**The mathematical InDE model**

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

\[
\frac{dT}{dT} = r_T T \left(1 - \frac{T}{T_{\text{max}}} + I\right) - \beta TV
\]

\[
E(t) = E(0) P_E(t) + \int_0^t \beta(T) V(t-s) P_E(t-s) \, ds
\]

\[
I(t) = I(0) P_I(t) + \int_0^t (\beta(T) V(t-s) P_E(t-s) - \gamma(T) I(t-s)) \, ds
\]

\[
\frac{dV}{dt} = (1-c)p - cV
\]

- Target cells regenerate at rate \(P_\text{E}(t)\) by infectious cells \(P_I(t)\) and is cleared at rate \(\gamma(T)\).
- \(P_E(t)\) or \(P_I(t)\) is the probability that a cell remains in the eclipse (or infectious) state for a time \(t\) before transitioning to the infections (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 \(f_E = -dP_E/dt\).

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 \(V\) are given by:

\[
\bar{T} = \frac{c}{\beta(T) I_{\text{max}}} E(t)
\]

\[
\bar{E} = \int_0^\infty \frac{E(s)da}{\beta(T) V(s)} \, ds
\]

\[
\bar{I} = \int_0^\infty \frac{I(s)da}{\beta(T) V(s)} \, ds
\]

\[
\bar{V} = \beta \left[ 1 + \frac{c}{\beta(T) I_{\text{max}}} (E(t) + I(t)) \right]
\]

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 \(f_{\text{max}} = 60\%\) of its original size with \(f_{\text{max}} = 8.7\%\) of it infected \((c = 0.95, \, e = 2.25\, d^{-1})\).
- The ODE model suggests only 0.005\% of the liver is infectible \((T_{\text{susceptible}} = T_{\text{max}}/20,000)\) leading to a more reasonable sized liver where only \(f_{\text{max}} = 0.003\%\) 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 \((\text{more likely} \sim 10\%\).

**Conclusions**

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

**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