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

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HIV now infects 40 millions adults worldwide
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
• 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
• 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
• Results from clinical trials expected by 2011.
Infected CD4$^+$ T cells

- Die at death rate $d$
- Cleared by CTLs at rate $p$, proportional to the density of both types

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
- Die at death rate $\delta$. 

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

Thus the model (without vaccination) is

\[
\frac{dT}{dt} = \pi - dT - pCT \\
\frac{dC}{dt} = \alpha CT - \delta C.
\]

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

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

Thus unstable iff \( \bar{C}' = (\alpha \pi - \delta d)/p \delta > 0 \)

• For the nontrivial steady state, the characteristic polynomial is

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

Thus stable whenever \( \bar{C} > 0 \).

\[ T=\text{infected } T \text{ cells} \quad \pi=\text{production rate} \quad d,\delta=\text{death rates} \]
\[ C=\text{CTLs} \quad \alpha=\text{proliferation rate} \quad p=\text{clearance rate} \]
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, $C^i$
- Given at regular times, $t_k$
- We assume the vaccine effect is instantaneous...
  ...this results in a series of impulsive differential equations.
According to impulsive theory, we can describe the nature of the impulse at time $r_k$ via the difference equation:

$$\Delta y \equiv y(r_k^+) - y(r_k^-) = f(r_k, y(r_k^-))$$
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
• The cycle is restarted
• It continues until the next “interruption”.

Infectected T cells

CTLs
The model (with vaccination)

- Thus, the impulsive model is

\[
\begin{align*}
\frac{dT}{dt} &= \pi - dT - pCT \\
\frac{dC}{dt} &= \alpha CT - \delta C \\
\Delta C &= C^i
\end{align*}
\]

\( t \neq t_k \)

\( t = t_k \).

\( T = \) infected \( T \) cells \quad \pi = \) production rate \quad d, \delta = \) death rates \quad C^i = \) vaccine strength

\( C = \) CTLs \quad \alpha = \) proliferation rate \quad p = \) clearance rate \quad t_k = \) vaccination time
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

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

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

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

Since

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

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

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

\[ T=\text{infected cells} \quad C=\text{CTLs} \]
\[ \alpha=\text{proliferation rate} \quad \delta=\text{death rate} \]
Defining $T_{\text{int}}$

• Define

$$T_{\text{int}} = e^{\int_0^\tau (\alpha T(u) - \delta) du}$$

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.

$T =$ infected $T$ cells  \hspace{1em} $\alpha =$ proliferation rate  \hspace{1em} $\delta =$ death rate  \hspace{1em} $t_k =$ vaccination time
An impulsive periodic orbit

- In particular, if $C(0^+) = \frac{C^i}{1-T_{\text{int}}}$

$T_{\text{int}}$=cell ratio measure  \hspace{1em} C=CTLs
\hspace{1em} C'=vaccine strength \hspace{1em} \tau=\text{vaccination period}$
An impulsive periodic orbit

- In particular, if $C(0^+) = \frac{C^i}{1-T_{\text{int}}}$

$$C(\tau^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}}.$$
An impulsive periodic orbit

- In particular, if $C(0^+) = \frac{C_i}{1 - T_{\text{int}}}$

$$C(\tau^-) = \frac{C_i T_{\text{int}}}{1 - T_{\text{int}}}$$

$$C(\tau^+) = \frac{C_i T_{\text{int}}}{1 - T_{\text{int}}} + C_i$$

$T_{\text{int}}$=cell ratio measure  $C=$CTLs  
$C'$=vaccine strength  $\tau=$vaccination period
An impulsive periodic orbit

In particular, if \( C(0^+) = \frac{C^i}{1 - T_{\text{int}}} \)

\[
C(\tau^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}}
\]

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

\[
= \frac{C^i}{1 - T_{\text{int}}}
\]

\( T_{\text{int}} = \) cell ratio measure  \( C = \) CTLs  
\( C^i = \) vaccine strength  \( \tau = \) vaccination period
An impulsive periodic orbit

- In particular, if $C(0^+) = \frac{C^i}{1-T_{\text{int}}}$

$$C(\tau^-) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}}$$

$$C(\tau^+) = \frac{C^i T_{\text{int}}}{1 - T_{\text{int}}} + C^i$$

$$= \frac{C^i}{1 - T_{\text{int}}}$$

$$= C(0^+).$$

$T_{\text{int}}=$ cell ratio measure  \( C=\text{CTLs} \)

$C^i=$ vaccine strength \( \tau=\text{vaccination period} \)
The orbit, with endpoints

• Thus we have an impulsive periodic orbit

\[ C'(t) = \frac{C^i e^{\int_0^t (\alpha T(u) - \delta) du}}{1 - T_{int}} \]

for \( 0 < t < \tau \)

• Endpoints of the impulsive orbit are

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

\( T_{int} = \text{cell ratio measure} \quad C = \text{CTLs} \quad C^i = \text{vaccine strength} \)
\( \alpha = \text{proliferation rate} \quad \delta = \text{death rate} \quad \tau = \text{vaccination period} \)
From the impulsive DEs, define

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

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

\[ \{ \phi(T(t), C(t)) = 0 : t = t_k \} \]

Impulsive effects

\( \pi = \) production rate
\( \delta, d = \) death rates
\( p = \) production rate
\( \alpha = \) proliferation rate
\( C^i = \) vaccine strength
\( t_k = \) impulse times
Impulsive Floquet Theory

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

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

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

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

\[
\begin{align*}
\xi(t_k^-) &= \xi(t_k^+) = T(\tau) \\
\eta(t_k^-) &= \frac{C^iT_{\text{int}}}{1 - T_{\text{int}}}
\end{align*}
\]

No impulse in T

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

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

\[
\xi(t^-_k) = \xi(t^+_k) = T(\tau)
\]
\[
\eta(t^-_k) = \frac{C^i T_{int}}{1 - T_{int}}
\]
\[
\eta(t^+_k) = \frac{C^i}{1 - T_{int}}
\]

**Legends:**
- \(T\) = infected T cells
- \(C^i\) = vaccine strength
- \(\tau\) = vaccination period
- \(t_k\) = impulse times
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

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

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

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

\(P, Q, \frac{\partial a}{\partial T}, \frac{\partial b}{\partial T}, \frac{\partial a}{\partial C}, \frac{\partial b}{\partial C}, \frac{\partial \phi}{\partial T}\) 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
P and Q explicitly

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

\((\xi, \eta) = (T, C)\) 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 $\xi(t^+_k) = \xi(t^-_k)$,

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

\[ (\xi, \eta) = (T, C) \text{ periodic orbit } t_k = \text{impulse times} \]
\[ P, Q = \text{differential equations} \]
\[ d, \delta = \text{death rates} \quad \alpha = \text{proliferation rate} \]
\[ \pi = \text{production rate} \quad p = \text{production rate} \]
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 \hspace{1cm} \( \alpha = \) proliferation rate

\( \pi = \) production rate \hspace{1cm} \( p = \) production rate
P and Q explicitly

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

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

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

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

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

\[
\begin{align*}
P &= \pi - d\xi(t_k^-) - p\eta(t_k^-)\xi(t_k^-) \\
P_+ &= \pi - d\xi(t_k^-) - p\eta(t_k^+)\xi(t_k^-) \\
Q &= \alpha \xi(t_k^-)\eta(t_k^-) - \delta\eta(t_k^-) \\
Q_+ &= \alpha \xi(t_k^-)\eta(t_k^+) - \delta\eta(t_k^+) .
\end{align*}
\]

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

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

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

\( \pi = \text{production rate} \quad p = \text{production rate} \)
Calculating $\Delta_1$

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

\[
Q = T_{\text{int}} Q_+ \\
P_+ T_{\text{int}} = (\pi - d\xi(t^-_k))T_{\text{int}} - \rho\eta(t^+_k)T_{\text{int}}\xi(t^-_k) \\
= (\pi - d\xi(t^-_k))T_{\text{int}} - \rho\eta(t^-_k)\xi(t^-_k)
\]

$(\xi, \eta) = (T, C)$ 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 $\eta(t_k^-) = \eta(t_k^+) T_{int}$ and $T_{int} < 1$,

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

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

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

\[
< P
\]
Calculating $\Delta_1$

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

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

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

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

\[
< P
\]

- 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 $T_{\text{int}} < 1$,

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

- It follows that

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

$(\xi, \eta) = (T, C)$ 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 $T_{int} < 1$,

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

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

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

$$< P$$

- It follows that

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

$$< \frac{1}{T_{int}}.$$

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

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

$\phi = \text{implicit impulse function}$

$d = \text{death rate}$

$\pi = \text{production rate}$

$p = \text{production rate}$
Calculating the nontrivial Floquet multiplier

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

(\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

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

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

(\(\xi, \eta\) = (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

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

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

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

\((\xi, \eta) = (T, C) \) periodic orbit  \(\tau = \)vaccination frequency  \(d = \)death rate

\(P, Q = \)differential equations  \(\pi = \)production rate  \(p = \)production rate
Calculating the nontrivial Floquet multiplier

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

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

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

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

\((\xi, \eta) = (T, C)\) periodic orbit \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

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

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

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

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

\[ < 1. \]

(\( \xi, \eta \))=(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
• 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
- 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.
Average # of infected T cells

- The average number of infected T cells during a single cycle of the impulsive periodic orbit is

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

A CTL recognising a tumour

\( T = \) infected cells  \( \tau = \) vaccination period
Infected T cell minimum

- Easy to show:

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

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

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

- Clearly this turning point is a minimum.

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

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

$T =$ infected $T$ cells  \hspace{1em} \pi =$ production rate  \hspace{1em} \delta =$ death rate  \hspace{1em} C^i =$ vaccine strength  \hspace{1em} T_{av} =$ av # cells
C =$ CTLs  \hspace{1em} \alpha =$ proliferation rate  \hspace{1em} p =$ clearance rate  \hspace{1em} \tau =$ vaccination period  \hspace{1em} (T_{tp}, C_{tp}) =$ T-cell min
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$$
\frac{dT}{dt} (T_{tp}, C_{tp}) = \pi - dT_{tp} - pC_{tp} T_{tp} = 0
$$

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

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

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

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

\( \pi = \text{production rate} \quad \delta, d = \text{death rates} \quad C^i = \text{vaccine strength} \)

\( \alpha = \text{proliferation rate} \quad \tau = \text{vaccination period} \quad T_{av} = \text{av # cells} \)
Clearance is theoretically possible

Thus, infection could theoretically be cleared...

...for a sufficiently strong vaccine or sufficiently frequent vaccinations

(ignoring latently infected cells and other reservoirs)

(although the impulsive assumptions break down as the limit approaches zero).
### Parameters

- Realistic parameters were simulated
- Desired average: $T_{av} = 2.6$ cells $\mu L^{-1}$ (instead of 3 cells $\mu L^{-1}$)
- 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$^{-1}$ $\mu L^{-1}$</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>$\mu L$ cells$^{-1}$ day$^{-1}$</td>
<td>Bonhoeffer et al. (2000)</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>0.067</td>
<td>$\mu L$ cells$^{-1}$ 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 $\mu$L$^{-1}$ that was applied every 122 days or fewer would ensure the average infected T cell count remained below 2.6 cells $\mu$L$^{-1}$. 
\( C^i = 35 \text{ cells } \mu \text{L}^{-1}, \tau = 120 \text{ days} \)
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 $\mu L^{-1}$). 

\begin{align*}
\text{CTL count} \\
0 & \quad 5 & \quad 10 & \quad 15 & \quad 20 & \quad 25 & \quad 30 & \quad 35 & \quad 40 \\
0 & \quad 200 & \quad 400 & \quad 600 \\
\text{Infected T cells / \mu L} \\
0 & \quad 0.5 & \quad 1 & \quad 1.5 & \quad 2 & \quad 2.5 & \quad 3 \\
0 & \quad 200 & \quad 400 & \quad 600 
\end{align*}
$C^i = 10 \text{ cells } \mu\text{L}^{-1}, \tau = 240 \text{ days}$
Infrequent vaccination

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

\( \pi = \) production rate

\( p = \) clearance rate

\( \delta = \) CTL death rates

\( d = \) infected T cell death rate

\( \alpha = \) proliferation rate

\( \tau = \) vaccination frequency

\( \tau \) vs variation in \( \pi \)

\( \tau \) vs variation in \( d \)

\( \tau \) vs variation in \( \delta \)

\( \tau \) vs variation in \( p \)

\( \tau \) vs variation in \( \alpha \)

\( \pi = \) production rate

\( p = \) clearance rate

\( \delta = \) CTL death rates

\( d = \) infected T cell death rate

\( \alpha = \) proliferation rate

\( \tau = \) vaccination frequency
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.
- 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
- 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
- The consequences of missing a single vaccination are more severe than missing a single drug dose.
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.

• 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

• 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, in revision*)