Asynchronous oscillations due to antigenic variation in Malaria Pf

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Outline

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Delays in disease

- Physical origins
  - + Latency time between compartments.
    Incubation time. Infectious time. Temporary Immunity.
  - + "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.

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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 λ, 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.

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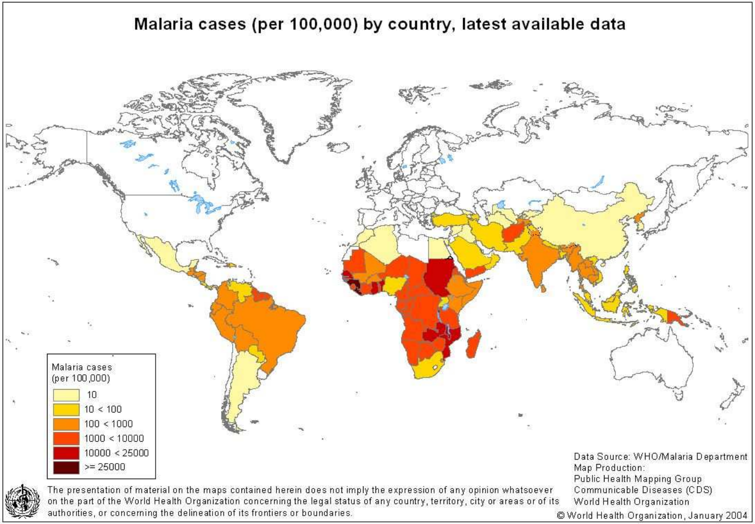
Malaria Map


Malaria cases (per 100,000) by country, latest available data
Malaria cases
(per 100,000)
10
10 < 100
100 < 1000
1000 < 10000
10000 < 25000
>= 25000
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.
Data Source: WHO/Malaria Department
Map Production:
Public Health Mapping Group
Communicable Diseases (CDS)
World Health Organization
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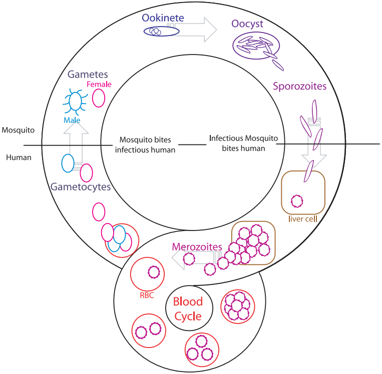
Malaria Life Cycle



- 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.

Plasomodium 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.
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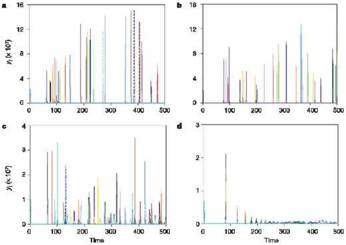
Antigenic variation in Plasomodium Falciparum

- 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 *hosts IR*.
  - + No external switching mechanism or rule is needed.



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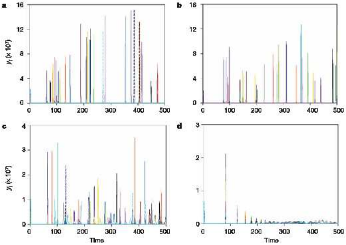

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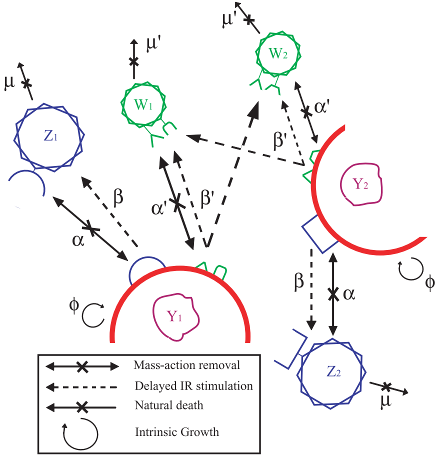
Model of Recker and Gupta

Bull. Math. Bio (2006) 68: 821-835



- 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.

$$\frac{dZ_j}{dT} = \beta Y_j|_{\mathcal{T}} - \mu Z_j$$

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

$$\frac{dW_j}{dT} = \beta' \sum_k \xi_{jk} Y_k|_{\mathcal{T}} - \mu' W_j$$

Delayed activation of IR (Mitchell & Carr)

$$Y_k|_{\mathcal{T}} = Y_k(t - \mathcal{T})$$

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.

$$\sum_k \xi_{jk} Y_k|_T \text{ with } \xi_{jk} = 1$$

$$\Rightarrow \sum_{k=1}^{n} Y_k|_T$$

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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 $(y_j, z_j, w_j) = (0, 0, 0)$

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

$$a = \sqrt{\frac{d\mu}{\phi}}, \quad b = \frac{\mu'}{\mu}, \quad c = \frac{\alpha\beta}{\alpha'\beta'} \quad \text{and } \tau = \sqrt{\frac{\mu\phi}{d}}\mathcal{T}.$$

$$0 < \mu \ll \mu' \ll 1$$

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

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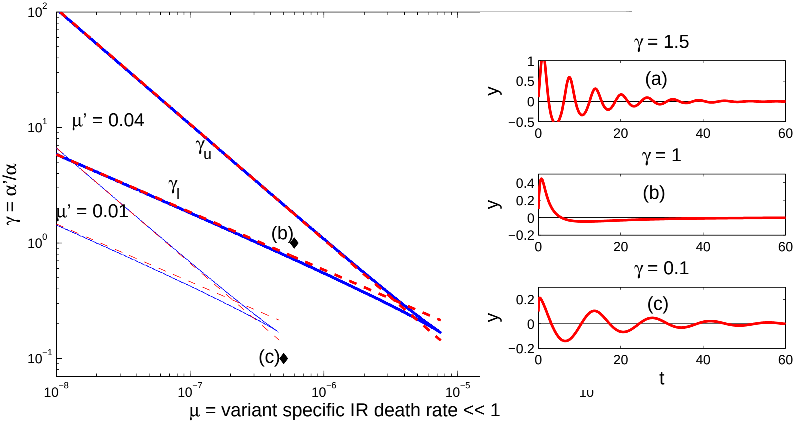
Synchronous linear stability
Decay: oscillatory or monotonic?



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 γ is sufficiently large or small then there are oscillations.
- Decreasing (increasing) the number of shared of minor epitopes *n*, shifts both critical values up (down).
- μ 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

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

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

- $E_{Z,W}$ = *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.

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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.

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Asynchronous linear stability

- $3 \times n$ system of equations.

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

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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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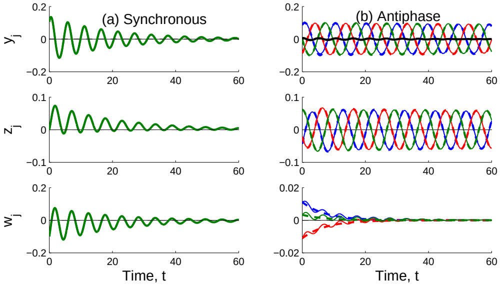
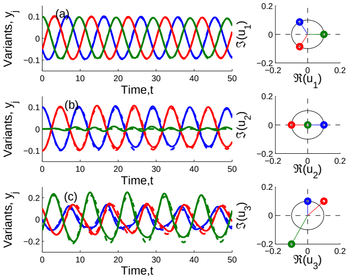


- Antiphase: $1 \to 2 \to 3 \to 1 \to \dots$
- Decay rates: synchronous vs. asynchronous

$$\sigma_s \sim -\frac{1}{2}\mu' \quad \text{faster than} \quad \sigma_{ap} \sim -\frac{1}{2}\mu$$

Long-time observation is async: NO DELAY



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- 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 . . .
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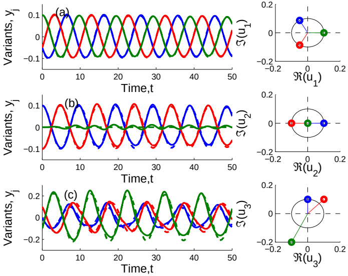

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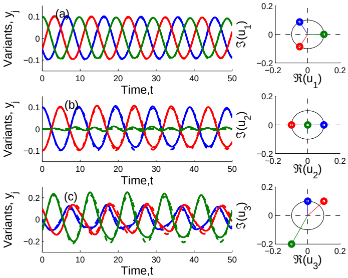

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Linear stability: $\tau \neq 0$

- Hopf bifurcation to persistent oscillations.
- Synchronous:

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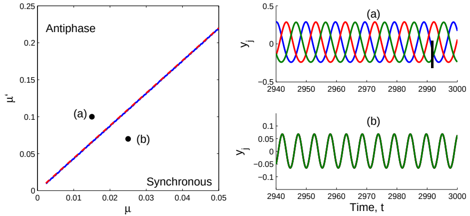

$$\text{slope} = \frac{n\alpha'\beta'}{\alpha\beta}$$

- Increasing $\mu \Rightarrow$ weakens specific IR
  - Cross-reactive IR $\gg$ specific IR
    $\Rightarrow$ Couples variants
    $\Rightarrow$ synchronous.
- Increasing $\mu' \Rightarrow$ weakens cross-reactive IR
  - Specific IR $\gg$ cross-reactive
    $\Rightarrow$ Decouples variants
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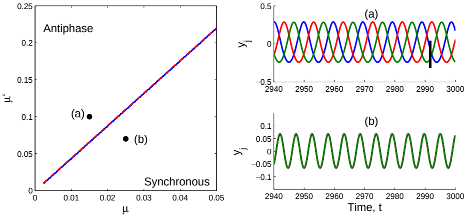
Sync vs. Antiphase: $\tau \neq 0$



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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 $y = \epsilon y^{(1)} + \epsilon^2 y^{(2)} + \dots$
- Expand the delay term:

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

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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.

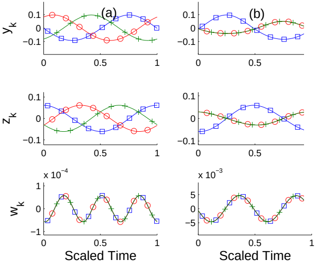
$$\begin{aligned} x_j^{(1)} &= -i\omega_h y_j^{(1)} + \text{e.d.t.}, \\ y_j^{(1)} &= \sum_{m=1}^{n-1} A_m(s) v_{jm} e^{i\omega_h t} + \text{c.c.} + \text{e.d.t.}, \\ w_j^{(1)} &= 0 + \text{e.d.t.}, \end{aligned}$$

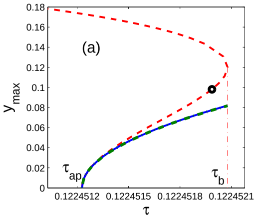
- $A_m(s)$, $m = 1, 2, \ldots, n-1$ are slowly varying amplitudes.
- Determined by solvability condition at $O(\epsilon^3)$.

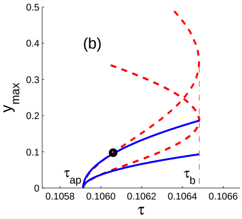
$$\frac{dA_m}{ds} = \tau_2(f_2 + ig_2)A_m + (f_3 + ig_3)\hat{A}_m + (f_4 + ig_4)\tilde{A}_n A^*_{n-m},$$

Two examples for $n = 3$

- (a) *Pure* antiphase with $A_1 \neq 0$, $A_2 = 0$
  $1 \to 2 \to 3 \to 1 \to \ldots$
- (b) *Combination* of basis $A_1 = A_2 \neq 0$
  $1 \to 2 \to 3 \to 1 \to \ldots \oplus 1 \to 3 \to 2 \to 1 \to \ldots$



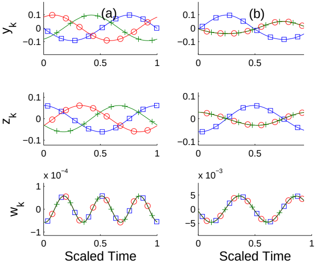


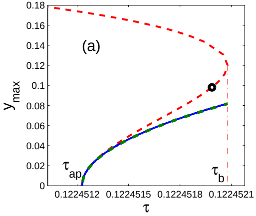


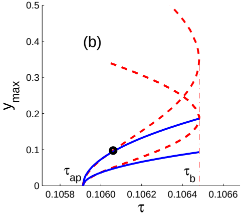
Two examples for $n = 3$

$$\text{(a) } \vec{y} \sim 2\sqrt{-\frac{f_2 \cdot (\tau - \tau_h)}{f_3}} \begin{pmatrix} \cos\left(\theta(t) + \frac{2\pi}{3}\right) \\ \cos\left(\theta(t) + \frac{4\pi}{3}\right) \\ \cos\left(\theta(t) + 0\right) \end{pmatrix} \qquad \text{(b) } \vec{y} = 2\sqrt{-\frac{f_2 \cdot (\tau - \tau_h)}{f_3 + 2f_4}} \begin{pmatrix} -1 \\ -1 \\ 2 \end{pmatrix} \cos\theta(t).$$

$$y_{max} \sim \frac{\phi E_Z}{E_Z + E_W}\sqrt{\frac{6}{\mu}(\mathcal{T} - \mathcal{T}_{ap})},$$

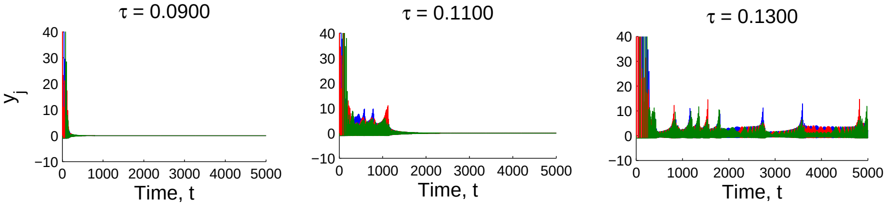






- ϕ or $E_Z \uparrow \Rightarrow$ larger amplitude.

Transient and persistent chaotic oscillations



Outline

Summary: synchronous oscillations

- Key model assumptions:
  + Variant specific + cross-reactive IR $\Rightarrow$ sequential dominance.
  + Variant specific $\mu \ll$ cross-reactive μ'.
- Synchronous oscillations:
  + Identify IR efficacies as useful parameters.

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

  + 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 $= \sum$ antiphase.
- 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 synch.
  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

Model of Recker and Gupta

- Recker et al., *Nature* (2004) 429:555-558
- Recker and Gupta, Bull. Math. Bio (2006) 68: 821-835
- De Leenheer and Pilyugin, *J. Biological Dynamics* (2008) 2:102-120
- Mitchell and Carr, *Bull. Math. Bio.* (2009) 72:590-610
- Blyuss and Gupta, *J. Math. Biol.* (2009) 58:923-937
- Mitchell and Carr, *submitted*

Warning! Taylor series with delay can be misleading

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

$$x' = -2x(t) + x(t-\tau)$$

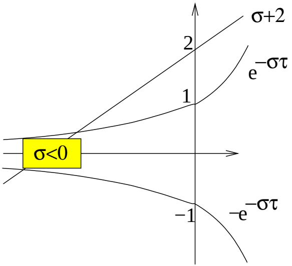
Let $x = e^{\lambda t}$

$$\lambda = -2 + e^{-\lambda\tau}$$

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

Consider the real-part equation

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



$\sigma < 0$: Exponentially decaying solutions

Small delay: $\tau \ll 1$

$$x' = -2x(t) + x(t-\tau)$$

$$x' = -2x(t) + [x(t) - \tau x'(t) + \frac{1}{2}\tau^2 x''(t) + \ldots]$$

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

$$\lambda = -2 + [1 - \tau\lambda + \frac{1}{2}\tau^2\tau^2]$$

$$\frac{1}{2}\tau^2\tau^2 - (\tau+1)\lambda + 1 = 0$$

$$\lambda = \frac{(\tau+1) \pm \sqrt{(\tau+1)^2 - 2\tau^2}}{\tau^2}$$

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