Introduction to Viral Dynamics Studies

Identify the important components of a model and what they mean.

Identify benefits and dangers of using mathematical models in HIV research

Identify possible studies which could be done

Discuss the design process for a viral dynamics study

Open to any suggestions about topics of interest

Theoretical models

- No data involved
- Identify (possibly) counter-intuitive features of disease processes;
- Prediction of long term outcomes;
- Generally more complex models with lots of compartments
- Not clear how to determine if one model is "better" than another (more accurate, better prediction?)
- Physicists and Engineers have spent decades,centuries developing their models for systems with relatively little noise.
- Should primarily be used for generating hypothesis to be tested experimentally.

"Applied" Models

- Models used with longitudinal data. Used to estimate dynamic features from data, eg viral set points or decay rates
- **Used to compare these parameters between different populations or compartments**
- **E.g. Treated vs untreated, semen vs plasma**
- Generally simpler with fewer compartments and parameters
- In some cases may be used to make predictions - but with caveats which must be transparent.
- Often presented in an opaque manner in the research literature.

Background

- Discovery of rapid turnover of virus and infected cells.

  Wei et.al.,Ho et.al,Nature 1995, Perelson et.al Science 1996

- Viral eradication with treatment is predicted using a model

  Perelson et.al. Nature 1997

- Lots of groups model HIV etiology and estimate decay rates

  1995-2006

- Viral setpoint is shown to be prognostic for disease outcome.

  Mellors et.al Annals Int. Med. 1997.

- Do other dynamic parameters have similar prognostic value?

  Would be interesting to conduct such studies

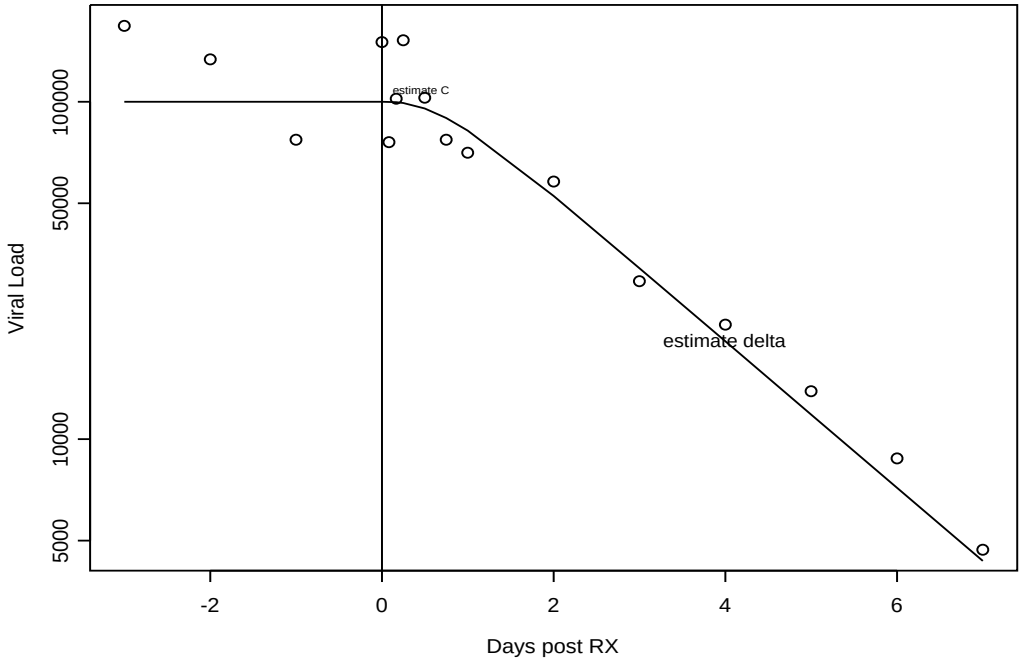
Estimation of parameters in viral dynamics models

Viral decay after treatment and infected cell turnover rates

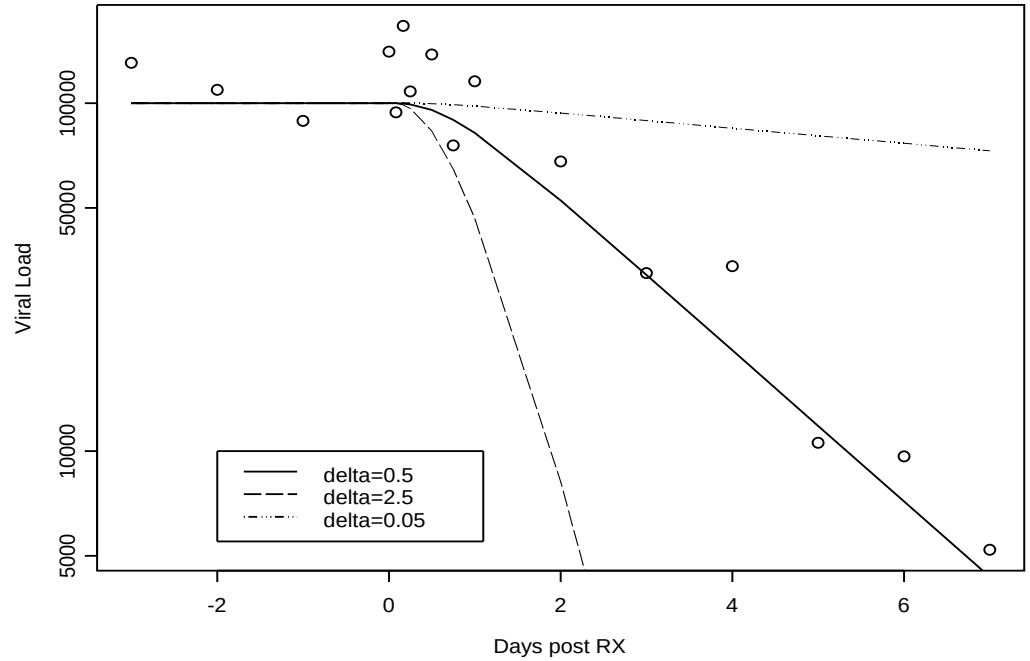
Perelson et.al. Science 1996

- Treatment with protease inhibitors does not halt the production of viral RNA, but stops virion formation so that viral RNA produced after treatment is non-infectious.
- Treatment "perturbs" viral steady state by halting production of infectious virus.
- Using measurements of **viral loads** after treatment, viral clearance and **infected cell** turnover rates are estimated using a model.
- The model provides the relationship between viral loads and infected cell turnover rate.

Example: simulated viral load up to 7 days post treatment



Decay rates CANNOT be estimated from steady state data



Model equations for viral decay after treatment

$$\begin{aligned}
\frac{dX}{dt} &= kTV_I - \delta X \\
\frac{dV_I}{dt} &= -cV_I \\
\frac{dV_{NI}}{dt} &= N\delta X - cV_{NI}
\end{aligned}$$

- X is the population of infected cells
- V_I is the population of infectious virus
- V_{NI} is the population of non-infectious virus
- $V = V_I + V_{NI}$ is the total **observed** viral load

Conclusions based on estimation of viral clearance and infected cell turnover.

- Estimates of δ (infected cell turnover rate) and c (viral RNA clearance rate) showed that infected cells and viral RNA are turning over rapidly and continuously during the long latent stage of HIV infection prior to AIDS
- Previously, it was thought that HIV was relatively inactive during the latent stage prior to development of AIDS
- Estimates of number of viral particles produced per day have been obtained using these estimates and explain why HIV escapes immune response and can easily becomes resistant to suboptimal treatment.
- Homework Find something very unusual in the presentation of the results in Perelson Science 1996 paper.