</td>
<td>diffusion rate for mosquitoes</td>
</tr>
<tr>
<td>( \gamma )</td>
<td>human recruitment rate</td>
</tr>
<tr>
<td>( c )</td>
<td>transmission probability per bite from ( I_M ) to ( S_H )</td>
</tr>
<tr>
<td>( d_H )</td>
<td>human death rate</td>
</tr>
<tr>
<td>( r )</td>
<td>recovery rate</td>
</tr>
<tr>
<td>( \Lambda )</td>
<td>mosquito recruitment rate</td>
</tr>
<tr>
<td>( b )</td>
<td>transmission probability per bite from ( I_H ) to ( S_M )</td>
</tr>
<tr>
<td>( d_M )</td>
<td>mosquito death rate</td>
</tr>
<tr>
<td>( \tau_H )</td>
<td>incubation period in humans</td>
</tr>
<tr>
<td>( \tau_M )</td>
<td>incubation period in mosquitoes</td>
</tr>
</tbody>
</table>

MODEL ANALYSIS

Since the generic mosquito-borne diseases model is for multiple mosquito-borne diseases, we want to investigate whether this model is able to reproduce malaria cases in four different districts in Sarawak. The actual cases are taken from Sarawak Weekly Epid News by Sarawak State Health Department as all malaria cases should be notified within 24 hours as reported by the Vector Borne Disease Control Section (Sarawak Health Department, 2012). Simulation results from the generic model are compared with actual prevalence in four districts in Sarawak, ie. Kapit, Song, Belaga and Marudi from week 39 in 2012 to week 22 in 2013, that is for 36 weeks. Parameters used are stated in Table 2.

As this system is made up of nonlinear partial differential equations, the model is discretized using the finite difference method. Crank Nicolson method is used as it is unconditionally stable for diffusion equations (Thomas, 1995). Firstly, let us start with equation (1) by writing it at the point \( (x_j,t^{j+\frac{1}{2}}) \). Thus

\[
\frac{\partial S_H(x_j,t^{j+\frac{1}{2}})}{\partial t} \approx \frac{S_H(x_j,t^{j+\frac{1}{2}}) - S_H(x_j,t^{j})}{\Delta t}
\]

will be written as \( S_H^{j+1} - S_H^j \). It is a centered difference approximation for \( S_H \) at \( (x_j,t^{j+\frac{1}{2}}) \). The term \( \frac{\partial^2 S_H(x_j,t^{j+\frac{1}{2}})}{\partial t^2} \) is approximated using the average of second centered differences for \( \frac{\partial^2 S_H(x_j,t^{j+\frac{1}{2}})}{\partial t^2} \) and \( \frac{\partial^2 S_H(x_j,t^j)}{\partial t^2} \). Similar approximation is carried out on the other populations, that is for infectious human, susceptible mosquito and infectious mosquito.

The equations after discretization and rearrangement are:

\[
S_H^{j+1} \left( \frac{-D_H}{2(\Delta t)^2} \right) + S_H^j \left( \frac{1}{\Delta t} \right) + \frac{\alpha D_H}{4(\Delta t)^2} (I_M^j + I_M^{j+1}) - \frac{d_H}{2} \right) + S_H^{j+1} \left( \frac{D_H}{2(\Delta t)^2} \right) + \gamma + S_H^j \left( \frac{1}{\Delta t} \right) - \frac{c \beta d_M}{4(\Delta t)^2} (I_M^j + I_M^{j+1}) - \frac{d_M}{2} \right) + S_H^{j+1} \left( \frac{D_M}{2(\Delta t)^2} \right) + \frac{g N_H^j}{1 + g N_H^j} I_H^j S_H^j - (d_H + r) I_H^j \right) \]

(5)
Table 2: Values of parameters used for Kapit, Song, Marudi and Belaga districts

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Kapit (dimensions)</th>
<th>Song</th>
<th>Marudi</th>
<th>Belaga</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$D_H$</td>
<td>10 km$^{-2}$ week$^{-1}$</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>$D_M$</td>
<td>10 km$^{-2}$ week$^{-1}$</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>$\gamma$</td>
<td>201 week$^{-1}$</td>
<td>201</td>
<td>201</td>
<td>201</td>
<td></td>
</tr>
<tr>
<td>$\lambda$</td>
<td>3.5 week$^{-1}$</td>
<td>3.5</td>
<td>3.5</td>
<td>3.5</td>
<td></td>
</tr>
<tr>
<td>$g$</td>
<td>2.8 week$^{-1}$</td>
<td>2.8</td>
<td>2.8</td>
<td>2.8</td>
<td></td>
</tr>
<tr>
<td>$c$</td>
<td>0.012</td>
<td>0.012</td>
<td>0.012</td>
<td>0.012</td>
<td></td>
</tr>
<tr>
<td>$d_H$</td>
<td>0.0000827 week$^{-1}$</td>
<td>0.0000827</td>
<td>0.0000827</td>
<td>0.0000827</td>
<td></td>
</tr>
<tr>
<td>$r$</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td>0.014</td>
<td></td>
</tr>
<tr>
<td>$\Lambda$</td>
<td>1056</td>
<td>1056</td>
<td>1056</td>
<td>1056</td>
<td></td>
</tr>
</tbody>
</table>

| $b$ | 0.47 | 0.47 | 0.47 | 0.47 |
| $d_M$ | 0.0485 week$^{-1}$ | 0.0485 | 0.0485 | 0.0485 |
| $\tau_H$ | 1.4 week | 1.4 | 1.4 | 1.4 |
| $\tau_M$ | 1.4 week | 1.4 | 1.4 | 1.4 |

Equations (5-8) form an algebraic system; hence the system is arranged in matrix form and solved simultaneously to obtain the numerical results. The initial data for susceptible and infectious compartments for both human and mosquito populations are polynomial functions. To obtain the actual density of infectious humans, actual cases in Song, Kapit, Belaga and Marudi can be obtained by dividing the prevalence of malaria to the area of each district. Then, the distances between these locations are calculated according to the latitude and longitude; thus we get $x = (\text{Song,Kapit,Belaga,Marudi}) = (0.43, 200, 375)$. 
Polynomial functions are found to better represent the density data for each of these locations. Hence, the initial data used are:

\[ I_H(\phi, x) = -1.55 \times 10^{-7} x^3 + 0.0001453 x^2 - 0.03891 x + 5.135, \]
\[ I_M(\psi, x) = -1.229 \times 10^{-11} x^3 + 8.003 \times 10^{-8} x^2 - 1.454 x + 0.001, \]
\[ S_H(\psi, x) = -8.067 \times 10^{-6} x^3 + 0.003249 x^2 - 0.05605 x + 7.624, \]
\[ S_M(\psi, x) = -1.697 \times 10^{-8} x^3 + 1.193 \times 10^{-5} x^2 - 0.002807 x + 0.3, \]
\[ \forall \psi \in [-\tau_{H,0}], \forall \psi \in [-\tau_{M,0}], x \in [0, 0.375]. \]

Neumann boundary condition is applied where

\[ \frac{\partial I_H(0,t)}{\partial x} = 0, \frac{\partial I_H(0,t)}{\partial x} = 0, \frac{\partial S_M(0,t)}{\partial x} = 0, \frac{\partial I_M(0,t)}{\partial x} = 0 \]
\[ \frac{\partial S_H(T, t)}{\partial x} = 0, \frac{\partial I_H(T, t)}{\partial x} = 0, \frac{\partial S_M(T, t)}{\partial x} = 0, \frac{\partial I_M(T, t)}{\partial x} = 0, \]

and
\[ \frac{\partial I_M(T, t)}{\partial x} = 0. \]

Since we do not have the data for mosquito population in the districts in Sarawak, the initial data for susceptible and infectious mosquito are estimated to fit the actual prevalence. To obtain best fit, the objective is to attain a very low root mean square error (RMSE). RMSE is the difference between the predicted and actual density and the smaller it is, the better. The parameter value for mosquito such as death rate \( d_M \) is determined by finding the best fit numerical result compared to prevalence in the four districts. For mosquito death rate, \( d_M \) if we consider the average lifespan of mosquito only in ideal situation, the parameter value will be around 0.333-0.5 week\(^{-1}\) [Kon and Labadin, to be published]. As it is not possible to measure directly the life span of mosquitoes in nature, the value is varied until we obtain the best fit curve. The values for mosquito death rate in the four locations differ and are lower than the predicted value for ideal situation. As it is challenging to decide on the value of the speed of the random movement of both human and mosquito populations, the diffusion rate for human population, \( D_H \) and mosquito population \( D_M \) are decided upon comparison of actual and simulation of the infectious human density.

Comparing Figure 1 which depicts the actual cases in Song, Kapit, Belaga and Marudi and the numerical result produced from the generic model in Figure 2, it is clear that the magnitude and behavior of the infectious human density is in good agreement for the different locations in time.

Next, we would like to compare the simulated infectious human density to that of the actual notified cases in each of the four districts. The initial conditions used are the same except for:

\[ I_M(\psi, x) = -6.857 \times 10^{-8} x^3 + 4.192 \times 10^{-5} x^2 - 0.007141 x + 0.4, \]
\[ \forall \phi \in [-\tau_{H,0}], \forall \psi \in [-\tau_{M,0}], x \in [0, 0.375]. \]

This is because the change in the initial data for infectious mosquito population actually increases the accuracy of the model in producing simulated cases which are similar to actual cases. Hence, the initial condition plays a vital role in getting a good approximation. The simulated density is graphed on the same axis as the actual cases to compare them visually and the RMSE is calculated.

In Figure 3, the density of weekly actual malaria cases in Song and the predicted cases increases from week 0 to week 35. The disease prevails in the population and displays similar behavior for both the actual and simulated cases. RMSE for this particular set of data is \( 6.2334 \times 10^{-4} \).

The numerical result of the generic model’s density of malaria infectious humans in Kapit resembles the actual notified cases closely as depicted in Figure 4. The RMSE is a low \( 4.5217 \times 10^{-4} \). Malaria cases surge from week 0 to week 35 and are alike in both cases. As shown in Figure 5, the actual density of infectious humans is slightly higher but both display similar growth of the disease until week 35. The RMSE is calculated to be \( 4.1168 \times 10^{-4} \). Finally, the actual prevalence of malaria in Marudi can be seen in Figure 5. The numerical result from the generic model shows a steady, almost linear increment while the notified cases exhibit a sharper increase up to week 5, then it continues to grow but at a slower rate. Both results agree that the disease prevails in Marudi by week 35. The RMSE for this comparison is \( 8.0379 \times 10^{-4} \).
CONCLUSION AND FUTURE WORK

A generic model for multiple mosquito-borne diseases is discussed in this paper. This generic model is formulated to be utilized for many different types of mosquito-borne diseases. Here, we would like to use this model to produce results for malaria. Simulations from this generic model are compared with actual malaria cases in four districts in Sarawak, namely Kapit, Song, Belaga and Marudi. Thirty-six weekly notified malaria cases are obtained from Sarawak State Health Department and compared with simulations. The spatio-temporal model is found to be able to reproduce actual cases in the four locations. The disease is endemic in all four districts. The simulated cases for Song and Kapit are found to be in good agreement with that of the actual notified cases. Numerical results for Belaga and Marudi shows similar behavior, that is the disease prevails in the population although the magnitudes slightly differ. In this study, it is found that the generic model for mosquito-borne diseases is able to reproduce malaria cases which correspond to the four districts in Sarawak. For future work, we would like to study whether this generic model is able to reproduce results...
for other mosquito-borne diseases such as dengue. Factors concerning spatial heterogeneity which contributes to the spread of diseases will also be identified and the optimal control measure can be determined.

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