Asynchronous oscillations due to antigenic variation in Malaria Pf

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Outline

Introduction

Modeling

Synchronous oscillations

Asynchronous oscillations

Summary

Additional material
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Synchronous oscillations

Asynchronous oscillations

Summary

Additional material
Delays in disease

- Physical origins
  - “Transit time” of biological process.

- Modeling
  - Constant coefficient ODEs: exponential distribution. “Easy” to analyze.
  - Delay DEs: step distributions.
Delays in disease

• Physical origins
  + “Transit time” of biological process.

• Modeling
  + Constant coefficient ODEs: exponential distribution. “Easy” to analyze.
  + Integro-differential Es: arbitrary distributions. “Hard” to analyze.
  + Delay DEs: step distributions.
Delay induced oscillations

- **ODE:** \( x(t)' = rx(t) \)
  - Let \( x(t) \sim \exp(\lambda t) \).
  - Characteristic equation: \( \lambda = r \).
  - There exists a single real value \( \lambda \), implying exponential growth or decay.

- **DDE:** \( x(t)' = rx(t - \tau) \)
  - Let \( x(t) \sim \exp(\lambda t) \).
  - Characteristic equation: \( \lambda = re^{-\lambda \tau} \).
  - Let \( \lambda = \sigma + i\omega \)
    
    \[ \sigma = re^{-\sigma \tau} \cos(\omega \tau), \quad \omega = -re^{-\sigma \tau} \sin(\omega \tau) \]
  - Transcendental equations with multiple solutions
  - Allows for oscillatory solutions to a first-order DDE.
Delay induced oscillations

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Malaria Map

Malaria cases (per 100,000) by country, latest available data

Data Source: WHO/Malaria Department
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization
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The presentation of material on the maps contained herein does not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or areas or of its authorities, or concerning the delineation of its frontiers or boundaries.
Malaria Life Cycle

- Inter-host vs. Intra-host
- Blood cycle
- Parasitized RBCs rupture $\rightarrow$ 10-30 new parasites.
- Parasite generations lead to fever, etc.
- PRBCs avoid splenic removal by cytoadhering to arterial walls.
- Must attack with immune response. Antibodies and T-Lymphocytes recognize antigens displayed on PRBCs.
Plasmodium Falciparum

- Four strains of malaria in humans.
- P. vivax is the most common.
- P. falciparum is the most dangerous.
  + Highest parasite load in host.
  + Cytoadhering leads to clogging of arteries in cerebrum. *cerebral malaria*
  + Leading cause of death in humans by malaria
Antigenic variation in Pf

- Evade the host’s IR and prolonged infection by changing the dominate genetic variant.
  - Parasite varies the major epitope on antigen PfEMP1.
  - Epitope: binding sites for immune response effectors.
- In the population there are \( \sim \) 60 variants defined by unique major epitopes
  - An individual will have \(<\,\,60\,(10-20)\) variants.
  - Variants will share minor epitopes.
- Individuals exhibit switching (oscillations) of the dominant variant.
  - Sequential dominance.
  - Prevents IR from maintaining a prolong attack against a single variant.
  - Evolutionary survival strategy.
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Antigenic variation in Plasmodium Falciparum

- Molecular switching mechanisms in a single cell are known.
- Coordination of the parasite population is not well understood.
- Recker et al. proposed an interaction between the variants via the minor epitopes.
  - Switching occurs as a natural dynamic of the host's IR.
  - No external switching mechanism or rule is needed.

Recker et al.,

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Recker et al.,

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Model of Recker and Gupta


- $Y_j$: variant $j$ parasitized red-blood cells.
- $Z_j$: variant $j$ specific immune response.
- $W_j$: cross-reactive immune response affecting variant $j$.
Model of Recker and Gupta

Parasitized RBCs: proliferation - removal due to IR.

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

Variant specific IR: stimulation - natural degradation.

\[ \frac{dZ_j}{dT} = \beta Y_j |_T - \mu Z_j \]

Cross-reactive IR: multi-variant stimulation - natural degradation.

\[ \frac{dW_j}{dT} = \beta' \sum_k \xi_{jk} Y_k |_T - \mu' W_j \]

Delayed activation of IR (Mitchell & Carr)

\[ Y_k |_T = Y_k (t - T) \]
Some assumptions

- **Specific IR** \((z)\) is long lived relative to the **cross-reactive IR** \((w)\).

\[
0 < \mu \ll \mu' \ll 1
\]

- Complete sharing of minor epitopes \(\Rightarrow\) global coupling.

\[
\sum_k \xi_{jk} Y_k|_\mathcal{T} \text{ with } \xi_{jk} = 1
\]

\[
\Rightarrow \sum_{k=1}^n Y_k|_\mathcal{T}
\]
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\[
\sum_{k} \xi_{jk} Y_k \big|_T \text{ with } \xi_{jk} = 1
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\[
\Rightarrow \sum_{k=1}^{n} Y_k \big|_T
\]
Steady states

- Disease free: \((Y_j, Z_j, W_j) = (0, 0, 0)\). Unstable.

- Nonuniform: \((Y_j, Z_j, W_j) \neq 0\). Unstable.

- Uniform: \((Y_j, Z_j, W_j) = (Y_0, Z_0, W_0)\). Stable.
Rescale and nondimensionalize

New variables are deviations from the uniform steady-state \((y_j, z_j, w_j) = (0, 0, 0)\)

\[
\begin{align*}
\frac{dy_j}{dt} &= -(z_j + w_j)(1 + y_j) \\
\frac{dz_j}{dt} &= \frac{c}{n} y_j|_\tau - az_j \\
\frac{dw_j}{dt} &= \frac{1}{n} \sum_{k=1}^{n} y_k|_\tau - abw_j,
\end{align*}
\]

\[
a = \sqrt{\frac{d\mu}{\phi}}, \quad b = \frac{\mu'}{\mu}, \quad c = \frac{\alpha\beta}{\alpha'\beta'}, \quad \text{and} \quad \tau = \sqrt{\frac{\mu\phi}{dT}}.
\]

\(0 < \mu \ll \mu' \ll 1\)
Synchronous vs. Asynchronous

- **Synchronous**: $y_j(t) = y(t)$, etc.
  \[
  \frac{1}{n} \sum_{k=1}^{n} y_k|_{\tau} = y(t)
  \]

- **Asynchronous**: $y_j(t) \neq y_k(t)$, etc

- The plan...
  + Synchronous linear stability
  + Asynchronous linear stability
  + Asynchronous nonlinear dynamics
Synchronous vs. Asynchronous

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Decay: oscillatory or monotonic?

\[ \gamma = \frac{\alpha'}{\alpha} \]

- \( \mu' = 0.04 \)
- \( \gamma_u \)

- \( \mu' = 0.01 \)
- \( \gamma_l \)

- \( \gamma = 1.5 \)
- \( (a) \)

- \( \gamma = 1 \)
- \( (b) \)

- \( \gamma = 0.1 \)
- \( (c) \)

\( \mu = \text{variant specific IR death rate} \ll 1 \)
Decay: oscillatory or monotonic?

\[ \gamma \equiv \frac{\alpha'}{\alpha} = \frac{\text{removal rate due to cross-reactive IR}}{\text{removal rate due to specific IR}} \]

- If \( \gamma \) is sufficiently large or small then there are oscillations.
- Decreasing (increasing) the number of shared or minor epitopes \( n \), shifts both critical values up (down).
- \( \mu \) can be set such that there are always decaying oscillations.
  - The variant-specific IR can be quite slow, while still being large enough to guarantee oscillations.
Decay: rates

\[
Decay \ rate \sim ab = \left[ \left( \frac{E_Z + E_W}{E_W} \right) \left( \frac{\mu'}{\phi} \right) \right]^{1/2},
\]

\[
E_Z \equiv \frac{\alpha \beta}{\mu} \quad \text{and} \quad E_W \equiv \frac{\alpha' (n \beta')}{\mu'}.
\]

- \( E_{Z,W} = \) efficacy of the specific and cross-reactive IR.
- The farther away one moves from the triangular region the variants oscillate with faster decay.
- Increasing the specific efficacy relative to the cross-reactive efficacy leads to faster decay.
Decay: rates

Decay rate \( \sim ab = \left[ \left( \frac{E_Z + E_W}{E_W} \right) \left( \frac{\mu'}{\phi} \right) \right]^{1/2} \),

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- The farther away one moves from the triangular region the variants oscillate with faster decay.
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Delayed IR

\[ \lambda^3 + a(1 + b)\lambda^2 + a^2 b \lambda + e^{-\lambda\tau}[(1 + q)\lambda + a(1 + qb)] = 0. \]

\[ \mathcal{T}_h = \frac{1}{\phi} \left( \frac{E_z + E_w}{E_w} \right). \]

- Parasite generation rate \( \phi \uparrow \Rightarrow \mathcal{T}_h \downarrow. \)
  System is more susceptible to delay induced oscillations.
- \( E_z \gg E_w \Rightarrow \mathcal{T}_h \uparrow. \)
  Decreases the sensitivity of the system.
- \( E_z \ll E_w \Rightarrow \mathcal{T}_h \sim 1/\phi. \)

Thus, just as a strong parasite generation rate and a strong cross-reactive IR lead to decaying oscillations in the case of instantaneous IR, they also decrease the minimum value of delay necessary to excite persistent oscillations.
Delayed IR

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Asynchronous linear stability

- $3 \times n$ system of equations.

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\begin{align*}
\frac{dy_j}{dt} &= -(z_j + w_j)(1 + y_j) \\
\frac{dz_j}{dt} &= \frac{c}{n}y_j|_\tau - az_j \\
\frac{dw_j}{dt} &= \frac{1}{n} \sum_{k=1}^{n} y_k|_\tau - abw_j,
\end{align*}
\]

- Characteristic equation with $3 \times n$ roots.

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

\[
\begin{align*}
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].
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Asynchronous linear stability

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$$
Sync vs. Antiphase eigenvectors

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

- \(n - 1\) roots from \(F_1\). Always stable.
- 3 roots from \(F_s\).
  - Same as synchronous case with “synchronized” eigenvector \(v_j = v\).
- 2\((n - 1)\) roots from \(F_{ap}\).
  - “ap” = antiphased eigenvectors

\[
\sum_{j=1}^{n} v_j^{(y)} = 0 \quad \Rightarrow \quad v_{jm}^{(y)} = e^{i2\pi jm/n},
\]
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Decay rates, NO DELAY

- **Antiphase**: $1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \rightarrow \ldots$

- **Decay rates**: synchronous vs. asynchronous

\[ \sigma_s \sim -\frac{1}{2\mu'} \text{ faster than } \sigma_{ap} \sim -\frac{1}{2\mu} \]
Long-time observation is async: NO DELAY

- Given an arbitrary initial condition...
- Complex oscillations can be decomposed into a sum of synchronous and antiphase oscillatory modes...
- The synchronous component decays fast...
- Observe some combination of antiphase oscillations...
  $\Rightarrow$ observe asynchronous oscillations.
Given an arbitrary initial condition...
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- Given an arbitrary initial condition...
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  ⇒ observe asynchronous oscillations.
Linear stability: $\tau \neq 0$

- Hopf bifurcation to persistent oscillations.
- Synchronous:
  \[
  T_s = \frac{1}{\phi} \left( \frac{E_z + E_w}{E_w} \right) .
  \]
- Antiphase
  \[
  T_{ap} = \frac{1}{\phi} \left( \frac{E_z + E_w}{E_z} \right) .
  \]
Sync vs. Antiphase: $\tau \neq 0$

- Increasing $\mu$ ⇒ weakens specific IR
  - Cross-reactive IR $\gg$ specific IR
  - Couples variants
  - synchronous.

- Increasing $\mu'$ ⇒ weakens cross-reactive IR
  - Specific IR $\gg$ cross-reactive
  - Decouples variants
  - asynchronous.
Sync vs. Antiphase: $\tau \neq 0$

**Increasing $\mu$ ⇒ weakens specific IR**
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**Increasing $\mu'$ ⇒ weakens cross-reactive IR**
- Specific IR $\gg$ cross-reactive
  - Decouples variants
  - asynchronous.

$slope = \frac{n\alpha'\beta'}{\alpha\beta}$
Hopf bifurcation to asynchronous oscillations

- Near Hopf point.
  \[ \tau = \tau_h + \epsilon^2 \tau_2. \]
- Multiple time scales \( t \) and \( s = \epsilon^2 t \).
- Expand \( y = \epsilon y^{(1)} + \epsilon^2 y^{(2)} + \ldots \)
- Expand the delay term:
  \[ y_j(t-\tau, s-\epsilon^2 \tau) = y_j \bigg|_{\tau_h} - \epsilon^2 \left( \tau_2 \frac{\partial y_j}{\partial t} \bigg|_{\tau_h} + \tau_h \frac{\partial y_j}{\partial s} \bigg|_{\tau_h} \right) + O(\epsilon^4), \]
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- Near Hopf point.
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- Multiple time scales \( t \) and \( s = \epsilon^2 t \).
- Expand \( y = \epsilon y^{(1)} + \epsilon^2 y^{(2)} + \ldots \)
- Expand the delay term:
  \[ y_j(t - \tau, s - \epsilon^2 \tau) = y_j|_{\tau_h} - \epsilon^2 \left( \tau_2 \left. \frac{\partial y_j}{\partial t} \right|_{\tau_h} + \tau_h \left. \frac{\partial y_j}{\partial s} \right|_{\tau_h} \right) + O(\epsilon^4), \]
Antiphase oscillations as basis

- The leading order, $O(\epsilon)$ problem is linear.

\[ \frac{\partial}{\partial t} \vec{Y}^{(1)} = J|_{\tau_h} \cdot \vec{Y}^{(1)}, \]

- Solution decomposed as a sum of the antiphase eigenvectors.

\[
\begin{align*}
    x_j^{(1)} &= -i\omega_h y_j^{(1)} + \text{e.d.t.}, \\
    y_j^{(1)} &= \sum_{m=1}^{n-1} A_m(s) v_{jm} e^{i\omega_h t} + \text{c.c.} + \text{e.d.t.}, \\
    w_j^{(1)} &= 0 + \text{e.d.t.},
\end{align*}
\]

- $A_m(s)$, $m = 1, 2, \ldots, n - 1$ are slowly varying amplitudes.
- Determined by solvability condition at $O(\epsilon^3)$.

\[
\frac{dA_m}{ds} = \tau_2(f_2 + ig_2)A_m + (f_3 + ig_3)\hat{A}_m + (f_4 + ig_4)\hat{A}_n A_{n-m}^*,
\]
Two examples for $n = 3$

- (a) *Pure* antiphase with $A_1 \neq 0$, $A_2 = 0$
  
  \[ 1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \rightarrow \ldots \]

- (b) *Combination* of basis $A_1 = A_2 \neq 0$
  
  \[ 1 \rightarrow 2 \rightarrow 3 \rightarrow 1 \rightarrow \ldots \oplus 1 \rightarrow 3 \rightarrow 2 \rightarrow 1 \rightarrow \ldots \]
Two examples for $n = 3$

(a) $\bar{y} \sim 2\sqrt{\frac{f_2 \cdot (\tau - \tau_h)}{f_3}} \begin{pmatrix} \cos \left(\theta(t) + \frac{2\pi}{3}\right) \\ \cos \left(\theta(t) + \frac{4\pi}{3}\right) \\ \cos(\theta(t) + 0) \end{pmatrix}$

(b) $\bar{y} = 2\sqrt{\frac{f_2 \cdot (\tau - \tau_h)}{f_3 + 2f_4}} \begin{pmatrix} -1 \\ -1 \\ 2 \end{pmatrix} \cos \theta(t)$

$y_{max} \sim \frac{\phi E_Z}{E_z + E_w} \sqrt{\frac{6}{\mu (T - T_{ap})}}$

- $\phi$ or $E_Z \uparrow \Rightarrow$ larger amplitude.
Transient and persistent chaotic oscillations

\[ \tau = 0.0900 \]

\[ \tau = 0.1100 \]

\[ \tau = 0.1300 \]
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Summary: synchronous oscillations

- **Key model assumptions:**
  - Variant specific + cross-reactive IR $\Rightarrow$ sequential dominance.
  - Variant specific $\mu \ll$ cross-reactive $\mu'$.

- **Synchronous oscillations:**
  - Identify IR efficacies as useful parameters.
  
  $E_Z \equiv \frac{\alpha \beta}{\mu}$ and $E_W \equiv \frac{\alpha'(n\beta')}{\mu'}$.

  - A large parasite generation rate and a strong cross-reactive IR favors oscillations.
  - Increases the sensitivity to persistent oscillations due to external "forces" such as a delayed IR.

- **Pulsating solutions** $\Rightarrow Y \approx 0$ for long times. Poorly timed measurements of the system could be misleading.
Summary: sync. vs async. oscillations

- Asynchronous oscillations $= \sum$ antiphasic.
- Synchronous: decay rate $E_W$ and is fast.
  Antiphase: decay rate $E_Z$ and is slow.
  Given arbitrary ICs, the likely observation is asynchronous oscillations.
- The frequency of async. is higher than synth.
  Forces the immune system to respond faster.
- Inc/dec $E_W$ relative to $E_Z$ strengthens/weakens coupling.
  - Strong coupling: synchronous oscillations.
  - “Balanced” coupling: sequential dominance.
  - Very weak coupling: uncoordinated oscillations.
Open questions

- Less than complete set of minor variants.
- Dynamics on network.
- Stronger physiologically based model.
Outline

Introduction

Modeling

Synchronous oscillations

Asynchronous oscillations

Summary

Additional material
Model of Recker and Gupta

- Mitchell and Carr, *submitted*
Warning! Taylor series with delay can be misleading

From R.D. Driver, “Ordinary and Delay Differential Equations”

\[ x' = -2x(t) + x(t - \tau) \]

Let \( x = e^{\lambda t} \)

\[ \lambda = -2 + e^{-\lambda \tau} \]

\[ \sigma + 2 = e^{-\sigma \tau} \cos(\omega \tau), \quad \omega = -e^{-\sigma \tau} \sin(\omega \tau) \]

Consider the real-part equation

\[ |\sigma + 2| \leq e^{-\sigma \tau} \]

\( \sigma < 0: \) Exponentially decay-ing solutions
Small delay: $\tau \ll 1$

\begin{align*}
x' &= -2x(t) + x(t - \tau) \\
x' &= -2x(t) + [x(t) - \tau x'(t) + \frac{1}{2}\tau^2 x''(t) + \ldots]
\end{align*}

Let $x = e^{\lambda t}$ and keep $O(\tau^2)$

\begin{align*}
\lambda &= -2 + [1 - \tau \lambda + \frac{1}{2}\tau^2 \lambda^2] \\
\frac{1}{2}\tau^2 \lambda^2 - (\tau + 1)\lambda + 1 &= 0 \\
\lambda &= \frac{(\tau + 1) \pm \sqrt{(\tau + 1)^2 - 2\tau^2}}{\tau^2}
\end{align*}

$\lambda_+ > 0$ for all $\tau$: Exponentially growing solutions. Must validate analytical results with numerical simulations.