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Stability and bifurcations in a model of antigenic variation in malaria

Konstantin B. Blyuss · Sunetra Gupta

Abstract   We examine the properties of a recently proposed model for antigenic variation in malaria which incorporates multiple epitopes and both long-lasting and transient immune responses. We show that in the case of a vanishing decay rate for the long-lasting immune response, the system exhibits the so-called "bifurcations without parameters" due to the existence of a hypersurface of equilibria in the phase space. When the decay rate of the long-lasting immune response is different from zero, the hypersurface of equilibria degenerates, and a multitude of other steady states are born, many of which are related by a permutation symmetry of the system. The robustness of the fully symmetric state of the system was investigated by means of numerical computation of transverse Lyapunov exponents. The results of this exercise indicate that for a vanishing decay of long-lasting immune response, the fully symmetric state is not robust in the substantial part of the parameter space, and instead all variants develop their own temporal dynamics contributing to the overall time evolution. At the same time, if the decay rate of the long-lasting immune response is increased, the fully symmetric state can become robust provided the growth rate of the long-lasting immune response is rapid.

Keywords   Malaria · Antigenic variation · Stability · Bifurcations · Synchronization

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1 Introduction

Several pathogens, including *Plasmodium falciparum* malaria and African trypanosomes, achieve immune escape by the so-called *antigenic variation* (see a recent review by Gupta [6]). The latter essentially refers to a process by which a pathogen keeps changing its surface proteins, thus preventing antibodies from recognizing and destroying it. Antigenic variation is achieved by exploiting a large repertoire of antigenic variants that differ in some of their epitopes. An important requirement here is that the variants must not be expressed all at the same time, as otherwise the resulting immune response will detect and destroy all of them, thus terminating the infection.

Here we examine a particular model of antigenic variation for *P. falciparum* malaria, put forward by Recker et al. [9]. Within this framework, each variant is assigned one major epitope, which is unique to that variant, and also several minor epitopes that are shared between different variants. Both types of epitopes elicit epitope-specific responses, but in the case of the minor epitopes these are cross-protective between variants that share them. A critical feature of the model is that the immune response to the major epitope (uniquely variant-specific) is long-lasting in comparison with the immune responses (frequently cross-protective) to the minor epitopes. Under these conditions, the dynamics may be characterized by sequential domination of different variants. Thus, the conclusion of the model is that effectively the host immune system can itself be responsible for prolonging the malaria infection and causing chronicity. Through numerical simulations and by analysing a caricature of the model involving complete synchrony between variants, Recker and Gupta [10] have shown that stronger cross-protective immune responses lead to prolonged length of infection and reduced severity of the disease. This was explained by the conflicting interaction of cross-protective and variant-specific immune responses.

In this paper, we perform a detailed study of this model with particular emphasis on stability aspects, as well as possible bifurcation scenarios. First, we consider the case when the variant-specific immune responses to the major epitopes do not decay. In this case, the phase space of the system possesses a very peculiar geometry with a high-dimensional surface of equilibria having different types of stability. We show, it is exactly this curious structure that causes successive re-appearance of different malaria variants in the dynamics until the specific immune responses reach sufficient protective level to prevent further appearance of given variants in the dynamics. If the specific immune responses can decay (even slightly), the dynamics is qualitatively different, as the phase space geometry changes significantly. Now it contains a large number of distinct equilibria with different number of non-zero variants, some of which can be related by the permutation symmetry of the system.

An interesting tool for investigating the dynamics is the imposition of synchrony among the variants. From mathematical perspective, in the case of complete synchrony the dimension of the system is drastically reduced. Here, we use the tools of synchronization theory to investigate the robustness of such state.

The outline of this paper is as follows. In the next section the model of cross-reactive immune response to malaria is introduced and its basic properties are discussed. Section 3 contains the analysis of a particular case when the decay rate of a long-lasting immune response vanishes. Numerical simulations will be presented that illustrate the behaviour of the system in this case. A general situation of arbitrary non-decaying specific immune responses is considered in Sect. 4. In Sect. 5 the stability of the fully symmetric state of the system is investigated by means of numerical computation of transverse Lyapunov exponents. The paper concludes in Sect. 6 with a discussion.

2 Model definition

In this section, we use the above-mentioned multiple epitope description to introduce a model of the interaction of malaria variants with the host immune system. Our derivation follows that of Recker et al. [9] with some refinements.

It is assumed that each antigenic variant i consists of a single unique major epitope, that elicits a long-lived (specific) immune response, and also of several minor epitopes that are not unique to the variant. Assuming that all variants have the same net growth rate ϕ, their temporal dynamics is described by the equation

$$\frac{dy_i}{dt} = y_i(\phi - \alpha z_i - \alpha' w_i), \tag{1}$$

where α and α' denote the rates of variant destruction by the long-lasting immune response z_i and by the transient immune response w_i, respectively, and index i spans all possible variants. The dynamics of the variant-specific immune response can be written in its simplest form as

$$\frac{dz_i}{dt} = \beta y_i - \mu z_i, \tag{2}$$

with β being the proliferation rate and μ being the decay rate of the immune response. Finally, the transient (cross-reactive) immune response can be described by the minor modification of the above Eq. (2):

$$\frac{dw_i}{dt} = \beta' \sum_{j \sim i} y_j - \mu' w_i, \tag{3}$$

where the sum is taken over all variants sharing the epitopes with the variant y_i. We shall use the terms long-lasting and specific immune response interchangeably, likewise for transient and cross-reactive.

To formalize the above construction, one can introduce the adjacency matrix A, whose entries A_{ij} are equal to one if the variants i and j share some of their minor epitopes and equal to zero otherwise. Obviously, the matrix A is always a symmetric matrix. Prior to constructing this matrix it is important to introduce a certain ordering of the variants according to their epitopes. For this purpose we shall use the *lexicographic* ordering, as explained below. To illustrate this, suppose we have a system of two minor

epitopes with two variants in each epitope, which is the simplest non-trivial system of epitope variants. In this case, the total number of variants is four, and they are enumerated as

$$
\begin{array}{ll}
1 & 11 \\
2 & 12 \\
3 & 21 \\
4 & 22
\end{array}
\tag{4}
$$

It is clear that for a system of m minor epitopes with n_i variants in each epitope, the total number of variants is given by

$$
N = \prod_{i=1}^{m} n_i.
\tag{5}
$$

Now that the ordering of variants has been fixed, it is an easy exercise to construct the adjacency matrix A of variant interactions. For the particular system of variants (4), this matrix has the form

$$
A = \begin{pmatrix}
1 & 1 & 1 & 0 \\
1 & 1 & 0 & 1 \\
1 & 0 & 1 & 1 \\
0 & 1 & 1 & 1
\end{pmatrix}.
\tag{6}
$$

In general, for a system of two minor epitopes with m variants in the first epitope and n variants in the second, the matrix A will be an $mn \times mn$ block matrix consisting of $n \times n$ blocks of ones along the main diagonal, with the rest of the matrix being filled with $n \times n$ identity matrices. For simplicity, in the rest of the paper we will concentrate on the case of two minor epitopes, but the results can easily be generalized for arbitrary number of minor epitopes. Using the adjacency matrix one can rewrite the system (1)–(3) in a vector form

$$
\frac{d}{dt} \begin{pmatrix} \mathbf{y} \\ \mathbf{z} \\ \mathbf{w} \end{pmatrix} = F(\mathbf{y}, \mathbf{z}, \mathbf{w}) = \begin{cases} \mathbf{y}(\phi \mathbf{1}_N - \alpha \mathbf{z} - \alpha' \mathbf{w}), \\ \beta \mathbf{y} - \mu \mathbf{z}, \\ \beta' A \mathbf{y} - \mu' \mathbf{w}, \end{cases}
\tag{7}
$$

where $\mathbf{y} = (y_1, y_2, \ldots, y_N)$, etc., $\mathbf{1}_N$ denotes a vector of the length N with all components equal to one, and in the right-hand side of the first equation multiplication is taken to be entry-wise so that the output is a vector again.

To better understand the symmetry of the system it is convenient to represent graphically relations between different variants. Figure 1 shows such relations in the case of two minor epitopes. One can observe that within each horizontal and each vertical stratum, the network of variants is characterized by an "all-to-all" coupling [2]. Besides this, if the number of variants in both minor epitopes is the same, then there
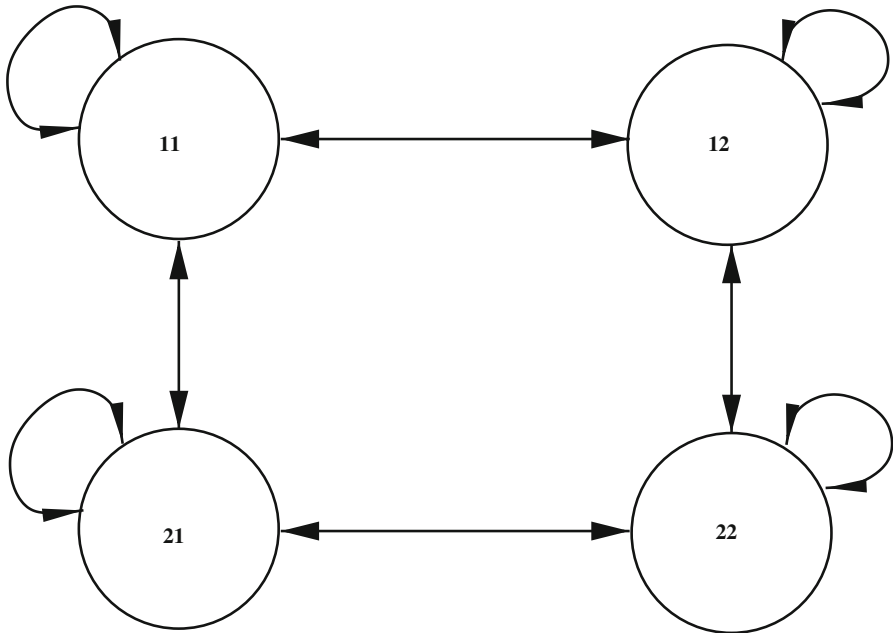
Fig. 1 Interaction of malaria variants in the case of two minor epitopes with two variants in each epitope

is an additional reflectional symmetry. Formally this means the system is equivariant with respect to the following symmetry group [5]

$$\mathcal{G} = \begin{cases} \mathbf{S}_m \times \mathbf{S}_n, & m \neq n, \\ \mathbf{S}_m \times \mathbf{S}_m \times \mathbb{Z}_2, & m = n. \end{cases} \tag{8}$$

This construction can be generalized in a straightforward way for a larger number of minor epitopes. It is noteworthy that each of the variants has exactly the same number of connections to other variants.

We finish this section by noting that the system (7) is well-posed, in that provided the initial conditions for this system are non-negative $\mathbf{y}(0) \geq 0$, $\mathbf{z}(0) \geq 0$, $\mathbf{w}(0) \geq 0$, the solutions satisfy $\mathbf{y}(t) \geq 0$, $\mathbf{z}(t) \geq 0$, $\mathbf{w}(t) \geq 0$, for all $t \geq 0$.

Remark In many cases it is reasonable to assume the initial conditions for the system (7) to be of the form ($\mathbf{y} \geq 0$, $\mathbf{z} = 0$, $\mathbf{w} = 0$). A possible exception is when the immune system has already built-up a long-lasting response from prior exposure to a certain variant. In this case, the initial condition for the system (7) will contain non-zero entries for some of $\mathbf{z}$ variables [10].

3 The case of non-decaying specific immune response

We begin our analysis of the system (7) by considering a particular case of vanishing decay rate of the long-lasting immune response $\mu = 0$ (some partial results for this

case have been obtained in [9]). In this case the only steady states of this system are given by

$$\mathbf{y} = \mathbf{w} = 0, \quad \mathbf{z} = \text{const.} \tag{9}$$

This is a rather degenerate situation as the fixed points are not separated in the phase space, but rather form an N-dimensional hypersurface with each point of it being a fixed point of the system (7). Linearization near one such fixed point has the eigenvalues $(-\mu')$ of multiplicity N, zero of multiplicity N, and the rest of the spectrum is given by

$$\phi - \alpha z_1, \phi - \alpha z_2, \ldots, \phi - \alpha z_N. \tag{10}$$

The generalized eigenvectors of the zero eigenvalue correspond to the N directions along the hypersurface of the fixed points. As long as there is at least one $z_i < \phi/\alpha$, the corresponding steady state is a saddle, otherwise it is a stable node. From the dynamical systems perspective, the case $\mu = 0$ corresponds to the so-called *bifurcations without parameters* [4]. Indeed, in the space $\{\mathbf{y} = \mathbf{w} = 0\}$ as one crosses the hyperplane $z_j = \phi/\alpha$, one of the eigenvalues crosses zero along the real axis. Furthermore, since the hypersurface $\{\mathbf{y} = \mathbf{w} = 0\}$ is in general high-dimensional, the cases of two or more eigenvalues crossing zero at the same time (this happens along the lines $z_i = z_j = \phi/\alpha, i \neq j$) are still generic, and these lead to "bifurcations" of a higher co-dimension. It is important to note that all these bifurcations are of the steady state type and there is no possibility of a Hopf bifurcation that could lead to temporally periodic solutions.

Figure 2 shows numerical simulations of a typical behaviour in the system (7) for $\mu = 0$. These results were obtained by integrating the system (7) using the variable order solver based on backward differentiation formulas to account for the stiffness of the system [12]. Initially most variants have quite high amplitudes, but as the time progresses, their amplitudes decrease as illustrated in Fig. 2a. Figure 2b and d illustrates this feature in more detail by showing the dynamics of a single variant and its specific immune response. With each subsequent re-appearance of the variant, the specific immune response to it is building up, and ultimately it reaches a protective level, which prevents this variant from ever re-appearing in the dynamics. As suggested by Fig. 2c, sometimes more than one variant appear at the same time, and this is very good from the immune system perspective, as it allows simultaneous destruction of all of these variants. The question of synchronization between different variants will be investigated in Sect. 5.

The fact that the system exhibits the jumps from one variant to another can be explained by the existence of the above-mentioned hypersurface of equilibria. When one of the variants decays, the trajectory approaches the neighbourhood of the hypersurface of equilibria, and since all points on this hypersurface are saddles of different dimensions, the trajectory is pushed away along the unstable manifold of one of these fixed points. This behaviour is reminiscent of that in the neighbourhood of a heteroclinic cycle [1,8], with the major difference being that in the present case the nodes of the cycle are not distinct but rather form a smooth hypersurface. There is a
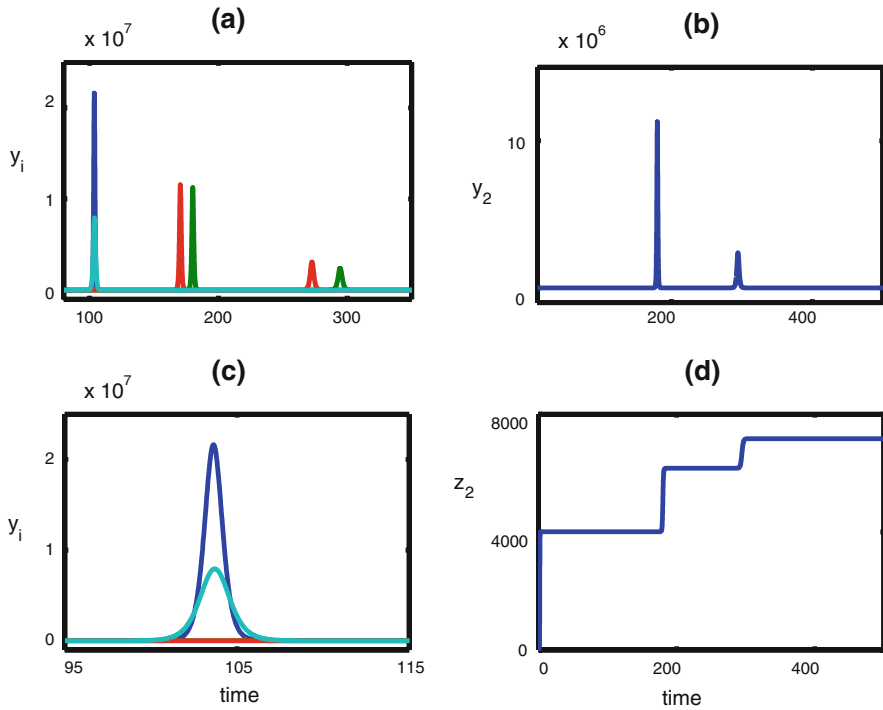
Fig. 2 Temporal dynamics of the system (7) with two variants in each of the two epitopes. Parameter values are $\alpha = \alpha' = 10^{-3}$, $\beta = \beta' = 10^{-4}$, $\mu = 0$, $\mu' = 0.02$, $\phi = 7.5$ [9]. **a** Time evolution of the variants y_i. **b** Dynamics of a single variant y_2. **c** The close-up of the initial stage of evolution of the variants. **d** Dynamics of the long-lasting immune response z_2

clear separation of time scales in the dynamics: the trajectories move quickly to/away from the invariant $\mathbf{w} - \mathbf{z}$ plane, and then they slowly move towards the hyper-axis $\mathbf{y} = \mathbf{w} = 0$ before the next iteration. With time, the phase space excursions between subsequent returns to the equilibrium manifold become shorter (they are restricted by the ever growing z variables), and eventually all trajectories converge to a point $\mathbf{T} = (\mathbf{y} = \mathbf{w} = 0, \mathbf{z} = (\phi/\alpha)\mathbf{1}_N)$. Similar behaviour takes place in the phase coordinates of other variants, which all approach the point $\mathbf{T}$. The importance of such a point for understanding the dynamics has been previously highlighted, for instance, in the analysis of adaptive control systems, where it gave rise to bad point bifurcations at which the close-loop systems could never be stabilised [11].

If during time evolution, the trajectory reaches the hyperplane $z_i = \phi/\alpha$ for some i, and at least one of y_i or w_i is different from zero, then this trajectory will escape the basin of attraction of the point $(\mathbf{y} = \mathbf{w} = 0, \mathbf{z} = (\phi/\alpha)\mathbf{1}_N)$ and instead it will asymptotically converge to the hypersurface of equilibria with the value of $z_i > \phi/\alpha$ without any further phase space excursions. This will happen provided the initial amount of a given variant is high enough. Figure 3a shows in red the projection of the stable manifold of the point on the reduced phase space of a single variant together with a representative trajectory in blue. In the same figure a trajectory in green illustrates
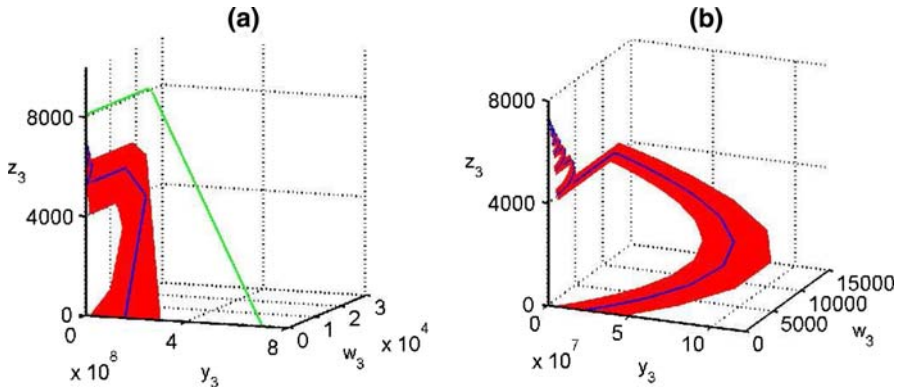
Fig. 3 **a** Reduced phase space of the system (7). **b** Close-up near the hypersurface of equilibria. Parameter values are the same as in Fig. 2

the scenario in which the protective level of immune response is reached within one parasitemia peak, and hence there are no further oscillations. In Fig. 3b we show the close-up of the phase dynamics in the neighbourhood of the hypersurface of equilibria. One can clearly observe recurrent oscillations of parasitemia, during which the specific immune response is monotonically increasing until it reaches the protective level.

Next we would like to discuss the issues of peak dynamics and the threshold for chronicity, which have been previously studied in Recker and Gupta [10]. The chronicity threshold is defined as the critical ratio of the variant destruction rates $\gamma_c = \alpha'/\alpha$, such that if $\gamma < \gamma_c$, then during the first peak the protective level of immunity will be reached, so that the system will display no further oscillations. There are several simplifying assumptions, which have to be made in order to derive analytical expressions for the solutions needed for the analysis of peak dynamics. First of all, it is reasonable to assume that all variants in the full system (7) are identical, and therefore this system can be replaced by

$$\dot{y} = y(\phi - \alpha z - \alpha' w),$$
$$\dot{z} = \beta y,$$
$$\dot{w} = \beta' n_c y - \mu' w,$$

where n_c is the number of connections for each variant, and $y_i = y$, etc. The second assumption is that for a single parasitemia peak the cross-reactive immune response does not have time to decay, i.e. for a peak dynamics we have $\mu' = 0$. This reduces the system to

$$\dot{y} = y(\phi - \alpha z - \alpha' w),$$
$$\dot{z} = \beta y, \qquad\qquad\qquad\qquad (11)$$
$$\dot{w} = \beta' n_c y.$$

Assuming zero initial conditions $z(0) = w(0) = 0$, which correspond to the absence of pre-existing specific or cross-reactive immune responses, the analytic expression

for the solutions of the system (11) can be found as

$$z(t) = \frac{1}{\psi}\left[\phi + \sqrt{2C_1\psi}\tanh\left(\sqrt{\frac{C_1\psi}{2}}(t + C_2)\right)\right],$$

$$y(t) = \frac{C_1}{\beta}\left[1 - \tanh\left(\sqrt{\frac{C_1\psi}{2}}(t + C_2)\right)^2\right],$$

(12)

where the integration constants C_1 and C_2 are given by

$$C_1 = \beta y_0 + \frac{\phi^2}{2\psi}, \quad C_2 = -\sqrt{\frac{2}{C_1\psi}}\text{arctanh}\left(\sqrt{\frac{C_1 - \beta y_0}{C_1}}\right),$$

and ψ is defined as

$$\psi = \frac{\alpha\beta + \alpha'n\beta'}{\beta}.$$

Initially, $y(t)$ monotonically increases, until it reaches its peak of $y = C_1$ exactly at $t = -C_2$, after which $y(t)$ is monotonically decreasing. Due to the symmetry of the solution, at $t = -2C_2$, y has the same value as it had at the initiation of parasitemia peak. By considering the equation for $y(t)$, one can argue that if at the end of the parasitemia peak the combined specific and cross-reactive immune response has reached the protective level of ϕ/α, then this will prevent further oscillations. Evaluating z and w at the end of parasitemia peak, we find the threshold for chronicity as

$$z(-2C_2) + w(-2C_2) > \phi/\alpha \quad \text{if} \quad \gamma < \gamma_c = \frac{\alpha'}{\alpha} = 2 + \frac{\beta}{n_c\beta'}.$$

If $\gamma < \gamma_c$, then during the first peak y should be sufficiently high to allow the build-up of protective immunity. Conversely, if $\gamma > \gamma_c$, then y will be too low for protective immunity to be reached within one peak, and therefore the system will display further oscillations [10].

It is important to note that the trajectories shown in red and blue in Fig. 3 satisfy the condition for chronicity $\gamma < \gamma_c$, but still for these trajectories the protective level of immune response is not reached within a single parasitemia peak. The reason for this discrepancy is due to the fact that in the system describing the peak dynamics, the cross-reactive immune response does not decay, because if it did, then at the end of the parasitemia peak the combined immunity would be below the protective level, and therefore further oscillations would occur, as shown in Fig. 3. This also highlights the importance of initial conditions, and in particular, the initial amount of variants, which may play a crucial role in whether or not the protective immunity level will be reached within one peak for the same parameter values.

4 General case

In the previous section we considered the case $\mu = 0$, in which the long-lasting immune responses can only grow with time, unless they are saturated at the level preventing further re-emergence of particular variants. For $\mu > 0$, the situation is drastically different as the hypersurface of equilibria no longer exists, and instead, it degenerates into two separate steady states. One of these is the origin ($\mathbf{y} = \mathbf{z} = \mathbf{w} = 0$), which is always a saddle with an N-dimensional unstable manifold and a $2N$-dimensional stable manifold. The other steady state originating from the hypersurface of equilibria is the fully symmetric equilibrium

$$y_i = \frac{\phi\mu\mu'}{\alpha\beta\mu' + \alpha'n_c\beta'\mu}, \quad z_i = \frac{\phi\beta\mu'}{\alpha\beta\mu' + \alpha'n_c\beta'\mu},$$
$$w_i = \frac{\phi\mu n_c\beta'}{\alpha\beta\mu' + \alpha'n_c\beta'\mu}, \quad i = \overline{1, N}, \tag{13}$$

where $n_c = m + n - 1$ is the number of connections for each variant. Using Fig. 1, this number can easily be interpreted as the number of elements in the horizontal and vertical strata, to which the current variant belongs. When considered in the context of a reduced system (11), in which all variants are assumed to behave in the same manner (see next section for further analysis of this case), this steady state is stable for all values of parameters, as shown in Recker and Gupta [10]. At the same time, this result does not hold for the full system (7), as the stability of the fully symmetric equilibrium does depend on parameters of the system. More specifically, the fully symmetric equilibrium can undergo Hopf bifurcation, thus giving rise to periodic occurrences of parasitemia peaks.

Figure 4a and b shows the boundary of the Hopf bifurcation in the parameter space of the system (7) with two variants in each of the two minor epitopes. These figures indicate that the higher is the decay rate of variant specific immune response, the larger should be the values of the relative immune efficiency $\gamma = \alpha'/\alpha$ and that of a ratio of proliferation rates β'/β to guarantee the occurrence of the Hopf bifurcation. The corresponding temporal evolution of variants in the parameter regime beyond the Hopf bifurcation is illustrated in Fig. 4c and d. One can observe periodic oscillations of all four variants, which have approximately the same maximum amplitudes and are slightly out-of-phase with each other. The plot of the dynamics of one variant shown in Fig. 4d indicates that peaks of parasitemia corresponding to this variant have decreasing amplitudes, and after several occurrences there are large periods of time when the variant is quiescent. Cross-reactivity between different variants causes subsequent re-appearance of large-amplitude oscillations after such periods of quiescence. The reason for this is as follows. The long-lasting and cross-reactive immune responses show anti-phase oscillations, which are quite regular both in amplitude and in period. These oscillations lead to a slightly irregular oscillations of the combined rate of variant destruction $\alpha z + \alpha' w$. Intervals of parasitemia peaks correspond to the combined variant destruction rate oscillating around the critical value of ϕ with long-lasting immune response increasing. After such intervals, the combined variant destruction
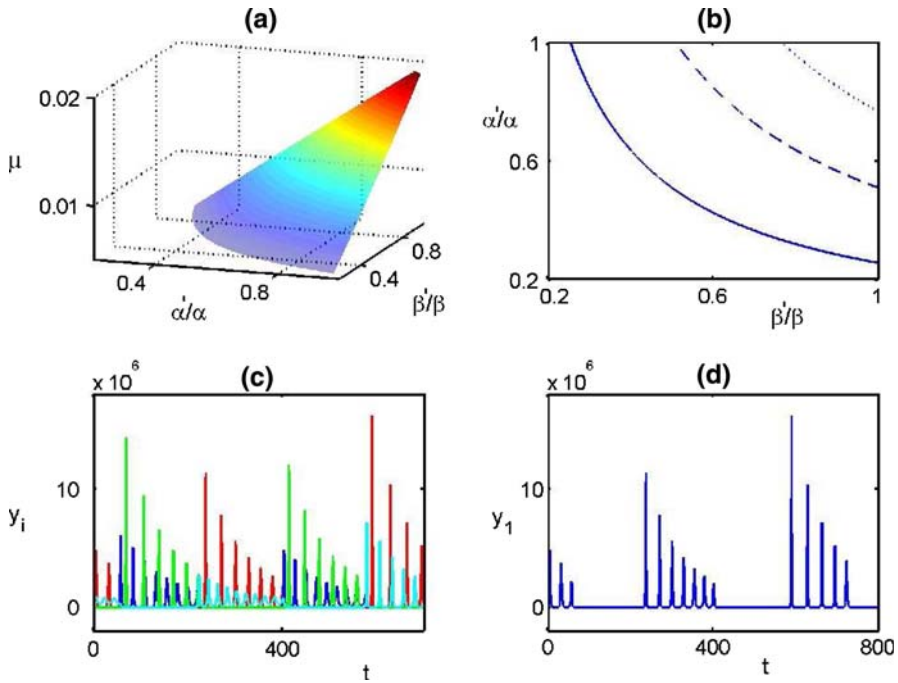
Fig. 4 a Boundary of Hopf bifurcation in a parameter space. **b** The two-parameter Hopf boundaries for different values of the specific response decay rate $\mu = 0.005$ (*solid*), $\mu = 0.01$ (*dashed*) and $\mu = 0.015$ (*dotted*). In (**a**) the fully symmetric steady state is unstable above the coloured surface, and in (**b**) it is unstable above each of the corresponding curves. **c** Temporal dynamics of variants 1, 2, 3 and 4. **d** Temporal dynamics of variant 1 showing periodic oscillations with large intermittent period of quiescence

rate stays above ϕ keeping the variant absent from the dynamics, and during this time the long-lasting immune response wanes, until it starts to recover during the next cycle. We emphasize that this dynamics can only occur in the case when the long-lasting immune response can decay, hence this feature could not be observed in the previously analysed case of $\mu = 0$.

Besides the origin and a fully symmetric equilibrium, the system also possesses $(2^N - 2)$ steady states characterized by a different number of non-zero variants y_i. One should notice that the symmetry of the system mentioned earlier implies that for a given number of non-zero variants, many of the corresponding steady states are symmetry-related. At the same time, one can identify several clusters of the steady states with different values of the steady states which cannot be transformed into each other by a symmetry. For example, if we consider the system with two variants in each of the two minor epitopes, then there exist six steady states with two non-zero variants. Introducing the notation

$$Y_1 = \frac{\phi\mu\mu'}{\beta'\alpha'\mu + \alpha\beta\mu'}, \quad Y_2 = \frac{\phi\mu\mu'}{2\beta'\alpha'\mu + \alpha\beta\mu'},$$

the steady states with non-zero variants 12, 13, 24 and 34 form one cluster:

$$E_{12} = (Y_2, Y_2, 0, 0, Z_2, Z_2, 0, 0, 2W_2, 2W_2, W_2, W_2),$$
$$E_{13} = (Y_2, 0, Y_2, 0, Z_2, 0, Z_2, 0, 2W_2, W_2, 2W_2, W_2),$$
$$E_{24} = (0, Y_2, 0, Y_2, 0, Z_2, 0, Z_2, W_2, 2W_2, W_2, 2W_2),$$
$$E_{24} = (0, 0, Y_2, Y_2, 0, 0, Z_2, Z_2, W_2, W_2, 2W_2, 2W_2),$$

while the steady states with non-zero variants 14 and 23 are in another cluster

$$E_{14} = (Y_1, 0, 0, Y_1, Z_1, 0, 0, Z_1, W_1, 2W_1, 2W_1, W_1),$$
$$E_{23} = (0, Y_1, Y_1, 0, 0, Z_1, Z_1, 0, 2W_1, W_1, W_1, 2W_1),$$

where $Z_{1,2} = \beta Y_{1,2}/\mu$ and $W_{1,2} = \beta' Y_{1,2}/\mu'$. All the steady states in the first cluster are related by permutation, and the steady states in the second cluster are also related by some permutation, but the steady states from the first cluster cannot be related to those in the second cluster. The reason for this becomes clear if one more closely analyses the structure of the adjacency matrix A given in (6). In the case of a steady state E_{ij} from the first cluster, both rows i and j of matrix A contain ones in positions i and j (i.e. the variants i and j cross-react with each other), while in the case of the second cluster the rows i and j contain only a single one in either position i or position j (i.e. the variants i and j are completely unrelated). Due to this difference the steady states from the two clusters are different and it is impossible to change from one cluster to another by permutation.

As far as stability of the steady states different from the origin and the fully symmetric equilibrium is concerned, they all are saddles of different dimensions. Even though they are unstable as steady states, it is possible for some of them to form some sort of a heteroclinic cycle.

Remark In the case when the number N of malaria variants participating in the dynamics exceeds four, the symmetry of the system increases the co-dimension of the Hopf bifurcation for the fully symmetric steady state. Moreover, the purely imaginary eigenvalues at the Hopf bifurcation would coincide, thus creating extra complications for the analysis by virtue of increasing the dimension of the centre manifold. Some details of possible bifurcation scenarios in systems with an "all-to-all" coupling can be found in [2,3], and the extension of those results should provide an insight into the effects of symmetry on the dynamics of system (7). The complete analysis of these effects will be presented elsewhere.

5 Robustness of the fully symmetric solution

An interesting dynamical regime occurs when, by virtue of initial conditions or time evolution, the system behaves in such a way that all variants are indistinguishable from each other, in other words, the system is in a state of complete symmetry. In this case, the dimension of the system reduces drastically from $3N$ to just three. As several insightful results have been obtained for this case [10], it is important to
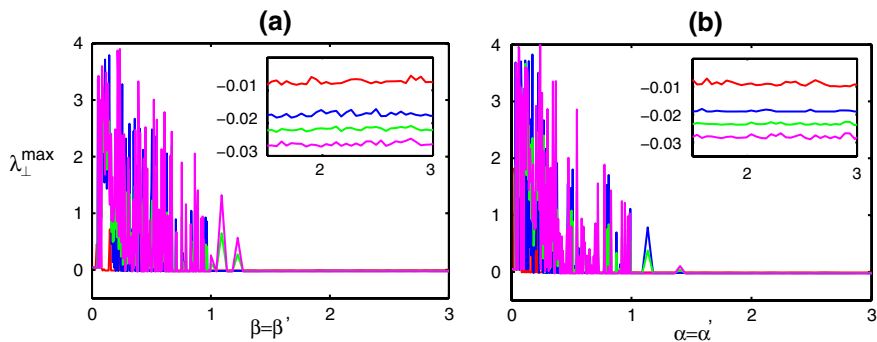
Fig. 5 Maximal transverse Lyapunov exponent as a function of parameters for $\mu = 0$ (top), $\mu = 0.01$, $\mu = 0.02$ and $\mu = 0.03$ (bottom). **a** Parameter values are $\phi = 7.5$, $\beta = \beta' = 1$, $\mu' = 0.02$. **b** Parameter values are $\phi = 7.5$, $\alpha = \alpha' = 1$, $\mu' = 0.02$

study how robust this state of complete symmetry is with respect to perturbations that attempt to break the symmetry. To characterize stability properties of the symmetric state one can use transverse Lyapunov exponents, as is customary in the studies of synchronization, see, for instance [7]. By analogy with synchronization theory we shall call the hypersurface of complete symmetry a *symmetry manifold*.

Writing ($y_i = y + \widetilde{y}_i$, $z_i = z + \widetilde{z}_i$, $w_i = w + \widetilde{w}_i$), one can split the total dynamics into that inside the symmetry manifold

$$
\begin{aligned}
\dot{y} &= y(\phi - \alpha z - \alpha' w), \\
\dot{z} &= \beta y - \mu z, \\
\dot{w} &= \beta' n_c y - \mu' w,
\end{aligned}
\tag{14}
$$

and the linearized dynamics in the transverse direction given by

$$
\frac{d}{dt}\begin{pmatrix} \widetilde{\mathbf{y}} \\ \widetilde{\mathbf{z}} \\ \widetilde{\mathbf{w}} \end{pmatrix} = DF(y\mathbf{1}_N, z\mathbf{1}_N, w\mathbf{1}_N)\begin{pmatrix} \widetilde{\mathbf{y}} \\ \widetilde{\mathbf{z}} \\ \widetilde{\mathbf{w}} \end{pmatrix},
$$

$$
DF(y\mathbf{1}_N, z\mathbf{1}_N, w\mathbf{1}_N) = \begin{pmatrix} (\phi - \alpha z - \alpha' w)\mathbf{I}_N & -\alpha y\mathbf{I}_N & -\alpha' y\mathbf{I}_N \\ \beta\mathbf{I}_N & -\mu\mathbf{I}_N & \mathbf{0}_N \\ \beta' A & \mathbf{0}_N & -\mu'\mathbf{I}_N \end{pmatrix}.
\tag{15}
$$

Here n_c is again the number of connections of a given variant, $\mathbf{0}_N$ and $\mathbf{I}_N$ denote $N \times N$ zero and unity matrices, respectively. The minimal condition for the stability (or robustness) of the symmetric state is that the maximum Lyapunov exponent associated with the system (15) has negative real part [7]. By solving Eqs. (15) in combination with (14), we determine the dependence of the leading Lyapunov exponent on the system parameters.

In Fig. 5 we show the results of numerical simulations for the maximal transverse Lyapunov exponent $\lambda_\perp^{\max}$. In both plots we kept the rates of variant destruction equal to each other $\alpha = \alpha'$ and also the proliferation rates were taken to be the same $\beta = \beta'$. Figure 5 indicates that for small values of $\alpha = \alpha'$ or $\beta = \beta'$, the fully symmetric state of the system is transversely unstable, as signified by the positive transverse Lyapunov exponent. This means that in such parameter regime different variants will not synchronize in time, hence it is unlikely to observe the fully symmetric state in experiment. However, when the variant destruction rates/proliferation rates are increased, the fully symmetric state becomes transversely stable, i.e. independently on initial conditions for each particular variants, they will all ultimately follow the same time evolution. The increase in the decay rate of the specific immune response μ plays a stabilizing role, since it lowers the values of of the maximal transverse Lyapunov exponent. The robustness of the fully symmetric state appears to be independent on the relative efficiency $\gamma = \alpha'/\alpha$ of immune responses.

6 Conclusions

In this paper, the temporal behaviour in a model of antigenic variation in malaria has been studied from a dynamical systems perspective. Using the model of immune response to multiple epitopes, we have demonstrated that when the long-lasting immune response does not decay, the system possesses a high-dimensional surface of equilibria, and these exhibit steady-state bifurcation without parameters, i.e. some part of the surface of equilibria consists of saddles of different dimensions, while another part contains stable nodes. The existence of these two parts of the surface of equilibria with different stability properties accounts for the observed patterns of behaviour of malaria variants, when different variants exhibit out-of-phase parasitemia peaks that decay with time. If the initial amounts of all variant are not very large, then phase space excursions between successive re-appearances of the variants become shorter as the time grows, and eventually all trajectories approach the single steady state **T** characterized by all coordinates equal to each other and equal to the value at the boundary between the saddles and the nodes on the surface of equilibria. If, however, an initial amount of a given variant is sufficiently high, then a trajectory with such initial condition will escape the basin of attraction of the above-mentioned point **T** by reaching the protective level of long-lasting immune response to a given variant while having either a non-zero transient response to this variant or a non-zero amount of the variant itself. In this case, the eventual time evolution of the solution will be different in that it will also approach the surface of equilibria but now it will be above the critical protective level without any further excursions in the phase space.

When both variant-specific and cross-reactive immune responses are allowed to decay with a certain rate, the dynamics are quite different. In this case the surface of equilibria disintegrates, and instead the phase space of the system contains a large number of distinct fixed points many of which are related to each other by the permutation symmetry of the variants. At the same time, they may form separate clusters which are not related by symmetry. Provided the decay rate of the specific immune response is high enough, the fully symmetric equilibrium will exhibit Hopf bifurcation,

thus giving rise to periodic oscillations of the variants. These oscillations appear to be out-of-phase for different variants, and such oscillations are separated by extended time intervals during which the amount of a variant is very small.

In order to investigate to what extent the results obtained in the approximation of complete symmetry between variants describe the general patterns of behaviour, we have numerically computed the transverse Lyapunov exponents of the fully symmetric state. This analysis indicates that while the fully symmetric state is not robust to small perturbations for small proliferation/variant destruction rates, the robustness is restored as these rates increase. In this case the dynamics of the completely symmetric system faithfully represents that of the full original system. Finally, we note that the robustness of complete synchronization between variants increases with the decay rate of the specific immune response.

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