Evaluating the effect of implementing biologically realistic delays on hepatitis C kinetics and associated estimates of antiviral efficacy

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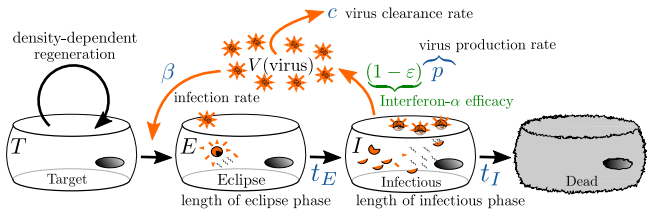
Introduction

- Hepatitis C is an infectious disease which causes severe inflammation of the liver.
- About 130–170 million people are chronically infected with the hepatitis C virus (HCV) worldwide according to the World Health Organization (WHO).
- Current therapy with interferon-α (IFN-α) and ribavirin is effective in controlling the infection in $\sim$50% of treated persons [3].
- Absence of a reliable in vitro cell culture model for HCV makes it difficult to characterize HCV kinetics.
- Mathematical models of HCV based on ordinary differential equations (ODEs) have helped characterize HCV kinetics in patients during antiviral therapy and determine antiviral efficacy and other parameters [4, 5].

The viral infection process



Target cells (T) are infectible by HCV (V) at rate (β).

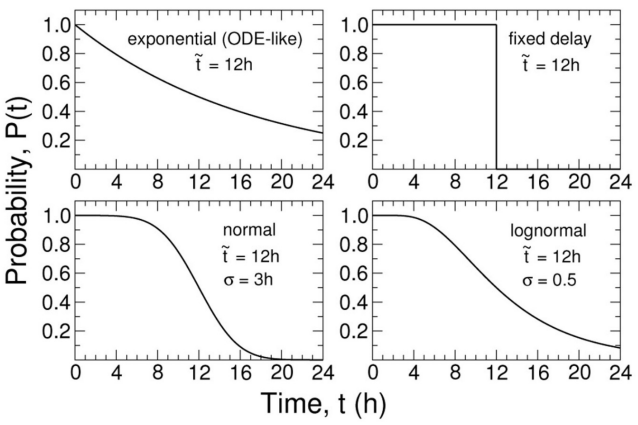
Eclipse cells (E) are recently infected cells which will become infectious cells (I) and begin producing virus after an average time $\langle t_E \rangle$ has elapsed.

Infectious cells (I) produce virus at constant rate p for an average time $\langle t_I \rangle$.

Dead cells (D) are those no longer producing virus.

Virus (V) is produced by infectious cells (I) at constant rate p which can be dampened, $p \to (1-\varepsilon)p$, by IFN-α treatment, and is cleared at rate c.

Different possible types of delays



- Delays define the time spent by a cell in a given state before transitioning to another.
- Biologically, a cell is not able to produce virus as soon as it is infected.
- Since an exponential distribution (ODE-like) allows immediate transitions, other distributions are more appropriate (e.g., fixed, normal, lognormal) [2].

Objective

To investigate whether a more realistic mathematical model for HCV i.e., one with

1. an eclipse phase between the moment of cell infection and when the cell starts to release virus; and
2. a realistic duration for cell lifespan and the length of the eclipse phase,

would lead to different conclusions about the role and efficacy of IFN-α treatment.

The mathematical InDE model

We define an integral and differential equation (InDE) model with an eclipse phase and flexible delay as follows

$$\frac{\mathrm{d}T}{\mathrm{d}t} = r_T T\left(1 - \frac{T+E+I}{T_{\max}}\right) - \beta T V$$

$$E(t) = E(0)P_E(t) + \int_0^t \beta T(s)V(s)P_E(t-s)\,\mathrm{d}s$$

$$I(t) = I(0)P_I(t) + \int_0^t P_I(t-s)E(0)f_E(s)\,\mathrm{d}s + \int_{s_2=0}^{t}\int_{s_1=0}^{s_2} \beta T(s_1)V(s_1)f_E(s_2-s_1)P_I(t-s_2)\mathrm{d}s_1\mathrm{d}s_2$$

$$\frac{\mathrm{d}V}{\mathrm{d}t} = (1-\varepsilon)pI - cV$$

- Target cells regenerate at rate (r_T) following logistic growth constrained by the maximum number of hepatocytes ($T_{\max}$).
- $P_E(t)$ (or $P_I(t)$) is the probability that a cell remains in the eclipse (or infectious) state for at least a time t before transitioning to the infectious (or dead) state.
- $f_E(t)$ is the probability density function for the time a cell will spend in the eclipse state before transitioning to the infectious state ($f_E = -\mathrm{d}P_E/\mathrm{d}t$).

The chronic infection steady state

Since treatment is administered when a patient suffers from chronic infection, it is simulated by setting the model to a steady state before applying treatment.

The steady state densities of uninfected ($\bar{T}$), eclipse ($\bar{E}$), and infectious ($\bar{I}$) cells and virions ($\bar{V}$) are given by

$$\bar{T} = \frac{c}{p\beta\langle t_I\rangle}$$

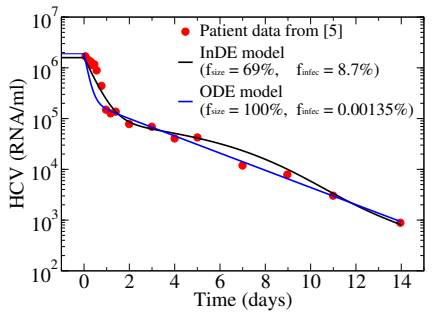
$$\bar{E} = \int_0^\infty \bar{E}(a)\mathrm{d}a = \int_0^\infty \beta\bar{T}\bar{V}P_E(a)\mathrm{d}a = \beta\bar{T}\bar{V}\langle t_E\rangle$$

$$\bar{I} = \int_0^\infty \bar{I}(a)\mathrm{d}a = \int_0^\infty \beta\bar{T}\bar{V}P_I(a)\mathrm{d}a = \beta\bar{T}\bar{V}\langle t_I\rangle$$

$$\bar{V} = \frac{1 - \frac{\bar{T}}{T_{\max}}}{\beta\left[\frac{1}{r_T} + \frac{\bar{T}}{T_{\max}}\left(\langle t_E\rangle + \langle t_I\rangle\right)\right]}$$

where a is age of infection at time t.

Biological considerations



Both fits are good (SSR of 0.28 (InDE) and 1.24 (ODE)), but...

- The InDE model suggests an infected liver size which is $f_{\text{size}} = 69\%$ of its original size with $f_{\text{infec}} = 8.7\%$ of it infected ($\varepsilon = 0.95$, $c = 2.25\ \mathrm{d}^{-1}$).
- The ODE model suggests only 0.005% of the liver is infectible ($T_{\text{susceptible}} = T_{\max}/20{,}000$) leading to a more reasonably sized liver where only $f_{\text{infec}} = 0.001\%$ of cells are infected.

It is believed that the hepatic liver does not shrink to more than $\sim$90% of its original size and is typically 3–75% infected [1] (more likely $\sim$10%).

Constraints on parameters

We apply the following biological constraints:

- The whole liver is susceptible and $T_{\max} = 10^{11}$ cells.
- The infected liver is $f_{\text{size}} = 90\%$ of an uninfected liver.
- $f_{\text{infec}} = 10\%$ of the liver is chronically infected.

such that in InDE model we can fix

$$\beta = \frac{\mathbf{c}}{\mathbf{p}\langle\mathbf{t_I}\rangle\mathbf{T}_{\max}\mathbf{f}_{\text{size}}(1-\mathbf{f}_{\text{infec}})}$$

$$\langle\mathbf{t_E}\rangle = \frac{\mathbf{f}_{\text{infec}}}{\mathbf{r_T}(1-\mathbf{f}_{\text{infec}})(1-\mathbf{f}_{\text{size}})} - \langle\mathbf{t_I}\rangle$$

leaving only $\mathbf{r_T}$, $\mathbf{p}$, $\mathbf{c}$, $\langle\mathbf{t_I}\rangle$ to fit.

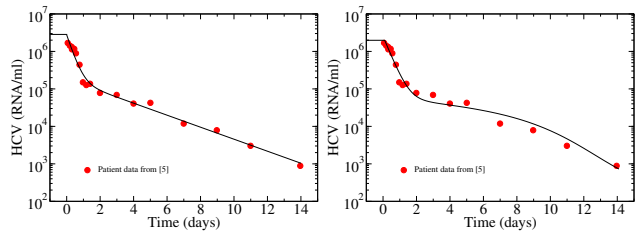
In the ODE model we can fix

$$\beta = \frac{\mathbf{c}\mathbf{r_T}(1-\mathbf{f}_{\text{size}})}{\mathbf{p}\mathbf{T}_{\max}\mathbf{f}_{\text{size}}\mathbf{f}_{\text{infec}}}$$

$$\langle\mathbf{t_I}\rangle = \frac{\mathbf{f}_{\text{infec}}}{\mathbf{r_T}(1-\mathbf{f}_{\text{infec}})(1-\mathbf{f}_{\text{size}})}$$

leaving only $\mathbf{r_T}$, $\mathbf{p}$, $\mathbf{c}$ to fit.

Fitting models to experiments



Fit of the ODE model (left) and InDE model (right) against the experimental viral titer.

Param.	ODE model	InDE model
ε	0.90	0.97
c	3.22 d^{-1}	2.19 d^{-1}
$\langle t_E\rangle$	–	1.13 d
$\langle t_I\rangle$	1.78 d	8.56 d
r_T	0.62 d^{-1}	0.11 d^{-1}
SSR	0.22	0.33
f_{size}	90%	90%
f_{infec}	10%	10%

Conclusion

The addition of: (1) an eclipse phase; (2) biologically realistic delays; and (3) biological constraints leads to different predictions about antiviral efficacy, viral clearance rate, and infected cell lifespans.

Future work

We will expand our model to include: (1) regeneration of infected cells; (2) use our model to fit more patient data and look for other deviations in parameters extracted.

References

[1] V. Agnello, G. Abel, G. B. Knight, and E. Muchmore. Detection of widespread hepatocyte infection in chronic hepatitis C. *Hepatology*, 28(2):573–584, August 1998.

[2] B. P. Holder and C. A. A. Beauchemin. Exploring the effect of implementing different biological delays in constructing kinetic models of influenza infection within a host or cell culture. *BMC Public Health*, 11(Suppl 1):S10, Feb 2011.

[3] M. P. Manns, J. G. McHutchison, S. C. Gordon, V. K. Rustgi, M. Shiffman, R. Reindollar, Z. D. Goodman, K. Koury, M. Ling, and J. K. Albrecht. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet*, 358(9286):958–965, 22 September 2001.

[4] A. U. Neumann, N. P. Lam, H. Dahari, D. R. Gretch, T. E. Wiley, T. J. Layden, and A. S. Perelson. Hepatitis C viral dynamics in vivo and the antiviral efficacy of interferon-α therapy. *Science*, 282(5386):103–107, 2 October 1998.

[5] T. C. Reluga, H. Dahari, and A. S. Perelson. Analysis of hepatitis C virus infection models with hepatocyte homeostasis. *SIAM J Appl Math*, 69(4):999–1023, January 2009.