Bifurcations and Patterns of Synchrony of Multi-Strain Infection Models

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Outline

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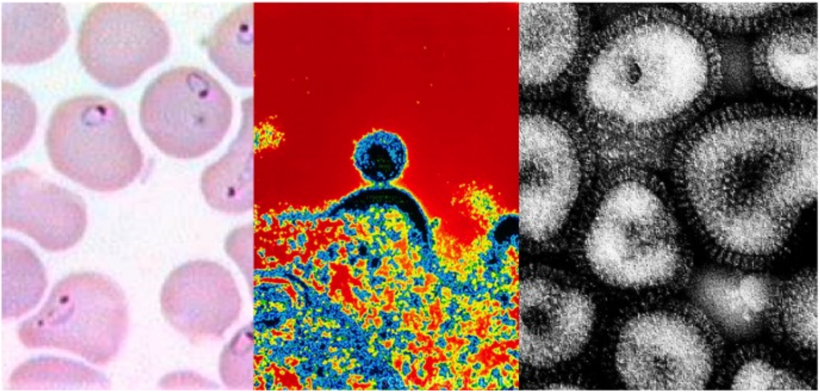
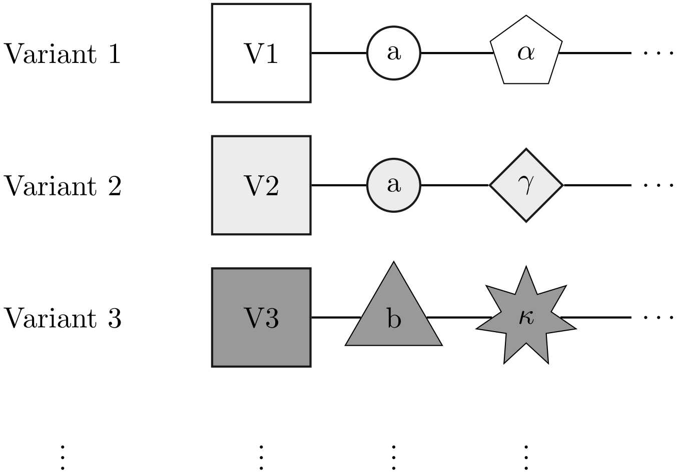
Multi-Strain Pathogens



Immune Response to Pathogens

- How does our body response to pathogens?
  - First step: Self Vs. non-self.
  - Recognize pathogens by chemical markers (e.g. proteins, carbohydrates) on the surface.
  - Different markers stimulate different types of CTLs.
  - Acquired immunity: Recognize, respond, purge and memorize.
  - Evolution of pathogens: Have multiple strains of the same pathogen.

Visualizing Variants, Antigens, and Epitopes



Unanswered Questions in Antigenic Variations

- How fast do variants switch?
- Is the expression of variants sequential or random?
- How is the phenotypic expression regulated?
- More importantly for us, how does it affect the hosts?

Strain Structure in Host Population

- Given the success of antigenic variation, there should be many pathogens variants.
- Theory suggests that many variants necessary for the strategy to succeed
- Clinically, distinct strains (strain structure) are often maintained within the host population.
- Example: switching of dominant strains of influenza occurs seasonally.
- Flu shots are only administer once a season.
- In same timescale, pathogens mutate and reproduce clonaly many times over.

Strain Structure: Limiting Factors

- Number of limiting factors has been suggested for the limited appearance of new strains.
- Biological compatibility (chemical) with binding sites on these target cells.
- Limited change with same genome
- Not all new variants can be successful.

Cross-Protective Immunity

- Genetically similar strains share antigens.
- A host gained partial immunity from a previous infection.
- Negatively impact on future infection by other strains that share allele.
- Protection is not fully effective, it may be enough to prevent infection.
- Assume that strains with same genetic info will encode the same antigens.

Outline

Multi-Strain Model by Gupta et al. (1998)

- z_i denotes the portion of population immune to strain i; w_i denotes the portion of the population which is immune to any strain j that shares allele with strain i; and y_i portion of the population that is infectious w.r.t. strain i.

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

- Force of infection: $\lambda_i = \beta y_i$.
- Effectiveness of cross-protection is denoted by γ.
- j is indexed over strains which share any allele with strain i, including i itself.
- Noted in (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.

Multi-Strain Model by Recker and Gupta (2005)

- Recker and Gupta (2005) added another compartment to model (1).

$$
\begin{aligned}
\dot{z}_i &= \lambda_i(1 - z_i) - \mu z_i, \\
\dot{w}_i &= (1 - w_i)\sum_{j\sim i}\lambda_j - \mu w_i, \\
\dot{v}_i &= (1 - v_i)\sum_{k\sim i}\lambda_k - \mu v_i, \\
\dot{y}_i &= \lambda_i\left((1 - w_i) + (1-\gamma_1)(w_i - z_i) + (1-\gamma_2)(v_i - z_i)\right) - \sigma y_i,
\end{aligned} \tag{2}
$$

- $j \sim i$ indicates the strains which share alleles with strain i.
- $k \sim i$ indicates the strains which share more than one allele with strain i.

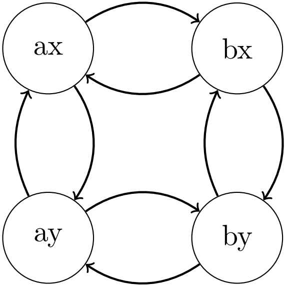
Clusters Formation

- Calvez et al. (2005) noticed that clusters of solutions form in the aforementioned models.
- Clusters (partial synchrony) can be in the form of steady-steady, periodic or chaotic solutions.
- Clustering seems to follow a pattern and Calvez et al. (2005) investigated numerically.
- We will investigate this clustering analytically.

Outline

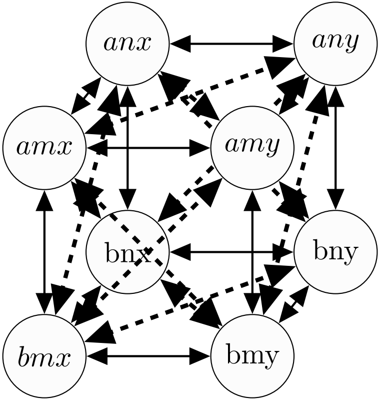
Recasting the Models (1)

- Let each node in the figure represents the set of differential equations in system (1).
- Directed graph gives a coupled cell representation of the 2 locus-2 allele form of the model by Gupta et al. (1998).
- Solid arrows indicate strains share alleles.
- Same shape of nodes denote the same set of differential equations.



Recasting the Models (2)

- For another example, the 3 locus-2 allele form of the model from Recker and Gupta (2005) is shown in the next figure
- Dashed arrows indicate strains share one allele.
- Solid arrows indicate strains share more than one allele.

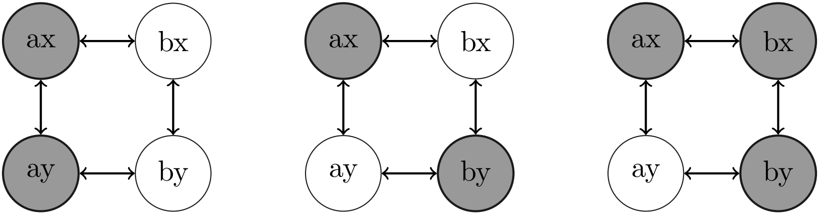


Balanced Colouring

- To continue the mathematical analysis, we need a concept called *balanced coloring*.
- Colour the nodes of the digraph to identify *synchrony patterns* that may occur.
- A colouring is *balanced* when all the nodes of the same colour receive the same set of inputs (directed edges).
- A balanced colouring with k colours is called a k-colouring.

Examples of 2-colour Patterns for $n_1 = 2$ and $n_2 = 2$.

- All nodes in Figure (a) and (b) receive the same kind of input based on the colour of node.
- Not the case in Figure (c).
- Biologically, not all strains can be synchronized after bifurcation.



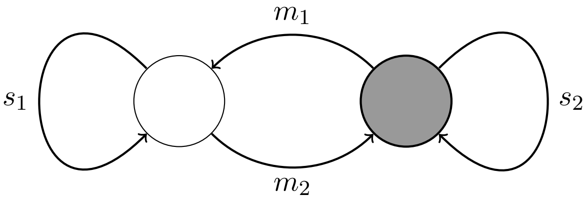
(a) (b) (c)

Quotient Network

- Simplify the system by analyzing its 2-colour quotient networks as shown in Golubitsky et al. (2005)
- Roughly speaking, a quotient network is a reduced network based on potential synchrony patterns of the larger network.
- Use colour to denote synchrony pattern (i.e. clustering) of the subsystems.
- 2-colour refers to the number of synchrony states.

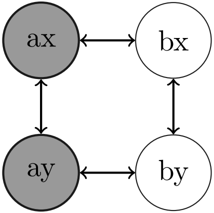
2-colour Quotient Network for System (1)

- Assume some balanced 2-colour pattern exist.
- s_i are self-connections.
- m_i are connections from the other set.

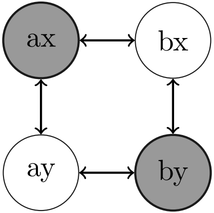


Examples of 2-colour Patterns for $n_1 = 2$ and $n_2 = 2$.

- Figure (a) corresponds to $s_i = 1$ and $m_i = 1$.
- Figure (b) corresponds to $s_i = 0$ and $m_i = 2$.
- There are multiple edges for (b).



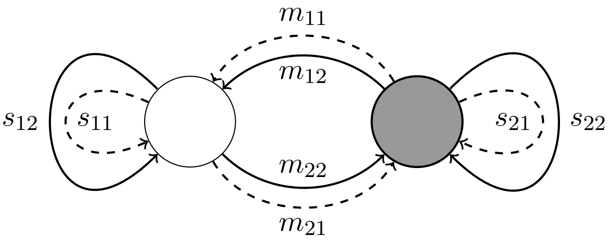
(a)



(b)

2-colour Quotient Network for System (2)

- Assume some balanced 2-colour pattern exist.
- s_{i1} and m_{i1} are self and non-self connections for dashed arrows.
- s_{i2} and m_{i2} are self and non-self connections for solid arrows.



Semi-Simple Double Zero Bifurcation

- We find semi-simple double zero bifurcation occurs for both systems.
- As a parameter varies, bifurcation occurs when eigenvalues from cross from the negative to the positive on the complex plane.
- Two zeros cross the simultaneously at critical point.
- Exist two linearly independent eigenvectors associated with the eigenvalues (semi-simple).
- Can apply centre manifold reduction to the systems.

Jordan canonical form and center manifold reduction

- Let n_c and n_s respectively be the numbers of eigenvalues with zero real-part and negative real-part of the Jacobian.
- For semi-simple double zero bifurcation, there would be two eigenvalues with zero real part and $2k-2$ eigenvalues with negative real part.
- The system can be rewritten in block matrix form as

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

- Centre Manifold Theorem guarantees that there exists a smooth manifold near the equilibrium point that captures the local behaviour
- Other coordinates are represented on the centre manifold as

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

Stability of semi-simple double zero bifurcation

- Following a centre manifold reduction, essential dynamics of the model have been reduced to

$$\begin{aligned}\dot{x}_1 &= f_1(x_1, x_2, \tilde{\beta}) \\ \dot{x}_2 &= f_2(x_1, x_2, \tilde{\beta})\end{aligned}, \quad \text{where } i \in \{1, 2\}. \tag{4}$$

- Bifurcation solutions are the intersections of the curves $f_{i0} = f_i(x_1, x_2, 0)$.
- We define

$$\mathbf{J}_0(\hat{x}_1, \hat{x}_2) = \begin{bmatrix} \frac{\partial \hat{f}_{10}(\hat{x}_1, \hat{x}_2, 0)}{\partial \hat{x}_1} & \frac{\partial \hat{f}_{10}(\hat{x}_1, \hat{x}_2, 0)}{\partial \hat{x}_2} \\ \frac{\partial \hat{f}_{20}(\hat{x}_1, \hat{x}_2, 0)}{\partial \hat{x}_1} & \frac{\partial \hat{f}_{20}(\hat{x}_1, \hat{x}_2, 0)}{\partial \hat{x}_2} \end{bmatrix} \tag{5}$$

  and σ_{i0} be the eigenvalues of $\mathbf{J}_0$.
- The bifurcating solution is stable when $\det \mathbf{J}_0 > 0$ and both of its eigenvalues have negative real part.

Stability Conditions for System (1)

- A direct calculation shows that the determinants are

$$\begin{aligned} D_1 &= 1, \\ D_2 &= \frac{\gamma(m_2 - s_1) - 1}{1 + s_1\gamma}, \\ D_3 &= \frac{\gamma(m_1 - s_2) - 1}{1 + s_2\gamma}, \\ \text{and} \quad D_4 &= \frac{[1 + \gamma(s_2 - m_1)][1 + \gamma(s_1 - m_2)]}{\gamma^2(s_1 s_2 - m_1 m_2) + \gamma(s_1 + s_2) + 1}. \end{aligned}$$

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

$$E_1 = \{1, 1\}, E_2 = \{-1, -D_2\},$$

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

Stability Conditions for System (2)

- The relevant determinants corresponding to the four equilibria are

$$\begin{aligned} D_1 &= 1, \\ D_2 &= \frac{\gamma_1(m_{21} - s_{11}) + \gamma_2(m_{22} - s_{12}) - 1}{1 + \gamma_1 s_{11} + \gamma_2 s_{12}}, \\ D_3 &= \frac{\gamma_1(m_{11} - s_{21}) + \gamma_2(m_{12} - s_{22}) - 1}{1 + \gamma_1 s_{21} + \gamma_2 s_{22}}, \\ \text{and} \quad D_4 &= \frac{C_1\gamma_1^2 + C_2\gamma_1 + C_3\gamma_1\gamma_2 + C_4\gamma_2 + C_5\gamma_2^2}{\sigma[B_1\gamma_1^2 + B_2\gamma_1 + B_3\gamma_2 + B_4\gamma_1\gamma_2 + B_5\gamma_2^2 + 1]}, \end{aligned}$$

  where $C_i(m_{11}, m_{12}, m_{21}, m_{22})$ are constant coefficients.
- The corresponding sets of eigenvalues of J_0 at each intersection of the conics are

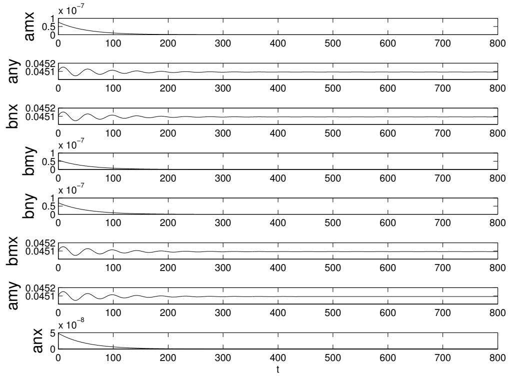
$$E_1 = \{1, 1\}, E_2 = \{-1, -D_2\},$$

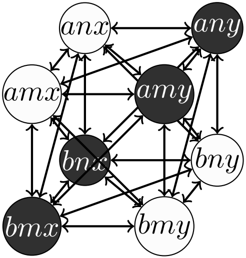
$$E_3 = \{-1, -D_3\}, \text{ and } E_4 = \{-1, -D_4\}.$$

Outline

Simulations for System (1)

- Levels of the y_{ij} are shown here.
- Cross-protection may cause strains to thrive or not.





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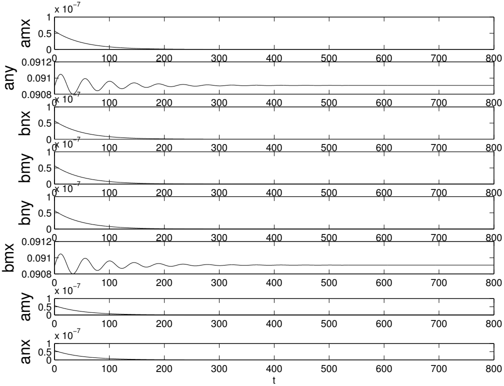
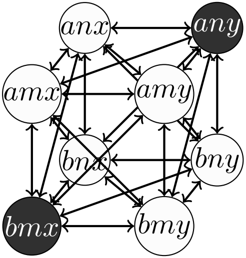
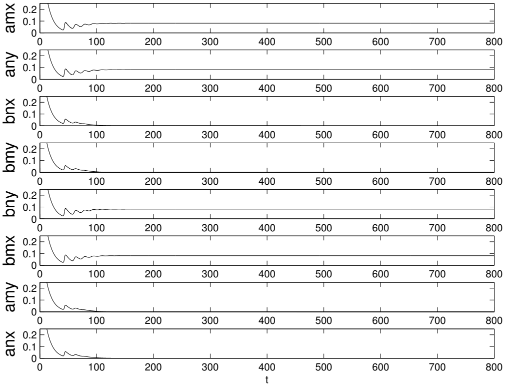
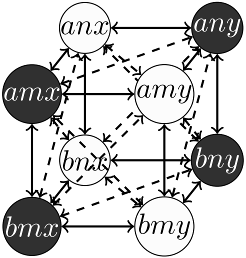




Simulations for System (2)

- Levels of the y_{ij} are shown here.





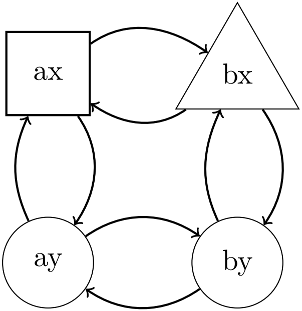
Outline

Biological Considerations

- Connect the strain structure observations and mathematical analysis.
- Strength of cross-protection and topology determine the strain structure.
- Was the strain space realistic?

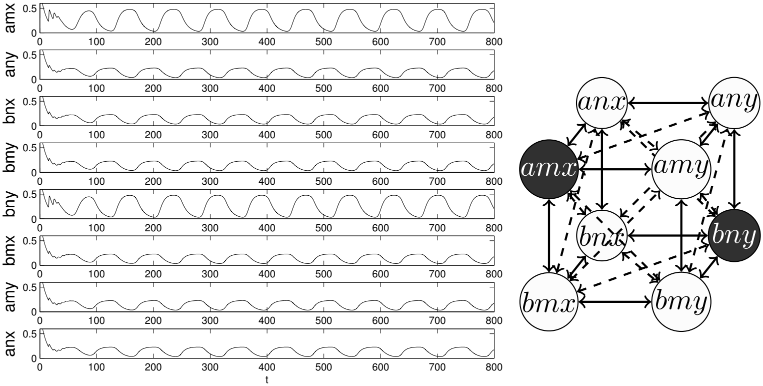
Mathematical Considerations

- Why not use the symmetry method?
  - Symmetry will likely not exist in a more realistic configuration.
- Suppose we the parameters of ax and bx are no longer identical the other systems:



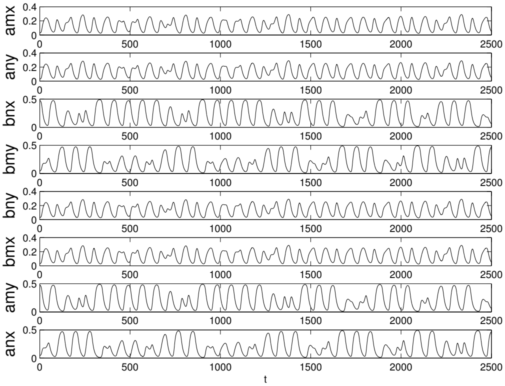
Other Possible Partial Synchrony Solutions

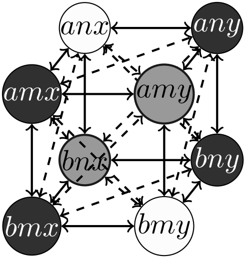
- Hopf bifurcation that follows 2-colour balanced synchrony pattern is possible.



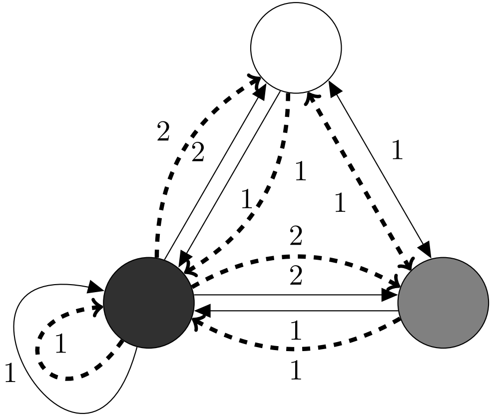
Simulations for System (2)

- Synchronized chaos is also possible.





Corresponding Quotient Network



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