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Instability of disease-free equilibrium in a model of malaria with immune delay

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ABSTRACT

A recent paper Ncube (2013) [11] considered the disease-free equilibrium in a mathematical model for intra-host dynamics of *Plasmodium falciparum* malaria with discrete immune time delay. The author showed that depending on system parameters, the disease-free steady state can be absolutely stable (i.e. asymptotically stable for arbitrary positive values of the time delay), or it can be asymptotically stable for sufficiently small values of the time delay and then undergo Hopf bifurcation once the time delay exceeds certain critical value. In this paper we show by direct calculation that the conclusions regarding stability and Hopf bifurcation of the disease-free equilibrium are incorrect, and, in fact, the disease-free equilibrium of the model is always unstable. Furthermore, we provide a general argument why the disease-free steady state of the model can never undergo Hopf bifurcation.

1. Introduction

In 2004, Recker and collaborators [1] proposed a mathematical model of immune response to *Plasmodium falciparum* malaria (to be referred to as *Recker model*), which postulates that in addition to a highly variant-specific immune response, the dynamics of each antigenic variant is also affected by cross-reactive immune responses against a set of epitopes not unique to this variant. This assumption implies that each antigenic variant experiences two types of immune responses: a long-lasting immune response against epitopes unique to it, and a transient immune response against epitopes that it shares with other variants. The main impact of this model lies in its ability to explain a sequential appearance of antigenic variants purely on the basis of cross-reactive inhibitory immune responses between variants sharing some of their epitopes, without the need to resort to variable switch rates or growth rates (see [2] for a discussion of several clinical studies in Ghana, Kenya and India, which support this theory).

In the case when long-lasting immune responses do not decay, numerical simulations in the original paper [1] showed that eventually all antigenic variants will be cleared by the immune system, with specific immune responses reaching protective levels preventing each of the variants from showing up again. Blyuss and Gupta [3] have demonstrated that the sequential appearance of parasitemia peaks during such immune clearance can be explained by the existence of a hypersurface of equilibria in the phase space of the system, with individual trajectories approaching this hypersurface and then being pushed away along stable/unstable manifolds of the saddle-centres lying on the hypersurface.

Under the assumption of *perfect synchrony*, when all variants are identical to each other, Recker and Gupta [4] have analysed peak dynamics and threshold for chronicity, while Mitchell and Carr [5] have investigated the additional effect of time delay in the development of immune response. De Leenheer and Pilyugin [6] have replaced linear growth of antigenic variants in the original model by the logistic growth, and have studied the effects of various types of cross-reactivity on the dynamics, ranging from no cross-reactivity to partial and complete cross-immunity. Mitchell and Carr [7] have studied the appearance of synchronous and asynchronous oscillations in the case of global coupling between variants (referred to as perfect cross immunity in [6]). More recently, the techniques of equivariant bifurcation theory have been used to study symmetry properties of the Recker model, with particular emphasis on understanding stability and clustering of different steady states in terms of their symmetry [8–10].

A recent paper [11] considered Recker model with discrete immune delay and showed that the disease-free equilibrium of this model can undergo Hopf bifurcation. To better understand why the conclusions drawn in that paper are wrong, we consider the time-delayed modification of the Recker model, which can be written as follows [11]

$$\begin{aligned}\dot{Y}_i(T) &= Y_i(T)[\phi - \alpha Z_i(T) - \alpha' W_i(T)],\\ \dot{Z}_i(T) &= \beta Y_i(T-T_d) - \mu Z_i(T),\\ \dot{W}_i(T) &= \beta' \sum_j c_{ij} Y_j(T-T_d) - \mu' W_i(T),\end{aligned} \tag{1}$$

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where Y_i denotes the amount of antigenic variant i, Z_i and W_i denote variant-specific and cross-reactive immune responses, respectively, ϕ is the parasite intrinsic growth rate, α and α' are removal rates associated with specific and cross-reactive immune responses, β and β' are the proliferation rates of immune responses, and μ and μ' are the decay rates of variant-specific and cross-reactive immune responses, T_d is the time delay associated with the development of immune response. The coefficients c_{ij} of the connectivity matrix describe cross-reactive interactions between different variants [1,3,6]. To facilitate the analysis, the author followed an earlier work of Mitchell and Carr [5] in two ways: all variants are taken to have identically the same temporal dynamics, i.e. $Y_i(t) = Y(t)$, $Z_i(t) = Z(t)$, $W_i(t) = W(t)$ for all i, and then the system is rescaled using as new independent variables $y(t)$, $z(t)$ and $w(t)$ deviations from the endemic steady state, which satisfy the system of equations

$$\begin{aligned} \dot{y} &= -(z+w)(1+y),\\ \dot{z} &= qy(t-\tau) - az,\\ \dot{w} &= y(t-\tau) - abw, \end{aligned} \tag{2}$$

where we have used the scaling [5,11]

$$Y(t) = Y_s[1+y(t)], \quad Z(t) = Z_s\left[1+\frac{1}{q}\left(\frac{p\mu}{\phi}\right)^{1/2} z(t)\right],$$
$$W(t) = W_s\left[1+\frac{\mu'}{\mu}\left(\frac{p\mu}{\phi}\right)^{1/2} w(t)\right], \quad T = \left(\frac{p\mu}{\phi}\right)^{1/2} t$$

and the new parameters are defined as follows

$$a = \left(\frac{p\mu}{\phi}\right)^{1/2}, \quad b = \frac{\mu'}{\mu}, \quad q = \frac{\alpha\beta}{\alpha' n\beta'}, \quad p = q + \frac{\mu}{\mu'}.$$

Here, τ is the rescaled time delay, n is the number of antigenic variants each given variant is connected to (in the case of all-to-all coupling considered in [7], this number is the same as the total number of variants), and the endemic steady state values of variables are given by

$$Y_s = \frac{\mu\phi}{\alpha' n\beta' p}, \quad Z_s = \frac{\phi q}{\alpha p}, \quad W_s = \frac{\mu\phi}{\alpha'\mu' p}.$$

For simplification of analysis, a new variable is introduced: $x = z + w$, which transforms the system (2) into the following system

$$\begin{aligned} \dot{x} &= (1+q)y(t-\tau) - abx - a(1-b)z,\\ \dot{y} &= -x(1+y),\\ \dot{z} &= qy(t-\tau) - az. \end{aligned} \tag{3}$$

System (3) has two steady states:

$$E_0 = (x_0, y_0, z_0) = \left(-\frac{1+qb}{ab}, -1, -\frac{q}{a}\right) \tag{4}$$

and

$$E_1 = (x_1, y_1, z_1) = (0,0,0). \tag{5}$$

Despite the fact that the steady state E_1 of the system (3) has all its components equal to zero, since the system (3) describes the dynamics of deviations from the uniform endemic steady state, the steady state E_1 actually corresponds to the *non-zero uniform endemic equilibrium* of the original system (1). Hence, although the stability analysis of the steady state E_1 performed in [11] is formally correct, it was erroneous to interpret it as a stability result for the disease-free equilibrium, as it rather provides information on stability of the non-zero uniform endemic equilibrium, which has been studied earlier by Mitchell and Carr [5,7], and Blyuss and Kyrychko [8,9]. At the same time, stability of the steady state E_0, which is a genuine disease-free steady state has remained unexplored. Furthermore, the assertion in [11] that the system (3) has a third non-uniform equilibrium is also incorrect, as the system (3) has only two steady states E_0 and E_1, and non-uniform equilibria with some Y_i variables being equal to zero and others being positive can only exist in the full original system (1), but not in its fully-synchronous truncation (3). Such equilibria have recently been systematically analysed for the Recker model with and without time delay using the techniques of equivariant bifurcation theory [8–10].

2. Stability of the disease-free steady state

To analyse stability of the disease-free steady state E_0, we linearise the system (3) near this steady state

$$\begin{aligned} \dot{x} &= (1+q)y(t-\tau) - abx - a(1-b)z,\\ \dot{y} &= -x_0 y - (1+y_0)x = \frac{1+qb}{ab} y,\\ \dot{z} &= qy(t-\tau) - az, \end{aligned} \tag{6}$$

where we have used the values of x_0 and y_0 from (4). Looking for solutions of the system (6) in the form

$$\begin{pmatrix} x\\ y\\ z \end{pmatrix} = \begin{pmatrix} c_1\\ c_2\\ c_3 \end{pmatrix} e^{\lambda t},$$

where $c_1, c_2, c_3 \in \mathbb{R}$, and $\lambda \in \mathbb{C}$, yields the characteristic polynomial for the eigenvalues λ is given by

$$\begin{aligned} D(\lambda) &= \det \begin{pmatrix} -ab-\lambda & (1+q)e^{-\lambda\tau} & -a(1-b)\\ 0 & \frac{1+qb}{ab} - \lambda & 0\\ 0 & qe^{-\lambda\tau} & -a-\lambda \end{pmatrix}\\ &= (ab+\lambda)(a+\lambda)\left(\frac{1+qb}{ab} - \lambda\right) = 0. \end{aligned}$$

Since all parameters a, b and q are positive, two roots of the characteristic polynomial $\lambda_1 = -ab$ and $\lambda_2 = -a$ are always negative, and the third one

$$\lambda_3 = \frac{1+qb}{ab}$$

is always positive, thus implying that the disease-free steady state E_0 is always unstable regardless of the value of the immune time delay τ. This, in turn, implies that the conclusions about possible absolute stability of the disease-free steady state as presented in [11] are wrong, and this steady state can never undergo Hopf bifurcation.

To get a better understanding of the phase space of the system and the reason why the disease-free steady state cannot undergo Hopf bifurcation, let us return to the system (1) and prove the following well-posedness result.

Theorem. *Let the initial condition for the system (1) be*

$$(Y_i(s) = Y_{i0}(s),\ Z_i(0) = Z_{i0},\ W_i(0) = W_{i0}), \quad Z_{i0} \geqslant 0, W_{i0} \geqslant 0,$$

$$Y_{i0}(s) \geqslant 0 \quad \text{for } s \in [-T_d, 0].$$

Then the solution $(Y(T), Z(T), W(T))$ of the system (1) will remain non-negative for all $T \geqslant 0$.

Proof. The proof of non-negativity of solutions is done by contradiction. Let us assume that for some $i = 1, .., N$, $T_1 > 0$ is the first moment of time when $Y_i(T_1) = 0$. In order for Y_i to become negative, one would need to have $dY_i/dT(T_1) < 0$, however, according

to the first equation in (1), we have $dY_i/dT(T_1) = 0$. Hence, Y_i can never become negative. Similarly, let us assume that T_2 is the first moment of time when some $Z_i(T_2) = 0$. For Z_i to become negative, one has to have $dZ_i/dT(T_2) < 0$, but according to the second equation in (1), at this moment we have

$$\dot{Z}_i(T_2) = \beta Y_i(T_2 - T_d) - \mu Z_i(T_2) = \beta Y_i(T_2 - T_d) \geqslant 0,$$

hence the contradiction. A similar argument can be used to show that $W_i(T) \geqslant 0$ for all $T \geqslant 0$. □

Let us now consider a solution of the system (1) with a non-negative initial condition. If the disease-free steady state $(Y_i, Z_i, W_i) = (0, 0, 0)$ were able to undergo Hopf bifurcation, provided this bifurcation is supercritical, one would have an oscillatory solution around the disease-free steady state. However, since these oscillations would occur around the point $(Y_i, Z_i, W_i) = (0, 0, 0)$, all components of the solution would have to become negative for some part of the period, thus violating the well-posedness theorem we have just proved. Therefore, we can conclude that the absence of Hopf bifurcation of the disease-free steady state is a natural consequence of the non-negativity of solutions.

3. Discussion

In this paper, we have considered the disease-free steady state of the Recker model and showed that this steady state is always unstable regardless of the value of time delay. Besides explicit computation of the eigenvalues, we have shown that the same conclusion follows from well-posedness of the system.

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