Synchronous versus asynchronous oscillations for antigenically varying \textit{Plasmodium falciparum} with host immune response

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We consider a deterministic intra-host model for \textit{Plasmodium falciparum} (\textit{Pf}) malaria infection, which accounts for antigenic variation between \textit{n} clonal variants of PfEMP1 and the corresponding host immune response (IR). Specifically, the model separates the IR into two components, specific and cross-reactive, respectively, in order to demonstrate that the latter can be a mechanism for the sequential appearance of variants observed in actual \textit{Pf} infections. We show that a strong variant-specific IR relative to the cross-reactive IR favours the asynchronous oscillations (sequential dominance) over the synchronous oscillations in a number of ways. The decay rate of asynchronous oscillations is smaller than that for the synchronous oscillations, allowing for the parasite to survive longer. With the introduction of a delay in the stimulation of the IR, we show that only a small delay is necessary to cause persistent asynchronous oscillations and that a strong variant-specific IR increases the amplitude of the asynchronous oscillations.

\textbf{Keywords: } malaria; antigenic variation; sequential dominance; global coupling; delay

\textbf{AMS Subject Classification: } 92C45; 92B25; 37G05; 39A23

1. Introduction

Of the species of parasites that cause malaria in humans, \textit{Plasmodium falciparum} (\textit{Pf}) is considered the most dangerous because it can cause cerebral malaria by clogging the arteries near the cerebrum [22]. It is the leading cause of death by malaria in humans [33]. \textit{Plasmodium} exhibits a complex life-cycle changing forms as it changes habitats. During the blood cycle, the parasite invades a healthy red blood cell; after approximately 48 hours (for \textit{Pf}), the parasitized red blood cell (PRBC) ruptures, releasing 10–30 new parasites. Each of these coordinated parasite ‘generations’ will cause a spike in the host’s febrile state, the primary symptom of the disease. PRBCs are able to avoid splenic destruction by cyto-adhering to the endothelial wall of a blood vessel and are thereby removed from blood circulation. However, these sequestered PRBCs display antigens on their surface and become targets for the host’s immune response (IR), such as antibodies or T-lymphocytes [3,9].

The parasite’s ability to alter exposed antigens is called antigenic variation; this prevents the IR from maintaining a prolonged attack against any single variant [5,11,25]. For \textit{Pf} the variation

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occurs in the antigen PfEMP1 and, more specifically, variations in its unique IR-binding site referred to as its major epitope [27]. Under a wide range of conditions, the population size of PRBCs corresponding to each immunologically distinct variant exhibits oscillations. Furthermore, it is observed that the oscillations of the variants appear asynchronously such that they switch from one variant to another; this is referred to as sequential dominance [23,26,27]. Biologically, the synchronous oscillations are a disadvantage to the parasite because an IR to every variant is stimulated simultaneously, clearing the disease at once and in less time than when the variants appear sequentially [11,25]. Thus, sequential dominance has been proposed as a survival mechanism for the parasite; it prolongs the duration of infection because the IR has to continually re-tune itself to attack the current dominant variant. A number of models have been proposed to account for sequential dominance [12,20,26].

We are interested in the model studied in [4,8,21,24,26], which prescribes the dynamics for an antigenically varying Pf infection with corresponding IR. The model is able to demonstrate that sequential dominance can occur without an explicitly imposed switching mechanism and that the host’s IR plays a critical role in causing the sequencing. In particular, the model separates the IR into two phenomenological components, variant-specific and cross-reactive. For any particular variant, the corresponding cross-reactive IR is stimulated by the presence of all other variants that display common minor epitopes.

An important assumption of the model we consider is that the cross-reactive IR decays quickly relative to the more long-lasting variant-specific response. In [24], it is assumed that specific immunity is acquired and remembered by the host to the extent that its decay is negligible. That is, they enforce the extreme case that the decay rate for the specific IR is zero. In addition, they induce synchrony between the variants by setting identical initial conditions and excluding asynchronous perturbations. The resulting simplified model is used to predict parameter conditions separating oscillatory versus exponential decay and to correlate the length of infection with the transient cross-reactive IR efficacy.

De Leenheer and Pilyugin [8] analyse different types of cross-immunity by choosing different couplings or connectivity matrices via common minor epitopes. They provide conditions for global stability of different steady-state solutions. In addition, they consider the system with and without a logistic term, representing a carrying capacity in the equation for parasite production.

Blyuss and Gupta [4] also compare the resulting dynamics for when specific IR decay is negligible and when it is not. Moreover, they consider a particular connectivity matrix between four variants. Given their connectivity matrix (coupling), they show that the uniform steady state, where all variants have the same non-zero value, is stable for some parameter values yet bifurcates to periodic parasitemia peaks for others due to an Hopf bifurcation. Non-uniform equilibria, representing extinction of some variants but not others, are found to be always unstable.

In our previous work with this model [21], we considered the case of purely synchronous oscillations as done in [24]. While this ignored the effect of antigenic variation, it allowed us to focus on the effect of the various rate constants. In particular, we determined conditions on the efficacies of the specific and cross-reactive IRs under which the uniform steady state, corresponding to persistent infection within the host, is a stable spiral or a node. The former predicts recurring oscillations of the parasitemia that decay to the uniform steady state, while the latter implies that protective immunity is obtained after the first peak, which inhibits further oscillations. In addition, we showed that a small delay in the activation of the host’s IR can cause the uniform steady state to undergo an Hopf bifurcation to oscillations. Under the assumption that the decay rate for specific IR is much lower than that for cross-reactive IR, we found that the critical delay-time causing oscillations is inversely proportional to the efficacy of the host’s cross-immunity. That is, a more effective cross-reactive IR tends to make the system more susceptible to delay-induced synchronous oscillations.
In this paper, we allow for the possibility of asynchronous oscillations. We consider the ideal case of complete global coupling among $n$ antigenic variants. In general, there are approximately $N = 60$ variants each corresponding to a particular $var$ gene for $Pf$ [25]. We assume that there is a subset of $n < N$ variants that have common minor epitopes. This will allow us to obtain results describing the competition between the synchronous or asynchronous oscillations. The synchronous oscillations are all in-phase such that the peak parasitemia for each variant occurs at the same time; an example is shown in Figure 1(a) for the case of $n = 3$ variants. For the asynchronous oscillations, the peaks of the variants occur at different times as described in [26]. We find that a basis to describe all possible asynchronous oscillations is with antiphase eigenvectors, defined such that the sum of their vector phases is zero. A specific type of asynchronous oscillation, where the oscillators follow each other in sequence, is referred to as an antiphase state (also referred to as splay states or ponies on a merry-go-round) [2,6,31,32]. One such example is shown in Figure 1(b), where three oscillators follow each other in the sequence $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \ldots$. The sequence $2 \rightarrow 1 \rightarrow 3 \rightarrow 2 \ldots$ would be another distinct antiphase state and both of these examples are described by the antiphase eigenvectors that we will define. Antiphase states in coupled oscillators are a direct result of the symmetry imposed by global coupling, which in the present study is due to the variants’ all sharing minor epitopes. Subsequently, we will use the abbreviations AP and SYNC to describe the antiphase and synchronous behaviour, respectively.

Because the highly complex interactions of the human IR following sequestration are condensed into only two phenomenological variables, precise estimates of the rate constants are difficult to acquire. However, in the next section, we rescale the the original model of Recker and Gupta [24] and Recker et al. [26] and define new parameters that are defined in terms of the ratios of original rate constants. This allows us to describe variant specific and cross-reactive IRs in terms of their overall efficacies. We then analyse the linear stability of the uniform steady state and quantify the decay rates for both transient SYNC or AP oscillations. We find that the decay rate of the SYNC oscillations is proportional to the decay rate of the cross-reactive IR and is relatively fast. In contrast, we find that the decay of the AP oscillations is proportional to the decay rate of the specific IR, which is relatively slow. Thus, given an arbitrary set of initial conditions that lead to transient oscillations, the synchronous component will rapidly decay so that the likely observation is the asynchronous oscillations. Finally, we obtain asymptotic approximations of transient AP oscillations under the case of instantaneous IR stimulation and compare with numerical simulations.

We also consider the effect of delaying the IR by a constant time lag. That is, there is a delay between changes in the $Pf$ population and production of corresponding immune effectors. Delays have been used in disease models with an IR in [17], and for malaria in particular in [13,18,19]. However, we are not aware of any reported measurements of IR delay times for $Pf$. That said, it is well known that the introduction of delays or time lags into dynamical systems models can excite persistent oscillations [16]. Thus, it is one possible mechanism for continued long-term infection in the host. Specifically, we find that even very small delays lead to an Hopf bifurcation yielding persistent SYNC or AP oscillations.

The delay also serves as a theoretical probe to understand the competition between SYNC and AP oscillations in this model. That is, the delay serves to perturb the system and determine when the system is more sensitive to AP versus SYNC oscillations. We demonstrate that by increasing the efficacy of the cross-reactive IR relative to the variant-specific IR, the delayed IR will lead to SYNC oscillations. This is a manifestation of the well known fact that for a general system of coupled oscillators, strong coupling tends to lead to synchronization [28]. In other words, if there were no cross-reactive IRs in the model, then the asynchronous behaviour results from applying arbitrary initial conditions to each variant because they are uncoupled and thus mutually independent of each other. Thus, incorporating the coupling via the cross-reactive IR into the model serves to organize interactions between variants while still allowing various types
of oscillations, namely, AP and SYNC. This suggests that the coupling must be strong enough to allow the variants to interact and organize yet weak enough to observe sequential dominance.

Finally, we study the nonlinear behaviour of the system and the oscillations that result from the delayed IR. Near the AP Hopf bifurcation, we show how the amplitude and frequency of persistent small-amplitude oscillations vary in terms of the parameters. Using numerical continuation and simulation, we identify intervals of the delay where the system settles back to the uniform steady-state versus exhibiting persistent oscillations. In the case of the latter, it turns out that most often the system exhibits large amplitude pulsating behaviour that appears chaotic. This indicates that the IR delay is too large for the subject to acquire protective immunity against the disease.

Our manuscript is organized as follows: in Section 2, we derive a non-dimensionalized model that will be the focus of our analysis in the rest of the paper. In Section 3, we determine the conditions that lead to either synchronous or asynchronous oscillations for the case of instantaneous IR and describe the properties of the oscillations. In Section 4, we consider the effect of a delayed IR. We conclude with a discussion of the paper’s results in Section 5.

2. Scaled model with global coupling

We consider the malaria model proposed by Recker and Gupta [24] in which we include a delay on the term representing IR stimulation. The delay, \( T \), represents the time between changes in parasitemia and the production of the corresponding immune effectors. The model is given by the system of delay differential equations as follows:

\[
\frac{dY_j}{dT} = \phi Y_j - \alpha Y_j Z_j - \alpha' Y_j W_j,
\]

\[
\frac{dZ_j}{dT} = \beta Y_j|_{T} - \mu Z_j,
\]

\[
\frac{dW_j}{dT} = \beta' \sum_k \kappa_{jk} Y_k|_{T} - \mu' W_j,
\]

(1)

where \( Y_k|_{T} = Y_k(T - T) \) represents a delay by time \( T \). The index, \( j \), separates the PRBC population, represented by \( Y_j \), into \( N \) classes or variants characterized by the unique major epitope of their displayed antigen. Each variant is produced at an intrinsic growth rate of \( \phi \) and destroyed when it comes into contact with either the immune effector \( Z_j \) or \( W_j \) at capture rates \( \alpha \) and \( \alpha' \), respectively. The specific IR, \( Z_j \), stimulated by the presence of the variant with the corresponding major epitope at a rate of \( \beta \) and decays with a rate \( \mu \). The cross-reactive IR, \( W_j \), is stimulated at a rate of \( \beta' \) by all variants with corresponding minor epitopes and decays at a rate of \( \mu' \). The former produces the summation term in Equation (1), which couples the subsystems for each variant \( k \) that shares a minor epitope with \( j \). A connectivity matrix, whose entries are \( \kappa_{jk} \), defines precisely how the variants share minor epitopes.

In [21], we analysed the case of complete synchronization between the strains such that \( Y_j(t) = Y(t), Z_j(t) = Z(t) \) and \( W_j(t) = W(t) \). Equations (1) then reduce to just three equations for \( Y, Z \) and \( W \) since the coupling term becomes

\[
\sum_k \kappa_{jk} Y_k|_{T} = nY|_{T}.
\]

(2)

In this paper, we relax the previous assumption by allowing asynchronous behaviour, i.e. \( Y_j(T) \neq Y_k(T) \) when \( j \neq k \). Also, we consider a subsystem of Equations (1) where \( \kappa_{jk} = 1 \) for all variants \( j, k = 1 \ldots n < N \) and neglect variants \( j = n + 1 \ldots N \). More specifically, every variant in the
subsystem has the same $n$ minor epitopes in common so that the summation in Equation (1) simplifies to

$$\sum_k \kappa_{jk} Y_k |_T = \sum_{k=1}^n Y_k |_T.$$  \hfill (3)

De Leenheer and Pilyugin [8] refer to Equation (3) as ‘perfect cross immunity’ because the cross-reactive IR corresponding to each variant is stimulated by all of the variants within the subsystem. Said another way, the variants are globally coupled to each other since they share all $n$ minor epitopes and thus regulate the production of $W_j$ for all $j = 1 \ldots n$.

In general, there are many equilibria to Equations (1), but there is only one that is strictly positive [8]. The non-positive equilibria have some of the $Y_j = 0$ and allow one to analyse the competitive exclusion principle by representing extinction of one or more of the variants [1,4,7,8,15]. We are not interested in the competition between steady states but, rather, the competition between either synchronous or asynchronous oscillations. In any case, we have checked that the non-positive equilibria are unstable to perturbations due to at least one positive eigenvalue (for $\tau = 0$). Thus, will consider oscillatory deviations from the uniform steady state, which is given by

$$Y_j = Y_s = \frac{\mu \phi}{\alpha' \beta' d}, \quad Z_j = Z_s = \frac{\phi c}{n \alpha d}, \quad \text{and} \quad W_j = W_s = \frac{\mu \phi}{\alpha' \mu' d},$$

where

$$c = \frac{\alpha \beta}{\alpha' \beta'}, \quad \text{and} \quad d = c + \frac{\mu}{\mu'}.$$  \hfill (5)

We introduce new variables that represent deviations from the uniform steady state by defining

$$Y_j = Y_s (1 + y_j),$$

$$Z_j = Z_s \left[ 1 + \frac{n}{c} \left( \frac{d \mu}{\phi} \right)^{1/2} z_j \right],$$

$$W_j = W_s \left[ 1 + \frac{\mu'}{\mu} \left( \frac{d \mu}{\phi} \right)^{1/2} w_j \right],$$

$$T = \left( \frac{d}{\mu \phi} \right)^{1/2} t.$$  \hfill (6)

We also let $x_j = z_j + w_j$ represent the total (specific plus cross-reactive) IR for the $j$th variant so that the change of variables yields the new dimensionless system

$$\frac{dy_j}{dt} = -x_j (1 + y_j),$$

$$\frac{dx_j}{dt} = \frac{c}{n} y_j |_T + \frac{1}{n} \sum_{k=1}^n y_k |_T - ax_j + a(1 - b) w_j,$$

$$\frac{dw_j}{dt} = \frac{1}{n} \sum_{k=1}^n y_k |_T - ab w_j,$$  \hfill (7)

with scaled constants given by

$$a = \sqrt{\frac{d \mu}{\phi}}, \quad b = \frac{\mu'}{\mu}, \quad c = \frac{\alpha \beta}{\alpha' \beta'} \quad \text{and} \quad \tau = \sqrt{\frac{\mu \phi}{a d} T}.$$  \hfill (8)
Rescaling the system to dimensionless quantities is preferred because the seven parameters in Equations (1) are absorbed into only three parameters in Equations (7). Also, the scaled parameters are expressed in terms of ratios of the rate constants in Equations (1), which are themselves difficult to estimate because the model compartmentalizes the host’s very complicated immune system into two phenomenological variables, \( Z \) and \( W \). The rescaled model allows us to explicitly focus our analysis on the relative strengths of the biological processes being studied. We note that some results of our analysis will be expressed in terms of the original rate constants and/or IR efficacies given by

\[
E_z = \frac{\alpha \beta}{\mu} \quad \text{and} \quad E_w = \frac{\alpha' n \beta'}{\mu'},
\]

which represent the overall effectiveness of the specific and cross-reactive IR, respectively [21]. For example, increasing \( \mu \) decreases \( E_z \) and thereby decreases the effectiveness of the specific IR because it decays at a faster rate. The efficacies will allow us to make certain comparisons between the types of IR later in the manuscript.

An important biological assumption is that the specific IR is long-lived as opposed to the more transient cross-reactive IR. This implies that \( \mu \ll \mu' \). Recker and Gupta [24] and Blyuss and Gupta [4] have analysed the extreme case \( \mu = 0 \). The case \( \mu \neq 0 \) has been addressed in [4,8,21,24]. Similar to [21], we maintain throughout this paper a non-zero-specific IR decay rate, \( \mu \), such that \( 0 < \mu \ll \mu' \). For this reason, we find that \( a \) is small while \( b = \mu'/\mu \) is large. In this paper, we will treat \( a \) as our small parameter and choose scalings for \( b \) such that \( a \ll 1 \ll b \). We generally keep \( c = O(1) \), although it can be argued as in [24] that the capture rate is greater for specific than for cross-reactive IR, i.e. \( \alpha > \alpha' \). Also, the number of variants in the globally coupled system, \( n \), can influence parameter sizes. Because there may be only a portion of the total number of variants present in the host sharing their minor epitopes, we choose \( n \) to be \( O(1) \) or larger and typically use \( n = 3 \) to demonstrate results in numerical simulations.

3. Instantaneous IR \((\tau = 0)\)

In this section, we consider the IR stimulation to be instantaneous by setting the delay to zero so that Equations (7) becomes a system of ordinary differential equations (ODEs). Initially, we will continue to include the \( \tau \) in the analysis so that we may use some of the early results later in Section 4.

In the first subsection, Section 3.1, we analyse the linear stability of the uniform steady state and find the decay rate and frequency of both AP and SYNC oscillations. In Section 3.2, we construct solutions for small amplitude AP oscillations and compare the results to numerical solutions. Of particular importance is that the AP eigenvalue is repeated \((n - 1)\) times corresponding to \((n - 1)\) distinct phase relationships among the variants. The latter are captured by the associated eigenvectors, which we describe in Sections 3.3.

3.1. Linear stability

We perform a linear-stability analysis of Equations (7) about the uniform steady state \((y_j = x_j = w_j = 0 \text{ for all } j)\) by looking for small solutions proportional to \( \exp(\lambda t) \). A global stability analysis via the Lyapunov function can be used to prove that the uniform steady state is stable [8]. However, specific knowledge of the linear eigenvalues will allow us to draw conclusions regarding the competition between SYNC versus AP oscillations. The Jacobian matrix for Equations (7)
that determines the eigenvalue $\lambda$ is a $3n$ by $3n$ block matrix of the form

$$J = \begin{bmatrix} D & E & E & \cdots \\ E & D & E & \cdots \\ \vdots & \vdots & \ddots & \ddots \end{bmatrix},$$

where $D$ and $E$ are given by

$$D = \begin{bmatrix} 0 & -1 & 0 \\ (c+1)e^{-\lambda \tau / n} & -a & a(1-b) \\ e^{-\lambda \tau / n} & 0 & -ab \end{bmatrix}$$

and

$$E = \begin{bmatrix} 0 & 0 \\ 0 & 0 \\ 0 & 0 \end{bmatrix}.$$

Due to the symmetry imposed by the global coupling, the determinant of $J - \lambda I$ is factorable and there are repeated roots. Specifically, the characteristic equation for $\lambda$ is

$$[F_1(\lambda) F_{ap}(\lambda, \tau)]^{n-1} F_s(\lambda, \tau) = 0,$$

where

$$F_1(\lambda) = \lambda + ab,$$

$$F_{ap}(\lambda, \tau) = \lambda^2 + a\lambda + \frac{c}{n} e^{-\lambda \tau},$$

$$F_s(\lambda, \tau) = \lambda^3 + a(1+b)\lambda^2 + a^2 b\lambda + e^{-\lambda \tau} \left[ \lambda \left( 1 + \frac{c}{n} \right) + a \left( 1 + \frac{bc}{n} \right) \right].$$

Equations (12) and (13) are valid for both zero and non-zero delay. We will now focus on the case when the IR is instantaneous, i.e. $\tau = 0$.

We consider first the factor $F_1$, which yields the repeated root $\lambda = -ab$, with multiplicity $n - 1$. Because $a$ and $b$ are strictly positive, these roots are always negative, indicating stability.

When the IR is instantaneous, $F_{ap}(\lambda, 0) = 0$ is a quadratic equation with solutions

$$\lambda_{ap} = -\frac{a}{2} \pm \sqrt{\left( \frac{a}{2} \right)^2 - \frac{c}{n}},$$

which have multiplicity $n - 1$. Because the parameters $a$ and $c$ are positive, even if the roots are real, both will be negative, indicating stability. However, feasible parameter values, namely $\mu \ll \mu' \ll 1$, force $a$ to be at least an order of magnitude smaller than $c/n$. As a result, the decay to the uniform steady state will be oscillatory with decay rate $|\Re[\lambda_{ap}]| = a/2$. Because these complex eigenvalues are repeated, they will have $(n - 1)$ associated eigenvectors. In Section 3.3, we show that these eigenvectors are representative of various types of AP solutions corresponding to different phase relationships between the oscillations of the major variants. For this reason, we associate the factor $F_{ap}$ with AP oscillations and use the subscript $ap$ when referring to quantities generated from $F_{ap}(\lambda, \tau) = 0$. In terms of the original parameters such that $\lambda t = (-\sigma + i\Omega)T$, the decay rate and frequency of the AP oscillations are given by

$$\sigma_{ap} \sim \frac{1}{2} \mu,$$

$$\Omega_{ap} \sim \sqrt{\phi \mu \left( \frac{E_z}{E_z + E_w} \right)}.$$

Decreasing the value of $\mu$ decreases $\sigma_{ap}$ and, thus, causes the AP oscillations to decay more slowly. The frequency for a single variant is $\Omega_{ap}$. For the case when the AP solution corresponds
to the variants oscillating sequentially (Figure 1(b)), then the clinical episodes of the host appear at a frequency $n\Omega_{ap}$ as the host responds to each variant peak.

The third factor in the characteristic equation, $F_s$, is precisely the characteristic equation we analysed in [21] for SYNC solutions. Therefore, we subsequently use the subscript $s$ when referring to quantities generated from $F_s(\lambda, \tau) = 0$. In [21], we found approximations of the eigenvalues under two scalings of the parameters, both of which were based on $\mu \ll \mu' \ll 1$. The result was that we determined parameter regions when there was either strictly exponential or oscillatory decay. We have reformulated the relevant result for this paper by assuming that $a \ll 1$, $b = O(1/a)$ and $c/n = O(a^{1/2})$. Under this scaling, the real and imaginary parts of the complex eigenvalues corresponding to SYNC oscillations when written in terms of the original parameter values are given by

$$\sigma_s \sim \frac{1}{2} \mu',$$

$$\Omega_s \sim \sqrt{\phi \mu' \left( \frac{E_w}{E_z + E_w} \right)}.$$  

For the SYNC oscillations, the decay rate is controlled by $\mu'$ as opposed to $\mu$. As mentioned previously, an important assumption in the design of Equations (1) is that the specific IR is long lasting, while the cross-reactive IR is relatively transient, i.e. $\mu' \gg \mu$. Thus, from Equations (15) and (16), we find that the SYNC oscillations will decay much faster than the AP oscillations (we have confirmed that this also holds for an alternative scaling of the parameters that also yield SYNC oscillations [21]). We also note that because all of the oscillations of the variants are synchronized, the frequency of SYNC clinical episodes is equal to $\Omega_s$.

3.2. **Transient antiphase oscillations for $\tau = 0$**

As discussed in the previous section, the uniform steady state is stable. However, transient oscillations that decay to the uniform steady state may be either AP or SYNC (Figure 1). In
this section, we present asymptotic approximations to the decaying AP oscillations, using results from Section 3.1 and continue the comparison between AP and SYNC behaviour. We consider antiphase oscillations by imposing the condition $\sum y_j = 0$ onto Equations (7) such that each variant then satisfies

$$\frac{dy_j}{dt} = -x_j(1 + y_j),$$
$$\frac{dx_j}{dt} = \frac{c}{n}y_j - ax_j + a(1 - b)w_j,$$
$$\frac{dw_j}{dt} = -abw_j.$$ (17)

For small solutions, we can solve the linearized version of Equations (17) to obtain approximations to transient AP oscillations, which are given by

$$y_j(t) \sim 2R_je^{-at/2}\cos(\omega t + \Phi_j),$$
$$x_j(t) \sim -2\omega R_je^{-at/2}\sin(\omega t + \Phi_j),$$
$$w_j(t) \sim w_k(0)e^{-abt},$$ (18)

where $R_j$ and $\Phi_j$ are constants given by the initial conditions. To observe AP oscillations in numerical simulations, the initial conditions must be chosen so that the antiphase condition, $\sum y_j = 0$ (or Equation (22)) is satisfied. One example is when $R_j = R$ such that the amplitudes are uniform, while the phases are chosen to be evenly spaced in the interval $[0, 2\pi]$, i.e. $\Phi_j = 2\pi j/n$. In Figure 1(b), we compare Equations (18) (dashed) to numerical solutions (solid) of Equations (7) with $\tau = 0$; the curves are so close as to be essentially indistinguishable. In this case, variants oscillated with phases ordered according to $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \ldots$. The small-amplitude, thick, solid curve in the plot of $y_j$ in Figure 1(b) represents the sum of the variants such that $\sum y_j \approx 0$. That is, the AP condition is satisfied despite the fact that the variants exhibit non-trivial oscillations.

Because each variant is coupled to the others via the global coupling term, we easily obtain SYNC oscillations by numerically solving Equations (7) with identical initial conditions (Figure 1(a)). By definition, the SYNC oscillations are in phase such that $y_j = y$ and, hence, $\sum y_j = ny$. For asymptotic approximations of transient SYNC oscillations, see [21].

The frequencies of AP and SYNC oscillations given by Equations (15) and (16) offer a few relevant biological implications, which we now explain. We first consider the effect of the parasite growth rate $\phi$. Both $\Omega_{ap}$ and $\Omega_s$ vary directly with the square root of the intrinsic growth rate of the parasite, $\phi$. Thus increasing the rate of producing, each variant increases the frequency of recurring clinical episodes. We next consider the effect of the IR efficacies $E_z$ and $E_w$ given in Equations (9). First consider the cross-reactive IR efficacy, $E_w$, to be fixed. As the specific IR efficacy $E_z$ is increased, $\Omega_{ap}$ increases and saturates to $\sqrt{\phi \mu}$, while $\Omega_s$ decreases to 0. This implies that a stronger specific IR tends to accelerate AP and asynchronous, oscillations of the variants, but decelerates the frequency of a synchronized parasitic attack. On the other hand, for fixed $E_z$, increasing $E_w$ will have the opposite effect, implying that a stronger cross-reactive IR will increase the frequency of synchronized clinical episodes and decrease the frequency of AP oscillations.

Finally, as predicted in the previous sections, the simulations confirm that AP oscillations, or the sequential appearance of antigenic variants, will lengthen the host’s duration of infection compared with the SYNC oscillations and, hence, promote the survival of the malaria parasite. In addition, we observe that the clinical frequency for peaks in the parasite load in the case of AP oscillations is greater than that of the SYNC oscillations due to the non-synchronized episodes of the individual variants.
3.3. Antiphase versus synchronous eigenvectors

In this section, we derive the eigenvectors associated with either $F_{ap}(\lambda, \tau) = 0$ or $F_s(\lambda, \tau) = 0$. We note that the results of this section are valid for both $\tau = 0$ and $\tau \neq 0$. The phase relationship between the oscillators is directly determined by the eigenvectors of the linear system. Due to the block nature of the Jacobian matrix, given by Equation (10), it suffices to study the subsystem corresponding to a single variant, $j$. Let $\vec{v}_j = (v_j^{(y)}, v_j^{(x)}, v_j^{(w)})$ be the subvector corresponding to the $j$th variant and consider the $j$th block-row of the Jacobian matrix, $J$. Because the blocks in $J$ form a diagonal, each subvector, $\vec{v}_j$, is multiplied by $D - \lambda I$, while the subvectors $\vec{v}_k \neq j$ are multiplied by $E$ such that we have

$$(D - \lambda I) \cdot \vec{v}_j + \sum_{k \neq j} E \cdot \vec{v}_k = 0, \quad (19)$$

where $D$ and $E$ are defined in Equation (11). The first and third rows from Equation (19) yield

$$v_j^{(x)} = -\lambda v_j^{(y)}$$
$$v_j^{(w)} = \frac{1}{\lambda + ab} \left( \frac{1}{n} \right) e^{-\lambda \tau} \sum_{k=1}^{n} v_k^{(y)}. \quad (20)$$

Note that the expression for $v_j^{(w)}$ does not depend on $j$, which indicates that the $w$ components for each eigenvector are identical. We substitute Equations (20) into the second row of Equation (19) and find that the $y$-components must satisfy

$$[F_1(\lambda)F_{ap}(\lambda)]^{1/(n-1)} v_j^{(y)} + \frac{1}{n} e^{-\lambda \tau} (\lambda + a) \sum_{k=1}^{n} v_k^{(y)} = 0. \quad (21)$$

In the following two subsections, we derive the specific eigenvectors corresponding to AP and SYNC terms for oscillatory solutions to Equations (7).

3.3.1. Antiphase eigenvectors

We now find expressions for the $(n - 1)$ AP eigenvectors associated with the repeated eigenvalue, $\lambda_{ap}$. Because $F_{ap}(\lambda_{ap}, \tau) = 0$ from Equation (21), we are left with the result (for notation convenience, we have switched the index from $k$ back to $j$)

$$\sum_{j=1}^{n} v_j^{(y)} = 0. \quad (22)$$

That is, each of the $(n - 1)$ eigenvectors must satisfy Equation (22), which we refer to as the antiphase condition. We introduce a second subscript $m$ to account for $m = 1 \ldots n - 1$ eigenvectors and define the $y$-components as

$$v_j^{(y)} = e^{i2\pi jm/n}, \quad (23)$$

where the $v_j^{(x)}$ and $v_j^{(w)} = 0$ are determined by Equations (20). It can be shown that the resulting eigenvectors are orthogonal and form a basis sufficient to span the space of solutions when $F_{ap}(\lambda_{ap}, \tau) = 0$. 

Each eigenvector defined by Equation (23) determines a unique phase ordering of the variants as they oscillate; a similar analysis has been done in the context of multimode lasers in [6,32]. As an example, consider the case \( n = 3 \). Then the \( y \)-components of the \( m = 1, 2 \) eigenvectors are

\[
\vec{v}_1^{(y)} = (e^{2\pi i/3}, e^{4\pi i/3}, 1) \\
\vec{v}_2^{(y)} = (e^{4\pi i/3}, e^{2\pi i/3}, 1).
\] (24)

In \( \vec{v}_1^{(y)} \) the first variant has phase \( 2\pi/3 \), the second \( 4\pi/3 \), and the third \( 2\pi \). Thus, the ordering of the variants as they oscillate is \( 1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \ldots \) (Figure 1(b)). On the other hand, in \( \vec{v}_2^{(y)} \) the phases are \( 4\pi/3, 2\pi/3, \) and \( 2\pi \) corresponding to the ordering \( 1 \rightarrow 3 \rightarrow 2 \rightarrow 1 \ldots \)

As mentioned above, these two vectors are sufficient to generate any set of vectors satisfying Equation (22). This allows us to express any observed AP state as a linear combination of these eigenvectors. For example, consider the vectors

\[
\vec{u}_1 = (i, 1 + i, -1 - 2i) \quad \text{and} \quad \vec{u}_2 = (1, -1, 0)
\]

which clearly satisfy Equation (22) and hence, can be written as the following linear combinations of the eigenvectors:

\[
\vec{u}_1 = -\frac{1}{2} - \left(1 - \frac{\sqrt{3}}{6}\right)i \vec{v}_1^{(y)} + \left(-\frac{1}{2} - \left(1 + \frac{\sqrt{3}}{6}\right)i\right) \vec{v}_2^{(y)} \\
\vec{u}_2 = \frac{1}{\sqrt{3}} \vec{v}_1^{(y)} + \frac{1}{\sqrt{3}} i \vec{v}_2^{(y)}.
\] (25)

These different asynchronous oscillations, represented by \( \vec{u}_1 \) and \( \vec{u}_2 \), are illustrated in Figure 2, where we compare the numerically computed solutions to Equations (7) (solid curves) to the analytical approximations given by Equations (18) (dotted curves) with appropriate initial conditions. Note that Figure 2(b) shows variants 1 and 2 oscillating perfectly out of phase while
variant 3 is near zero, corresponding to the vector \( \mathbf{u}_2 = (1, -1, 0) \). Biologically, this implies that although there are three variants present within the host, only two are oscillating, while the third is essentially at steady state.

As was mentioned in the introduction, the \((n - 1)\) AP eigenvectors that serve as a basis to describe general asynchronous oscillations should be distinguished from the so-called AP states. The latter refer to the specific case when the phases of the oscillators are evenly distributed on the circle such that one oscillator follows another, e.g. for \( n = 3 \), \( 1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \ldots \) or \( 1 \rightarrow 3 \rightarrow 2 \rightarrow 1 \ldots \). An example is shown in Figure 1(b). More generally, for \( n \) oscillators, there are \((n - 1)!\) distinct antiphase states corresponding to different sequencing of the oscillators [2,6,31,32].

3.3.2. **Synchronized eigenvectors**

In the case of complete synchronization, all of the oscillators are in-phase. Thus, \( \tilde{v}_j = \tilde{v}_k \) for all variants \( j, k \) such that we can set \( v_j^{(y)} = v^{(y)} \). If we make this substitution into Equation (21), we obtain

\[
F_s(\lambda, \tau)v^{(y)} = 0,
\]

(26)

where \( F_s \) is defined in Equation (13). Thus, we have confirmed that for synchronous oscillations, we must satisfy the condition \( F_s(\lambda, \tau) = 0 \), which determine the eigenvalues \( \lambda_s \) as given by Equation (16).

4. **Delayed IR**

Up to this point, we have considered the case of instantaneous IR stimulation with \( \tau = 0 \). In this section, we consider non-zero values for \( \tau \), which is a measure of the time it takes the antigen to stimulate a corresponding IR. From a linear stability analysis, we determine the parameter conditions that cause an Hopf bifurcation to either AP or SYNC oscillations of the variants. We then perform a weakly nonlinear analysis to describe the solutions that emerge from an AP-type Hopf bifurcation and note that the SYNC case can be found in [21].

4.1. **Linear stability**

We reanalyse the characteristic equation, Equation (12), for the case of a delayed IR when \( \tau \neq 0 \). Since both equations \( F_{ap}(\lambda, \tau) = 0 \) and \( F_s(\lambda, \tau) = 0 \) contain the exponential expression, \( e^{-\lambda \tau} \), the equations are transcendental and may have infinitely many solutions. To determine when there is an Hopf bifurcation, we look for solutions for which \( \Re[\lambda] = 0 \), i.e. \( \lambda = i \omega \). As with the case of no delay, \( F_{ap} \) is associated with AP oscillations, while \( F_s \) is associated with SYNC oscillations.

For \( F_{ap}(\lambda, \tau) = 0 \) we obtain

\[
\omega_{ap} = \sqrt{-\frac{a^2}{2} + \sqrt{\frac{a^4}{4} + \left(\frac{c}{n}\right)^2}},
\]

\[
\tau_{ap} = \frac{1}{\omega_{ap}} \arctan \left( \frac{a}{\omega_{ap}} \right).
\]

Equations (27) are expressions for the frequency, \( \omega_{ap} \), and delay time, \( \tau_{ap} \), at the Hopf bifurcation. That is, there is a change in stability when the delay time \( \tau \) is increased or decreased from \( \tau_{ap} \).
We can find simpler expressions than Equations (27) by looking for small delay and assuming that $a \ll 1$ and $c/n = O(1)$. To leading order, we find that

$$\omega_{ap} \sim \frac{c}{n} \quad \rightarrow \quad \Omega_{ap} = \sqrt{\frac{\mu \phi}{E_z + E_w}} \left( \frac{E_z}{E_z + E_w} \right),$$
$$\tau_{ap} \sim \frac{an}{c} \quad \rightarrow \quad \tau_{ap} = \frac{1}{\phi} \left( \frac{E_z + E_w}{E_z} \right),$$

(28)

which corresponds to the least value of the delay when there is an Hopf bifurcation. We note that the right arrow indicates that the quantity has been scaled back into original time units, $T$, such that $\omega T = \Omega T$. Also, the frequency of the AP oscillations, $\Omega_{ap}$, at the Hopf bifurcation, Equation (28), is equivalent to that when there is no delay, Equation (15), because the delay excites the natural oscillations of the system. As $\tau$ is increased from zero and reaches $\tau_{ap}$, $\Re[\lambda]$ changes from negative to positive, indicating that the uniform steady state becomes unstable. More specifically, we derive an approximation for $\Re[\lambda]$ by substituting $\tau = \tau_{ap} + \tau_1$ and $\lambda = \sigma_{ap} + i\omega_{ap}$ into $F_{ap}(\lambda, \tau) = 0$ where $\tau_1 \sim \sigma_{ap} \ll 1$ to obtain

$$\sigma_{ap} \sim \frac{(c/n)\omega_{ap}}{a \sin(\omega_{ap}\tau_{ap}) + 2\omega_{ap} \cos(\omega_{ap}\tau_{ap})}(\tau - \tau_{ap}),$$

(29)

which is linear in $\tau$ and exhibits a positive slope for small positive delay. Thus, as $\tau$ is increased beyond $\tau_{ap}$, $\sigma_{ap}$ switches from negative to positive, indicating that the uniform steady state becomes unstable via an Hopf bifurcation to AP oscillations.

We now look for potential bifurcation points from the third term in the characteristic equation by setting $F_s(\lambda, \tau) = 0$. As we discussed in the previous section, this is the characteristic equation for SYNC solutions that we studied in [21] in which we found approximations for delay and frequency at the bifurcation point. We reproduce relevant results to this analysis by looking for purely imaginary eigenvalues under the assumptions $a \sim \tau_s \ll 1$ and $c/n = O(1)$ to obtain

$$\omega_s \sim \sqrt{\frac{1 + c}{n}} \quad \rightarrow \quad \Omega_s^{(H)} = \sqrt{\phi \left( \frac{\mu E_z + \mu' E_w}{E_z + E_w} \right)},$$
$$\tau_s \sim \frac{a (b + c/n)}{(1 + c/n)^2} \quad \rightarrow \quad \tau_s = \frac{1}{\phi} \left( \frac{E_z + E_w}{E_w} \right).$$

(30)

We note that $\Omega_s^{(H)}$ is greater than $\Omega_s$ (Equation (16)), where the latter was derived for $c/n \ll 1$. In addition, when $c/n \ll 1$, $\Omega_s^{(H)}$ simplifies to $\Omega_s$. Our reason for choosing $c/n = O(1)$ here is in obtaining the critical delay time $\tau_s$ and will be made apparent in the next paragraph. We again approximate $\Re[\lambda]$ for the SYNC case by substituting $\tau = \tau_s + \tau_1$ and $\lambda = \sigma_s + i\omega_s$ into $F_s(\lambda, \tau) = 0$, where $\tau_1 \sim \sigma_s \ll 1$. We find that

$$\sigma_s \sim \frac{\omega_s a (1 + bc/n)}{\omega_s \tau_s (1 + c/n) + (a^2 b - 3\omega_s^2) \sin(\omega_s \tau_s) + 2\omega_s a (1 + b) \cos(\omega_s \tau_s)}(\tau - \tau_s),$$

(31)

which corresponds to the least value of the delay when there is an Hopf bifurcation. Small values of the delay and parameter $a$ produce a positive coefficient for $(\tau - \tau_s)$ so that the uniform steady state is unstable for $\tau > \tau_s$. Equations (29) and (31) are plotted in Figure 3 as the ‘s’ and ‘+’s, respectively, and are nearly coincident with numeric solutions of the characteristic equation which are given by the solid curves [10].

The least values of $\tau_{ap}$ and $\tau_s$ are given by Equations (28) and (30), respectively. The Hopf bifurcation from the stable uniform steady state to oscillatory solutions will occur at $\tau = \tau_h$ given
Figure 3. Two possible Hopf bifurcations. Parameter values can be tuned, so that the Hopf bifurcation occurs at (a) \( \tau_h = \tau_{ap} \) given by Equation (27) or (b) \( \tau_h = \tau_s \) given by Equation (30). Analytical approximations of \( \Re[\lambda] \), indicated by the ×’s and +’s, are given by Equations (29) and (31), respectively. Numerical approximations of \( \Re[\lambda] \) are represented by the solid curves [10]. Parameters: same as those in Figure 1 except (a): \( \mu = 0.015, \mu' = 0.1 \); (b): \( \mu = 0.025, \mu' = 0.07 \).

Figure 4. Left: The boundary between AP versus SYNC behaviour found from Equation (32) (dashed) and numerically evaluating \( \tau_{ap} = \tau_s \) from Equations (27) and (30) (solid). Points (a) and (b) show choices for \( \mu \) and \( \mu' \) which produce (a) AP and (b) SYNC behaviour, respectively. Right: Numerical simulations [30] of Equations (7) demonstrate the contrasting persistent oscillations using the indicated values for \( \mu \) and \( \mu' \) and similar initial conditions. Parameters are the same as those in Figure 3.

by the minimum of the two, i.e. \( \tau_h = \min\{\tau_{ap}, \tau_s\} \). Thus, if the parameters are such that \( \tau_h = \tau_{ap} \), then the oscillations that exist for \( \tau > \tau_{ap} \) will be asynchronous (Figure 4(a)), while if the parameters are such that \( \tau_h = \tau_s \), the oscillations will be synchronous (Figure 4(b)). By considering when \( \tau_{ap} = \tau_s \), we can determine the parameter conditions that favour AP versus SYNC oscillations. From Equations (28) and (30), we find that the bifurcation points are equal when

\[
\mu' = \left(\frac{n}{c} + 2\right) \mu.
\]

The result is a line in the \((\mu, \mu')\)-plane, which is plotted in Figure 4; our analytical result is the dotted line and is coincident with the result of numerically examining the roots of the characteristic equation shown as the solid line. SYNC solutions emerge from the Hopf bifurcation for values of \((\mu, \mu')\) below the line, while AP solutions emerge for \((\mu, \mu')\) above the line. Thus, for fixed
increasing $\mu'$ corresponding to increasing the decay rate of the specific IR favours SYNC oscillations. Alternatively, if we fix $\mu$ and increase $\mu'$ corresponding to increasing the decay rate of the cross-reactive IR, then AP solutions are favoured. These observations are consistent with the linear-stability results for no delay, where the decay rate of the AP solutions was $-\mu/2$ so that larger $\mu$ favours the SYNC oscillations, while the decay rate of the SYNC solutions was $-\mu'/2$ so that larger $\mu'$ favours AP solutions. The slope of the line is controlled by the factor $n/c = (n\alpha'\beta')/(\alpha\beta)$. Thus, increasing the influence of the cross-reactive IR through a larger number of shared minor epitopes $n$, a higher removal rate of the parasite $\alpha'$, or a greater stimulation of the cross-reactive IR $\beta'$, will lead to a larger slope and thus a larger region that favours the SYNC oscillations. In contrast, increasing the influence of the variant-specific IR with either $\alpha$ or $\beta$ decreases the slope of the line and favours AP oscillations. Taking all of these effects together, we can generally state that a stronger cross-reactive IR relative to the variant specific IR tends to synchronize the oscillations of the variants, while the opposite favours asynchronous oscillations, or sequential dominance. As alluded to in the introduction, this is a manifestation of the well-understood property of coupled oscillators that strong coupling tends to synchronize the oscillators [28]. On the other hand, if the coupling (cross-reactive IR efficacy, $E_w$) is weak, the oscillators operate in a seemingly independent manner. For this reason, we argue that the cross-reactive IR should be weak enough to avoid absolute synchronization yet strong enough to allow the variants to organize.

4.2. Antiphase and asynchronous oscillations

In this section, we analyse the Hopf bifurcation leading to antiphase oscillations. We note that bifurcation analysis for the SYNC case has been done in [21]. We assume that the parameter values are set such that $F_{ap}(i\omega_{ap},\tau_{ap}) = 0$ so that an Hopf bifurcation occurs for delay and frequency values given by Equations (27); for convenience, from here on, we will use the subscript $h$ instead of $ap$. We will validate our analysis by comparing our results to numerical simulations [30] and continuation [10].

We consider delay values near $\tau_h$ by defining a small parameter, $\eta$, which controls the size of the deviation of the delay time from the Hopf bifurcation value, i.e.

$$\tau = \tau_h + \eta^2\tau_2.$$  

(33)

We introduce a new slow time scale $s = \eta^2t$ and assume state variables depend on $t$ and $s$, where oscillatory behaviour occurs in time scale $t$ and slow evolution of the amplitude of oscillations occurs in the long time scale $s$. With the new slow time scale, the delay term in Equation (7) expands as (see [21,29] for a discussion of the validity of this expansion)

$$y_j(t - \tau, s - \eta^2\tau) = y_j|_{\tau_h} - \eta^2\left(\tau_2 \frac{\partial y_j}{\partial t}|_{\tau_h} + \tau_h \frac{\partial y_j}{\partial s}|_{\tau_h}\right) + O(\eta^4),$$  

(34)

where the subscript indicates the $j$th oscillator. We look for small-amplitude solutions such that the state variables have asymptotic expansions of the form, $y = \eta y^{(1)} + \eta^2 y^{(2)} + \ldots$ where the parenthetical superscript indicates the order of the perturbation analysis. We note that at this point, we make no assumptions on the sizes of the non-dimensional parameters and proceed with the analysis treating all coefficients as $O(1)$. We are able to do this because, as we shall see, looking for small-amplitude solutions that satisfy the AP condition would result in a leading order problem that is solvable. Once we obtain a general bifurcation equation, we will take advantage of the small parameters to simplify the result.
We expand the delay and dependent variables as described above, substitute into Equations (7) and obtain the leading order problem given by

$$\frac{\partial}{\partial t} \tilde{Y}^{(1)} = J|_{\tau_h} \cdot \tilde{Y}^{(1)},$$

(35)

where $\tilde{Y}^{(1)} = (y_1^{(1)}, x_1^{(1)}, w_1^{(1)}, \ldots, y_n^{(1)}, x_n^{(1)}, w_n^{(1)})$ and $J|_{\tau_h}$ is the Jacobian defined by Equation (10) evaluated at $\tau = \tau_h$. The solution to Equation (35) is a linear combination of the product terms $\tilde{v}_j e^{i\omega_h t}$, where the $\tilde{v}_j$ correspond to the AP eigenvectors described in Section 3.3, and the $\lambda$ satisfy the characteristic equation given by Equation (12). Because we have tuned the parameters to be near the AP Hopf bifurcation point, $\lambda = i \omega_h$ will be an $(n - 1)$-repeated root to $F_{ap}(i \omega_h, \tau_h) = 0$. In addition, there will be $(n - 1)$ ‘decaying’ eigenvalues corresponding to $F_1(\lambda) = 0$ and three ‘decaying’ SYNC eigenvalues corresponding to $F_4(\lambda, \tau) = 0$. Thus, the leading order solution for the $j$th variant is

$$y_j^{(1)} = \sum_{m=1}^{n-1} A_m(s) v_{jm} e^{i\omega_h t} + \text{c.c.} + \text{e.d.t.},$$

$$x_j^{(1)} = -i \omega_h y_j + \text{e.d.t.},$$

$$w_j^{(1)} = 0 + \text{e.d.t.},$$

(36)

where c.c. stands for complex conjugate and e.d.t. represents all of the exponentially decaying terms. Thus, $A_m$ describes the slowly varying amplitude of oscillations of the variants whose phase order is specified by the $m$th eigenvector.

The next steps are typical for the method of multiple scales [14], so here we summarize only the main results; however, the details can be found in the appendix. We continued our analysis until $O(\eta^2)$, where to avoid secular terms we require the slowly evolving amplitudes $A_m(s)$ to satisfy $(n - 1)$ solvability conditions. Specifically, we find that for $m = 1 \ldots (n - 1)$,

$$\frac{dA_m}{ds} = \tau_2(a_2 + ib_2) A_m + (a_3 + ib_3) \hat{A}_m + (a_4 + ib_4) \hat{A}_n A^*_{n-m}.$$  \hspace{1cm} (37)

where the $a_j$’s and $b_j$’s are real constants given by Equations (A13) in the appendix. $A^*$ is the complex conjugate of $A$, and $\hat{A}$ and $\hat{A}$ are nonlinear combinations of the $A_m$ given by Equations (A3) and (A14), respectively. The solvability conditions given by Equations (37) form a system of ODEs that is not easily solved for general $n$ because the definitions for $\hat{A}_m$ and $\hat{A}_n$ are complicated. In fact, for $n = 4$ further analysis becomes intractable. However, we can obtain results and insights from the case $n = 3$ with eigenvectors given by Equations (24). We substitute the polar form of the complex amplitude, $A_m(s) = R_m(s) e^{i\Phi_m(s)}$, into Equations (37) and find that the equations for the amplitudes and phases decouple. Specifically, we find $2(n - 1) = 4$ ODEs for $R_m(s)$ and $\Phi_m(s)$, $m = 1, 2$, where the equations for the $R_m$ are given by

$$\frac{dR_1}{ds} = \tau_2 a_2 R_1 + a_3 R_1^3 + 2a_4 R_1 R_2^2,$$

$$\frac{dR_2}{ds} = \tau_2 a_2 R_2 + a_3 R_2^3 + 2a_4 R_2 R_1^2.$$  \hspace{1cm} (38)

We do not consider the equations for the phases $\Phi_1$ and $\Phi_2$ because they do not affect the amplitudes and, as described below, we look for constant amplitude solutions so that the phases provide only a frequency correction to $\omega_h$.

We are interested in periodic solutions to the original equations. In terms of the slowly evolving amplitudes, this corresponds to the $R_j$ being a constant and, hence, $dR_m/ds = 0$. Thus,
We note that the amplitude is not uniform between variants in this case. More specifically, the amplitude of each variant is the same, while the phases are evenly spaced in Equations (38) become two algebraic equations for \( R_1 \) and \( R_2 \). Recall that \( R_1 \) is the amplitude of the eigenvector \( \vec{v}_1 \), which corresponds to the variants oscillating with phases such that they appear in the order \( 1 \to 2 \to 3 \to 1 \to \ldots \). For \( R_2 \), corresponding to \( \vec{v}_2 \), the variants oscillate in the order \( 1 \to 3 \to 2 \to 1 \to \ldots \). Thus, the general solution is a sum of these two specific solutions. That is, we can rewrite the leading order solution \( y_j^{(1)} \) as a linear combination of the \( n - 1 = 2 \) eigenvectors:

\[
y_j^{(1)} = (A_1 \vec{v}_1^{(y)} + A_2 \vec{v}_2^{(y)}) e^{i\omega_0 t} + \text{c.c.} = (R_1 \vec{v}_1^{(y)} + R_2 \vec{v}_2^{(y)} e^{i\Delta}) e^{i\theta(t)} + \text{c.c.},
\]

where \( \Delta = \Phi_2 - \Phi_1, \theta(t) = \omega_0 t + \Phi_1 \), and \( y_j^{(1)} = (y_1^{(1)}, y_2^{(1)}, y_3^{(1)}) \), whose components are given in Equations (36).

We illustrate two possible AP periodic solutions stemming from the Hopf bifurcation. The first case corresponds to a pure antiphase solution with \( R_1 \neq 0, R_2 = 0 \), while the second is a mix of the two general antiphase states such that \( R_1 = R_2 \). For the first case, substitute \( R_2 = 0 \) and \( dR_1/ds = 0 \) into Equations (38) and (39) to obtain

\[
\vec{y} \sim 2 \sqrt{-\frac{a_2(\tau - \tau_h)}{a_3}} \begin{pmatrix} \cos \left( \theta(t) + \frac{2\pi}{3} \right) \\ \cos \left( \theta(t) + \frac{4\pi}{3} \right) \\ \cos \left( \theta(t) + 0 \right) \end{pmatrix}.
\]

This is the case where the amplitude of each variant is the same, while the phases are evenly spaced by a difference of \( 2\pi/n = 2\pi/3 \). The coefficients \( a_2 \) and \( a_3 \), defined in Equation (A13), are quite complicated to analyse explicitly, so we simplify them by considering \( a \ll 1, b = O(a^{-1/2}) \), and \( c, n = O(1) \). In this case, the amplitude in Equation (40) can be rewritten to obtain the simplified bifurcation equation as follows:

\[
y_{\max} \sim \frac{c}{na} \sqrt{\frac{6}{a}} (\tau - \tau_h) \quad \rightarrow \quad y_{\max} \sim \frac{\phi E_z}{E_z + E_w} \sqrt{\frac{6}{\mu}} (T - T_{ap}),
\]

where the right arrow indicates that we have returned to original time units, using the time-scale factor given in Equations (6). (Note that the coefficient in front of the square root is 1/\( T_{ap} \). However, for clarity in the discussion below, we have left the result in terms of the efficacies.) The amplitude for persistent AP oscillations is \( O(a^{-3/2}) \), which indicates that it grows very quickly with the delay for values near the Hopf bifurcation since \( a \ll 1 \). This explains why the range for \( \tau \) in Figure 5 is so small. In Figure 5(a), the amplitudes given by Equations (40) and (41) are plotted along with numerical continuation [10], and the phases of the evenly spaced AP oscillations can clearly be seen in Figure 6(a). We now consider what influence the two types of IR have on the amplitude of the persistent AP oscillations. For fixed \( E_w \), strengthening the specific IR efficacy, \( E_z \), increases the amplitude of the AP oscillations. In contrast, for fixed \( E_z \), a stronger cross-reactive IR efficacy, \( E_w \), will decrease the amplitude. We have observed that, in general, whether the AP oscillations are small amplitude and nearly harmonic or large amplitude and pulsating, a stronger specific IR relative to the cross-reactive IR increases the amplitude of those observations.

The second case is obtained by substituting \( R_1 = R_2 \) and \( dR_1/ds = 0 \) into Equations (38) and (39), which yields

\[
\vec{y} = 2 \sqrt{-\frac{a_2(\tau - \tau_h)}{a_3 + 2a_4}} \begin{pmatrix} -1 \\ -1 \\ 2 \end{pmatrix} \cos \theta(t).
\]

We note that the amplitude is not uniform between variants in this case. More specifically, the amplitude for \( y_3 \) will be twice as that for \( y_1 \) and \( y_2 \). Also, the phase for \( y_3 \) will be \( \pi \) out of phase
Figure 5. Bifurcating branches of two periodic solutions stemming from the degenerate AP Hopf bifurcation for the (a) uniform-amplitude and (b) dual-amplitude AP oscillations. Numerical continuation [10] is plotted as the dashed curves while the analytical results given by Equations (40) and (42) are shown as the solid curves in (a) and (b), respectively. The result given by Equation (41) is the dotted-dashed curve in (a) and is coincident with the solid curve such that they are indistinguishable. Parameters are the same as those in Figure 3, except that (a) $\mu = 0.035$, $\mu' = 0.25$ and (b) $\mu = 0.025$, $\mu' = 0.15$. Both choices of parameter values lie above the line in Figure 4, and, thus, the Hopf bifurcation occurs at $\tau_{ap}$ as opposed to $\tau_s$.

Figure 6. Periodic solutions associated with the black circles on the bifurcation diagrams in Figure 5: (a) uniform-amplitude AP oscillations corresponding to $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \ldots$ and (b) dual-amplitude AP oscillations corresponding to $1, 2 \rightarrow 3 \rightarrow 1, 2 \ldots$. The squares, circles and crosses are used to indicate the different $j = 1, 2, 3$ variants; thus, in (b) where the circles and crosses are on the same curve, indicating synchronization between variants 2 and 3. The solutions are numerically computed [10] and scaled so that the period is $P = 1$. Because $w_j \sim \sum y_j, j = 1, 2, 3$ and these are AP oscillations, then $w_j \approx 0$. Parameters are the same as those in Figure 5.
with the others. Numerically [10], we find that this AP solution is unstable; we therefore do not offer a simplified form of the amplitude coefficient, as we did for Equation (40). However, in general, as with the previous AP case, a stronger specific IR leads to larger amplitude oscillations. We illustrate the validity of our analysis by plotting the two amplitudes given by Equation (42) along with numerical continuation [10] in Figure 5(b). The periodic solutions along this branch are shown in Figure 6(b).

For both cases, described above, the initial bifurcation is supercritical in that a new branch of periodic solutions overlaps with the unstable branch corresponding to the steady state. However, as shown in Figure 5(a) and (b), the branch of periodic solutions exhibits a turning point at $\tau_b$, where the latter is only slightly larger than $\tau_{ap}$. Continuing on the branch for $\tau < \tau_b$, all of the AP solutions are unstable. In Figure 7, we zoom out on Figure 5(a) and see that there is another turning point at $\tau_c$ such that the branch turns back to the right. In general, the delay times $\tau_c$ and $\tau_b$ are the critical values separating different asymptotic states as we will describe below.

In Figures 8 and 9, we show the time evolution [30] for initial conditions close to and far from the steady state, respectively, for different values of the delay. We begin by describing Figure 8 for small initial conditions. In Figure 8(a), the delay is less than the Hopf bifurcation value ($\tau < \tau_{ap}$)
such that the uniform steady state is asymptotically stable and the initial perturbation decays to zero. In Figure 8(b), the delay is greater than that at the Hopf bifurcation point but less than that at the turning point such that $\tau_{ap} < \tau < \tau_b$ (Figure 5(a)). In this case, the uniform steady state is unstable and the system asymptotes to the periodic AP oscillations. For $\tau > \tau_b$, the steady state is unstable and the small-amplitude AP solutions no longer exist. For these larger values of the delay, the system exhibits complex large-amplitude pulsations (Figure 9(c)).

In Figure 9, we consider the evolution of large initial perturbations from the uniform steady state. Figure 9(a) shows the case when $\tau < \tau_c$ and the uniform steady state is the only stable set; thus, all initial perturbations decay to zero. At the other extreme when $\tau > \tau_b$ the uniform steady state is unstable and the system exhibits complex large-amplitude pulsations, which we assume to be chaotic (Figure 9(c)). For values of delay in the interval $\tau_c < \tau < \tau_b$, either the steady state or small amplitude oscillations are stable. However, as shown in Figure 9(b), the transient oscillations leading to these states exhibit the complex pulsating oscillations similar to those for large delay when $\tau > \tau_b$.

For all initial conditions, we have tested, the system eventually settles to one of the simpler limit sets (uniform steady state or the AP oscillations), but that can take a significant amount time. That said, we have only considered initial histories that are constant; we have not attempted a detailed analysis to determine whether in fact there is a second stable limit set for intermediate values of the delay, and we have not tried to more precisely define the value of the delay when the transient complex pulsations transition to persistent complex pulsations. Thus, it is possible that there is bi-stability between the simple limit sets and some more complex attractor, but we have not observed it.

Biologically, two critical values of the delay, namely $\tau_c$ and $\tau_{ap}$, serve as thresholds for the different behaviours mentioned above. If the host’s IR is regulated by the delayed parasite with a time lag less than $\tau_c$, then oscillations will not persist but decay to the endemic steady state following a few recurring peaks of the parasite population. This is consistent with the host acquiring and maintaining immunity to the disease. In contrast, for an immune deficient host such that the time lag is greater than $\tau_c$, persistent peaks of parasite load are likely if $\tau < \tau_{ap}$ and inevitable if $\tau > \tau_{ap}$. In the latter case, the host cannot acquire protective immunity due to the time lag between changes in parasite load and stimulation of corresponding immune effectors. In the case of the former, the transient may be so long that from the point of view of the patient, the disease is effectively permanent.

5. Discussion

Antigenic variation in Pf manifested as sequential dominance of the variants is a survival strategy. In considering Equations (1) with global coupling in which each variant shares minor epitopes,
we are able to make comparisons between synchronous and asynchronous oscillations of the parasite load and IR for each variant. In particular, the asynchronous oscillations can be completely described in terms of antiphase oscillations, where the symmetry of the latter allows for analytical description. We preface the rest of our discussion by again emphasizing that we considered the special case of global coupling, whereas a more complex coupling topology could make our observations more nuanced.

The first part of our analysis was to rescale the state variables and parameters in Section 2 to obtain Equations (7). The main advantage of the rescaled model, particularly for a phenomenological model where specific values of the parameters are difficult to obtain, is that it allows us to focus on ratios of the original rate constants. For example, while in the figure captions, we quote values for the original parameters defined in Equations (1), we were simulating the non-dimensional model, Equations (7), that use the ratios \( \frac{a}{b} \) and \( c \). Thus, our results can be considered more widely applicable to parameter values leading to similar non-dimensional parameter ratios.

In the case of an instantaneous IR, we find that the decay rate of the SYNC oscillations is proportional to the decay of the cross-reactive IR, while the decay of AP oscillations is proportional to the decay of the variant-specific IR. A fundamental assumption built into Equations (1) is that the former decays much faster than the latter. Thus, in general, synchronous oscillations will decay faster than asynchronous oscillations, making the observation of the latter more likely. Increasing the efficacy of the variant-specific IR relative to the cross-reactive IR increases the frequency of AP oscillations but decreases the frequency of the SYNC oscillations. In addition, the ‘clinical’ frequency of asynchronous oscillations will be higher than that of a single variant as the patient responds to each oscillating variant in sequence. Thus, Equations (1) allows for increased survival of the parasite via sequential dominance not only by decreasing the decay rate of asynchronous oscillations, but also by forcing the host’s IR to respond more rapidly.

The behaviour of the cross-reactive IR variable \( w_j \) is distinctly different between the SYNC and AP oscillations because \( \frac{dw_j}{dt} \sim \sum_{j=1}^{n} y_j \). For AP oscillations the sum is identically zero. Thus, in terms of the original variable \( W_j \), the SYNC oscillations will cause \( W_j \) to oscillate with non-zero amplitude and at the same frequency as \( Y_j \). However, in the case of AP oscillations, \( W_j \) will be at approximately the uniform steady-state value. Thus, we have the prediction that asynchronous oscillations and sequential dominance tend to decrease the net activity of the cross-reactive IR.

In the case of a delayed IR, we see that only a small delay is necessary to cause persistent oscillations that do not decay. In terms of the original parameters, the value of the delay for an Hopf bifurcation is given by Equation (29). For a long-lived variant-specific IR relative to the cross-reactive IR, and all other processes being relatively equal, then the efficacy of the variant-specific IR \( E_z \) will be much larger than that of the cross-reactive IR, \( E_w \). The value of a delay at the Hopf bifurcation is then \( \tau_{ab} \sim 1/\phi \). Thus, the more aggressive the parasite is, the more susceptible the host will be to experiencing persistent oscillations. Further, even before the delay is increased to the Hopf bifurcation value, there can be long-lived, large-amplitude complex pulsations that appear to be a chaotic transient. For larger delays, the pulsations persist and do not decay. From a weakly nonlinear analysis of AP oscillations, we can quantify how the amplitude of oscillations depends on the efficacies of the IR. We find that a stronger variant-specific IR relative to the cross-reactive IR increases the amplitude of the oscillations. Numerically, we find that this relationship holds true even when the amplitudes are so large that our analytical result is not necessarily asymptotically valid.

Introduction of the delayed IR also serves as a useful probe into the the sensitivity of the system to either the SYNC or AP oscillations. Without delay, we observed that the AP oscillations decay more slowly and have a higher frequency. With delay, we observe that increasing the efficacy of the variant-specific IR relative to the cross-reactive IR increases the sensitivity of the system
to AP or asynchronous oscillations. This is consistent with the generic behaviour observed in coupled oscillators, where strong coupling tends to synchronize, while for weak coupling, the oscillators are more apt to behave independently. Thus, some coupling among the variants is necessary because without it a variant with an initially very low population will stay small; the coupling will allow small population variants to increase as the previously high-population variants weaken the host. However, for long-term survival of the parasite, the coupling should be weak enough to avoid absolute synchronization, enabling the parasite to exhibit sequential dominance.

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Appendix. Weakly nonlinear analysis using the method of multiple scales

In this section, we supplement the analysis described in Section 4.2 with additional details. The leading order solution to Equation (35) is a linear combination of the AP eigenvectors and can thus be written as

\[ y_j^{(1)} = \sum_{m=1}^{n-1} A_m v_{jm} e^{i\omega h t} + \text{c.c.} + \text{e.d.t.} \]

\[ x_j^{(1)} = -i\omega_h \sum_{m=1}^{n-1} A_m v_{jm} e^{i\omega h t} + \text{c.c.} + \text{e.d.t.}, \quad (A1) \]

where c.c. denotes the complex conjugate and e.d.t. represents exponentially decaying terms. Because the parameters are defined so that \( \tau_h = \tau_{ap} \), all eigenvalues except for the repeated \( \lambda_{ap} \) will have negative real parts and are therefore neglected in the rest of this analysis.

The \( O(\eta^3) \) problem can be written as

\[ \frac{\partial Y^{(2)}}{\partial t} = J|_{\tau_h} \cdot Y^{(2)} + i\omega_h Ge^{2i\omega_h t}, \quad (A2) \]

where \( Y^{(2)} = (y_1^{(2)}, x_1^{(2)}, w_1^{(2)}, \ldots, y_n^{(2)}, x_n^{(2)}, w_n^{(2)}) \) and \( J|_{\tau_h} \) is the Jacobian matrix given by Equation (10) and evaluated at \( \tau = \tau_h \). The \( y \) components of \( G = (G_1, 0, 0, \ldots, G_n, 0, 0) \) are generated by the nonlinearity, \( x_j^{(1)} y_j^{(1)} \), and are given by

\[ G_j = \left( \sum_{m=1}^{n-1} \tilde{A}_m v_{jm} \right)^2 \equiv \sum_{m=1}^{n-1} \tilde{A}_m v_{jm}, \quad (A3) \]

where \( \tilde{A}_m \) is defined to be the complex coefficients of \( v_{jm} \) attained when expanding \( G_j \). We mention here that when \( m = n \), \( \tilde{A}_n \) is the coefficient associated with \( v_{jm} \), which is simply number 1 because \( \tilde{v}_n \) is a vector of all ones corresponding to SYNC solutions. The solution, \( Y^{(2)} \), will consist of a homogeneous part and a particular part. However, for this problem, we find that it is only the particular part that will give rise to secular terms at \( O(\eta^3) \), and so we focus only on it. We find that

\[ y_{part}^{(2)} = \tilde{P} e^{2i\omega_h t} + \text{c.c.} = (P_1^{(y)}, P_1^{(x)}, P_1^{(w)}, \ldots, P_n^{(y)}, P_n^{(x)}, P_n^{(w)}) e^{2i\omega_h t} + \text{c.c.} \]

\[ p_j^{(y)} = p_1 \sum_{m=1}^{n-1} \tilde{A}_m v_{jm} + p_2 \tilde{A}_n \]

\[ p_j^{(x)} = i\omega_h (1 - 2p_1) \sum_{m=1}^{n-1} \tilde{A}_m v_{jm} + i\omega_h (1 - 2p_2) \tilde{A}_n \]

\[ p_j^{(w)} = p_3 \tilde{A}_n, \quad (A4) \]
where $p_1$, $p_2$, and $p_3$ are constants defined by

\[
p_1 = \frac{d_2}{F_{ap}(2\omega_h, \tau_h)}
\]

\[
p_2 = \frac{d_2}{F_{ap}(2\omega_h, \tau_h) + nd_1}
\]

\[
p_3 = \frac{d_2e^{-i2\omega_h \tau_h}}{(2\omega_h + ab)(F_{ap}(2\omega_h, \tau_h) + nd_1)}
\]

\[
d_1 = \frac{1}{n}e^{-i2\omega_h \tau_h} \left[ 1 + \frac{a(1-b)}{2i\omega_h + ab} \right]
\]

\[
d_2 = \frac{-2\omega^2_h}{n} + i\omega_h.
\]

(A5)

We note that since $w_j^{(1)} = 0$ from Equations (36), the leading-order approximation for $w$ is obtained here at $O(\eta^2)$. Thus, the $w_j$'s should be an order of magnitude smaller than the $y_j$'s or $x_j$'s. Also, because the expression for $P_w^{(n)}$ is independent of $j$, we confirm that the $w_j$'s are synchronous as shown in Figure 6.

The $O(\eta^3)$ problem can be written as

\[
\frac{\partial Y^{(3)}}{\partial t} + \frac{\partial Y^{(1)}}{\partial s} = J_1 |_{\tau_h} \cdot Y^{(3)} + \Psi_D + \Psi_{NL},
\]

(A6)

where $\Psi_D$ and $\Psi_{NL}$ are the $O(\eta^3)$ terms from the Taylor expansion of the delayed term $y_j |_{\tau}$ and the product $x_j y_j$, respectively. With explanations to follow, we define them here as

\[
\Psi_{NL} = \left( \begin{array}{cccc}
-x_1^{(1)} y_1^{(2)} - x_1^{(2)} y_1^{(1)} & 0 & \cdots & 0 \\
0 & 0 & \cdots & 0 \\
\vdots & \vdots & \ddots & \vdots \\
-x_n^{(1)} y_n^{(2)} - x_n^{(2)} y_n^{(1)} & 0 & \cdots & 0 \\
\end{array} \right), \quad \Psi_D = \left( \begin{array}{cccc}
0 & \cdots & 0 & 0 \\
-c \frac{n}{n} \left( \frac{\partial y_j^{(1)}}{\partial t} \right) |_{\tau_h} + \tau_h \frac{\partial y_j^{(1)}}{\partial s} |_{\tau_h} & 0 & \cdots & 0 \\
0 & \cdots & 0 & 0 \\
0 & \cdots & 0 & 0 \\
\end{array} \right),
\]

(A7)

where the superscript represents the order in the perturbation analysis and the subscript indicates the variant or oscillator. Zeroes occur in the second and third rows of $\Psi_{NL}$ since the nonlinear term occurs only in the equation for $y_j$ in Equations (7). The definition of $\Psi_D$ requires more explanation. Recall Equation (34), where we expanded the delayed term, $y_j(t-\tau, s-\eta^2 \tau)$, using a Taylor series to obtain

\[
y_j |_{\tau} = y_j |_{\tau_h} - \eta^2 \left[ \tau_2 \frac{\partial y_j}{\partial t} |_{\tau_h} + \tau_h \frac{\partial y_j}{\partial s} |_{\tau_h} \right] + \cdots.
\]

(A8)

Note that the equations for $x_j$ and $w_j$ in Equations (7) contain the sum over all variants of $y_j |_{\tau}$. However, the $O(\eta^3)$ part of this sum is ignored since it simplifies to zero in the following way:

\[
O(\eta^3) \text{ part of } \sum_{j=1}^{n} y_j |_{\tau} \sim \eta^2 \frac{1}{n} \sum_{j=1}^{n} \left[ \tau_2 \frac{\partial y_j}{\partial t} |_{\tau_h} + \tau_h \frac{\partial y_j}{\partial s} |_{\tau_h} \right]
\]

\[
= \eta^2 \frac{1}{n} \sum_{j=1}^{n} \left[ \tau_2 \eta \frac{\partial y_j^{(1)}}{\partial t} |_{\tau_h} + \tau_h \eta \frac{\partial y_j^{(1)}}{\partial s} |_{\tau_h} \right]
\]

\[
= \eta^3 \frac{1}{n} \sum_{j=1}^{n} \left[ \tau_2 \frac{\partial}{\partial t} \sum_{m=1}^{n-1} A_m v_{jm} e^{i\omega_h (t-\tau_h)} + \tau_h \frac{\partial}{\partial s} \sum_{m=1}^{n-1} A_m v_{jm} e^{i\omega_h (t-\tau_h)} \right]
\]

where $\sum_{j=1}^{n} y_j |_{\tau}$
\[ n \eta e^{-i \omega h \tau_h} \left[ \sum_{j=1}^{n-1} (i \omega_h) A_m v_{jm} + \tau_h \sum_{m=1}^{n-1} \frac{\partial A_m}{\partial s} v_{jm} \right] e^{i \omega h t} \]

\[ = n \eta e^{-i \omega h \tau_h} \left[ \sum_{m=1}^{n-1} (i \omega_h) A_m \sum_{j=1}^{n} v_{jm} + \tau_h \sum_{m=1}^{n-1} \frac{\partial A_m}{\partial s} \sum_{j=1}^{n} v_{jm} \right] e^{i \omega h t} \]

\[ = 0 \]

since \( \sum_{j=1}^{n} v_{jm} = 0 \) by Equation (22). Thus, the delayed summation terms in the equations for \( x_j \) and \( w_j \) (see Equations (7)) have no contribution at \( O(\eta^3) \) and are neglected in defining \( \Psi_D \), leaving only the contribution from the non-summed term, \( (c/n)y_j \), in the \( x_j \) equation.

The homogeneous solution to Equation (A6) would contain secular terms \( \sim te^{i \omega h t} \), which become unbounded as \( t \rightarrow \infty \). We avoid this by using the Fredholm alternative, which requires us to first solve the homogeneous adjoint problem which is

\[ -i \omega_h Y_{HA} = (J|\tau_h)^* \cdot Y_{HA}, \quad (A9) \]

where \((J|\tau_h)^*\) denotes the conjugate transpose of the Jacobian matrix, \( J|\tau_h \). The solution, \( Y_{HA} = (y_{H1}, x_{H1}, w_{H1}, \ldots, y_{Hn}, x_{Hn}, w_{Hn}) \) to Equation (A9) is given by

\[ y_{Hj} = v_{jm} \]

\[ x_{Hj} = \frac{1}{i \omega_h - a} y_{Hj} \]

\[ w_{Hj} = \frac{-a(1 - b)}{(i \omega_h - a)(i \omega_h - ab)} y_{Hj}. \quad (A10) \]

where \( v_{jm} \) is the \( j \)th entry of some AP eigenvector, \( m = 1, \ldots, n - 1 \). That is, the homogeneous adjoint solution can be defined in terms of any of the \( n - 1 \) degenerate eigenvectors, which are mutually orthogonal. We eliminate secular terms by setting the following dot product to zero:

\[ Y_{HA}^* \cdot \left( \Psi_D + \Psi_{NL} - \frac{\partial Y^{(1)}}{\partial s} \right) = 0. \quad (A11) \]

Since the homogeneous adjoint solution, Equation (A10), can be defined in terms of any of the \( n - 1 \) eigenvectors, we obtain \( n - 1 \) separate solvability conditions that, when taken together, form a system of ODEs that determine the behaviour of the complex amplitude, \( A_m(s) \). For each, \( m = 1, \ldots, n - 1 \), we have

\[ C_1 \frac{dA_m}{ds} = C_2 \tau_2 A_m + C_3 \hat{A}_m + C_4 \tilde{A}_n A_{n-m}^* - m, \quad (A12) \]

where complex constants are given by

\[ C_1 = 2i \omega_h + a - \frac{c}{n} e^{-i \omega h \tau_h} \]

\[ C_2 = i \omega_h \frac{c}{n} e^{-i \omega h \tau_h} \]

\[ C_3 = \left( \omega_h^2 - i \omega_h a \right) \left( 1 - \frac{d_2}{F_{ap}(2i \omega_h, \tau_h)} \right) \]

\[ C_4 = n(\omega_h^2 - i \omega_h a) \left( 1 - \frac{d_2}{F_{ap}(2i \omega_h, \tau_h) + nd_4} \right) \]

\[ a_2 + ib_2 = \frac{C_2}{C_1} \]

\[ a_3 + ib_3 = \frac{C_3}{C_1} \]

\[ a_4 + ib_4 = \frac{C_4}{C_1} \]

(A13)

and \( \hat{A}_j \) is defined by expanding the following product:

\[ \left( \sum_{m=1}^{n-1} \hat{A}_m v_{jm} \right) \left( \sum_{m=1}^{n-1} A_m^* v_{jm} \right) = \sum_{k=1}^{n} \hat{A}_j v_{jk}. \quad (A14) \]

Equation (A12) appears as Equation (34) in the main text.