Understanding the complex patterns observed during hepatitis B Virus therapy - Supplementary material

Andrea Carracedo Rodriguez*, Matthias Chung*, Stanca M Ciupe*¶
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Positivity and boundness. We first establish the positivity and boundness of model

\[
\begin{align*}
\frac{dT}{dt} &= r_T T \left(1 - \frac{T + I}{K}\right) - \beta(1 - \eta)VT, \\
\frac{dI}{dt} &= r_I I \left(1 - \frac{T + I}{K}\right) + \beta(1 - \eta)VT - \delta I, \\
\frac{dV}{dt} &= (1 - \epsilon)pI - cV.
\end{align*}
\] (1)

subject to initial conditions

\[
T(0) = T_0 > 0, \quad I(0) = I_0 > 0, \quad V(0) = V_0 > 0, \quad T(0) + I(0) \leq K.
\] (2)

Proposition 1. The solutions of (1) subject to (2) are positive on \([0, b)\) for some \(b > 0\).

Proof. Note that (1) is locally Lipschitz at \(t = 0\). Therefore, a solution exists and is unique on \([0, b)\) for some \(b > 0\). Assume that there exists \(t_1 \in (0, b)\) such that \(V(t_1) = 0\) and all variables are positive on \([0, t_1]\). For all \(t \in [0, t_1]\)

\[
\frac{dV}{dt} = (1 - \epsilon)pI - cV \geq -cV,
\]

and so

\[V(t_1) \geq V_0 e^{-ct_1} > 0,\]
a contradiction. Therefore \(V(t) > 0\) for all \(t \in [0, t_1]\).

Proposition 2. If \(\max\{r_T, r_I\} > \min\{d_T, \delta\}\), then any solution \((T(t), I(t))\) of (1) subject to (2) remains bounded on \([0, b)\) for some \(b > 0\).

Proof. Let \(F = T + I\), \(r_{\max} = \max\{r_T, r_I\}\) and \(d_{\min} = \min\{d_T, \delta\}\). Then

\[
\frac{dF}{dt} \leq s + r_{\max} F \left(1 - \frac{F}{K}\right) - d_{\min} F
\]

\[
= s + (r_{\max} - d_{\min}) F - \frac{r_{\max} F^2}{K}
\]

\[
= -\frac{r_{\max}}{K} (F - X)(F - Y),
\]

where

*Corresponding author

¶Corresponding author
\[ X = \frac{r_{\text{max}} - d_{\text{min}} + \sqrt{(r_{\text{max}} - d_{\text{min}})^2 + \frac{4sr_{\text{max}}}{K}}}{-2s}, \]

\[ Y = \frac{r_{\text{max}} - d_{\text{min}} - \sqrt{(r_{\text{max}} - d_{\text{min}})^2 + \frac{4sr_{\text{max}}}{K}}}{-2s}. \]

Then

\[ \int \frac{dF}{(F - X)(F - Y)} \leq \int \frac{r_{\text{max}}}{K} dt \]

\[ \frac{1}{X - Y} \ln |F - X| + \frac{1}{Y - X} \ln |F - Y| \leq -\frac{r_{\text{max}}}{K} t \]

\[ \frac{|F - X|}{|F - Y|} \leq \exp \left( -\frac{(X - Y)r_{\text{max}}}{K} t \right). \]

and, since \( r_{\text{max}} > d_{\text{min}}, \)

\[ F(t) \leq \frac{X - Y \exp \left( -\frac{(X - Y)r_{\text{max}}}{K} t \right)}{1 - \exp \left( -\frac{(X - Y)r_{\text{max}}}{K} t \right)}. \]

Note that \( X - Y > 0, \) and so \( F(t) \) is bounded. Therefore \( T(t) \) and \( I(t) \) are bounded.

\[ \square \]

**Proposition 3.** Any solution \((T(t), I(t))\) of (1) subject to (2) is positive on \([0, b)\) for some \( b > 0. \)

**Proof.** We first show positivity for \( F. \) Assume that there exists \( t_1 \in (0, b) \) such that \( F(t_1) = 0 \) and all variables are positive on \([0, t_1). \) Assume also that \( T \) and \( I \) are bounded on \([0, t_1), \) i.e., there exist \( M_1 \) and \( M_2 \) such that \( T(t) \leq M_1 \) and \( I(t) \leq M_2 \) for all \( t \in [0, t_1). \) Then for all \( t \in [0, t_1] \)

\[ \frac{dF}{dt} \geq r_{\text{min}}F \left( 1 - \frac{F}{K} \right) - d_{\text{max}}F \]

\[ \geq r_{\text{min}}F \left( -\frac{M_1 + M_2}{K} \right) - d_{\text{max}}F \]

\[ = -\tilde{c}F, \quad \tilde{c} > 0 \]

and so

\[ F(t_1) \geq F_0 e^{-\tilde{c}t_1} > 0 \]

a contradiction. Then \( F(t) > 0 \) for all \( t \in [0, t_1]. \) Since we assume all the variables positive on \([0, t_1), \) this implies that both \( T(t) \) and \( I(t) \) are positive for all \( t \in [0, t_1]. \)

\[ \square \]
**Proposition 4.** If \( \max\{r_T, r_I\} > \min\{d_T, \delta\} \), then any solution \( V(t) \) of (1) subject to (2) remains bounded on \([0, b)\) for some \( b > 0 \).

**Proof.** If \( I(t) \) is bounded on \([0, b)\), then there exists a number \( M > 0 \) such that
\[
M \geq (1 - \epsilon)p \sup_{t \in [0, b)} I(t).
\]

Then for any \( t \in [0, b) \) we have
\[
\frac{dV}{dt} = (1 - \epsilon)p - cV \leq M - cV,
\]
and so
\[
V(t) \leq \max\left\{ V_0, \frac{M}{c} \right\}.
\]

\hfill \square

**Stability analysis.** We study the local asymptotic stability of system (1)’s equilibria for \( \epsilon = \eta = 0 \). The system has four equilibria: a liver death equilibria \( E^* = (0, 0, 0) \), a disease-free equilibrium \( E_0 = (K, 0, 0) \), a chronic infection equilibrium with total liver infection
\[
E^{\text{tot.liv}} = \left( 0, \frac{K(r_I - \delta)}{r_I}, \frac{pK(r_I - \delta)}{cr_I} \right),
\]
and a chronic equilibrium with partial liver infection
\[
E = \left( \frac{c\delta R_0(r_T - r_I) + r_T}{\beta p(R_0\delta + r_T - r_I)}, \frac{c\delta r_T(R_0 - 1)}{\beta p(R_0\delta + r_T - r_I)}, \frac{\delta r_T(R_0 - 1)}{\beta(R_0\delta + r_T - r_I)} \right),
\]
where
\[
R_0 = \frac{\beta pK}{c\delta} \tag{3}
\]
is the basic reproduction number, representing the number of secondary infections induced by an infected cell in a naive population.

**Proposition 5.** The liver death equilibrium is unstable.

**Proof.** The Jacobian matrix for the system is
\[
J = \begin{pmatrix}
    r_T \left(1 - \frac{2T+I}{K}\right) & -r_T \frac{T}{K} & -\beta T \\
    -r_I \frac{T}{K} & r_I \left(1 - \frac{T+2I}{K}\right) - \delta & \beta T \\
    0 & p & -c \\
\end{pmatrix}.
\]

When evaluated at \( E^* \), \( J \) becomes:
\[
J = \begin{pmatrix}
    r_T & 0 & 0 \\
    0 & r_I - \delta & 0 \\
    0 & p & -c \\
\end{pmatrix},
\]
whose eigenvalues \( \lambda_1 = r_T > 0 \) and \( \lambda_2 = r_I - \delta > 0 \). Therefore \( E^* \) is unstable.

\hfill \square
Proposition 6. The free disease equilibrium is locally asymptotically stable if $R_0 < 1$.

Proof. The Jacobian matrix for the system evaluated at $E_0$ becomes:

$$J = \begin{pmatrix} -r_T & -r_T & -\beta K \\ 0 & -\delta & \beta K \\ 0 & p & -c \end{pmatrix},$$

whose eigenvalues are negative when $R_0 < 1$.

Proposition 7. The equilibrium $E_{\text{tot.liv}}$ exists when $r_I > \delta$, is locally asymptotically stable when

$$R_0 \frac{r_I - \delta}{r_T} > 1,$$

and is unstable otherwise.

Proof. $E_{\text{tot.liv}}$ exists when $r_I > \delta$. It can be shown that the characteristic equation for $E_{\text{tot.liv}}$ is given by

$$\left(\lambda - \frac{r_T \delta}{r_I} + \frac{\beta p K (r_I - \delta)}{r_I c}\right)(\lambda + c)(\lambda + r_I - \delta) = 0,$$

with eigenvalue $\lambda_1 = \frac{r_T \delta}{r_I} - \frac{\beta p K (r_I - \delta)}{r_I c} < 0$ when $R_0 \frac{r_I - \delta}{r_T} > 1$. Since the other two eigenvalues are always negative, this condition is enough to ensure local asymptotic stability of equilibrium $E_{\text{tot.liv}}$.

Proposition 8. The equilibrium $E$ is locally asymptotically stable if $r_I > \delta$ and

$$1 < R_0 \text{ and } R_0 \frac{r_I - \delta}{r_T} < 1.$$  \hfill $\square$

The proof is messy and it will not be presented here.

When the treatment is initiated, we assume that the chronic equilibrium $E$ is stable, i.e. $1 < R_0 < \frac{r_T}{r_I - \delta}$. A successful combination drug therapy $0 < \epsilon \leq 1$ and $0 < \eta \leq 1$ will lead to virus clearance if the clearance equilibrium in the presence of therapy, $E_0^d = (K,0,0)$ (same as $E_0$ in the absence of therapy), becomes the locally asymptotically stable steady state. This occurs when

$$\mathcal{R} = (1 - \epsilon)(1 - \eta)R_0 < 1.$$  \hfill (5)
Figure S1: Samples for bi-phasic (dark blue dots) and tri-phasic (red to light blue dots) $V(t)$ dynamics for: (A) fixed $r_T/r_I = 2.5$; (B) fixed $r_T/r_I = 1$; (C) fixed $\epsilon = 0.9$; and (D) fixed $\epsilon = 0.99$; (E) fixed $\delta = 0.01$. The other parameters are as in Table 2.
Figure S2: Division of the samples for bi-phasic and tri-phasic virus pattern based on the number of years to virus clearance for: (A) fixed $\epsilon = 0.9$; (B) fixed $\epsilon = 0.99$. The other parameters are as in Table 2.
Figure S3: Density of bi-phasic (blue) and tri-phasic (pink) $V(t)$ samples versus: (A) Liver turnover; (B) Net liver gain, for $\epsilon = 0.99$, $r_T/r_I = 2.5$, $0.01 \leq \delta \leq 0.1$ d$^{-1}$ and $\tau = 100$ days.