Predicting the potential impact of a cytotoxic T-lymphocyte HIV vaccine: How often should you vaccinate and how strong should the vaccine be?

Robert Smith?

The University of Ottawa
HIV vaccines

- HIV now infects 33 million adults worldwide
HIV vaccines

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• An HIV vaccine represents the best hope of controlling the disease
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- An HIV vaccine represents the best hope of controlling the disease
- $682 million is spent on HIV vaccine research annually.
Cytotoxic T Lymphocytes (CTLs)

- Cells with the ability to identify and destroy virally infected cells in the body
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- Activated via specific recognition of viral fragments
Cytotoxic T Lymphocytes (CTLs)

- Cells with the ability to identify and destroy virally infected cells in the body
- Activated via specific recognition of viral fragments
- One of the body’s best natural defence mechanisms.
CTL vaccines

- If CTLs can be boosted at regular intervals, they can attack infected T-helper cells
CTL vaccines

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• A vaccine that stimulates the CTL response has been described as the best hope for control of HIV
CTL vaccines

- If CTLs can be boosted at regular intervals, they can attack infected T-helper cells.
- A vaccine that stimulates the CTL response has been described as the best hope for control of HIV.
- Such a post-infection “vaccine” would be administered regularly and indefinitely.
Infected CD4\(^+\) T cells

- Die at death rate \(d\)
Infected CD4$^+$ T cells

- Die at death rate $d$
- Cleared by CTLs at rate $p$, proportional to the density of both types
Infected CD4⁺ T cells

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Key approximation:
Infected CD4$^+$ T cells

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- We assume the production rate of infected cells is constant, $\pi$
Infected CD4$^+$ T cells

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Key approximation:
- We assume the production rate of infected cells is constant, $\pi$
  (thus we use a steady-state viral load approximation when estimating parameters).
CTLs

- Proliferate at rate $\alpha$, proportional to density of both CTLs and infected T cells

*Three CTLs (blue) annihilate target cells (red)*
CTLs

- Proliferate at rate $\alpha$, proportional to density of both CTLs and infected T cells
- Die at death rate $\delta$.

*Three CTLs (blue) annihilate target cells (red)*
The model without vaccination

• Thus the model (without vaccination) is
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\[
\begin{align*}
\frac{dT}{dt} &= \pi - dT - pCT \\
\frac{dC}{dt} &= \alpha CT - \delta C.
\end{align*}
\]

\(T = \) infected T cells \(\pi = \) production rate \(d, \delta = \) death rates

\(C = \) CTLs \(\alpha = \) proliferation rate \(p = \) clearance rate
Steady states

Two steady states:
Steady states

Two steady states:

• trivial
  (no CTLs)

\[(\hat{T}, \hat{C}) = \left( \frac{\pi}{d}, 0 \right)\]

- \(T\)=infected T cells
- \(\pi\)=production rate
- \(d, \delta\)=death rates
- \(C\)=CTLs
- \(\alpha\)=proliferation rate
- \(p\)=clearance rate
Steady states

Two steady states:

• trivial (no CTLs)
  \((\hat{T}, \hat{C}) = \left( \frac{\pi}{d}, 0 \right)\)

• nontrivial (coexistence)
  \((\bar{T}, \bar{C}) = \left( \frac{\delta}{\alpha}, \frac{\alpha \pi - \delta d}{p \delta} \right)\).

\(T=\)infected \(T\) cells \(\pi=\)production rate \(d, \delta=\)death rates \(C=\)CTLs \(\alpha=\)proliferation rate \(p=\)clearance rate
Stability

- For the trivial steady state, the Jacobian is
For the trivial steady state, the Jacobian is

\[ J|_{(\hat{T},\hat{C})} = \begin{bmatrix} -d & -\frac{p\pi}{d} \\ 0 & \frac{\alpha\pi}{d} - \delta \end{bmatrix} \]

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- **π** = production rate
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- **α** = proliferation rate
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Thus unstable iff \( \bar{C} = (\alpha\pi - \delta d)/p\delta > 0 \)

• For the nontrivial steady state, the characteristic polynomial is

\[
\text{det}(J|_{(\bar{T},\bar{C})} - \lambda I) = \lambda^2 + (d + p\bar{C})\lambda + p\delta\bar{C}/\alpha
\]

\( T=\text{infected T cells} \quad \pi=\text{production rate} \quad d,\delta=\text{death rates} \)

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Stability

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  \[ J|_{(\hat{T},\hat{C})} = \begin{bmatrix} -d & -\frac{p\pi}{d} \\ 0 & \frac{\alpha\pi}{d} - \delta \end{bmatrix} \]
  Thus unstable iff \( \bar{C}' = (\alpha\pi - \delta d)/p\delta > 0 \)

- For the nontrivial steady state, the characteristic polynomial is
  \[ \det(J|_{(\bar{T},\bar{C})} - \lambda I) = \lambda^2 + (d + p\bar{C})\lambda + p\delta\bar{C}/\alpha \]
  Thus stable whenever \( \bar{C}' > 0 \).

\( \bar{T} = \text{infected } T \text{ cells} \quad \pi = \text{production rate} \quad d,\delta = \text{death rates} \)
\( C = \text{CTLs} \quad \alpha = \text{proliferation rate} \quad p = \text{clearance rate} \)
Stability

Hence:
Stability

Hence:

- the trivial steady state is unstable iff the nontrivial steady state exists in the positive plane
Stability

Hence:

- the trivial steady state is unstable iff the nontrivial steady state exists in the positive plane.
- the nontrivial steady state is asymptotically stable whenever it exists in the positive plane.
Nontrivial $eq^m$ absent $\iff$ trivial $eq^m$ stable
Nontrivial $eq^m$ stable in the positive plane
Vaccination

- A fixed boost of CTLs, $C^i$
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- Given at regular times, $t_k$
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Vaccination

- A fixed boost of CTLs, $C^i$
- Given at regular times, $t_k$
- We assume the vaccine effect is instantaneous...

...this results in a series of *impulsive differential equations.*
Impulsive effect

• According to impulsive theory, we can describe the nature of the impulse at time $r_k$ via the difference equation
Impulsive effect

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\[ \Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-)) \]
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$$\Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-))$$

- Difference equation
- Depends on the time of impulse and the state immediately beforehand.
Impulsive DEs

- Solutions are continuous for $t \neq r_k$

Thousands of HIV particles emerging from an infected T-cell

$r_k$ = impulse time
Impulsive DEs

- Solutions are continuous for $t \neq r_k$
- Solutions undergo an instantaneous change in state when $t = r_k$.

Thousands of HIV particles emerging from an infected T-cell

$r_k=$impulse time
Putting it together

- The model thus consists of a system of ODEs (infected T cells and CTLs) together with a difference equation (CTL boost).
Impulsive interruption

- The impulsive effect "interrupts" the continuous trajectories
Impulsive interruption

- The impulsive effect "interrupts" the continuous trajectories
- The cycle is restarted
Impulsive interruption

- The impulsive effect “interrupts” the continuous trajectories.
- The cycle is restarted.
- It continues until the next “interruption”.

![Graph showing the relationships between infected T cells and CTLs over time.](image-url)

**Infected T cells**

**CTLs**
The model (with vaccination)

- Thus, the impulsive model is
The model (with vaccination)

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\[
\frac{dT}{dt} = \pi - dT - pCT \quad t \neq t_k \\
\frac{dC}{dt} = \alpha CT - \delta C \quad t \neq t_k \\
\Delta C = C^i \quad t = t_k.
\]

<table>
<thead>
<tr>
<th>T=infected T cells</th>
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Implicit solution within a cycle

• Since

\[ C' = C(\alpha T - \delta) \]

*T=infected cells  C=CTLs  \alpha=proliferation rate  \delta=death rate*
Implicit solution within a cycle

• Since

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\[ \int_0^t \frac{dC}{C} = \int_0^t (\alpha T(u) - \delta) \, du \]

\[ T = \text{infected cells} \quad C = \text{CTLs} \]
\[ \alpha = \text{proliferation rate} \quad \delta = \text{death rate} \]
Implicit solution within a cycle

- Since

\[ C' = C(\alpha T - \delta) \]

\[ \int_0^t \frac{dC}{C} = \int_0^t (\alpha T(u) - \delta) du \]

\[ \therefore C(t) = C(0)e^{\int_0^t (\alpha T(u) - \delta) du} \]

\( T = \) infected cells  \( C = \) CTLs  
\( \alpha = \) proliferation rate  \( \delta = \) death rate
Defining $T_{\text{int}}$

- Define

where $\tau = t_{k+1} - t_k$ is the vaccine administration interval (assumed constant)

- $T_{\text{int}}$ is a measure of the ratio of the number of CTLs at the end of an impulsive cycle to those at the beginning

$T=\text{infected T cells}$, $\alpha=\text{proliferation rate}$, $\delta=\text{death rate}$, $t_k=\text{vaccination time}$
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$T=$infected T cells  \( \alpha \)=proliferation rate  
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where $\tau = t_{k+1} - t_k$ is the vaccine administration interval (assumed constant)

- $T_{int}$ is a measure of the ratio of the number of CTLs at the end of an impulsive cycle to those at the beginning

- Thus, $T_{int} < 1$ is necessary for an impulsive orbit to exist.

$T=$infected $T$ cells  $\alpha=$proliferation rate  
$\delta=$death rate  $t_k=$vaccination time
An impulsive periodic orbit

• In particular, if $C(0^+) = \frac{C^i}{1-T_{\text{int}}}$
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C(\tau^+) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}} + C^i
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$T_{\text{int}}$=cell ratio measure  $C=$CTLs  $C'=$vaccine strength  $\tau=$vaccination period
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= \frac{C^i}{1 - T_{\text{int}}}
\]

\[
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- \( T_{\text{int}} \) = cell ratio measure
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- \( C^i \) = vaccine strength
- \( \tau \) = vaccination period
The orbit, with endpoints

- Thus we have an impulsive periodic orbit
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\[ C'(t) = \frac{C^i e^{\int_0^t (\alpha T(u) - \delta) du}}{1 - T_{int}} \]

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for \(0 < t < \tau\)

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Endpoints of the impulsive orbit are

- \( T_{int} \) = cell ratio measure
- \( C \) = CTLs
- \( C^i \) = vaccine strength
- \( \alpha \) = proliferation rate
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The orbit, with endpoints

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• Endpoints of the impulsive orbit are

\[ C(0^+) = \frac{C^i}{1 - T_{\text{int}}} \quad \text{and} \quad C(\tau^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}} . \]

\( T_{\text{int}} = \) cell ratio measure \( C = \) CTLs \( C^i = \) vaccine strength \( \alpha = \) proliferation rate \( \delta = \) death rate \( \tau = \) vaccination period
Impulsive Floquet Theory

- From the impulsive DEs, define
Impulsive Floquet Theory

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\[ P(T, C) = \pi - dT - pCT \]
\[ Q(T, C) = \alpha CT - \delta C \]
\[ a(T, C) = 0 \]
\[ b(T, C) = C^i, \]

\( \pi \) = production rate
\( \delta, d \) = death rates
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\alpha(T, C) = 0 \\
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\]

with the (differentiable) function \( \phi \) defined implicitly by

\[
\{ \phi(T(t), C(t)) = 0 : t = t_k \}
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Reworks impulse times as a smooth function.
Impulsive Floquet Theory

- Let \((\xi, \eta)\) define the periodic orbit
Impulsive Floquet Theory

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• Then
Impulsive Floquet Theory

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- Then

\[\xi(t_k^-) = \xi(t_k^+) = T(\tau)\]

\(T=\text{infected } T \text{ cells}\) \(C=\text{vaccine strength}\) 
\(\tau=\text{vaccination period}\) \(t_k=\text{impulse times}\)
Impulsive Floquet Theory

• Let \((\xi, \eta)\) define the periodic orbit

Then

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No impulse in \(T\)

\(T=\text{infected T cells}\) \quad \(C_i=\text{vaccine strength}\)

\(\tau=\text{vaccination period}\) \quad \(t_k=\text{impulse times}\)
Impulsive Floquet Theory

- Let \((\xi, \eta)\) define the periodic orbit
- Then

\[
\xi(t_k^-) = \xi(t_k^+) = T(\tau)
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\[
\eta(t_k^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}}
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\xi(t_k^-) & = \xi(t_k^+) = T(\tau) \\
\eta(t_k^-) & = \frac{C^i T_{int}}{1 - T_{int}} \\
\eta(t_k^+) & = \frac{C^i}{1 - T_{int}}.
\end{align*}
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No impulse in T

\(T=\text{infected } T \text{ cells} \quad C^i=\text{vaccine strength} \quad \tau=\text{vaccination period} \quad t_k=\text{impulse times}\)
Nontrivial 2D Floquet multiplier

- The nontrivial Floquet multiplier is

\[(\xi, \eta) = (T, C) \] periodic orbit
\[t_k = \text{impulse times}\]
\[P, Q = \text{differential equations}\]
\[a, b = \text{impulsive effects}\]
\[\phi = \text{implicit impulse function}\]
Nontrivial 2D Floquet multiplier

• The nontrivial Floquet multiplier is

\[ \mu_2 = \Delta_1 \exp \left[ \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \right] \]

\((\xi, \eta)\) = (T, C) periodic orbit  \(t_k\) = impulse times
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• where

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• where

$$\Delta_1 = \frac{P_+ \left( \frac{\partial b}{\partial C} \frac{\partial \phi}{\partial T} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial T} \right) + Q_+ \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial a}{\partial C} \frac{\partial \phi}{\partial T} + \frac{\partial \phi}{\partial C} \right)}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} ;$$

$(\xi, \eta)=(T,C)$ periodic orbit $t_k=$impulse times
$P,Q=$differential equations $a,b=$impulsive effects
$\phi=$implicit impulse function
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\mu_2 = \Delta_1 \exp \left[ \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \right]
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\]

\(P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial T}\) and \(\frac{\partial \phi}{\partial C}\) are computed at the point \((\xi(t_k^-), \eta(t_k^-))\) and \(P_+ = P(\xi(t_k^+), \eta(t_k^+)), Q_+ = Q(\xi(t_k^+), \eta(t_k^+))\).

- \((\xi, \eta) = (T, C)\) periodic orbit \(t_k = \) impulse times
- \(P, Q = \) differential equations \(a, b = \) impulsive effects
- \(\phi = \) implicit impulse function
Nontrivial 2D Floquet multiplier

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\[ \mu_2 = \Delta_1 \exp \left[ \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \right] \]

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\[ \Delta_1 = \frac{P_+ \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial T} \right) + Q_+ \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial a}{\partial C} \frac{\partial \phi}{\partial T} + \frac{\partial \phi}{\partial C} \right)}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} \] ;

\( P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial T} \) and \( \frac{\partial \phi}{\partial C} \) are computed at the point \((\xi(t_k^-), \eta(t_k^-))\) and \( P_+ = P(\xi(t_k^+), \eta(t_k^+)) \), \( Q_+ = Q(\xi(t_k^+), \eta(t_k^+)) \).

\((\xi, \eta) = (T, C)\) periodic orbit \( t_k = \) impulse times
\( P, Q = \) differential equations \( a, b = \) impulsive effects
\( \phi = \) implicit impulse function
Nontrivial 2D Floquet multiplier

• The nontrivial Floquet multiplier is

\[ \mu_2 = \Delta_1 \exp \left[ \int_0^T \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) \, dt \right] \]

where

\[ \Delta_1 = \frac{P_+ \left( \frac{\partial a}{\partial T} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial T} \right) + Q_+ \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial a}{\partial C} \frac{\partial \phi}{\partial T} + \frac{\partial \phi}{\partial C} \right)}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} \] ;

\[ P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial T} \] and \( \frac{\partial \phi}{\partial C} \) are computed at the point \( (\xi(t_k^-), \eta(t_k^-)) \) and \( P_+ = P(\xi(t_k^+), \eta(t_k^+)) \), \( Q_+ = Q(\xi(t_k^+), \eta(t_k^+)) \).

\( (\xi, \eta) = (T, C) \) periodic orbit \( t_k = \) impulse times
\( P, Q = \) differential equations \( a, b = \) impulsive effects
\( \phi = \) implicit impulse function
Nontrivial 2D Floquet multiplier

- The nontrivial Floquet multiplier is

\[ \mu_2 = \Delta_1 \exp \left[ \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) \, dt \right] \]

where

\[ \Delta_1 = \frac{P_+ \left( \frac{\partial a}{\partial T} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial T} \right) + Q_+ \left( \frac{\partial a}{\partial T} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial C} \right)}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} \; ; \]

\[ P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial C} \text{ and } \frac{\partial \phi}{\partial C} \] are computed at the point \( (\xi(t_k^-), \eta(t_k^-)) \) and \( P_+ = P(\xi(t_k^+), \eta(t_k^+)) \), \( Q_+ = Q(\xi(t_k^+), \eta(t_k^+)) \).

\( (\xi, \eta) = (T, C) \) periodic orbit \( t_k = \) impulse times

\( P, Q = \) differential equations \( a, b = \) impulsive effects

\( \phi = \) implicit impulse function
Nontrivial 2D Floquet multiplier

- The nontrivial Floquet multiplier is

\[ \mu_2 = \Delta_1 \exp \left[ \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \right] \]

where

\[ \Delta_1 = \frac{P \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial T} \right) + Q \left( \frac{\partial a}{\partial T} \frac{\partial \phi}{\partial C} - \frac{\partial b}{\partial T} \frac{\partial \phi}{\partial C} + \frac{\partial \phi}{\partial C} \right)}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} \right] . \]

\( P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial T} \) and \( \frac{\partial \phi}{\partial C} \) are computed at the point \( (\xi(t_k^-), \eta(t_k^-)) \) and \( P_+ = P(\xi(t_k^+), \eta(t_k^+)) \), \( Q_+ = Q(\xi(t_k^+), \eta(t_k^+)) \).

\( (\xi, \eta) = (T, C) \) periodic orbit \( t_k = \) impulse times
\( P, Q = \) differential equations \( a, b = \) impulsive effects
\( \phi = \) implicit impulse function
P and Q explicitly

• Since \( \xi(t^+_k) = \xi(t^-_k) \),

\( (\xi,\eta) = (T,C) \) periodic orbit \( t_k=\)impulse times
\( P,Q=\)differential equations
\( d,\delta=\)death rates \( \alpha=\)proliferation rate
\( \pi=\)production rate \( p=\)production rate
P and Q explicitly

- Since \( \xi(t_k^+) = \xi(t_k^-) \),

\[
P = \pi - d\xi(t_k^-) - p\eta(t_k^-)\xi(t_k^-)
\]

\((\xi, \eta) = (T, C)\) periodic orbit \( t_k = \text{impulse times} \)

\( P, Q = \text{differential equations} \)

\( d, \delta = \text{death rates} \quad \alpha = \text{proliferation rate} \)

\( \pi = \text{production rate} \quad p = \text{production rate} \)
P and Q explicitly

Since \( \xi(t_k^+) = \xi(t_k^-) \),

\[
P = \pi - d\xi(t_k^-) - p\eta(t_k^-)\xi(t_k^-) \\
P_+ = \pi - d\xi(t_k^-) - p\eta(t_k^+)\xi(t_k^-)
\]

(\( \xi, \eta \) = (T,C) periodic orbit \( t_k \) = impulse times \( P,Q \) = differential equations \( d,\delta \) = death rates \( \alpha \) = proliferation rate \( \pi \) = production rate \( p \) = production rate)
P and Q explicitly

• Since $\xi(t_k^+) = \xi(t_k^-)$,

$$P = \pi - d\xi(t_k^-) - p\eta(t_k^-)\xi(t_k^-)$$

$$P_+ = \pi - d\xi(t_k^-) - p\eta(t_k^+)\xi(t_k^-)$$

$$Q = \alpha\xi(t_k^-)\eta(t_k^-) - \delta\eta(t_k^-)$$

$(\xi, \eta) = (T, C)$ periodic orbit $t_k = \text{impulse times}$

$P, Q = \text{differential equations}$

$d, \delta = \text{death rates}$  $\alpha = \text{proliferation rate}$

$\pi = \text{production rate}$  $p = \text{production rate}$
P and Q explicitly

Since \( \xi(t_k^+) = \xi(t_k^-) \),

\[
P = \pi - d\xi(t_k^-) - p\eta(t_k^-)\xi(t_k^-)
\]

\[
P_+ = \pi - d\xi(t_k^-) - p\eta(t_k^+)\xi(t_k^-)
\]

\[
Q = \alpha\xi(t_k^-)\eta(t_k^-) - \delta\eta(t_k^-)
\]

\[
Q_+ = \alpha\xi(t_k^-)\eta(t_k^+) - \delta\eta(t_k^+).
\]
Calculating $\triangle_1$

- Since $\eta(t^-_k) = \eta(t^+_k)T_{\text{int}}$ and $T_{\text{int}} < 1$, 

---

$(\xi, \eta) = (T, C)$ periodic orbit $t_k=$ impulse times $P, Q =$ differential equations

$\phi =$ implicit impulse function $d =$ death rate

$\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

• Since $\eta(t^-_k) = \eta(t^+_k)T_{\text{int}}$ and $T_{\text{int}} < 1$,

$$Q = T_{\text{int}}Q_+$$

$(\xi, \eta) = (T, C)$ periodic orbit $t_k =$ impulse times $P, Q =$ differential equations
$\phi =$ implicit impulse function $d =$ death rate
$\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t_k^-) = \eta(t_k^+)T_{\text{int}}$ and $T_{\text{int}} < 1$,

  \[ Q = T_{\text{int}}Q_+ \]

  \[ P_+T_{\text{int}} = (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^+)T_{\text{int}}\xi(t_k^-) \]

$(\xi, \eta) = (T, C)$ periodic orbit $t_k =$ impulse times
$P, Q =$ differential equations
$\phi =$ implicit impulse function $d =$ death rate
$\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t_k^{-}) = \eta(t_k^{+})T_{\text{int}}$ and $T_{\text{int}} < 1$,

$$Q = T_{\text{int}}Q_+$$

$$P_+T_{\text{int}} = (\pi - d\xi(t_k^{-}))T_{\text{int}} - p\eta(t_k^{+})T_{\text{int}}\xi(t_k^{-})$$

$$= (\pi - d\xi(t_k^{-}))T_{\text{int}} - p\eta(t_k^{-})\xi(t_k^{-})$$

$(\xi, \eta) = (T, C)$ periodic orbit $t_k =$ impulse times

$P, Q =$ differential equations

$\phi =$ implicit impulse function $d =$ death rate

$\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t_k^-) = \eta(t_k^+)T_{\text{int}}$ and $T_{\text{int}} < 1$,

\[
Q = T_{\text{int}}Q_+ \\
\]
\[
P_+T_{\text{int}} = (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^+)T_{\text{int}}\xi(t_k^-) \\
= (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^-)\xi(t_k^-) \\
< P
\]

$(\xi, \eta) = (T, C)$ periodic orbit $t_k =$ impulse times $P, Q =$ differential equations $\phi =$ implicit impulse function $d =$ death rate $\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t^-_k) = \eta(t^+_k)T_{int}$ and $T_{int} < 1$,

\[
Q = T_{int}Q_+ \quad P + T_{int} = (\pi - d\xi(t^-_k))T_{int} - p\eta(t^+_k)T_{int}\xi(t^-_k) = (\pi - d\xi(t^-_k))T_{int} - p\eta(t^-_k)\xi(t^-_k) < P
\]

- It follows that

$(\xi, \eta) = (T, C)$ periodic orbit $t_k =$ impulse times $P, Q =$ differential equations $\phi =$ implicit impulse function $d =$ death rate $\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t_k^-) = \eta(t_k^+)T_{\text{int}}$ and $T_{\text{int}} < 1$,

$$\begin{align*}
Q &= T_{\text{int}}Q_+ \\
P_{+}T_{\text{int}} &= (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^+)T_{\text{int}}\xi(t_k^-) \\
&= (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^-)\xi(t_k^-) \\
&< P
\end{align*}$$

- It follows that

$$\begin{align*}
\Delta_1 &= \frac{P + \frac{\partial \phi}{\partial T} + Q + \frac{\partial \phi}{\partial C}}{P + \frac{\partial \phi}{\partial T} + Q + \frac{\partial \phi}{\partial C}}
\end{align*}$$

$(\xi, \eta) = (T, C)$ periodic orbit $t_k=$ impulse times $P, Q =$ differential equations $\phi =$ implicit impulse function $d =$ death rate $\pi =$ production rate $p =$ production rate
Calculating $\Delta_1$

- Since $\eta(t_k^-) = \eta(t_k^+)T_{\text{int}}$ and $T_{\text{int}} < 1$,

\[ Q = T_{\text{int}} Q_+ \]

\[ P + T_{\text{int}} = (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^+)T_{\text{int}}\xi(t_k^-) \]

\[ = (\pi - d\xi(t_k^-))T_{\text{int}} - p\eta(t_k^-)\xi(t_k^-) \]

\[ < P \]

- It follows that

\[ \Delta_1 = \frac{P + \frac{\partial \phi}{\partial T} + Q + \frac{\partial \phi}{\partial C}}{P \frac{\partial \phi}{\partial T} + Q \frac{\partial \phi}{\partial C}} \]

\[ < \frac{1}{T_{\text{int}}} \]

(\(\xi, \eta\) = (T, C) periodic orbit \(t_k\) = impulse times \(P, Q\) = differential equations \(\phi\) = implicit impulse function \(d\) = death rate \(\pi\) = production rate \(p\) = production rate)
Calculating the nontrivial Floquet multiplier

\[ \mu_2 < \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( \frac{\partial P}{\partial T} (\xi(t), \eta(t)) + \frac{\partial Q}{\partial C} (\xi(t), \eta(t)) \right) dt \]

\( (\xi, \eta) = (T, C) \) periodic orbit \quad \tau = \text{vaccination frequency} \quad d = \text{death rate} \\
P, Q = \text{differential equations} \quad \pi = \text{production rate} \quad p = \text{production rate}
Calculating the nontrivial Floquet multiplier

\[ \mu_2 < \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \]

\[ = \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( -d - p\eta(t) + \alpha\xi(t) - \delta \right) dt \]

\((\xi, \eta) = (T, C)\) periodic orbit \quad \tau = \text{vaccination frequency} \quad d = \text{death rate} \quad \pi = \text{production rate} \quad p = \text{production rate} \]
Calculating the nontrivial Floquet multiplier

\[ \mu_2 < \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \]

\[ = \frac{1}{T_{\text{int}}} \exp \int_0^\tau (-d - p\eta(t) + \alpha \xi(t) - \delta) dt \]

\[ = \frac{1}{T_{\text{int}}} \exp \left( - \int_0^\tau (d + p\eta(t)) dt \right) \exp \left( \int_0^\tau (\alpha \xi(t) - \delta) dt \right) \]

\((\xi, \eta) = (T, C)\) periodic orbit \quad \tau = \text{vaccination frequency} \quad d = \text{death rate} \quad P, Q = \text{differential equations} \quad \pi = \text{production rate} \quad p = \text{production rate}
Calculating the nontrivial Floquet multiplier

\[
\mu_2 < \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt
\]

\[
= \frac{1}{T_{\text{int}}} \exp \int_0^\tau (-d - p\eta(t) + \alpha\xi(t) - \delta) dt
\]

\[
= \frac{1}{T_{\text{int}}} \exp \left( - \int_0^\tau (d + p\eta(t)) dt \right) \exp \left( \int_0^\tau (\alpha\xi(t) - \delta) dt \right)
\]

\[
= \frac{1}{T_{\text{int}}} \exp \left( - \int_0^\tau (d + p\eta(t)) dt \right) T_{\text{int}}
\]

\((\xi, \eta) = (T, C)\) periodic orbit  \(\tau =\) vaccination frequency  \(d =\) death rate  
\(P, Q =\) differential equations  \(\pi =\) production rate  \(p =\) production rate
Calculating the nontrivial Floquet multiplier

\[ \mu_2 < \frac{1}{T_{\text{int}}} \exp \int_0^\tau \left( \frac{\partial P}{\partial T}(\xi(t), \eta(t)) + \frac{\partial Q}{\partial C}(\xi(t), \eta(t)) \right) dt \]

\[ = \frac{1}{T_{\text{int}}} \exp \int_0^\tau (-d - p\eta(t) + \alpha \dot{\xi}(t) - \delta) dt \]

\[ = \frac{1}{T_{\text{int}}} \exp \left( - \int_0^\tau (d + p\eta(t)) dt \right) \exp \left( \int_0^\tau (\alpha \dot{\xi}(t) - \delta) dt \right) \]

\[ = \frac{1}{T_{\text{int}}} \exp \left( - \int_0^\tau (d + p\eta(t)) dt \right) T_{\text{int}} \]

\[ < 1. \]

(\( \xi, \eta \) = (T, C) periodic orbit \( \tau \) = vaccination frequency \( d \) = death rate \( P, Q \) = differential equations \( \pi \) = production rate \( p \) = production rate)
Orbital asymptotic stability

• Hence, the nontrivial impulsive Floquet multiplier lies inside the unit circle
Orbital asymptotic stability

- Hence, the nontrivial impulsive Floquet multiplier lies inside the unit circle
- Thus, the impulsive periodic orbit is
Orbital asymptotic stability

- Hence, the nontrivial impulsive Floquet multiplier lies inside the unit circle
- Thus, the impulsive periodic orbit is
  a) orbitally asymptotically stable and
Orbital asymptotic stability

- Hence, the nontrivial impulsive Floquet multiplier lies inside the unit circle.
- Thus, the impulsive periodic orbit is
  a) orbitally asymptotically stable and
  b) has the property of asymptotic phase.
A caveat

• Although this orbit exists and is stable it might not be unique
A caveat

- Although this orbit exists and is stable it might not be unique
- In particular, there might be impulsive orbits with more than one impulse per period
A caveat

- Although this orbit exists and is stable it might not be unique
- In particular, there might be impulsive orbits with more than one impulse per period
- However, this does not appear to be the case, for the parameter ranges under consideration.
The average number of infected T cells during a single cycle of the impulsive periodic orbit is

\[ T_{av} \equiv \frac{1}{\tau} \int_0^\tau T(u)du. \]

\( T = \text{infected cells} \quad \tau = \text{vaccination period} \)

A CTL recognising a tumour
Infected T cell minimum

- Easy to show:

\[ T = \text{infected T cells} \quad C = \text{CTLs} \quad t_k = \text{vaccination time} \]
Infected T cell minimum

- Easy to show:

\[
\frac{dT}{dt}(t_k^+) < \frac{dT}{dt}(t_k^-)
\]
Infected T cell minimum

- Easy to show:

\[
\frac{dT}{dt}(t^+_k) < \frac{dT}{dt}(t^-_k)
\]

\[
\frac{dT}{dt} = 0 \text{ only once per cycle}
\]

\(T=\text{infected T cells} \quad C=\text{CTLs} \quad t_k=\text{vaccination time}\)
Infected T cell minimum

- Easy to show:

\[
\frac{dT}{dt}(t_k^+) < \frac{dT}{dt}(t_k^-)
\]

\[
\frac{dT}{dt} = 0 \quad \text{only once per cycle}
\]

- Denote this turning point by \((T_{tp}, C_{tp})\)

\[T=\text{infected T cells} \quad C=\text{CTLs} \quad t_k=\text{vaccination time}\]
Infected T cell minimum

- Easy to show:

\[ \frac{dT}{dt}(t^+_k) < \frac{dT}{dt}(t^-_k) \]

\[ \frac{dT}{dt} = 0 \quad \text{only once per cycle} \]

- Denote this turning point by \((T_{tp}, C_{tp})\)
- Clearly this turning point is a minimum.

\(T=\text{infected T cells} \quad C=\text{CTLs} \quad t_k=\text{vaccination time}\)
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^-)$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

\begin{align*}
T &= \text{infected } T \text{ cells} \\
\pi &= \text{production rate} \\
\delta &= \text{death rate} \\
C^i &= \text{vaccine strength} \\
T_{av} &= \text{av # cells} \\
C &= \text{CTLs} \\
\alpha &= \text{proliferation rate} \\
p &= \text{clearance rate} \\
\tau &= \text{vaccination period} \\
(T_{tp}, C_{tp}) &= \text{T-cell min}
\end{align*}
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^-)$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

$$\frac{dT}{dt} (T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp}T_{tp} = 0$$

$T$=infected T cells  \( \pi \)=production rate  \( \delta \)=death rate  \( C \)=vaccine strength  \( T_{av} \)=av # cells

$C$=CTLs  \( \alpha \)=proliferation rate  \( p \)=clearance rate  \( \tau \)=vaccination period  \((T_{tp}, C_{tp})\)=T-cell min
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^-)$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

$$\frac{dT}{dt} (T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp} T_{tp} = 0$$

$$\pi - \left( d + \frac{pC^i T_{int}}{1 - T_{int}} \right) T_{av} < 0$$

$T=$infected $T$ cells  \( \pi = \)production rate \( \delta = \)death rate \( C^i = \)vaccine strength \( T_{av} = \)av # cells
$C=$CTLs \( \alpha = \)proliferation rate \( p = \)clearance rate \( \tau = \)vaccination period \( (T_{tp}, C_{tp}) = T\)-cell min
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^*)$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

$$\frac{dT}{dt}(T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp}T_{tp} = 0$$

$$\pi - \left(d + \frac{pC_{i}T_{int}}{1 - T_{int}}\right)T_{av} < 0$$

$$\pi - \left(d + \frac{pC_{i}e^{\alpha \tau T_{av} - \delta \tau}}{1 - e^{\alpha \tau T_{av} - \delta \tau}}\right)T_{av} < 0$$

$T=$infected $T$ cells  $\pi=$production rate  $\delta=$death rate  $C_{i}=$vaccine strength  $T_{av}=$av # cells

$C=$CTLs  $\alpha=$proliferation rate  $p=$clearance rate  $\tau=$vaccination period  $(T_{tp}, C_{tp})=$T-cell min
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^-)$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

$$\frac{dT}{dt} (T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp}T_{tp} = 0$$

$$\pi - \left( d + \frac{pC^i T_{int}}{1 - T_{int}} \right) T_{av} < 0$$

$$\pi - \left( d + \frac{pC^i e^{\alpha \tau T_{av} - \delta \tau}}{1 - e^{\alpha \tau T_{av} - \delta \tau}} \right) T_{av} < 0$$

Thus

$T =$ infected $T$ cells  $\pi =$ production rate  $\delta =$ death rate  $C^i =$ vaccine strength  $T_{av} =$ av # cells
$C =$ CTLs  $\alpha =$ proliferation rate  $p =$ clearance rate  $\tau =$ vaccination period  $(T_{tp}, C_{tp}) =$ T-cell min
Estimating the vaccination period

Since $T_{tp} < T_{av}$, $C_{tp} > C(\tau^{-})$ and $T_{int} = e^{\alpha \tau T_{av} - \delta \tau}$,

$$\frac{dT}{dt} (T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp} T_{tp} = 0$$

$$\pi - \left( d + \frac{pC^{i} T_{int}}{1 - T_{int}} \right) T_{av} < 0$$

$$\pi - \left( d + \frac{pC^{i} e^{\alpha \tau T_{av} - \delta \tau}}{1 - e^{\alpha \tau T_{av} - \delta \tau}} \right) T_{av} < 0$$

Thus

$$\tau < \frac{1}{\delta - \alpha T_{av}} \ln \left( 1 + \frac{pC^{i} T_{av}}{\pi - dT_{av}} \right).$$

$T =$ infected $T$ cells $\pi =$ production rate $\delta =$ death rate $C^{i} =$ vaccine strength $T_{av} =$ av # cells

$C =$ CTLs $\alpha =$ proliferation rate $p =$ clearance rate $\tau =$ vaccination period $(T_{tp}, C_{tp}) =$ T-cell min
Infected T cells can be kept arbitrarily low

- It follows that the average number of infected T cells can be kept as low as desired, by appropriate choice of $\tau$ and $C^i$.

$\pi$ = production rate  $\delta, d$ = death rates  $C^i$ = vaccine strength
$\alpha$ = proliferation rate  $\tau$ = vaccination period  $T_{av}$ = av # cells
Infected T cells can be kept arbitrarily low

- It follows that the average number of infected T cells can be kept as low as desired, by appropriate choice of \( \tau \) and \( C^i \)
- In particular,

\[ \pi = \text{production rate} \quad \delta, d = \text{death rates} \quad C^i = \text{vaccine strength} \]
\[ \alpha = \text{proliferation rate} \quad \tau = \text{vaccination period} \quad T_{\text{av}} = \text{av # cells} \]
Infected T cells can be kept arbitrarily low

- It follows that the average number of infected T cells can be kept as low as desired, by appropriate choice of $\tau$ and $C_i$
- In particular,

$$
\lim_{{T_{av} \to 0}} \left[ \frac{1}{\delta - \alpha T_{av}} \ln \left( 1 + \frac{C_i T_{av}}{\pi - d T_{av}} \right) \right] = 0^+ .
$$

$\pi =$ production rate  $\delta,d =$ death rates  $C_i =$ vaccine strength
$\alpha =$ proliferation rate  $\tau =$ vaccination period  $T_{av} =$ av # cells
Clearance is theoretically possible

Thus, infection could theoretically be cleared...
Clearance is theoretically possible

Thus, infection could theoretically be cleared... (ignoring latently infected cells and other reservoirs)
Clearance is theoretically possible

Thus, infection could theoretically be cleared... (ignoring latently infected cells and other reservoirs)

...for a sufficiently strong vaccine or sufficiently frequent vaccinations
Clearance is theoretically possible

Thus, infection could theoretically be cleared... (ignoring latently infected cells and other reservoirs)

...for a sufficiently strong vaccine or sufficiently frequent vaccinations (although the impulsive assumptions break down as the limit approaches zero).
Parameters

• Realistic parameters were simulated

\[ \pi = \text{production rate} \quad \delta,d = \text{death rates} \quad \rho = \text{production rate} \]
\[ \alpha = \text{proliferation rate} \quad \tau = \text{vaccination period} \quad T_{av} = \text{av # cells} \]
Parameters

- Realistic parameters were simulated
- Desired average: $T_{av} = 2.6 \text{ cells } \mu\text{L}^{-1}$

\[\pi=\text{production rate} \quad \delta, d=\text{death rates} \quad p=\text{production rate} \quad \alpha=\text{proliferation rate} \quad \tau=\text{vaccination period} \quad T_{av}=\text{av # cells}\]
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Parameters

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• Desired average: \( T_{av} = 2.6 \text{ cells } \mu\text{L}^{-1} \) (instead of 3 cells \( \mu\text{L}^{-1} \))
• Parameter estimates:

\[ \pi = \text{production rate} \quad \delta, d = \text{death rates} \quad p = \text{production rate} \]
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Parameters

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- Desired average: $T_{av} = 2.6 \text{ cells } \mu\text{L}^{-1}$
  (instead of 3 cells $\mu\text{L}^{-1}$)
- Parameter estimates:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Units</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\pi$</td>
<td>1.5</td>
<td>cells day$^{-1}$ $\mu\text{L}^{-1}$</td>
<td>de Boer &amp; Perelson (1998)</td>
</tr>
<tr>
<td>$d$</td>
<td>0.5</td>
<td>day$^{-1}$</td>
<td>Essunger &amp; Perelson (1994)</td>
</tr>
<tr>
<td>$p$</td>
<td>0.05</td>
<td>$\mu\text{L} \text{ cells}^{-1}\text{day}^{-1}$</td>
<td>Bonhoeffer et al. (2000)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.067</td>
<td>$\mu\text{L} \text{ cells}^{-1}\text{day}^{-1}$</td>
<td>de Boer &amp; Perelson (1998)</td>
</tr>
<tr>
<td>$\delta$</td>
<td>0.2</td>
<td>day$^{-1}$</td>
<td>de Boer &amp; Perelson (1998)</td>
</tr>
</tbody>
</table>

$\pi =$ production rate  $\delta, d =$ death rates  $p =$ production rate
$\alpha =$ proliferation rate  $\tau =$ vaccination period  $T_{av} =$ av # cells
\[ \tau < \frac{1}{\delta - \alpha T_{av}} \ln \left( 1 + \frac{pC_i T_{av}}{\pi - dT_{av}} \right). \]
How strong and how often?

A CTL boost of 35 cells µL⁻¹ that was applied every 122 days or fewer would ensure the average infected T cell count remained below 2.6 cells µL⁻¹.
$C^i = 35 \text{ cells } \mu\text{L}^{-1}, \ \tau = 120 \text{ days}$
An overestimate

• The inequality is an overestimate
An overestimate

- The inequality is an overestimate
- A CTL boost of 35 cells administered every 120 days produced an actual average of 2.02 cells $\mu\text{L}^{-1}$
An overestimate

- The inequality is an overestimate
- A CTL boost of 35 cells administered every 120 days produced an actual average of 2.02 cells $\mu$L$^{-1}$
  (better than the desired 2.6 cells $\mu$L$^{-1}$).
$C^i = 10 \text{ cells } \mu\text{L}^{-1}, \ \tau = 240 \text{ days}$
Infrequent vaccination

- Low or infrequent vaccination has minimal effect on the infected T cell counts
Infrequent vaccination

- Low or infrequent vaccination has minimal effect on the infected T cell counts
- A CTL boost of 10 cells administered every 240 days produced an actual average of 2.65 cells $\mu$L$^{-1}$
Infrequent vaccination

- Low or infrequent vaccination has minimal effect on the infected T cell counts
- A CTL boost of 10 cells administered every 240 days produced an actual average of 2.65 cells μL\(^{-1}\) (worse than the desired 2.6 cells μL\(^{-1}\)).
How accurate is the approximation?

• Modelling the change in CTL numbers by an instantaneous change is obviously an approximation
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How accurate is the approximation?

- Modelling the change in CTL numbers by an instantaneous change is obviously an approximation.
- In reality, CTLs take $\sim 14$ days to reach peak values.
- This might be too coarse for an impulsive approximation...
- ...so we ran numerical simulations to test the accuracy of the results.
A reasonable approximation

[Graph showing the comparison between impulsive and nonimpulsive trajectories of infected T cells over time (days)].

- Impulsive trajectory
- Impulsive average
- Nonimpulsive trajectory
- Nonimpulsive average
An overestimate

• Thus, the impulsive approximation overestimates the average number of infected cells
An overestimate

• Thus, the impulsive approximation overestimates the average number of infected cells
• It follows that the actual average will be lower if our recommendations are implemented.
Sensitivity of parameters

- All parameters may vary, to some extent
Sensitivity of parameters

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• We used the most up-to-date estimates, but individuals will have different characteristics
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• All parameters may vary, to some extent
• We used the most up-to-date estimates, but individuals will have different characteristics
• To calculate sensitivity, we varied each parameter individually, while holding all others at median values
• Our output parameter is the vaccination frequency.
Sensitivity of parameters

\[ \pi = \text{production rate} \]
\[ p = \text{clearance rate} \]
\[ \delta = \text{CTL death rates} \]
\[ d = \text{infected T cell death rate} \]
\[ \alpha = \text{proliferation rate} \]
\[ \tau = \text{vaccination frequency} \]
Limitations

- The impulsive orbit is orbitally asymptotically stable, but may not necessarily attract all trajectories
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- There may be higher order impulsive orbits
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- Results may be sensitive to parameter variation.
Limitations

• The impulsive orbit is orbitally asymptotically stable, but may not necessarily attract all trajectories
• There may be higher order impulsive orbits
• Estimates are only reasonable during the asymptomatic phase of infection
• Results may be sensitive to parameter variation
• Impulsive Floquet theory is not easily extendable to higher-order models.
Implications for weak vaccines

- A small increase in the vaccine strength may result in a significantly larger range of possible vaccination intervals when the boost is low.
Implications for weak vaccines

• A small increase in the vaccine strength may result in a significantly larger range of possible vaccination intervals when the boost is low.

• Thus, CTL vaccines whose strength is too low would be less desirable, even if the frequency could be tolerated.
Attractiveness of such vaccines

- Currently, the only treatment option is antiretroviral drugs
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• Such drugs have harsh side effects, lead to drug resistance and require frequent daily administration
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- Such drugs have harsh side effects, lead to drug resistance and require frequent daily administration
- A CTL vaccine would offset the daily pill burden.
Potential drawbacks

- Logistical difficulties in administering regular vaccines to large populations
Potential drawbacks

- Logistical difficulties in administering regular vaccines to large populations
- The consequences of missing a single vaccination are more severe than missing a single drug dose.
Future work

- Adherence to a regular CTL vaccine
Future work

- Adherence to a regular CTL vaccine
- The effects of fluctuations in the vaccination time, even if administered quasi-regularly
Future work

• Adherence to a regular CTL vaccine
• The effects of fluctuations in the vaccination time, even if administered quasi-regularly
• Consequences of vaccine “resistance”.
Summary

• A CTL vaccine pulsed at regular intervals can keep the average number of infected CD4$^+$ T cells arbitrarily low, by choosing appropriate vaccination intervals and strength of the vaccine
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• A CTL vaccine pulsed at regular intervals can keep the average number of infected CD4$^+$ T cells arbitrarily low, by choosing appropriate vaccination intervals and strength of the vaccine.

• The estimate is overconservative, so this will actually result in a lower average number of infected T cells than theoretically predicted.
Conclusions

- A post-infection CTL vaccine would be highly desirable, assuming perfect patient adherence
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• Such a vaccine would offer a realistic alternative to the daily pill burden of antiretroviral drug therapy
Conclusions

• A post-infection CTL vaccine would be highly desirable, assuming perfect patient adherence
• Such a vaccine would offer a realistic alternative to the daily pill burden of antiretroviral drug therapy
• We recommend that such a vaccine should be available for self-administration by patients.
Key reference

- R.J. Smith? and E.J. Schwartz, Predicting the potential impact of a cytotoxic T-lymphocyte HIV vaccine: how often should you vaccinate and how strong should the vaccine be? *(Mathematical Biosciences 2008, 212:180-187)*