Bifurcation, stability, and cluster formation of multi-strain infection models

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Abstract Clustering behaviours have been found in numerous multi-strain transmission models. Numerical solutions of these models have shown that steady-states, periodic, or even chaotic motions can be self-organized into clusters. Such clustering behaviours are not a priori expected. It has been proposed that the cross-protection from multiple strains of pathogens is responsible for the clustering phenomenon. In this paper, we show that the steady-state clusterings in existing models can be analytically predicted. The clusterings occur via semi-simple double zero bifurcation from the quotient networks of the models and the patterns which follow can be predicted through the stability analysis of the bifurcation. We calculate the stability criteria for the clustering patterns and show that some patterns are inherently unstable. Finally, the biological implications of these results are discussed.

Keywords Multi-strain infection model · Semi-simple double zero bifurcation · Clustering · Stability

Mathematics Subject Classification (2000) 34C23 · 37G10 · 62P10

1 Introduction

Pathogens, such as viruses and parasites, are detected by the immune system via chemical on their surface. Based on the chemical detected, the immune system sends specific antibodies to clear away the pathogen (Coico and Sunshine 2009). Some pathogens can present themselves as many different variants in order to avoid detection,

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prolong infection, and infect another host. Many diseases, such as AIDS (Nowak et al. 1995a), malaria (Recker et al. 2004), dengue fever (Recker et al. 2009), and the common flu (Omori et al. 2010) are caused by pathogens that present themselves with many subtypes.

Each strain or subtype of the pathogen elicits specific immune response from the immune system. Some of these strains share epitopes, so they can also incite immune responses that will target multiple subtypes. Immune responses that target multiple types of such responses are called *cross-protective* or *cross-reactive*. If the host is infected by one particular subtype, it may be partially protected against another variant. Scientists have devised various within-host (Nowak et al. 1995a; Nowak et al. 1995b; Gjini et al. 2010) and epidemiological models (Gog and Grenfell 2002; Omori et al. 2010) to better understand the underlying dynamics of the multi-strain infections. Many of these models separate different strains into subsystems of differential equations that are coupled based on the biological situations (Gupta et al. 1998; Recker and Gupta 2005). These aforementioned models may be difficult to study analytically due to the high number of strains, and even higher number of differential equations involved, as well as the complex dynamics arising from the nonlinear couplings.

Given the difficulty in analyzing these models, different methods for bifurcation and stability analyses of them have been discussed in various papers (Dawes and Gog 2002; Guo et al. 2008). In similar fashion to the aforementioned papers, we will show that the groupoid formalism, established by Golubitsky et al. (2005), is an apt tool for analyzing multi-strain epidemiology models. This method is an evolution of the earlier symmetry method and this newer method can analyze systems that do not have symmetry present (Golubitsky and Stewart 2006). The use of the symmetry method for various topics in mathematical biology has been well established (Golubitsky et al. 1999; Buono and Golubitsky 2001; Buono and Palacios 2004) and the groupoid formalism has been used to study a multi-strain *in vivo* model of *Plasmodium falciparum* (Chan and Yu 2012). Similar to this paper, Chan and Yu (2012) also studied local bifurcations of a multi-strain model, but they did not discuss the use of center manifold reduction in combination with the groupoid formalism.

To demonstrate the application of the groupoid formalism to multi-strain epidemiological models, we will analyze the local bifurcations in two models. The first model by Gupta et al. (1998) studied the effects of cross-immunity in multi-strain epidemiology and there are three compartments describing the dynamics pertaining to each strain. For each strain *i*, there is a portion of the population (z_i) which is immune and there is another portion which is infectious (y_i) . Furthermore, there is another portion of the population (w_i) which is immune to any strain *j* that shares allele with strain *i*. In this model, the dynamics particular to each strain are described by

$$\dot{z}_{i} = \lambda_{i}(1 - z_{i}) - \mu z_{i},
\dot{w}_{i} = (1 - w_{i}) \sum_{j \sim i} \lambda_{j} - \mu w_{i},
\dot{y}_{i} = \lambda_{i} \left((1 - w_{i}) + (1 - \gamma)(w_{i} - z_{i}) \right) - \sigma y_{i},$$
(1)

where $\lambda_i = \beta y_i$ is the force of infection term and *j* is indexed over strains which share any allele with strain *i*, including *i* itself. As noted by Gupta et al. (1998), the

behaviour of the model is largely unaffected by the exact functional form of the force of infection term λ_i , so we choose the same form used by Recker and Gupta (2005). We use the parameter β to represent the factors affecting the transmission of strain *i*. As for the other parameters, $1/\mu$ and $1/\sigma$ are respectively the average life expectancy of the host and the average duration of the infections. The strength of cross-protection as a result of the share allele is measured by the parameter γ . Hence, the probability of transmission by any strain *j* is reduced by a factor of $(1 - \gamma)$.

The second model by Recker and Gupta (2005) may be considered as a continuation of other multi-strain multi-lcous epidemiology models, such as the one by Gupta et al. (1998) and another by Ferguson and Andreasen (2002). Specifically, the model by Recker and Gupta (2005) studied the effect of the number of variants shared between different strains on strain-structure. With z_i , w_i , and y_i similarly defined as in model (1), another compartment is added. The new class, v_i , denotes the portion of the population that are immune to strains that share more than one allele with strain *i*. For this model, the system describing the dynamics of each strain *i* has the form

$$\begin{aligned} \dot{z}_{i} &= \lambda_{i}(1 - z_{i}) - \mu z_{i}, \\ \dot{w}_{i} &= (1 - w_{i}) \sum_{j \sim i} \lambda_{j} - \mu w_{i}, \\ \dot{v}_{i} &= (1 - v_{i}) \sum_{k \sim i} \lambda_{k} - \mu v_{i}, \\ \dot{y}_{i} &= \lambda_{i} \left((1 - w_{i}) + (1 - \gamma_{1})(w_{i} - z_{i}) + (1 - \gamma_{2})(v_{i} - z_{i})) - \sigma y_{i}, \end{aligned}$$

$$(2)$$

where $\lambda_i = \beta_i y_i$ is the force of infection, $j \sim i$ indicates the strains which share alleles with strain *i*, and $k \sim i$ indicates the strains which share more than one allele with strain *i*.

As noticed by Calvez et al. (2005), the solutions of strains in the previously mentioned models and other related models (Gupta et al. 1996; Gupta and Galvani 1999) may form clusters of partially synchronized solutions. It has been shown numerically that solutions within each cluster may synchronize as steady-state, periodic, or even chaotic solutions. In this paper, we will show that the clustering behaviour found in the model by Gupta et al. (1998) as well as the one by Recker and Gupta (2005) can be analytically explained through the groupoid formalism. Specifically, the steadystate clusterings are formed via semi-simple double zero bifurcation of their 2-colour quotient networks. For each of the models, we assume the subsystems describing the dynamics of the strains have the same parameter values.

The rest of the paper is organized as follows. In Sect. 2, we outline the general approach in finding and understanding the related bifurcation and clustering patterns resulting from the bifurcation. Specific calculations related to each model are illustrated in Sect. 3. In Sect. 4, we numerically demonstrate the analytic results found in Sect. 3. Finally, conclusions and discussions are given in Sect. 5.

2 General approach

As mentioned in Sect. 1, we will show analytically that the clustering solutions of some multi-strain infection models are the results of semi-simple double zero bifurcation of

their 2-colour quotient networks. Given that the general approach to both models is the same, we provide our approach to the problem in this section and leave the specific details to each model in Sect. 3.

The steps presented in Sects. 2.1 and 2.2 are appropriate for any epidemiological models that can be described by the groupoid formalism. In Sect. 2.3, we restricted the scope of this paper to the general 2-colour case of the models by Gupta et al. (1998) and Recker and Gupta (2005), but one may extend the analysis to more complicated colouring patterns as necessary. Our discussions in Sects. 2.4 and 2.5 are specific to analyzing the semi-simple double zero bifurcations in the aforementioned general 2-colour quotient networks and one may adapt these steps to analyze other types of bifurcations.

2.1 Coupled cell network representation

The first step in this analysis is to represent the models of Gupta et al. (1998) and Recker and Gupta (2005) as coupled cell networks by the groupoid formalism introduced by Stewart et al. (2003) and refined by Golubitsky et al. (2005). This method is a systematic way to represent systems of coupled differential equations using directed graphs and analyze synchronization patterns resulting from bifurcations. Each node in the directed graph represents a specific set of differential equations. Shapes of the nodes denote specific set of differential equations, so identical sets of differential equations are represented in the graph with nodes of the same shape. In the two models, the dynamics related to each strain is described by system (1) or (2). In each model, all strains have the same parameter values, so all the nodes in the graph have the same shape.

Similarly, each directed edge, or arrow, in the graph represents the coupling between different sets of differential equations. In our cases, two sets of differential equations are coupled if they share alleles. Based on the model by Gupta et al. (1998), there is only one type of coupling terms, so there would be one type of arrows. As for the model by Recker and Gupta (2005), there are different types of couplings based on the number of shared alleles between strains. In this case, two different types of edges represent different couplings.

Having defined the sets of nodes and edges for each of the models, we now represent these models as coupled cell networks. For example, if we let each node in Fig. 1 represent the differential equations of system (1), then this directed graph gives a coupled cell representation of the 2 locus–2 allele form of the model by Gupta et al. (1998). As mentioned before, each strain has identical parameters, so all of them are represented with a circle in the digraph. Given that only one type of couplings is present in the system, there is only one type of arrows. For another example, the 3 locus–2 allele form of the model from Recker and Gupta (2005) is shown in Fig. 2.

Again, based on the identical parameter assumption, we only have one type of nodes in this figure. As we can see from system (2), there are two types of couplings in this model, so correspondingly, we have two different types of edges in its coupled cell network.

We want to point out that the directed graph of the coupled cell network is conceptually similar to the idea of strain space as discussed by Ferguson and Galvani (2003).

Fig. 1 The directed graph representing the coupled cell network of the 2 locus–2 allele form of the model by Gupta et al. (1998): each *node* represents the set of differential equations in system (1) and each *arrow* represents the coupling between strains that share allele; alleles $\{a, b\}$ are used at the first locus and alleles $\{x, y\}$ at the second locus

Fig. 2 The three-dimensional directed graph representing the coupled cell network of the 3 locus-2 allele form of the model by Recker and Gupta (2005): each node represents the set of differential equations in system (2); a dashed arrow represents the coupling between two strains when they only share one allele and a solid arrow represents the coupling between two strains when they share more than one allele; allele sets $\{a, b\}, \{m, n\}, \text{ and } \{x, y\}$ are used respectively at the first, second, and third locus; double headed arrows minimizing the number of arrow drawn, are used to indicate that there is an arrow originating from each node of the pair



Various authors (Gog and Swinton 2002; Gog and Grenfell 2002; Calvez et al. 2005) have used undirected graphs to represent the relationship between the strains in their models.

2.2 Possible 2-colouring patterns

To study the possible clustering formations after bifurcation, the concept of balanced colouring in a coupled cell network is needed (Golubitsky et al. 2005). We need a way to indicate patterns of synchrony and this can be achieved rigorously using equivalence relations to partition the nodes of the system. We can partition the nodes in the directed graph according to some equivalence relation \bowtie . Conversely, any partition of the nodes will also form an equivalence relation. If all the nodes of the same class receive the same input sets, then such colouring is *balanced*.

We can graphically check whether a particular equivalence relation, \bowtie , is balanced. In the directed graph, nodes are of the same colour if they are in the same \bowtie -equivalence class. Then, we colour the tails of these nodes using the same colour as well. An



Fig. 3 Three possible different colouring patterns for the 2 locus–2 allele form of the model by Gupta et al. (1998), where *black* and *white* represent the two possible classes in each of the coupled cell network. **a** In this case, each black node receives one input from a white node and one input from a black node. Similarly, each white node receives two inputs from white nodes, but no input from a black node. **b** In this case, each black node receives two inputs from white nodes, but no input from a black node. Similarly, each white node receives two inputs from black nodes and no input from a white node. **c** In this case, there are three black nodes. Node bx receives inputs only from other black nodes. Nodes *ax* and *by* receive inputs from black and white nodes.

equivalence relation, \bowtie , is balanced if and only if the inputs of the nodes in the same class have isomorphic inputs, i.e. same number of edges that have the same colour. A colouring pattern with *k* colours is a *k*-colouring of the system. To illustrate balanced colouring, we have provided a few different 2-colourings of the aforementioned 2 locus–2 allele example in Fig. 3. We can see that the networks in Fig. 3a and b are balanced while the network in Fig. 3c is not.

The models by Gupta et al. (1998) and Recker and Gupta (2005) can accommodate finite number of strains of pathogens in the system. Since each node represents the dynamics generated by one strain of the pathogen, there would be the same number of nodes in the coupled cell network. As such, it will not be feasible to study all balanced k-colourings for all the possible m locus—n allele forms of the multi-strain models. Instead of studying all possible k-colourings, we restrict the scope of this study to only the possible balanced 2-colourings.

2.3 Quotient networks

For the general *m* locus–*n* allele form of the multi-strain model, there would be n^m strains. Suppose *k* is the number of differential equations in the system required to describe the dynamics of each strain. To analyze possible bifurcations of the model, we would have to deal with a kn^m -dimensional system. Instead of directly dealing with the potentially high-dimensional system, we can use the balanced colourings of the coupled cell network to reduce the system to its quotient network and analyze a less complicated network (Golubitsky et al. 2005). Given that we are only interested in 2-colourings of the system, we only need to study a 2k-dimensional system after the quotient reduction.

From any balanced 2-colourings, we can always reduce the systems based on models to the quotient networks shown in Figs. 4 and 5. Each balanced colouring induces



Fig. 4 The directed graph representing the general quotient network for all balanced 2-colourings of the model by Gupta et al. (1998): The topological parameters, s_i , indicating the number of self-connections for each class, and similarly, the topological parameters, m_i , indicating the number of connections received from the other class, for $i \in \{1, 2\}$



Fig. 5 The directed graph representing the general quotient network for all balanced 2-colourings of the model by Recker and Gupta (2005): The parameters, s_{i1} and s_{i2} , indicating respectively the number of *dashed* and *solid* self-connections received for each class, and similarly, the parameter, m_{i1} and m_{i2} indicating respectively the number of *dashed* and *solid* connections received from the other class

a canonical quotient network. The nodes of the quotient network represent the equivalence classes in a balanced *interception*-equivalence relation. Because we are interested in the 2-colourings, there would be two nodes in the quotient network. From the balanced colouring, we pick one node from each colour class to define the parameters of the quotient network. Given that the nodes of the same equivalence class receive isomorphic inputs, the choice of nodes for each class does not change the resulting quotient network. For each equivalence class, we define inputs received by the nodes representing this class in the quotient network to be identical to the inputs received by the node we selected in the original network.

To reduce the complexity of the digraph of the quotient network, we denote the number of inputs on the digraph of the quotient network with their topological parameters shown in the figures. Details for constructing quotient networks from balanced *k*-colourings can be found in the works by Golubitsky et al. (2005) and Golubitsky and Stewart (2006). For example, the colouring pattern in Fig. 3a corresponds to quotient parameters $m_i = 1$ and $s_i = 1$; similarly, the colouring pattern in Fig. 3b corresponds to quotient parameters $m_i = 2$ and $s_i = 0$.

2.4 The semi-simple double zero bifurcation

After forming the coupled cell networks and quotient reductions, we can now begin the dynamic analysis. For each of these models, we show that a semi-simple double zero bifurcation occurs from the trivial equilibrium of the quotient network. At a locally stable equilibrium, a bifurcation occurs when some of the eigenvalues with negative

real part cross smoothly from the left side of the complex plane into the right side due to changes in the system parameters. Hence, we must understand the eigenvalue structure of the Jacobian in order to understand the type of bifurcation occurring.

Suppose spec (**J**) = { $\sigma_1, ..., \sigma_n$ }, then σ_i is a repeated eigenvalue for **J** if there is a *j*, such that $\sigma_i = \sigma_j$ and $i \neq j$. Let κ_i , the *algebraic multiplicity*, be the number of times σ_i is repeated and let η_i , the *geometric multiplicity*, be the number of linearly independent eigenvectors associated with σ_i . By the definition of eigenvalues, we must have $\kappa_i \geq \eta_i$. An eigenvalue is called *semi-simple* when $\kappa_i = \eta_i$. Thus, a *semi-simple double zero bifurcation* refers to the bifurcation of a twice repeated zero eigenvalue associated with two linearly independent eigenvectors.

2.5 Jordan canonical form and center manifold reduction

With a semi-simple double zero bifurcation, we can further simplify the system by transferring it to its Jordan canonical form. To start, we perform a linear change of coordinates so that the bifurcation occurs at $(\mathbf{x}, \tilde{\beta})^T = (\mathbf{0}, 0)^T \in \mathbb{R}^{2k+1}$, where \mathbf{x} is the generalized coordinates of the system and $\tilde{\beta}$ is the bifurcation parameter.

Let n_c and n_s respectively be the numbers of eigenvalues with zero real-part and negative real-part of the Jacobian. For this type of bifurcation, there would be two eigenvalues with zero real part and 2k - 2 eigenvalues with negative real part. Using the eigenvectors of J to form a transformation matrix, the system can be rewritten in block matrix form as

$$\dot{\mathbf{x}}_c = \mathbf{A}\mathbf{x}_c + \mathbf{f}(\mathbf{x}_c, \mathbf{x}_s) \dot{\mathbf{x}}_s = \mathbf{B}\mathbf{x}_s + \mathbf{g}(\mathbf{x}_c, \mathbf{x}_s)$$
 ($\mathbf{x}_c, \mathbf{x}_s$) $\in \mathbb{R}^2 \times \mathbb{R}^{2k-2}$, (3)

where $\mathbf{A} \in \mathbb{R}^{2\times 2}$ and $\mathbf{B} \in \mathbb{R}^{(2k-2)\times(2k-2)}$. With the eigenvalues having zero realpart, the Centre Manifold Theorem guarantees that there exists a smooth manifold $W_c = \{(\mathbf{x}_c, \mathbf{x}_s) | \mathbf{x}_s = \mathbf{h}(\mathbf{x}_c)\}$ near the equilibrium point such that the local behaviour in the centre direction of the system is qualitatively the same as that on the manifold (Wiggins 2003). The 2k - 2 nonessential generalized coordinates are represented on the centre manifold as

$$x_{i+2} = h_i = a_i x_1^2 + b_i x_2^2 + c_i \tilde{\beta}^2 + d_i x_1 x_2 + e_i x_1 \tilde{\beta} + f_i x_2 \tilde{\beta} + \cdots$$

where $i \in \{1, ..., 2k - 2\}$.

By differentiating $\mathbf{x}_s = \mathbf{h}(\mathbf{x}_c)$, we get $\dot{\mathbf{x}}_s = D\mathbf{h}(\mathbf{x}_c)\dot{\mathbf{x}}_c$. Substituting the equations in (3) into the previous identity and rearranging the equation, we get

$$D\mathbf{h}(\mathbf{x}_c)[\mathbf{A}\mathbf{x}_c + \mathbf{f}(\mathbf{x}_c, \mathbf{h}(\mathbf{x}_c))] - \mathbf{B}\mathbf{h}(\mathbf{x}_c) - \mathbf{g}(\mathbf{x}_c, \mathbf{h}(\mathbf{x}_c)) = 0.$$
(4)

Coefficients of the expansions h_i can be explicitly calculated by solving Eq. (4). Using these coefficients, we can express the dynamics on the centre manifold as

$$\dot{\mathbf{x}}_c = \mathbf{A}\mathbf{x}_c + \mathbf{f}(\mathbf{x}_c, \mathbf{h}(\mathbf{x}_c), \boldsymbol{\beta}).$$
(5)

2.6 Stability of semi-simple double zero bifurcation

Following the centre manifold reduction, essential dynamics of the model has been described by

$$\dot{x}_1 = f_1(x_1, x_2, \beta)
\dot{x}_2 = f_2(x_1, x_2, \tilde{\beta}),$$
(6)

where $i \in \{1, 2\}$ and f_i 's are scalar nonlinear functions representing the same dynamics in Eq. (5). Given that a semi-simple double zero bifurcation occurs, we now explicitly calculate the stability conditions for the bifurcating solutions (looss and Joseph 1990, Chapter V.8). To proceed, we define a convenient set of coordinates and their corresponding equations as

$$\hat{x}_i = \frac{x_i}{\tilde{\beta}} \text{ and } \hat{f}_i = \frac{f_i(x_1, x_2, \beta)}{\tilde{\beta}^2} = 0.$$
 (7)

At the bifurcation value of $\tilde{\beta} = 0$, the equations $\hat{f}_{i0} = \hat{f}_i(\hat{x}_1, \hat{x}_2, 0)$ are conic sections and the points of intersections of these two conics are the possible bifurcation solutions. These conics can have two, three or four intersection points. The trivial solution (0, 0) is always one of the intersection points. To find the stability of bifurcation solutions, let

$$\mathbf{J}_{0}(\hat{x}_{1}, \hat{x}_{2}) = \begin{bmatrix} \frac{\partial \hat{f}_{10}(\hat{x}_{1}, \hat{x}_{2}, 0)}{\partial \hat{x}_{1}} & \frac{\partial \hat{f}_{10}(\hat{x}_{1}, \hat{x}_{2}, 0)}{\partial \hat{x}_{2}} \\ \frac{\partial \hat{f}_{20}(\hat{x}_{1}, \hat{x}_{2}, 0)}{\partial \hat{x}_{1}} & \frac{\partial \hat{f}_{20}(\hat{x}_{1}, \hat{x}_{2}, 0)}{\partial \hat{x}_{2}} \end{bmatrix}$$
(8)

and σ_{i0} be the eigenvalues of \mathbf{J}_0 . Similarly, let \mathbf{J} be the Jacobian for system (6) and σ_i be its eigenvalues. Because of the parametrization chosen in Eq. (7), a direct calculation shows that $\mathbf{J}(\tilde{\beta}) = \tilde{\beta}\mathbf{J}_0 + \mathcal{O}(\tilde{\beta}^2)$. The determinants and the eigenvalues of \mathbf{J} and \mathbf{J}_0 are related as

$$\det \mathbf{J} = \tilde{\beta}^2 \det \mathbf{J}_0 + \mathcal{O}(|\tilde{\beta}^3|)$$

and

$$\sigma_i = \tilde{\beta}\sigma_{i0} + \mathcal{O}(|\tilde{\beta}^2|).$$

For small values of $\hat{\beta}$, the determinants and the eigenvalues of **J** and **J**₀ have the same sign. If det **J**₀ = $\sigma_{10}\sigma_{20} < 0$, one of σ_{10} or σ_{20} must be positive and the bifurcating solution must be unstable. When det **J**₀ > 0, the real parts of σ_{10} and σ_{20} must have the same sign. Hence, the bifurcating solution is stable when det **J**₀ > 0 and both of its eigenvalues have negative real part. In each of the multi-strain models, we have found that there are four intersection points for the respective conics. Detailed calculations pertaining to each model are presented in Sect. 3.

3 Bifurcation and stability analysis

In the previous section, we outlined the necessary steps to understand the clustering patterns of the multi-strain models. Specific details of the calculations are presented here.

3.1 The model by Gupta et al. (1998)

For the general m locus–n allele form of the model by Gupta et al. (1998), the dynamics of each strain is described by system (1). To understand the possible strain partitions, we analyze the quotient network obtained from any 2-colour pattern.

Let each node in Fig. 4 represent system (1). Combining the topological parameters, each node in the 2-colour quotient model represents

$$\begin{aligned} \dot{z}_i &= \lambda_i (1 - z_i) - \mu z_i, \\ \dot{w}_i &= ((1 + s_i)\lambda_i + m_i\lambda_j)(1 - w_i) - \mu w_i, \\ \dot{y}_i &= \lambda_i \left((1 - w_i) + (1 - \gamma)(w_i - z_i) \right) - \sigma y_i, \end{aligned}$$

where $\lambda_i = \beta y_i$ and *i* denotes the index for one of the nodes and *j* denotes the index for the other node in Fig. 4. Equilibrium points of the quotient system are

$$\mathbf{p}_{1} = (0, 0, \dots, 0)^{T},
\mathbf{p}_{2} = (z_{1}^{*}, w_{1}^{*}, y_{1}^{*}, 0, w_{2}^{*}, 0)^{T},
\mathbf{p}_{3} = (0, w_{2}^{*}, 0, z_{1}^{*}, w_{1}^{*}, y_{1}^{*})^{T},
and \mathbf{p}_{4} = (z_{3}^{*}, w_{3}^{*}, y_{3}^{*}, z_{3}^{*}, w_{3}^{*}, y_{3}^{*})^{T},$$

where z_1^* , w_1^* , y_1^* , w_2^* , z_3^* , w_3^* , and y_3^* are implicit equilibrium expressions. At \mathbf{p}_1 or \mathbf{p}_4 , both nodes of the quotient system have identical states. Hence, \mathbf{p}_1 corresponds to the trivial equilibrium and \mathbf{p}_4 corresponds to a fully synchronous nontrivial equilibrium in the quotient system as well as the larger network. At the other two equilibrium states, \mathbf{p}_2 and \mathbf{p}_3 , the two nodes are asynchronized in the quotient system. These equilibrium points correspond to possible partial synchrony patterns in the larger network.

After transferring the system to its Jordan canonical form at the trivial equilibrium, the Jacobian at this point is

$$\mathbf{J} = \begin{bmatrix} \beta - \sigma & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta - \sigma & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu \end{bmatrix}.$$

Given that the parameters of the system are always positive, the system is locally stable at the equilibrium for $\beta - \sigma < 0$. To simplify the computation, we substitute

the parameter β with $\tilde{\beta} \triangleq \beta - \sigma$. Hence, the newly transformed system undergoes a semi-simple double zero bifurcation at $\tilde{\beta} = 0$ and the system can be written as

$$\dot{\mathbf{x}}_{c} = \mathbf{A}\mathbf{x}_{c} + \mathbf{f}(\mathbf{x}_{c}, \mathbf{x}_{s})$$
$$\dot{\mathbf{x}}_{s} = \mathbf{B}\mathbf{x}_{s} + \mathbf{g}(\mathbf{x}_{c}, \mathbf{x}_{s}) \qquad (\mathbf{x}_{c}, \mathbf{x}_{s}) \in \mathbb{R}^{2} \times \mathbb{R}^{4},$$
(9)

where

$$\mathbf{A} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix},$$
$$\mathbf{B} = \begin{bmatrix} -\mu & 0 & 0 & 0 \\ 0 & -\mu & 0 & 0 \\ 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & -\mu \end{bmatrix},$$

and \mathbf{f} as well as \mathbf{g} are nonlinear functions of the system after the transformation.

As described in Sect. 2.5, we can now reduce the system to the centre manifold. For i = 1, ..., 4, let

$$x_{i+2} = h_i = a_i x_1^2 + b_i x_2^2 + c_i \tilde{\beta}^2 + d_i x_1 x_2 + e_i x_1 \tilde{\beta} + f_i x_2 \tilde{\beta} + \cdots$$
(10)

Then,

$$D\mathbf{h} = \begin{bmatrix} 2a_1x_1 + d_1x_2 + e_1\tilde{\beta} & 2b_1x_2 + d_1x_1 + f_1\tilde{\beta} \\ 2a_2x_1 + d_2x_2 + e_2\tilde{\beta} & 2b_2x_2 + d_2x_1 + f_2\tilde{\beta} \\ 2a_3x_1 + d_3x_2 + e_3\tilde{\beta} & 2b_3x_2 + d_3x_1 + f_3\tilde{\beta} \\ 2a_4x_1 + d_4x_2 + e_4\tilde{\beta} & 2b_4x_2 + d_4x_1 + f_4\tilde{\beta} \end{bmatrix}.$$
 (11)

By substituting Eqs. (9), (10) and (11) into Eq. (4), we obtain the necessary equations to determine the 24 coefficients for the expansions and thus, the centre manifold as well.

After the centre manifold reduction, we find that the two conics necessary to study the stability of the possible solutions are

$$\begin{aligned} \hat{f}_{10}(\hat{x}_1, \hat{x}_2) &= -\frac{\sigma(s_1\gamma + 1)}{m_2} \hat{x}_1^2 + \hat{x}_1 - \frac{\sigma^2\left(\gamma m_1 m_2 + (m_2\gamma - 2 - 2s_1\gamma)\right)}{\mu m_2} \hat{x}_1 \hat{x}_2 \\ &+ \frac{\left(m_1 m_2(1 + s_2\gamma) + m_2(s_2 + 1)(\gamma - 1) - (s_2 + 1)^2(1 + s_1\gamma)\right)}{m_2 \mu^2} \hat{x}_2^2 \\ \hat{f}_{20}(\hat{x}_1, \hat{x}_2) &= -\gamma \sigma \hat{x}_1 \hat{x}_2 + \hat{x}_2 + \frac{\sigma^2(\gamma - 1)}{\mu} \hat{x}_2^2. \end{aligned}$$

In this case, the four intersections of the two conics are

$$\hat{\mathbf{x}}_1^* = (0, 0)$$

$$\begin{aligned} \hat{\mathbf{x}}_{2}^{*} &= \left(\frac{m_{2}}{\sigma(1+s_{1}\gamma)}, 0\right), \\ \hat{\mathbf{x}}_{3}^{*} &= \left(\frac{1+s_{2}}{\sigma(1+s_{2}\gamma)}, \frac{\mu}{\sigma^{2}(1+s_{2}\gamma)}\right), \\ \text{and} \quad \hat{\mathbf{x}}_{4}^{*} &= \left(\frac{\mu(\gamma(m_{2}-s_{1})-1)}{\sigma^{2}\gamma(\gamma(m_{1}m_{2}-s_{1}s_{2})-(s_{1}+s_{2})-1)}, \\ \frac{\gamma(m_{2}(m_{1}+1)-s_{1}(s_{2}+1))-m_{2}-s_{2}-1}{\sigma^{2}\gamma(\gamma(m_{1}m_{2}-s_{1}s_{2})-(s_{1}+s_{2})-1)}\right). \end{aligned}$$

Performing the necessary inverse operations, we find that each $\hat{\mathbf{x}}_i^*$ corresponds to equilibrium points \mathbf{p}_i of the quotient system. To check the stability at each point, we must calculate the determinant found in Eq. (8) and the corresponding eigenvalues at each point. A direct calculation shows that the determinants are

$$D_1 = 1,$$

$$D_2 = \frac{\gamma(m_2 - s_1) - 1}{1 + s_1 \gamma},$$
(12)

$$D_3 = \frac{\gamma(m_1 - s_2) - 1}{1 + s_2 \gamma},\tag{13}$$

and
$$D_4 = \frac{[1 + \gamma(s_2 - m_1)][1 + \gamma(s_1 - m_2)]}{\gamma^2(s_1s_2 - m_1m_2) + \gamma(s_1 + s_2) + 1}.$$
 (14)

The corresponding sets of eigenvalues of J_0 at each intersection of the conics are

$$E_1 = \{1, 1\},\$$

$$E_2 = \{-1, -D_2\},\$$

$$E_3 = \{-1, -D_3\},\$$
and $E_4 = \{-1, -D_4\}.\$

For the semi-simple double zero bifurcation, a particular bifurcating solution is stable when the determinant is positive while both corresponding eigenvalues remain negative. We see that the trivial equilibrium is alway unstable while the other three solutions can be stable depending on the topological parameters and the strength of cross-protection parameter, γ .

Using the stability results of the bifurcating solutions, we now explain formation of clusters. As mentioned in Sect. 2.3, each node of the quotient network represents a subset of nodes of the larger network. At \mathbf{p}_2 or \mathbf{p}_3 , the two nodes of the quotient network have different solutions from each other, so the corresponding subsets of nodes in the larger network must also have different solutions. Hence, when \mathbf{p}_2 or \mathbf{p}_3 is stable, each subset would be synchronized to a solution, but these two sets must be non-overlapping. In other words, all steady-states partial synchrony corresponding to 2-colours patterns are the direct results of stable bifurcation from the trivial equilibrium to \mathbf{p}_2 or \mathbf{p}_3 .

Furthermore, we can look to the parameter values of the stability conditions to understand which specific synchrony pattern may occur. Expressions in (12), (13) and (14) are respectively responsible for the stability of equilibria \mathbf{p}_2 , \mathbf{p}_3 , and \mathbf{p}_4 . These expressions are the combination of the strength of cross-protection parameter from the differential system and more importantly, the topological parameters. The topological parameters represent some balanced 2-colourings on the quotient network. Hence, only the balanced partial synchrony patterns with parameters that could lead to stable bifurcating solutions at \mathbf{p}_2 or \mathbf{p}_3 would be observed. Numerical examples of different synchrony patterns of this model will be illustrated in Sect. 4.

On the other hand, if the conditions are such that \mathbf{p}_4 is stable, instead of a partially synchronized pattern, all the nodes would be synchronized to one state. When this equilibrium is stable, the two nodes in the quotient network have the same solutions. Thus, the two subsets of the nodes in the larger network must also have the same solution.

While we found synchrony-breaking behaviour through the occurrence of a semisimple double zero bifurcation, we note that partial-synchrony via synchrony-breaking bifurcations can occur through other types of bifurcations. As long as the bifurcation is stable and the corresponding colouring is balanced, partial synchrony would be possible. For example, Chan and Yu (2012) found stable partial synchrony through a synchrony-breaking Hopf bifurcation.

3.2 The model by Recker and Gupta (2005)

As mentioned in Sect. 1, the model from Recker and Gupta (2005) is an extension of the model in Gupta et al. (1998). The authors incorporated a new compartment for individuals being non-susceptible to pathogens strains sharing more than one allele with a particular strain i. This new compartment introduces a new type of coupling and thus there will be two types of arrows in the coupled cell network representation of the system. Instead of reducing the system to the quotient network shown in Fig. 4, any balanced 2-colourings of the system can be reduced to the quotient network shown in Fig. 5.

Based on the equations in (2), each node in Fig. 5 has the form

$$\begin{aligned} \dot{z}_i &= \lambda_i (1 - z_i) - \mu z_i, \\ \dot{w}_i &= ((1 + s_{i1} + s_{i2})\lambda_i + (m_{i1} + m_{i2})\lambda_j)(1 - w_i) - \mu w_i, \\ \dot{v}_i &= \left((1 + s_{i2})\lambda_i + m_{i2}\lambda_j\right)(1 - v_i) - \mu v_i, \\ \dot{y}_i &= \lambda_i \left((1 - w_i) + (1 - \gamma_1)(w_i - z_i) + (1 - \gamma_2)(v_i - z_i)\right) - \sigma v_i, \end{aligned}$$

where $\lambda_i = \beta y_i$, *i* denotes the index for one node and *j* denotes the index for the other node in Fig. 5. The equilibrium points of the quotient system are

$$\mathbf{p}_1 = (0, 0, \dots, 0)^T, \mathbf{p}_2 = (z_1^*, w_1^*, v_1^*, y_1^*, 0, w_2^*, v_2^*, 0)^T,$$

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$$\mathbf{p}_3 = (0, w_2^*, v_2^*, 0, z_1^*, w_1^*, v_1^*, y_1^*)^T,$$

and
$$\mathbf{p}_4 = (z_3^*, w_3^*, v_3^*, y_3^*, z_3^*, w_3^*, v_3^*, y_3^*)^T,$$

where z_1^* , w_1^* , v_1^* , y_1^* , w_2^* , z_3^* , w_3^* , v_3^* , and y_3^* are implicit equilibrium expressions. Similar to the previous system, both nodes of the quotient system have identical states at \mathbf{p}_1 or \mathbf{p}_4 . Again, \mathbf{p}_1 corresponds to the trivial equilibrium and \mathbf{p}_4 corresponds to a fully synchronous nontrivial equilibrium in the quotient system as well as the larger network. Furthermore, for the other two equilibrium states, \mathbf{p}_2 and \mathbf{p}_3 , the two nodes are again asynchronized in the quotient systems. They correspond to possible partial synchrony patterns in the larger network.

Subsequent to transforming the system to its Jordan canonical form at the trivial equilibrium, the Jacobian at this point is

$$\mathbf{J} = \begin{bmatrix} \beta - \sigma & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \beta - \sigma & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\mu \end{bmatrix}$$

We perform similar simplification as before and transform the parameter β with $\tilde{\beta} \triangleq \beta - \sigma$. With $\tilde{\beta}$ as the bifurcation parameter, this system also undergoes a semisimple double zero bifurcation at $\tilde{\beta} = 0$ and this system can be written as

$$\dot{\mathbf{x}}_{c} = \mathbf{A}\mathbf{x}_{c} + \mathbf{f}(\mathbf{x}_{c}, \mathbf{x}_{s}) \dot{\mathbf{x}}_{s} = \mathbf{B}\mathbf{x}_{s} + \mathbf{g}(\mathbf{x}_{c}, \mathbf{x}_{s})$$
 ($\mathbf{x}_{c}, \mathbf{x}_{s}$) $\in \mathbb{R}^{2} \times \mathbb{R}^{6}$, (15)

where

$$\mathbf{A} = \begin{bmatrix} 0 & 0 \\ 0 & 0 \end{bmatrix},$$

$$\mathbf{B} = \begin{bmatrix} -\mu & 0 & 0 & 0 & 0 & 0 \\ 0 & -\mu & 0 & 0 & 0 & 0 \\ 0 & 0 & -\mu & 0 & 0 & 0 \\ 0 & 0 & 0 & -\mu & 0 & 0 \\ 0 & 0 & 0 & 0 & -\mu & 0 \\ 0 & 0 & 0 & 0 & 0 & -\mu \end{bmatrix},$$

and \mathbf{f} as well as \mathbf{g} are nonlinear functions of the system after the transformation.

We again follow the method in Sect. 2.5 and reduce the system to its centre manifold. For i = 1, ..., 6, let

$$x_{i+2} = h_i = a_i x_1^2 + b_i x_2^2 + c_i \tilde{\beta}^2 + d_i x_1 x_2 + e_i x_1 \tilde{\beta} + f_i x_2 \tilde{\beta} + \cdots$$
 (16)

Then,

$$D\mathbf{h} = \begin{bmatrix} 2a_1x_1 + d_1x_2 + e_1\tilde{\beta} & 2b_1x_2 + d_1x_1 + f_1\tilde{\beta} \\ 2a_2x_1 + d_2x_2 + e_2\tilde{\beta} & 2b_2x_2 + d_2x_1 + f_2\tilde{\beta} \\ 2a_3x_1 + d_3x_2 + e_3\tilde{\beta} & 2b_3x_2 + d_3x_1 + f_3\tilde{\beta} \\ 2a_4x_1 + d_4x_2 + e_4\tilde{\beta} & 2b_4x_2 + d_4x_1 + f_4\tilde{\beta} \\ 2a_5x_1 + d_5x_2 + e_5\tilde{\beta} & 2b_5x_2 + d_5x_1 + f_5\tilde{\beta} \\ 2a_6x_1 + d_6x_2 + e_6\tilde{\beta} & 2b_6x_2 + d_6x_1 + f_6\tilde{\beta} \end{bmatrix}.$$
(17)

By substituting Eqs. (15), (16) and (17) into Eq. (4), we obtain the necessary equations to determine the thirty-six coefficients for the expansions and thus, the centre manifold as well.

In this case, we find that the conics for stability calculations are

$$\begin{split} \hat{f}_{10}(\hat{x}_1, \hat{x}_2) &= -\frac{\sigma^2 (m_{21}\gamma_1 s_{22} + \gamma_2 m_{22} - \gamma_1 m_{22} s_{21} - m_{22} + m_{21}\gamma_1)}{m_{22}\mu} \hat{x}_1^2 + \hat{x}_1 \\ &- \frac{\sigma (\gamma_1 m_{21} + \gamma_2 m_{22})}{m_{22}} \hat{x}_1 \hat{x}_2, \\ \hat{f}_{20}(\hat{x}_1, \hat{x}_2) &= -\frac{\sigma^3 \left((1 + s_{22})(1 + s_{22} + m_{22}) + \right)}{m_{22}\mu^2} \hat{x}_1^2 \\ &- \frac{\sigma^2}{m_{22}\mu} \hat{x}_1 \hat{x}_2 + \hat{x}_2 - \frac{\sigma (1 + s_{11}\gamma_1 + s_{12}\gamma_2)}{m_{22}} \hat{x}_2^2, \end{split}$$

and intersections of these two conics are

$$\begin{aligned} \hat{\mathbf{x}}_{1}^{*} &= (0, 0), \\ \hat{\mathbf{x}}_{2}^{*} &= \left(0, \frac{m_{22}}{\sigma(1 + \gamma_{1}s_{11} + \gamma_{2}s_{12})}\right), \\ \hat{\mathbf{x}}_{3}^{*} &= \left(\frac{\mu}{\sigma^{2}(1 + \gamma_{1}s_{21} + \gamma_{2}s_{22})}, \frac{m_{22}}{\sigma(1 + \gamma_{1}s_{21} + \gamma_{2}s_{22})}\right), \\ \text{and} \quad \hat{\mathbf{x}}_{4}^{*} &= \left(\frac{\mu[(m_{21} - s_{11})\gamma_{1} + (m_{22} - s_{12})\gamma_{2} - 1]}{\sigma^{2}[B_{1}\gamma_{1}^{2} + B_{2}\gamma_{1} + B_{3}\gamma_{1}\gamma_{2} + B_{4}\gamma_{2} + B_{5}\gamma_{2}^{2} + 1]}, \\ \frac{A_{1}\gamma_{1} + A_{2}\gamma_{2} + m_{22} + s_{22} + 1}{\sigma[B_{1}\gamma_{1}^{2} + B_{2}\gamma_{1} + B_{3}\gamma_{2} + B_{4}\gamma_{1}\gamma_{2} + B_{5}\gamma_{2}^{2} + 1]} \right), \end{aligned}$$

where

$$A_{1} = (s_{11} - m_{21})(1 + s_{22}) + m_{22}(s_{21} - m_{11}),$$

$$A_{2} = s_{12} - m_{22} - m_{12}m_{22} + s_{12}s_{22},$$

$$B_{1} = s_{11}s_{21} - m_{11}m_{21},$$

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$$B_2 = s_{11} + s_{21},$$

$$B_3 = s_{12} + s_{22},$$

$$B_4 = s_{12}s_{21} - m_{12}m_{21} - m_{11}m_{22} + s_{22}s_{11},$$

and
$$B_5 = s_{12}s_{22} - m_{12}m_{22}.$$

Performing the necessary inverse operations, we find that each $\hat{\mathbf{x}}_i^*$ corresponds to equilibrium points \mathbf{p}_i of the quotient system. The relevant determinants corresponding to the four equilibria are

$$D_1 = 1,$$

$$D_2 = \frac{\gamma_1(m_{21} - s_{11}) + \gamma_2(m_{22} - s_{12}) - 1}{1 + \gamma_1 s_{11} + \gamma_2 s_{12}},$$
(18)

$$D_3 = \frac{\gamma_1(m_{11} - s_{21}) + \gamma_2(m_{12} - s_{22}) - 1}{1 + \gamma_1 s_{21} + \gamma_2 s_{22}},$$
(19)

and
$$D_4 = \frac{C_1 \gamma_1^2 + C_2 \gamma_1 + C_3 \gamma_1 \gamma_2 + C_4 \gamma_2 + C_5 \gamma_2^2}{\sigma [B_1 \gamma_1^2 + B_2 \gamma_1 + B_3 \gamma_2 + B_4 \gamma_1 \gamma_2 + B_5 \gamma_2^2 + 1]},$$

where

$$C_{1} = m_{11}m_{21} + s_{11}s_{21} - s_{21}m_{21} - m_{11}s_{11},$$

$$C_{2} = s_{11} - m_{21} + s_{21} - m_{11},$$

$$C_{3} = (m_{21} - s_{11})(m_{12} - s_{22}) + m_{22}(m_{11} - m_{21})$$

$$C_{4} = s_{12} - m_{22} + s_{22} - m_{12},$$
and
$$C_{5} = m_{12}m_{22} + s_{12}s_{22} - s_{22}m_{22} - m_{12}s_{12}.$$

The corresponding eigenvalues of J_0 at each intersection of the conics are

$$E_1 = \{1, 1\},$$

$$E_2 = \{-1, -D_2\},$$

$$E_3 = \{-1, -D_3\},$$

and $E_4 = \{-1, -D_4\}.$

Like the previous model, the trivial intersection point \mathbf{p}_1 is always unstable because both the eigenvalues are always positive. We can see that for parameters such that D_i are positive, the corresponding eigenvalues are necessarily negative. Once again, the other three equilibrium solutions can be stable depending on the topological parameters and the strength of cross-protection parameters, γ_1 and γ_2 .

Given that the stability scenarios of the bifurcating solutions of this model are the same as the previous model, the reasons for cluster formation and a specific pattern to occur are also the same and they will not be repeated here. Numerical examples of different synchrony pattern for this model will also be illustrated in Sect. 4.

4 Numerical results

In this section, we numerically demonstrate some possible clustering patterns.

4.1 Numerical results of the model by Gupta et al. (1998)

There are three possible 2-colour patterns for the 2 locus–2 allele version of the model from Gupta et al. (1998) and they are shown in Fig. 3. Already mentioned in Sect. 2.2, the pattern shown in Fig. 3c is not a balanced colouring, so it does not occur numerically. The pattern in Fig. 3a is balanced and in its 2-colour quotient form, the parameter values are $s_i = 1$ and $m_i = 1$. Similarly, the pattern in Fig. 3b is also balanced and in its 2-colour quotient form, the parameter values are $s_i = 0$ and $m_i = 2$. Analytically, we calculate from Eqs. (12) and (13) that for the clustering to be stable, we must have

$$m_i - s_j > \frac{1}{\gamma}.$$
 (20)

Given that γ is a positive parameter, a direct calculation shows that the pattern in Fig. 3a cannot occur and the pattern in Fig. 3b will occur for appropriate choice of γ . The numerical results in Fig. 6 agree with the analytic predictions. The two patterns shown are symmetrical to each other and they are induced by choosing different initial conditions.

Extending the 2 locus–2 allele form, numerical results and the corresponding 2-colour patterns of the 3 locus–2 allele model are shown in Figs. 7 and 8. Clusters of numerical solutions found in Figs. 7a and 8a correspond to the colouring patterns shown in Figs. 7b and 8b, respectively. We can derive the corresponding parameters for the 2-colour quotient network from the balanced colouring. Combining the topo-



Fig. 6 Simulation results of the 2 locus–2 allele form of system (1) for $\sigma = 10$, $\gamma = 0.85$, $\mu = 0.02$, $\beta = 15$, showing the clustering patterns of z_i for each strain. The patterns in **a** and **b** are obtained by using different initial conditions



Fig. 7 Results for the 3 locus–2 allele version of the model from Gupta et al. (1998): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.1$, $\gamma = 0.58$, $\mu = 0.02$ with identical initial conditions for strains *any*, *bnx*, *bmx* and *amy*; and **b** the balanced 2-colour pattern corresponding to the numerical results, with each dark node receiving four inputs from white nodes and two from the other dark nodes; similarly, each white node receiving four inputs from dark nodes and two from the other white nodes, and the corresponding 2-colour quotient network having the parameter values $m_i = 4$ and $s_i = 2$



Fig. 8 Results for the 3 locus–2 allele version of the model from Gupta et al. (1998): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.1$, $\gamma = 0.58$, and $\mu = 0.02$ with identical initial conditions for strains *any* and *bmx*; and **b** The balanced 2-colour pattern corresponding to the numerical results and with each dark node receiving six inputs from white nodes and none from the other dark node; similarly, each white node receiving one input from dark nodes and five from the other white nodes, and the corresponding 2-colour quotient network having the parameter values $m_1 = 2$, $s_1 = 4$, $m_2 = 6$ and $s_2 = 0$

logical parameters as well as the system parameters, a direct calculation shows that the stability condition in Eq. (20) is satisfied.

Based on the stability expressions shown and the numerical results found in Figs. 7 and 8, we see that different patterns can emerge under identical parameter conditions.



Fig. 9 Results for 3 locus–2 allele version of the model from Gupta et al. (1998): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.1$, $\gamma = 0.45$, $\mu = 0.02$ with mixed initial conditions; and **b** the corresponding coupled cell system showing that all strains being synchronized in identical steady-state

Calvez et al. (2005) noticed the appearance of a particular pattern which is dependent on initial conditions. The simulation results shown in Figs. 7 and 8 are simulated with identical parameter values but different initial conditions. This phenomenon is possible because both patterns satisfy the stability condition found for balanced 2colourings.

On the other hand, we can change the system parameter values such that the clustering no longer occurs. In Fig. 9, we have decreased the value of γ so that, along with the topological parameters corresponding to the network in Fig. 8b, the inequality in Eq. (20) is no longer satisfied.

4.2 Numerical results of the model by Recker and Gupta (2005)

For the model by Recker and Gupta (2005), the stability criterion obtained from Eqs. (18) and (19) is

$$\gamma_1(m_{i1} - s_{j1}) + \gamma_2(m_{i2} - s_{j2}) > 1, \tag{21}$$

where *i* denotes the index for one node and *j* denotes the index for the other node in Fig. 5. For this model, the numerical results and the corresponding balanced 2-colouring of the 3 locus–2 allele form of the system are shown in Figs. 10 and 11. Applying Eq. (21) to the topological parameters of the quotient networks in Figs. 10b and 11, we see that these patterns are clearly stable.

Like the previous model, we can choose the system parameter values such that the clustering patterns become unstable. In Fig. 12, we decrease γ_1 and γ_2 so that the clustering disappears and all the strains are synchronized.



Fig. 10 Results for the 3 locus–2 allele version of the model from Recker and Gupta (2005): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.2$, $\gamma_1 = 0.5$, $\gamma_2 = 0.8$, $\mu = 0.09$ with identical initial conditions for strains *amx*, *any*, *bny*, and *bmx*; and **b** the balanced 2-colour pattern corresponding to the numerical results, and the corresponding 2-colour quotient network having the parameter values $m_{ij} = 2$ and $s_{ij} = 1$, for $i, j \in \{1, 2\}$



Fig. 11 Results for the 3 locus–2 allele version of the model from Recker and Gupta (2005): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.2$, $\gamma_1 = 0.5$, $\gamma_2 = 0.8$, $\mu = 0.09$ with identical initial conditions for strains *amx* and *bny*; and **b** the balanced 2-colour pattern corresponding to the numerical results and the corresponding 2-colour quotient network having the parameter values $m_{1i} = 1$, $m_{2i} = 3$, $s_{1i} = 2$ and $s_{2i} = 0$, for $i \in \{1, 2\}$

4.3 Periodic and chaotic motions

As shown numerically by Gupta et al. (1998) and Recker and Gupta (2005), the two models discussed in this work may have cyclical and chaotic solutions for some parameter values. Since our previous discussion in Sect. 3 is limited to the semi-simple double zero bifurcation and periodic solutions arise from Hopf bifurcations,



Fig. 12 Results for the 3 locus–2 allele version of the model from Recker and Gupta (2005): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.2$, $\gamma_1 = 0.45$, $\gamma_2 = 0.48$, $\mu = 0.09$; and **b** the corresponding coupled cell system showing that all strains being synchronized in identical steady-staten



Fig. 13 Results for the 3 locus–2 allele version of the model from Recker and Gupta (2005): **a** Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.2$, $\gamma_1 = 0.5$, $\gamma_2 = 0.8$, $\mu = 0.09$ with identical initial conditions for strains *amx*, *any*, *bny*, and *bmx*, and **b** The balanced 2-colour pattern corresponding to the numerical results, and the corresponding 2-colour quotient network having the parameter values $m_{ij} = 2$ and $s_{ij} = 1$, for $i, j \in \{1, 2\}$

our previous work based on bifurcation and stability analysis does not apply here. In this section, we will investigate these two types of solutions numerically.

For the model by Recker and Gupta (2005), we can see from Fig. 13a and b that periodic solutions of the system correspond to balanced colourings of the networks in Figs. 10b and 11b. While our bifurcation and stability analysis does not apply here, the results from balanced colouring seem to correspond to the clustering of periodic solutions. This result suggests that partial synchrony patterns of periodic solutions may also arise from bifurcations of the quotient network. Like our previous results obtained based on the semi-simple double zero bifurcations, these different patterns of synchrony can be induced numerically using different initial conditions.





Fig. 14 Results for the 3 locus–2 allele version of the model from Recker and Gupta (2005): 11A Simulated time history of z_i for $\sigma = 10$, $R_0 = 1.2$, $\gamma_1 = 0.5$, $\gamma_2 = 0.8$, $\mu = 0.09$ with identical initial conditions for strains *amx* and *bny*; and 11B The balanced 2-colour pattern corresponding to the numerical results and the corresponding 2-colour quotient network having the parameter values $m_{1i} = 1$, $m_{2i} = 3$, $s_{1i} = 2$ and $s_{2i} = 0$, for $i \in \{1, 2\}$

While keeping the parameter values the same as that for the periodic solutions, we see from Fig. 14a that chaotic solutions may occur under different initial conditions. Like the other solutions of the system, the different strains also synchronize with each other chaotically. The synchrony pattern of the synchronized chaos corresponds to the balanced colouring shown in Fig. 14b. The corresponding quotient network for this balanced colouring is shown in Fig. 14c. While the numerical solutions in Figs. 13a, b, and 14a are all produced using the same parameter values, their respective balanced colourings do not have the same number of equivalence classes. This result suggests that, for any given set of parameter values, the basin of attraction of the system may contain multiple stable regions corresponding to multiple patterns of balanced colourings.

5 Discussion and conclusion

In this paper, we introduced the groupoid formalism by Golubitsky et al. (2005) as a method for analyzing multi-strain epidemiology models. This approach takes advan-

tage of the fact that strains in many multi-strain models are treated as interconnected subsystems. Each of the subsystem is represented as a node of the digraph and the couplings between them are represented by edges. We can now further simplify the system by analyzing its quotient network. Using these simplifications, we were able to provide analytic insights to the local bifurcations. Furthermore, we were able to explain partial synchrony between the solutions of different strains through the groupoid framework and stability analysis of the bifurcating solutions.

Specifically, we applied this framework to the models by Gupta et al. (1998) and Recker and Gupta (2005). Both of these are multi-strain models that compartmentalize the dynamics pertaining one strain to a subsystem of differential equations. While both models are multi-strain epidemiology models, there were different motivations and assumptions. Because of these differences, the two different models have different coupled cell network representations and different quotient networks as well. Even with the differences, the bifurcation and stability analysis on the quotient networks of both models turned out to be quite similar. We were able to prove that semi-simple double zero bifurcations from the trivial equilibrium occur for both models. Aside from proving that such bifurcations exist, we also calculated the specific bifurcating solutions and their stability criteria.

With the stability criteria of the bifurcating solutions known explicitly, we showed that the partial synchrony observed numerically are the results of stable bifurcating solutions. The results show that the bifurcating solutions in which the two nodes of the quotient network do not synchronize with each other are possible. Since the two nodes of the quotient network represent different subsets of nodes of the larger network, the asynchronous steady-state bifurcating solutions of the quotient network imply that the subsets of nodes of the larger network will have different solutions. Thus, we have analytically explained how clustering of strains occur.

Calvez et al. (2005) analyzed a modified version of the model by Gupta et al. (1998) and they stated that "which cluster structure occurs in reality depends mostly on the level of cross-protection" and our results from the stability analysis certainly support their statement. One can see from Eqs. (20) and (21) that the cross-protection parameters, γ for model (1) as well as γ_1 and γ_2 for model (2), are important in the stability criteria. However, we show that cross-protection is not the only factor governing the appearance of distinct strain structure. The topological parameters from a balanced colouring pattern also factor into the appearance of strain clustering.

Aside from determining that appearance of strain structure is directly tied with the stability of bifurcating solutions, the clustering pattern that may occur is also of interest. Calvez et al. (2005) stated that it is "not clear why some cluster structures arise while others do not", but we were able to determine the pattern using the idea of balanced colourings from the groupoid formalism. As required by the method, only balanced colourings may occur, so some cluster structures cannot occur.

Furthermore, balanced colourings are characterized by their topological parameters from the quotient network representation. Through our stability analysis, we show that these parameters are important to stability and some patterns do not lead to stable bifurcating solutions. Thus, only balanced clustering structure with patterns that give stable bifurcating solutions may occur. Given system parameters, we observed in Sect. 4 that more than one balanced colouring may be stable. In such situations, the initial conditions may determine which of the pattern appear in numerical simulations.

The transition from one pattern to another can be observed from the differences between Figs. 7 and 9. As we decrease the parameter, γ , for model (1), the stable discrete strain structure in Fig. 7a is destabilized and the strain structure disappeared. Based on this observation, we may conclude that strain structure found in the model by Gupta et al. (1998) is related to the effectiveness of cross-immunity. The more effective the cross-protection, the more likely the discrete strain structure appears. This observation is consistent with the idea that discrete strain structure is a result of immune selection. In a similar fashion, we can destabilize the discrete strain structure found in the model by Recker and Gupta (2005) by decreasing the parameters, γ_1 and γ_2 . For this model, the transition from discrete strain structure to no structure can be observed in Figs. 10 and 12.

In addition to partially synchronized steady-states, partially synchronized periodic and chaotic solutions have also been observed numerically. Unlike the analysis performed by Dawes and Gog (2002), our bifurcation and stability analysis is local and limited to steady-states. While our work is not directly applied to study these phenomena, we would like to mention that the strain structures shown in Fig. 13a and b match the patterns found in Figs. 10b and 11b. This agreement between numerical results and balanced colourings suggest that other bifurcations, possibly secondary, may occur from the quotient network causing the oscillatory behaviour. Besides 2-colour balanced colouring being compatible with clusters of periodic solutions, we also observe that the chaotic synchronization shown in Fig. 14a also agrees with the balanced 3-colouring shown in Fig. 14b.

A few possibilities exist for future works and we shall discuss them here. For bifurcation and stability, we have restricted the analysis to 2-colourings of the systems. Given that there is strong agreement between the chaotic synchronization and a balanced 3-colouring, it is clear that more complicated synchrony patterns are possible. Since each colour of a colouring represents a subset of nodes, analyses for patterns with higher number of colours are necessary to understand the possible dynamics.

Secondly, Dawes and Gog (2002) suggested the configuration of the strain space with symmetries, such as a ring structure, may have affected the overall system and we have continued to study strain-spaces with symmetries in this work as well. Some of the symmetries are present because we have assumed that all strains have identical parameters. This identical assumption leads to identical nodes, identical couplings, and thus possible symmetries in the directed graph of the coupled cell representation. Biologically, it would be unlikely that all strains behave identically, thus the identical parameter assumption is not realistic. Choosing different parameters for various strains in the strain-space would provide a more realistic model. We have also assumed that all possible strains of the *m* locus–*n* allele model are present in the system and the effects of cross-immunity exist identically and perfectly between strains that share alleles. Since these assumptions are used for mathematical convenience and the groupoid method applied to topologies without symmetries, it would be interesting to study more realistic strain-spaces motivated by biological evidence that have less symmetries.

Ultimately, as our knowledge of multi-strain pathogens and their interactions with hosts increases, the demand for mathematical models that can describe newly observed phenomena grows as well. In order to keep up with these needs, mathematical models have become more intricate and complex over time. We have provided a method to understand these models in a manner that has not been done before. This method also allows newer models to have fewer assumptions and increase the realism. Understanding gained from utilizing this method may provide invaluable insights.

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