Modeling HCV Antivirals

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Outline

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Challenges of Drug Discovery

• *Paracelsus* (1493-1541) Known as 'The Father of Medicine' said "All that man needs for health and healing has been provided by God in nature, the challenge of science is to find it." Also known as 'The Father of Toxicology, he said, "All things are poison and nothing is without poison, only the dose permits something not to be poisonous."

• Little and much have changed …

*http://en.wikipedia.org/wiki/Paracelsus#Biography*
Drug Development Process

Of 10,000 compounds in basic research, on average only five will enter clinical testing and just one will make it to the market. (Source: PhRMA, March 2005)

By the year 2000 R&D costs for a single drug had exceeded $800M. Only 3 of 10 drugs recouped their R&D investment.
Applied Mathematics, Computing and Modeling

• Understanding
  – Moving from Qualitative to Quantitative
  – More compact representation of *knowledge* that is easier to disseminate.

• Efficiency
  – Can reduce cycle time or increase productivity via elimination of empirical work or redundant testing.

• Towards the Elimination of Animal Testing
  – Imaging and image processing enables longitudinal studies of animal reducing N (for humans and nonhumans).
  – Some mathematical models are better predictors then corresponding “animal models”.

• Many Contributors
  – Applied Computer Science and Mathematics (ACSM)
  – Biometrics Research
  – Clinical Statistics
  – Epidemiology
  – Metabolism
  – Molecular Profiling
  – Pharmacology and many others…
Background*

• Hepatitis C virus (HCV) is currently the major cause of parenterally-transmitted non-A, non-B hepatitis (NANB-H).

• In the majority of cases, infection by HCV results in a chronic disease characterized by liver inflammation and in some cases, slow progression to cirrhosis, liver failure and/or hepatocellular carcinoma.

• There is no vaccine available for HCV and current therapy with interferon alpha (IFNα) and the nucleoside analog ribavirin produces complete response in less than half of treated persons infected with genotype 1, the predominant genotype in the US and many other countries.

• It is estimated that 3% (> 170 million) of the world’s population and 2% (> 4 million) of the US population is affected by the disease.

• HCV is transmitted primarily through direct percutaneous exposure to blood and is the most common chronic blood-borne infection in the US.

HCV Replication Cycle

1. Virus binding and internalization
2. Cytoplasmic release and uncoating
3. Internal ribosomal entry site (IRES)-mediated translation and polyprotein processing
4. RNA replication
5. Packaging and assembly
6. Virion maturation and release

A cartoon of the HCV cell structural. HCV RNA replication occurs in a specific, self-constructed membrane, the membranous web (MW). Positive and negative strand RNA are each
Modeling & Simulation

• How can this system be modeled?
• What parts of the system are observable?
• What are the important variables?
• How much detail is necessary?
Perelson Model

• Basic Continuum Assumptions
  – Uniform infection of the liver hepatocytes.
  – Significant viron count.
  – Significant infected cell count.
  – Constant kinetics rates (production and clearance).

• Simplifying assumptions
  – $T$ is constant

• Some Implied Limitations
  – Early infection
  – Sustained viral clearance to cure
Perelson Model
Compartmental Representation

Uninfected Cells ($T$) \( \rightarrow \) Infected Cells ($I$) \( \rightarrow \) Virons ($V$)

\[ dT \times (1-\eta) \beta VT \]

\[ s \]

\[ \delta I \]

\[ (1-\varepsilon)pI \]

\[ cV \]

Perelson Model
ODE Representation

\[
\begin{align*}
\frac{dT}{dt} &= s - d \ T - (1 - \eta) \beta VT \\
\frac{dl}{dt} &= (1 - \eta) \beta VT - \delta I \\
\frac{dV}{dt} &= (1 - \varepsilon) pI - cV
\end{align*}
\]

where $T$ is the number of uninfected cells, $I$ is the number of infected cells, and $V$ is the number of virons; new hepatocytes are produced at rate $s$, and die at rate $d$, and are infected at rate $\beta$; infected hepatocytes are cleared at rate $\delta$, and produce new virons at rate $p$; virons are cleared at rate $c$. 
Perelson Model - Conclusions

- Biphasic decline in viral load implies blocking of virion production, not infection of hepatocytes
- Major initial effect of interferon-α is to block virion production or release
- Estimated mean virion half-life 2.7 hours
- Pretreatment production and clearance of $10^{12}$ virions per day
- Estimated infected cell death rate exhibited large interpatient variation (corresponding $t_{1/2}$ 51.7 to 70 days), was inversely correlated with baseline viral load
Modifications to Perelson Model

- Liver size (sum of healthy + infected cells) is constant
- Explicit account for viron loss during infection
- Rate constants refit to our data for nucleoside polymerase inhibitor in chimps
Constrained Total Hepatocyte Model
Compartmental Representation

\[ T + I = T_0 \]
Constrained Total Hepatocyte Model

ODE Representation

\[ \begin{align*}
  T & \xrightarrow{\rho} 2T \\
  T + V & \xrightarrow{\beta} I \\
  I \xrightarrow{(1-\epsilon f(t))p} I + V \\
  I & \xrightarrow{\delta} I \\
  V & \xrightarrow{c} V \\
 \end{align*} \]

\[\begin{align*}
  I'(t) &= -\delta I(t) + \beta T(t) V(t) \\
  T'(t) &= \rho T(t) - \beta T(t) V(t) \\
  V'(t) &= (1 - \epsilon f(t)) p I(t) - c V(t) - \beta T(t) V(t) \\
\end{align*}\]

\[ (T_0 = T(t) + I(t)) \Rightarrow (I'(t) = -T'(t)) \]

\[ -\delta I(t) + \beta T(t) V(t) = -(\rho T(t) - \beta T(t) V(t)) \]

\[ \rho = \frac{\delta I(t)}{T(t)} \]

\[\begin{align*}
  I'(t) &= \beta (T_0 - I(t)) V(t) - \delta I(t) \\
  V'(t) &= p (1 - \epsilon f(t)) I(t) - c V(t) - \beta (T_0 - I(t)) V(t) \\
\end{align*}\]
Steady State Analysis

Steady State

Uninfected

\[ \bar{I}(\infty) = 0 \]

\[ \mathcal{V}(\infty) = 0 \]

Infected

\[ \bar{I}(\infty) = -\frac{c \delta + \beta (\delta - p(1 - \epsilon f(\infty))) T_0}{\beta (\delta - p(1 - \epsilon f(\infty)))} \]

\[ \mathcal{V}(\infty) = -\frac{c \delta + \beta (\delta - p(1 - \epsilon f(\infty))) T_0}{c \beta} \]
Steady State Analysis

Stability Numerical Eigenvalues Numerical Eigenvalues
without treatment ($\epsilon = 0$) with treatment ($\epsilon = 0.9995$)

Uninfected $\{+, \pm\}$ $\{-8.97598, 0.0559827\}$ $\{-8.67016, -0.249841\}$

Infected ? $\{-8.27301, -0.0607397\}$ $\{-1.41155, 1.5346\}$

• Results Differ from HIV as:
  – Without treatment the uninfected steady state is unstable and will evolve to the stable infected steady state
    • Therefore, initial infection will not spontaneously clear.
  – With treatment the infected steady state is unstable.
    • Therefore, infected steady state must be driven to the stable uninfected steady state with continuous treatment.
Viral Time Course Under Therapy

\[ \varepsilon = 0.999 \]

- Viral clearance
- Infected clearance
- Reinfection
- Rebound
Infected Cell Ratio and Cure Boundary

The infected cell ratio

\[ i = \frac{I}{T_0} \]

is derived from the differential equations as

\[ i = \frac{1}{(1-\varepsilon)pT_0} \left( \frac{dV}{dt} + cV \right). \]

The cure boundary is the steady state value of the infected cell ratio.

\[ i_b = 1 - \frac{c\delta}{\beta(1-\varepsilon)pT_0} \]

If the ratio is positive then the infected cells are never cleared. Otherwise if \( i_b \) is zero or negative then all the infected hepatocytes are cleared - a cure.
Viral Time Course Under Therapy
Above and below the cure boundary

36 weeks of therapy

\[ \epsilon = 0.25 \]
\[ \epsilon = 0.40 \]

LOQ

H IU mL^{-1}

\( \varphi \) (IU mL^{-1})

time (d)
Data Fitting

Nucleoside Polymerase Inhibitor in Chimps

![Graphs showing viral load over time for different treatments.](image)
Clinical Trial Design

• Can we use our model and its simulation to predict the outcome from a clinical trial?

• Can we estimate
  – the confidence interval about the mean time to cure, \( i.e., \) duration of therapy to achieve SVR?
  – probability of break through?
  – the confidence interval about the mean time to rebound for a given duration of therapy?

• Can we help minimize the cost and/or the cycle time of a trial?
Stochastic Parameter Sensitivity

All parameters varied under normal distribution with standard deviation of 10% of parameter value; 1000 simulations.
Discrete Modeling

• Need
  – ODE model gives the mean time, but says nothing about distribution
  – When few virons remain, random fluctuations in behavior significant
  – Want to determine the variance of treatment times to complete cure

• Implementation
  – Use parameters from Neumann et al. 1998 for human, our fitted values for a polymerase inhibitor in chimps
  – Stochastic Simulation Algorithm (Gillespie et al.)
  – Convert ODEs into discrete events with exponential probability distributions
  – Use continuous model until hourly stochastic variation > 1%
    • Continuous model starts with $\sim 10^{11}$ virons, $\sim 10^{11}$ infected hepatocytes
    • Stochastic model begins at $\sim 10^4$ virons, $\sim 10^6$ infected hepatocytes
Stochastic Modeling
Gillespie Algorithm

- Individual events vs. statistical ensemble
- Rate constants define propensity of events
- Sum of propensities define time between events
A Stochastic Process in Action

Healthy Hepatocytes

Infected Hepatocytes

Choose an event at random

\[ T + V \xrightarrow{\beta} I \]

\[ I \xrightarrow{1 - e^{f(t)P}} I + V \]

\[ I \xrightarrow{\delta} I \]

\[ V \xrightarrow{c} I \]

\[ T + I = T_0 \]

infected ($\beta$)
Distribution of Simulated Time to Cure
Continuous Interferon α in humans

Virons

Infected Hepatocytes

time (d)

frequency

time (d)
Distribution of Simulated Time to Cure 36 week Interferon α in humans

- 92% of the runs cured during treatment
- 3.8% cured after treatment
- 3.2% remained infected

- 36 weeks not enough time to clear all the infected cells

\( H_L = H_{\Omega} L \)
Phase I Trial Design

• When should blood samples be taken for PK and viral load determination?

• Can we use a 5-day per week study center instead of a 7-day per week center?
Parameters varied with normal distribution about nominal values with a 20% standard deviation.
Analytic Parameter Sensitivity
Viral load and parameter sensitivity for 3 doses
Phase I Trial Design

Effect of Enrollment Day on Data Fitting

- First panel shows model for 7-day per week study site
- Other panels show results for 5-day per week study site on given enrollment day
- Enrollment on Monday-Thursday is quite acceptable
- Enrollment on Friday leads to data loss and much less confident data fitting
- Ability to use 5-day site saves approx. $2500 per patient
Business Impact of the HCV Infection Modeling

• We have a better understanding of the disease process under therapy, especially when traditional biomarkers fail to show the presence of disease, and we can design better treatment regimens.

• Modeling has shown that a less expensive clinical trial design can yield data of the same quality and utility as that from a more comprehensive and more expensive design.
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