A Mathematical Model to Assess the Impact of Temperature on the Virulence of Vector-borne Pathogens

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Abstract

It is expected that the increase in global temperature will lead to an expansion of the geographical spread, and an increase in the incidence, of tropical infections. However, the trend in severity of those infections as a function of the increase in temperature is still unknown. Suppose that two strains of a given parasite are competing for the same host. It is possible to demonstrate that, in general, the strain with an evolutionarily stable strategy,
that is, the one that wins the competition, is the one with the highest value of the basic reproduction number, \( R_0 \). Now, let us consider the case of a vector-borne infection. In this case, \( R_0 \) is dependent on the temperature, which influences the mosquitoes’ dynamics, and on the virulence of the parasite. We want to know which combination of environmental temperature \( T \) and virulence \( \nu \) maximizes \( R_0(T, \nu) \). We demonstrate, in this case, that the increase in temperature is associated with a decrease in parasite virulence.

**Keywords:** virulence, temperature, models, basic reproduction number

**INTRODUCTION**

The evolution of virulence has been the subject of formal analysis for decades [1-9]. Theoretical work has shown that parasites should evolve intermediate levels of virulence [1], [2], [10-13]. These intermediate levels of virulence have been attributed to a tradeoff between intra-host replication by the parasite and the negative effect that such replication has on inter-host transmission [8]. In cases where intra-host replication increases the host mortality, virulence tends to decrease, whereas virulence tends to increase in cases where intra-host replication results in higher transmissibility [2].

The ecology of virulence, in particular the impact of climatic factors on parasite virulence [8], [14], has received little attention. In the case of vector-borne infections, climate has been suggested as the most significant driver of disease [14]. This is particularly significant nowadays when important global changes in temperature are occurring at a dramatic rate [14]. However, the impact of an increase in temperature on the virulence of vector-borne parasites is still unknown.

We propose a model to evaluate the impact of temperature increase on the evolution of virulence. The model is intended to answer the question of which combination of environmental temperature \( T \) and virulence \( \nu \) maximizes \( R_0(T, \nu) \). This is based on the assumption that the strain with the highest \( R_0 \) is evolutionarily stable [13], that is the maximum \( R_0(T, \nu) \) is an Evolutionarily Stable Strategy (ESS) [15]. For this, we calculate the value of virulence that maximizes \( R_0(T, \nu) \) and then study how this optimal \( \nu \) changes as temperature increases.

This paper is organized as follows. After this brief introduction, we present the mathematical developments involved in the hypothesis relating virulence and temperature. We then show the result of a numerical exercise in which we demonstrate the relationship between temperature and virulence. This is followed by a section in which we carry out a sensitivity analysis. Finally, in the final section we discuss our results and their biological implications.
THE MODEL

The model is designed for a vector-borne infection [16-17] and assumes that the transmission parameter is dependent on the temperature and that the removal rate is dependent on parasite virulence, defined as the capacity of the parasite to replicate within the host. The exception is the probability of a vector acquiring the infection from an infectious host, which is assumed to be dependent on the parasitemia; that is, virulence. Virulence is generally defined as the decrease in host fitness [18]. Here we assume virulence as the capacity of the parasite to replicate within the host in the sense that the more virulent the parasite strain, the higher the parasitemia. This is assumed directly related to the instantaneous mortality rate, and indirectly related to the recovery rate from parasitemia.

Let us consider the expected lifetime production of new infections generated by a single infected host per susceptible host in the population, which is Dieckmann's [19] reproductive value, $R$

$$R = \int_{0}^{\infty} \beta(T,\nu) \exp[-u(T,\nu)] ds$$  \hspace{1cm} (1)

where $\beta(T,\nu)$ is the transmission rate, dependent on the temperature, $T$, and on the parasite virulence, $\nu$, and $u(T,\nu)$ is the removal rate from the infectious condition, dependent on the same variables. Now, let us consider the case of a vector-borne infection. In this case the transmission rate is

$$\beta(T,\nu) = m(T)a^2(T)b\exp(-\mu_m(T)\tau(T))c(\nu)/\mu(T)$$  \hspace{1cm} (2)

and the removal rate from the infectious condition is

$$u(\nu) = [\alpha_H(\nu) + \gamma_H(\nu)]$$  \hspace{1cm} (3)

where $m$ is the density of mosquitoes as related to humans, $a$ is the average daily biting rate of the vector, $b$ is the fraction of actually infective bites to humans, $\alpha_H$ is the disease induced mortality rate in humans, $\gamma_H$ is the human recovery rate from the infection, $c$ is the fraction of actually infective bites to mosquitoes, $\mu_m$ is the natural mortality rate of mosquitoes, and $\tau$ is the extrinsic incubation period of the parasite. Therefore equation (1) turns to be the expression of the Ross-Macdonald basic reproduction number [20]:

$$R = \int_{0}^{\infty} \beta(T,\nu) \exp[-u(T,\nu)] ds$$
\[ R_0(T, \nu) = \frac{m(T)\alpha^2(T)b \exp(-\mu_M(T)\tau(T))c(\nu)}{\mu_M(T)[\alpha_H(\nu) + \gamma_H(\nu)]} \]  

(4)

Note that, for the sake of generality, we consider the infectious terms as dependent on the temperature, except for the probabilities of infection to humans, \( b \), and to mosquitoes, \( c(\nu) \), the latter being dependent on virulence \( \nu \). In addition, the removal rate from the infectious condition is composed of terms dependent on virulence \( \nu \).

The mosquitoes’ density, \( m \), is a well-known parameter that is strongly dependent on the environmental temperature, insofar as the higher the temperature, the greater the abundance of mosquitoes, up to a certain maximum temperature [21]. The mosquitoes’ daily average biting rate, \( a \), was also assumed to be a function of environmental temperature, based on the fact that blood digestion is accelerated by a rise in temperature [22]. Adult mosquitoes’ mortality rate as a function of temperature, \( \mu(T) \), was based on work by Russel and Rao [23], who demonstrated an increase in mosquitoes’ mortality. The extrinsic incubation period, \( \tau \), is a parameter known since the 1940s to be strongly dependent on temperature [24]. Finally, the probability of infection to mosquitoes, \( c \), was assumed to be dependent on virulence based on the fact that higher parasite virulence is an inevitable consequence of higher rates of reproduction within the host and, therefore, higher parasitemia, thus making a higher concentration of inoculate available for the vectors [5].

The term for removal from the infectious condition (equation 3), has all its terms dependent on virulence. This is based on the assumption that higher parasitemia causes higher mortality to hosts, \( \alpha_H \), and lower recovery rates from the infection, \( \gamma_H \).

Assuming the following forms for the functions describing the parameters that compose \( R_0(T, \nu) \):

\[
\begin{align*}
c(\nu) &= c_0(1 - e^{-\kappa_1 \nu}) \\
\alpha_H(\nu) &= \alpha_0(1 - e^{-\kappa_2 \nu}) \\
\gamma_H(\nu) &= \gamma_0(1 + e^{-\kappa_3 \nu}) \\
a(T) &= a_0(1 - e^{-\kappa_4 T}) \\
m(T) &= m_0(1 - e^{-\kappa_5 T}) \\
\mu_M(T) &= \mu_0(1 - e^{-\kappa_6 T}) \\
\tau(T) &= \tau_0(1 - e^{-\kappa_7 T})
\end{align*}
\]  

(5)

with the parameters shown in table 1, chosen to result in values compatible with the literature [25], we can analyse the relationship between virulence and temperature. This
will be done by finding the values of virulence \( \nu \) that maximizes \( R_0(T, \nu) \) and then study how this optimal \( \nu \) changes as temperature changes. First, we calculate

\[
\frac{\partial}{\partial \nu} R_0(T, \nu) = \frac{\partial c(\nu) / \partial \nu}{c(\nu)} - \left\{ \frac{1}{\partial \alpha(\nu) / \partial \nu + \partial \gamma(\nu) / \partial \nu} \right\} \left[ \frac{\partial \alpha(\nu) / \partial \nu + \partial \gamma(\nu) / \partial \nu} {\partial \nu} \right] = 0
\]

and then change the values of temperature to see how those changes affect this maximum fitness. This is done by keeping this maximum fitness fixed, calculated for an initial temperature from equation (6), and see what levels of virulence result in this value for each temperature value chosen.

<p>| Table 1. Values of the parameters composing equation (5). |
|-------------------------------|---------|</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( c_0 )</td>
<td>1</td>
</tr>
<tr>
<td>( c_0 )</td>
<td>( 2 \times 10^{-1} )</td>
</tr>
<tr>
<td>( \gamma_0 )</td>
<td>( 10 )</td>
</tr>
<tr>
<td>( \alpha_0 )</td>
<td>5</td>
</tr>
<tr>
<td>( m_0 )</td>
<td>( 10^5 )</td>
</tr>
<tr>
<td>( \mu_0 )</td>
<td>( 10^1 )</td>
</tr>
<tr>
<td>( \tau_0 )</td>
<td>5</td>
</tr>
<tr>
<td>( \kappa_1 )</td>
<td>( 8 \times 10^{-2} )</td>
</tr>
<tr>
<td>( \kappa_2 )</td>
<td>( 10 )</td>
</tr>
<tr>
<td>( \kappa_3 )</td>
<td>( 10^2 )</td>
</tr>
<tr>
<td>( \kappa_4 )</td>
<td>( 10^2 )</td>
</tr>
<tr>
<td>( \kappa_5 )</td>
<td>( 10^{-5} )</td>
</tr>
<tr>
<td>( \kappa_6 )</td>
<td>( 5 \times 10^{-1} )</td>
</tr>
<tr>
<td>( \kappa_7 )</td>
<td>( 10^{-2} )</td>
</tr>
</tbody>
</table>

**RESULTS**

In this section, we present a hypothetical situation that is intended only to exemplify, with a numerical case, the theory provided in the previous section. Therefore, the results are actually an illustration of the qualitative analysis intended.

In figure 1, we show the result of the numerical simulation of equation (4) with the functional shapes of the parameters as in equation (5) and numerical values as in table 1.
Figure 1. The Basic Reproduction Number as in equation (4) with the functional shapes of the parameters as in equation (5) and numerical values as in table 1.

Note that $R_0(T, \nu)$ reaches a maximum value with variation in virulence and then drops slightly to a stable value. It is also noteworthy that $R_0(T, \nu)$ changes more intensely with temperature than with virulence. This is a result of the functional shape and parameter values of the components of $R_0(T, \nu)$.

Now, if we change the values of the temperature we can assess what values of virulence keeps that maximum $R_0(T, \nu)$ obtained with the initial value of temperature. The result is shown in figure 2.
Figure 2. Effect of the increase in temperature on parasite virulence.

Note that, as $R_0(T,\nu)$ is more sensitive to the temperature than to the virulence (see below) an increase in the temperature causes such an increase in $R_0(T,\nu)$ that the parasite can reduce its virulence and still keep its EES.

**Sensitivity of the model to the parameters**

In order to estimate the sensitivity of the model to the parameters composing $R_0(T,\nu)$ we calculated the partial derivatives of $R_0(T,\nu)$ with reference to each one of the factors [26].

We begin by taking the partial derivative of $R_0(T,\nu)$ with respect to each of the variables temperature and virulence, that is from equation (4) we take first $\frac{\partial R_0(T,\nu)}{\partial T}$, which assumes the form:
\[
\frac{\partial R_0(T, \nu)}{\partial T} = m_0 \kappa e^{-\kappa T} \left( a_0(1-e^{-\kappa T}) \right)^2 + 2m_0(1-e^{-\kappa T})a_0(1-e^{-\kappa T})a_0\kappa e^{-\kappa T} \times
\]

\[
\times b \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] \times
\]

\[
\left\{ \mu_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T}) \right] \right\} +
\]

\[
+m_0(1-e^{-\kappa T})(a_0(1-e^{-\kappa T}))^2 \times
\]

\[
\times (-bc \exp \left[ -T^2 \tau_0(1-e^{-\kappa T})\mu_0(1-e^{-\kappa T}) \right] \times
\]

\[
T^2 \tau_0(1-e^{-\kappa T})\mu_0 \kappa e^{-\kappa T} + T^2 \mu_0(1-e^{-\kappa T})\tau_0 \kappa e^{-\kappa T} +
\]

\[
+ 2T \tau_0(1-e^{-\kappa T})\mu_0(1-e^{-\kappa T}) \times \left[ \mu_0(1-e^{-\kappa T})(a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T})) \right]^4 +
\]

\[
\frac{bc \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right]}{T^2 \mu_0(1-e^{-\kappa T})}(a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T})) \right]^3
\]

\[
= m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right]^2 \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] \times
\]

\[
\times \kappa e^{-\kappa T} - m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right]^2 b \times
\]

\[
\times \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] c_0(1-e^{-\kappa T}) \times
\]

\[
\times \mu_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T}) + \kappa e^{-\kappa T} - \kappa \gamma_0 e^{-\kappa T} \right]
\]

\[
= m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right] \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] \times
\]

\[
\times \kappa e^{-\kappa T} - m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right]^2 b \times
\]

\[
\times \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] c_0(1-e^{-\kappa T}) \times
\]

\[
\times \mu_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T}) + \kappa e^{-\kappa T} - \kappa \gamma_0 e^{-\kappa T} \right]
\]

\[
\frac{\partial R_0(T, \nu)}{\partial \nu} \quad \text{(7)}
\]

Then, we take $\frac{\partial R_0(T, \nu)}{\partial \nu}$, which results in:

\[
\frac{\partial R_0(T, \nu)}{\partial \nu} = m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right] \exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] \times
\]

\[
\times \kappa e^{-\kappa T} - m_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) \right]^2 b \times
\]

\[
\exp \left[ -\mu_0(1-e^{-\kappa T})\tau_0(1-e^{-\kappa T}) \right] c_0(1-e^{-\kappa T}) \times
\]

\[
\times \mu_0(1-e^{-\kappa T})\left[ a_0(1-e^{-\kappa T}) + \gamma_0(1+e^{-\kappa T}) + \kappa e^{-\kappa T} - \kappa \gamma_0 e^{-\kappa T} \right]
\]

\[
\frac{\partial R_0(T, \nu)}{\partial \nu} \quad \text{(8)}
\]

Applying the same numerical values as those used to construct figure (1) in equations (7) and (8) we conclude that the model is more than 40 times more sensitive to temperature than to virulence.

In terms of the functional forms chosen for the parameters (with the exception of $b$ that was considered as constant through all the calculations) this results in:

\[
\frac{\partial R_0}{\partial a} = \frac{2ambc}{\mu_M(a_H + \gamma_H)} \quad \text{(9)}
\]

\[
\frac{\partial R_0}{\partial m} = \frac{a^2bc}{\mu_M(a_H + \gamma_H)} \quad \text{(10)}
\]
which in terms of the functions as in equations (5) and table 1 result in the relative sensitivity scale as in table 2:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relative Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \frac{\partial R_0}{\partial \mu_m} )</td>
<td>0.038397</td>
</tr>
<tr>
<td>( \frac{\partial R_0}{\partial \gamma} )</td>
<td>0.016344</td>
</tr>
<tr>
<td>( \frac{\partial R_0}{\partial c} )</td>
<td>0.015486</td>
</tr>
<tr>
<td>( \frac{\partial R_0}{\partial \alpha_H} )</td>
<td>0.007479</td>
</tr>
<tr>
<td>( \frac{\partial R_0}{\partial m} )</td>
<td>0.000159</td>
</tr>
</tbody>
</table>

Therefore, with the forms chosen for the parameters, the model is more sensitive to variations in the mosquitoes’ mortality rate than to the other parameters.

**DISCUSSION**

Although our results are obviously strongly dependent on the form chosen for the temperature and virulence dependence of the parameters of \( R_0 \), expressed in the relations...
(5), we believe that we have demonstrated that for the set of conditions applied a clear decrease trend in virulence is observed with the increase in temperature. Other relationships between the parameters and the temperature and virulence could produce different outcomes from the model. However, we think that the forms chosen are reasonable in the sense that they reproduce what should be expected to happen for subtle variations in both temperature and virulence.

The most strongly evidence-based relationship is the one between the size of the mosquito population and temperature. This was based on the observation that higher temperature and the absence of drying result in an increased production of adult mosquitoes [27]. The mosquito’s longevity, in contrast, decreases with temperature [28], which justifies the relationship chosen for mosquito mortality rate $\mu_M$ and temperature.

It is possible that the relationship that deserves a more detailed justification is the non-linear relationship between the probability of vector infection and virulence. We chose that form based on recent empirical entomological evidence that a reduction in the number of platelets facilitates transmission to the mosquitoes for hemorrhagic fevers like dengue (Ribeiro, personal communication).

Several significant variables could influence the evolution of virulence, such as precipitation, humidity, and host density, among others. It should be expected that all climate parameters influence mosquitoes’ density and behavior. However, we would like to stress that all climatic variables co-vary with temperature [29] and so their variation over the course of the observations are of the same magnitude as that of temperature. As for host density, it is known [18] that when host density is low, virulence is constrained to low levels, whereas if host density is high, a wide range of virulence can be associated with the parasite. However, vector-borne infections (as well as sexually transmitted infections, see [1]) are not influenced by host density [30], but rather by vector density.

Finally, a word about the possible biological mechanisms behind the mathematical formalism presented in this paper, which showed a negative correlation between virulence and temperature. Suppose there exists a pathogen strain 1 with virulence $\nu_1$ and a competing strain 2 with virulence $\nu_2$, where $\nu_2 > \nu_1$. Suppose that strain 1 is the wild type, transmitted in an environment with temperature $T_1$ by mosquitoes that bite at rate $a_1$. If the local temperature rises to $T_2$, then the mosquitoes’ biting rate will increase from $a_1$ to $a_2$ for $T_2 > T_1$. In addition, all the parameters related to temperature would make transmission more efficient with a higher level of temperature. For the functions chosen, transmission is increased both by an increase in temperature and in virulence. However, as the morel is more than 40 time more sensitive to temperature than to virulence, an increase in the former implies that the parasite can afford to decrease is replication capacity, saving biological energy, and still keeping itself in a ESS. This is because he increase in temperature more than offset the decrease in virulence.

We believe that our model can serve as a template for future investigation of the impact of climate change on the virulence of parasites. As mentioned above, other relationships between the parameters that compose parasite fitness could be chosen and the methods here
Mathematical model

proposed could help to investigate this topic of utmost importance in modern epidemiology.

Acknowledgements.
The authors would like to thank an anonymous reviewer, whose comments and suggestions were determinant to the improvement of the original manuscript. This work was supported by grants from LIM01-HCFMUSP, FAPESP, CNPq and FAPERJ.

References


Received: June 1, 2014