Introduction to Modeling and Simulation

- Introduction
- Pharmacokinetics and pharmacodynamics
- Modeling and simulation in drug development
- Modeling and simulation in design of a clinical trial – a case study
“Modeling and simulation:”

• Means many different things to many different people

• A “hot” topic in numerous application areas

• Computer science, engineering, operations research, biology and biomedicine...

• Here: Modeling and simulation related to the study of human health and treatment of disease

• In particular, M&S in drug development, design of clinical trials, and design of treatment strategies
Introduction

Premise: Use mathematical-statistical models as the basis for (probabilistic) simulation

• How would the entire population fare if all individuals followed a particular treatment strategy?

• How would a sample of individuals from the population fare in a clinical trial to evaluate and/or compare treatments? How large would the trial have to be to detect a real difference between treatments in the population?

• Try things out on “virtual subjects” . . .

• . . .to gain insight on the best approaches to try in real subjects
Introduction

**Required:** In most implementations

- Suitable *mathematical model(s)* of (usually) *individual-level* behavior, possibly *linked* together

- Suitable *statistical models(s)* of *individual-level* and *population-level* behavior

- Models must be *fully specified* $\implies$ (*ideally*) based on *data* from *preliminary studies* (but often some model components based on assumptions and conjecture. . . )
Pharmacokinetics and pharmacodynamics

**Historically:** One of the first instances of this brand of M&S

- *Population pharmacokinetic-pharmacodynamics (PK/PD)*
- *Pharmacokinetics (PK): “What the body does to the drug”*
- *ADME processes*: absorption, distribution, metabolism, excretion dictate *concentrations of drug* in the body over time
- *Pharmacodynamics (PD): “What the drug does to the body”*

- What kind of *responses* result from achieved concentrations?

- “*Response*” is a health outcome that is *straightforward* to ascertain; e.g., *viral load* in HIV-infected subjects, occurrence of an *adverse event* (evaluation of *safety*), a “*biomarker*”

- “*Response*” may *not* be the health outcome of ultimate interest (more later)…
Pharmacokinetics and pharmacodynamics

**Usual paradigm:** Look only at *dose-response* relationship

**PK/PD premise:**

- Understanding what goes on *between* dose and response leads to *greater insight*

- E.g., for developing *dosing regimens* that achieve *therapeutic objective*, minimize *toxicity*...

- ...and can be tailored to take account of *subject characteristics*
Pharmacokinetics and pharmacodynamics

\[ \text{dose} \rightarrow PK \rightarrow \text{concentration} \rightarrow PD \rightarrow \text{response} \]
Pharmacokinetics and pharmacodynamics

Basic assumptions and principles:

- There is an “effect site” where drug will have its effect
- Magnitudes of response (good and bad) depend on drug concentration at the site of action
- Drug cannot be placed directly at effect site, must move there
- Concentrations at the effect site are determined by ADME
- Concentrations must be kept high enough to produce a desirable response, but low enough to avoid toxicity

⇒ “Therapeutic window”

- (Usually) cannot measure concentration at effect site directly, but can measure in blood/plasma/serum; reflect those at site
Pharmacokinetics and pharmacodynamics

- Absorption
- Elimination

Time (hr)

Concentration (mg/L)
Pharmacokinetics and pharmacodynamics

![Graph showing absorption, elimination, therapeutic window, and duration of effect over time and concentration.]

- Absorption
- Elimination
- Therapeutic Window
- Duration of Effect

Time (hr)

Concentration (mg/L)
Pharmacokinetics and pharmacodynamics

**Multiple dosing:** Ordinarily, *sustaining doses* are given to *replace* drug eliminated, *maintain* concentrations in therapeutic window over time

- *Steady state*

**Frequency, amount for multiple-dose regimen governed by:**

- *ADME*

- *Width* of therapeutic window

**Ultimate objective:** Determine *multiple dosing regimens* that keep concentrations in the therapeutic window...
Pharmacokinetics and pharmacodynamics

Principle of superposition:

[Graph showing concentration over time for different doses]
Pharmacokinetics and pharmacodynamics

Effect of different frequency: Same dose and ADME characteristics
Pharmacokinetics and pharmacodynamics

Effect of different elimination characteristics: Same dose and frequency
Recall: Can learn about ADME from concentration-time data in the context of a PK model embedded in a hierarchical statistical model

- Can apply the principle of superposition to investigate dosing regimens that would keep concentrations in the therapeutic window for most subjects

- Must take into account variation in ADME across subjects. Identical dosing regimen can lead to very different concentrations in different subjects

- Identify subject characteristics that require tailored recommendations to achieve desired concentrations
Pharmacokinetics and pharmacodynamics

How to determine the therapeutic window?

- This is where PD comes in...

- Study response-concentration within subjects and how it varies across subjects

- Subjects who achieve the same concentrations can show very different responses

- Must characterize features underlying this variation in response

**Ideal**: PK/PD study

- Ascertain concentrations over time and measure responses for each subject

- Develop a mathematical-statistical model that links descriptions of PK and PD
Pharmacokinetics and pharmacodynamics

Example: PK/PD study of argatroban

- Anti-coagulant
- Early clinical study with $m = 37$ subjects receiving 4-hour IV infusion at rates (doses) of 1 to 5 $\mu$g/kg/min of argatroban
- $PK$ (blood samples) at (30, 60, 90, 115, 160, 200, 240, 245, 250, 260, 275, 295, 320) min
- $PD$: additional samples at 5–9 time points, measured activated partial thromboplastin time (aPTT, the response)

Objectives:

- Characterize concentrations for range of potential doses
- Evaluate extent and nature of PK and PD variation
- Describe relationship between aPTT and argatroban concentration
Pharmacokinetics and pharmacodynamics

Infusion rate 1.0 µg/kg/min

Infusion rate 4.5 µg/kg/min
Pharmacokinetics and pharmacodynamics
Pharmacokinetics and pharmacodynamics

Response-concentration for 4 subjects:

Subject 15

Subject 19

Subject 28

Subject 33
Pharmacokinetics and pharmacodynamics

Model for individual PK: For subject $i$

$$Y_{ij}^{(1)} = f^{(1)}(t_{ij}, U_i, \theta_{PK,i}) + \epsilon_{ij}^{(1)}$$

- Blood samples to be assayed for argatroban concentrations $(Y_{i1}^{(1)}, \ldots, Y_{in_i}^{(1)})^T$ at times $(t_{i1}, \ldots, t_{in_i})^T$

- Subject $i$ assigned to receive *intravenous infusion* at rate $R_i$ ($\mu$/kg/min) for $t_{inf} = 240$ minutes

- *One-compartment IV infusion model*, $U_i = (R_i, t_{inf})$

$$f^{(1)}(t_{ij}, U_i, \theta_{PK,i}) = \frac{R_i}{Cl_i} \left\{ \exp \left( -\frac{Cl_i}{V_i} t^\dagger_{ij} \right) - \exp \left( -\frac{Cl_i}{V_i} t_{ij} \right) \right\}$$

$$t^\dagger_{ij} = \begin{cases} 0, & t_{ij} \leq t_{inf}, \\ t_{ij} - t_{inf}, & t_{ij} > t_{inf} \end{cases}$$

$$\theta_{PK,i} = (\log Cl_i, \log V_i)^T$$
Pharmacokinetics and pharmacodynamics

Model for individual PD: For subject $i$

$$Y_{ij}^{(2)} = f^{(2)}(s_{ij}, U_i, \theta_{PK,i}, \theta_{PD,i}) + \epsilon_{ij}^{(2)}$$

- Blood samples to be assessed for aPTT measurements $(Y_{i1}^{(2)}, \ldots, Y_{ir_i}^{(2)})^T$ at times $(s_{i1}, \ldots, s_{ir_i})^T$ (possibly different from the PK times)

- **Key**: PD response depends on concentration at the *effect site*, *(not concentration in blood/plasma/serum)*

- **Here**: The blood *is* the effect site
Pharmacokinetics and pharmacodynamics

**Result:** PD model depends on concentration in PK model *directly*

- **“Emax model”:** A standard *empirical* representation of response-concentration relationships

\[
f^{(2)}(s_{ij}, U_i, \theta_{PK,i}, \theta_{PD,i}) = E_0 + \frac{E_{\text{max}i} - E_0}{1 + EC_{50i}/c_{ij}}
\]

\[
\theta_{PD,i} = (E_0, E_{\text{max}i}, EC_{50i})^T, \quad c_{ij} = f^{(1)}(s_{ij}, U_i, \theta_{PK,i})
\]

- **Standard assumption:** Dependence is on *expected concentration* at \(s_{ij}, E(Y_{ij}^{(1)}|U_i, \theta_{PK,i}) = f^{(1)}(s_{ij}, U_i, \theta_{PK,i})
\]

- Would be reasonable if *dominant* source of *intra-individual variation* is *measurement error*

**Individual-specific parameter:** \(\theta_i = (\theta_{PK,i}^T, \theta_{PD,i}^T)^T\)

- Write \(f^{(1)}(t, U_i, \theta_i), f^{(2)}(t, U_i, \theta_i)\)
Pharmacokinetics and pharmacodynamics

**Individual model:** \( Y_i = (Y_i^{(1)T}, Y_i^{(2)T})^T, i = 1, \ldots, m \)

- \( Y_i^{(1)} = (Y_{i1}^{(1)}, \ldots, Y_{in_i}^{(1)})^T \) at times \( (t_{i1}, \ldots, t_{in_i})^T \), PK concentrations
- \( Y_i^{(2)} = (Y_{i1}^{(2)}, \ldots, Y_{ir_i}^{(2)})^T \) at times \( (s_{i1}, \ldots, s_{ir_i})^T \), PD responses

**Combined model**

\[
Y_i = \begin{pmatrix}
    f(1)(U_i, \theta_i) \\
    f(2)(U_i, \theta_i)
\end{pmatrix}
\begin{pmatrix}
    \epsilon_i^{(1)} \\
    \epsilon_i^{(2)}
\end{pmatrix}
\]

- Assumptions on *joint conditional probability distribution* of \( Y_i^{(1)} \) and \( Y_i^{(2)} \) given \( U_i, \theta_i \Rightarrow p(y_i|u_i, \theta_i) \)
- E.g., do we expect *correlation* among elements of \( \epsilon_i^{(1)} \) and \( \epsilon_i^{(2)} \)?
Pharmacokinetics and pharmacodynamics

**Population model:** As usual $\theta_i = h(A_i, \beta) + b_i$

- *Among individual covariates* $A_i$, could be associated with both PK and PD parameters

- Assume $b_i = \mathcal{N}_p(0, D)$, $p = 5$ here

- $\theta = (\theta_{PK,i}^T, \theta_{PD,i}^T)^T \implies$ are elements of $\theta_{PK,i}$ and $\theta_{PD,i}$ correlated?

**Implied hierarchical model:**

1. *Individual model:* $p(y_i|u_i, a_i, b_i, \beta, \alpha)$

2. *Population model:* $p(b_i|\zeta)$
Pharmacokinetics and pharmacodynamics

Concentration-time for 4 subjects:

Subject 13

Subject 17

Subject 24

Subject 33
Pharmacokinetics and pharmacodynamics

Response-concentration for 4 subjects:

- **Subject 15**
- **Subject 19**
- **Subject 28**
- **Subject 33**
Pharmacokinetics and pharmacodynamics

Based on fit of hierarchical model: *Simulation*

- Estimates $\hat{\beta}$, $\hat{\alpha}$, $\hat{\zeta}$ and *standard errors*

- Can generate $N_{\text{sim}}$ "*virtual subjects*" by generating $\theta_i$ and then $Y_i$ from assumed *probability models* at each stage evaluated at a range of values $\beta$, $\alpha$, $\zeta$ based on estimates and standard errors

- $\Longrightarrow$ choose different sets of values for $(\beta, \alpha, \zeta)$

- Different *infusion rates* $R_i$, *infusion lengths* $t_{\text{inf}}$

- $N_{\text{sim}}$ "*large*" $\Longrightarrow$ effective *knowledge of the population* under different infusion strategies
Simulation procedure: For $i = 1, \ldots, N_{\text{sim}}$

- Generate $b_{i}^{\text{sim}}$ from $p(b_{i}|\zeta)$

- **Subject population**: Specify a *joint probability distribution* for all relevant covariates $A_{i}$, $p(a_{i})$, and generate $A_{i}^{\text{sim}}$ from $p(a_{i})$

- Form $\theta_{i}^{\text{sim}} = h(A_{i}^{\text{sim}}, \beta) + b_{i}^{\text{sim}}$

- Generate *“inherent”* PK and PD trajectories under chosen infusion strategy $U_{i}$ from $f^{(1)}(t, U_{i}, \theta_{i}^{\text{sim}})$, $f^{(2)}(t, U_{i}, \theta_{i}^{\text{sim}})$

- Can add within-subject *deviations* according to *intra-individual probability model* depending on $\alpha$ to obtain *“virtual data”* at intermittent *design points* $\Rightarrow$ “virtual future clinical study”
Pharmacokinetics and pharmacodynamics

Result:

• Can use “virtual inherent trajectories” to evaluate extent of population variation in PK and PD under different strategies, assess likely therapeutic window

• E.g., predict likely responses and/or toxic effects under different achieved concentrations

• Can inspect the results of “virtual studies” to evaluate sample size $m$ and numbers and placement of time points $n_i$, $r_i$ required to achieve desired precision for estimation of $\beta$, $\zeta$
Pharmacokinetics and pharmacodynamics

**In general:** *Effect site* is *not* blood/plasma/serum

- *Hysteresis, time lag* between plasma concentration and response
- *Popular approach for hysteresis:* Add a hypothetical “*effect compartment*” to the overall individual model
- drug is “*absorbed*” into “*effect compartment*” at fractional rate of *elimination* from central PK compartment
- Many other approaches, can get very fancy

**Alternative PD models:** Other *disease progression* models for response as a function of achieved concentrations are possible

- E.g., an *HIV dynamic model* where *efficacy* of PIs and RTIs depends on *achieved PK concentrations* or *underlying PK behavior*
Pharmacokinetics and pharmacodynamics

Summary: Population PK/PD modeling

- Provides a complete description of the time course of drug concentrations and resulting responses
- Provides insight into the extent of variability and systematic associations with subject characteristics
- Provides a mechanistic basis for simulation of effects on the population of proposed dosing strategies . . .
- . . . and for carrying out “virtual studies” to assess design suitability, precision, etc, of possible actual studies
M&S in drug development

Motivation:

- **Cost** of developing a new drug from conception to approval by the US Food and Drug Administration (FDA) is estimated at $600-950 million

- **Classical drug development paradigm**:
  - **R&D, drug discovery, preclinical testing** (5/5000 compounds go on to human testing)
  - **Phase 1** (safety, small trials) (70% go on)
  - **Phase 2** (efficacy, moderate-size trials) (33% go on)
  - **Phase 3** (effectiveness; compare against control, large, confirmatory studies) (25% make it)
  - **New Drug Application (NDA)** (less than 2 of original 5000 are approved)
M&S in drug development

Traditional approach: Which doses to study?

- Phase 1 dose selection based on very small number of subjects and statistically questionable studies
- Phase 2 doses carried forward from Phase 1 in studies of efficacy and further safety
- Phase 3 dose selection (one or two levels only) often involves guesswork

- Poor dose selection can “kill” a promising compound

FDA and pharmaceutical industry: Urgent need for new, more efficient approaches that integrate and exploit information

- Modeling and simulation has been promoted as one key approach
- Has gained considerable traction over the past decade
M&S in drug development

Challenge and Opportunity on the Critical Path to New Medical Products

FDA
U.S. Department of Health and Human Services
Food and Drug Administration
March 2004
M&S in drug development

Idea: Exploit accumulating information and other knowledge at each phase to develop and update a modeling and simulation framework to assist in dose selection and study design

- **Ideal**: PK/PD study from the same subjects + information on how PD response is related to the ultimate clinical endpoint of interest (e.g., time to death, myocardial infarction within 30 days, time to cancer recurrence, etc)

- Plus information on how PK/PD parameters are systematically associated with subject demographics (i.e., among subject covariates) and the distribution of demographics in the population

- **Realistically**: May have to integrate information from different sources and make assumptions on relationships (no data)

- **Key leap-of-faith assumption**: How PD response is associated with clinical endpoint
Moreover: For simulation to design future clinical studies

- Must acknowledge realities of subject drop-out, non-compliance with drug regimens
- Must specify the statistical analysis that will be performed; e.g., for a Phase 3 confirmatory trial, a simple hypothesis test appropriate for the type of clinical endpoint comparing drug to control
Simulation of drug effects on population: For a particular dosing regimen

- **Subject population**: A joint probability distribution for all relevant covariates $A_i$, $p(a_i) \implies$ generate $A_i$

- **Hierarchical PK/PD model**: Individual model $p(y_i|u_i, a_i, b_i, \beta, \alpha)$ and population model $p(b_i|\zeta)$ $\implies$ generate $b_i$ and hence $\theta_i = h(A_i, \beta) + b_i$

- $\implies$ Generate “Inherent” PK and PD trajectories
Simulation of drug effects on population, continued:

- **Clinical outcome model**: For clinical endpoint $E_i$, e.g., time to death or indicator of MI 30 days after initiation of drug, $p(e_i|u_i, a_i, b_i, \beta)$, e.g.,

$$P(E_i = 1|U_i, A_i, b_i, \beta, \delta) = \frac{\exp(\delta_0 + \delta_1 \bar{f}^{(2)}_i)}{1 + \exp(\delta_0 + \delta_1 \bar{f}^{(2)}_i)}$$

$$\bar{f}^{(2)}_i = \text{cumulative expected PD response over first 15 days}$$

$$= \int_{0}^{15} f^{(2)}(s, U_i, \theta_i) \, ds$$
**Simulation of drug effects on population, continued:**

- Or for $E_i$ a time to event, hazard rate model

$$\lim_{ds \to \infty} ds^{-1} P[s \leq E_i \leq s + ds|E_i \geq s, \{f^{(2)}(u, U_i, \theta_i), 0 \leq u \leq s\}] = \lambda_0(s) \exp\{\delta f^{(2)}(s, U_i, \theta_i)\}$$

for **baseline hazard** $\lambda_0(s)$

- **Here**: Hazard of event depends on *current value of biomarker*

- **“Proportional hazards”**

- **In general**: A **statistical model** based on conjecture (may want to try several)

- Generation of observed concentrations and responses $Y_i$ (i.e., adding within-subject deviations) may not be necessary here
**M&S in drug development**

Simulation of a future clinical trial:

- Decide on *dosing regimen* $DR$ (includes amount, dosing interval, etc), to be compared to *control*, *sample size* $m$, intermittent *sampling times*, final *statistical analysis* to be performed

- Simulate $N_{sim}$ trials, each of size $m$

- Evaluate the proportion of the $N_{sim}$ trials for which the *hypothesis* that drug is *superior* is rejected (*statistical power*)
Simulation of a single trial: For $i = 1, \ldots, m$

- **Subject population**: A joint probability distribution for all relevant covariates $A_i$, $p(a_i) \implies$ generate $A_i$

- **Inclusion/exclusion criteria**: Some subjects with certain characteristics are excluded; continue generating subjects until $m$ have been included

- **Randomization**: Each subject is randomized to drug or control

- **Hierarchical PK/PD model**: Individual model $p(y_i|u_i, a_i, b_i, \beta, \alpha)$ and population model $p(b_i|\zeta) \implies$ Generate $b_i$ and hence $\theta_i = h(A_i, \beta) + b_i$

- **Control subjects**: Do not receive drug; e.g., generate $\theta_{PD,i}$ only $\implies$ response $E_{0i}$ in *Emax model*, HIV dynamics with no drug
Simulation of a single trial: For $i = 1, \ldots, m$

- **Non-compliance to regimen**: May depend on underlying $\theta_i$ and $A_i$ and/or on evolving $Y_{ij}^{(2)}$ (*PD responses*); e.g., a subject in an HIV trial may stop or skip therapy if viral load looks good; probability model for *deviations from DR* conditional on $\theta_i, A_i, Y_{ij}^{(2)}, s_{ij} \leq t \implies$ generate a *non-compliance pattern*

- **Missed visits**: May depend on underlying $\theta_i$ and $A_i$ and/or on evolving $Y_{ij}^{(2)}$ (*PD responses*); e.g., a subject in an HIV trial may skip a visit because viral load is below limit $\implies$ generate *missed visit pattern*

- **Drop-out**: May depend on underlying $\theta_i$ and $A_i$ and/or on evolving $Y_{ij}^{(2)}$ (*PD responses*); e.g., a subject in an HIV trial may leave the study based on declining CD4 count; probability model for *drop-out* at time $t$ conditional on $\theta_i, A_i, Y_{ij}^{(2)}, s_{ij} \leq t \implies$ generate a *drop-out time $D_i$*
Simulation of a single trial: For $i = 1, \ldots, m$

- **Clinical outcome model**: $p(e_i|u_i, a_i, b_i \beta)$; for some subjects, $E_i > D_i$, so $E_i$ is *missing*

- **Analyze data**: *Observed* part of $Y_i$ and *observed clinical endpoints*  
  → incorporating methods/conventions for handling of *missing data*, *non-compliance*, *drop-out*

**Result**: Conduct $N_{\text{sim}}$ trials, summarize results

- Does the proposed design achieve the desired *statistical power*?

- Can try different trial designs possible with available resources and identify *most efficient*

- Can gain information on the resources required; is a trial *feasible*? *worth doing*?
Summary:

• The review of M&S here only touches the surface of the kinds of M&S explorations possible

• Many opportunities for mathematical modelers and statisticians interested in mathematical-statistical modeling in industry, academia, and at the FDA
M&S in design of a clinical trial

**Case study:** A simple use of M&S to inform the design of a clinical trial

- **Multidisciplinary collaboration** supported by a grant from the National Institute of Allergy and Infectious Diseases (NIAID)

- **Main players:** Immunologist/infectious disease clinician (*Eric Rosenberg*, MGH), statistician (*Marie*, NCSU), applied mathematician/control theorist (*Tom*, NCSU)

- **Big picture:** Use mathematical-statistical modeling of disease progression and simulation to design antiretroviral (*ARV*) therapies to manage HIV infection and clinical trials to study them

- Design and carry out a clinical trial in subjects with acute HIV infection assisted by M&S

- Collect extensive data to inform refined modeling → more sophisticated strategies and trials
Eric’s practice at MGH: A 47 year old male presents to the ER

- 102.5 °F fever, headache nausea/vomiting, rash, ...
- MSM, recent unprotected sex, ...
- Tests for CMV, EBV, influenza negative
- HIV ELISA positive
- HIV RNA (viral load) > 750,000 copies/ml
- CD4+ T cell count = 432 cells/µl

Diagnosis: Acute HIV infection

- Within weeks of initial infection
M&S in design of a clinical trial
Question: Should this individual be treated with ARV therapy?
### M&S in design of a clinical trial

<table>
<thead>
<tr>
<th>Disadvantages</th>
<th>Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High cost, side effects, QoL</td>
<td>Delay of costs, side effects, risks</td>
</tr>
<tr>
<td>Unknown long term risks of ARV</td>
<td>Delay of drug resistance</td>
</tr>
<tr>
<td>Acquisition of drug resistance</td>
<td><em>Preservation of HIV-specific immune response</em></td>
</tr>
<tr>
<td>Limitation of future ARV options</td>
<td><em>Opportunity for treatment interruption</em></td>
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**Premise:** Cycles of treatment *interruption* and *re-initiation* may *augment* immune response and allow patient to maintain *viral control*

- Brief, *controlled* viral exposure may serve as a “*self-vaccination*”
- ???
M&S in design of a clinical trial

The famous “Berlin patient”:

- Epididymitis, day 15–22
- Hepatitis A, day 121–137
- Treatment stopped, day 176
M&S in design of a clinical trial

Current state of affairs:

- Whether or not and how to use ARV therapy during acute infection is not known

- Treatment interruption may be useful in acute infection, but the optimal approach is not known

Structured treatment interruption (STI):

- Non-adaptive (non-dynamic) strategies – planned in advance, e.g., cycles of 8-weeks-on/8-weeks-off, terminal interruption

- Adaptive (dynamic) strategies – decisions to interrupt and re-initiate based on rules taking patient information as input, e.g., stop or start based on CD4+ T cell count or viral load
STI studies so far: Mixed results

- CPCRA "Strategies for Management of Antiretroviral Therapy" (SMART) trial (El-Sadr, Neaton, et al., 2006) in chronically-infected subjects

- Compared continuous ARV therapy to an adaptive STI strategy ("drug conservation") – on-off ARV treatment dictated by CD4+ T cell count

- Stopped early (∼ 5500 subjects), drug conservation ⇒ 2x risk of primary endpoint (AIDS or death)
M&S in design of a clinical trial

Our premise: Strategies so far may have been unfortunately chosen

- Based on “educated guesses,” expert opinion, pieced-together clinical evidence
- E.g., CD4 thresholds in SMART chosen after much debate...
- ...and decision rules did not include viral load (or other info)
- ⇒ it is premature to dismiss treatment interruption and adaptive treatment strategies for managing HIV infection
- Use mathematical-statistical modeling and simulation and control theory to design adaptive treatment strategies that do well in the population and clinical trials to study them
- In particular, can such an approach be used to determine the best way to manage patients from the time of acute infection?
Our proposal: Base this on a mathematical-statistical model describing HIV dynamics at the individual and population levels

- No PK model, no “hard” clinical endpoint (clinical endpoint is viral load)
- At the time, relatively simple HIV dynamic model (individual level)
  \[ \dot{x}(t, \theta_i) = g\{t, x(t, \theta_i), \theta_i\} \]
- Hierarchical statistical model to describe variation in dynamics across the population of acutely infected individuals
- Develop model based on intensive longitudinal data collected by Eric in his practice on viral loads, CD4 counts from a cohort of ≥ 270 acutely-infected subjects for ≈ 12 years
Model for within-subject dynamics: \( s = 7 \) states

\[
\begin{align*}
\dot{T}_1 &= \lambda_1 - d_1 T_1 - \{1 - \epsilon_1 u(t)\}k_1 V_I T_1 \\
\dot{T}_2 &= \lambda_2 - d_2 T_2 - \{1 - f\epsilon_1 u(t)\}k_2 V_I T_2 \\
\dot{T}_1^* &= \{1 - \epsilon_1 u(t)\}k_1 V_I T_1 - \delta T_1 - m_2 E T_1^* \\
\dot{T}_2^* &= \{1 - f\epsilon_1 u(t)\}k_2 V_I T_2 - \delta T_2 - m_2 E T_2^* \\
\dot{V}_I &= \{1 - \epsilon_2 u(t)\}10^3 N_T \delta (T_1^* + T_2^*) - c V_I - \{1 - \epsilon_1 u(t)\} \rho_1 10^3 k_1 T_1 V_I \\
&\quad - \{1 - f\epsilon_1 u(t)\} \rho_2 10^3 k_2 T_2 V_I \\
\dot{V}_{NI} &= \epsilon_2 u(t)10^3 N_T \delta (T_1^* + T_2^*) - c V_{NI} \\
\dot{E} &= \lambda_E + \frac{b_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_b} E - \frac{d_E (T_1^* + T_2^*)}{(T_1^* + T_2^*) + K_d} E - \delta_E E
\end{align*}
\]

- \( \theta = (\lambda_1, d_1, \epsilon_1, k_1, \ldots) \) plus initial conditions

- Observable: CD4 count = \( T_1 + T_1^* \), viral load = \( V_I + V_{NI} \)

- \( u(t) = \) ARV input at \( t \) (\( 0 \leq u(t) \leq 1, 0 = \text{off}, 1 = \text{on} \)
M&S in design of a clinical trial

Patient #14

CD4+ T-cells / ul

virus copies/ml

0 200 400 600 800 1000 1200 1400 1600

0 200 400 600 800 1000 1200 1400 1600

0 10 5 10^5 10^0

data
fit w/ half
fit w/ all
Hierarchical model:

- \( Y_{ij} = (Y_{ij}^{(1)}, Y_{ij}^{(2)})^T = \text{total CD4, viral load at } t_{ij} \) (viral load left-censored)

- \( f\{t, U_i(t), \theta_i\} = \mathcal{O}x\{t, U_i(t), \theta_i\} = [(f^{(1)}\{t, U_i(t), \theta_i\}, f^{(2)}\{t, U_i(t), \theta_i\})]^T \)

- No among individual covariates \( A_i \)

- Individual model: \( p(y_i | u_i, b_i, \beta, \alpha) \) for full data; implied \( p(z_i, \delta_i | u_i, b_i, \beta, \alpha) \) for observed data

- Population model: \( \theta_i = \beta + b_i, \ p(b_i | \zeta) \)

- Suitable population model chosen by comparing “virtual profile” distributions (VL, CD4) to those from Multicenter AIDS Cohort Study (MACS, \( u(t) \equiv 0 \)) and Eric’s data (various \( u(t) \)) \( \Rightarrow \) mixture of normal distributions
Armed with this framework: Use to design treatment strategies and clinical trials

Our first step: Proof of principle – can we use this capability to assist in designing a clinical trial in acute HIV infection?

- Is it better to give ARV for some period following acute infection (“train” the immune system, “self-vaccinate”) followed by terminal interruption...

- A non-adaptive treatment strategy

- ...or is it better to give no treatment at all until later (delay drug resistance, etc)

- Primary clinical endpoint – VL set point at 12 months
M&S in design of a clinical trial

Which strategies to study? $u(t) \equiv 0$ vs. strategies of the form

$$
\begin{align*}
  u(t) &= 1, \quad 0 \leq t \leq \tau \\
  &= 0, \quad t > \tau
\end{align*}
$$

for termination times $\tau = 3, 4, \ldots, 12$ months

Approach: Evaluate effects of candidate strategies on the (virtual) population by simulation

- Insight into which strategies to study based on their anticipated effects on the entire population
Strategy $u(t)$ with $\tau = 6$: 100 “virtual” “inherent” viral load trajectories with ARV therapy terminated at 6 months, i.e., $u(t) = 1$, $0 \leq t \leq 6$, $u(t) = 0$, $t > 6$
Different termination times $\tau$: Means of 15,000 “virtual” CD4 and viral load data profiles with $u(t) = 1$, $0 \leq t \leq \tau$, $u(t) = 0$, $t > \tau$, $\tau = 0, 3, 4, \ldots, 12$ months.
Summary:

- Based on this (simple) HIV dynamic model, *no differences expected*
- Simple model does not represent adequately the *immune response*
- Since the grant was awarded, we have developed a *refined model*
- Simulations with the *refined model* show larger *subpopulations* with *lowered VL set point* for larger $\tau$ . . .
- . . .but are less reliable (very little data on immune response)

Result: Study ARV under *more than one termination time*

- $\tau = 3$ ("*short-term*") and $\tau = 8$ months ("*long-term*"
**M&S in design of a clinical trial**

**Trial schema:** 1/2 pts randomized to ARV, 1/2 pts to no ARV
M&S in design of a clinical trial

Design: 3 year accrual period, 1 year follow-up

- 36 subjects, 2:1:1 randomization to none, 3 months, 8 months
- Standard sample size considerations for primary VL comparison at 12 months
- **Intensive visit schedule**—collect CD4, VL, CTLs, viral fitness, etc
- Data collection more frequent when dynamics are anticipated to *be changing* (e.g., in the weeks *after ARV termination*) based on the *mathematical model*

- **So far:** Have enrolled 6 subjects
Next step: Armed with more informative data (e.g., measurements reflecting aspects of immune response) from the trial

- Develop and validate more realistic HIV dynamic models...
- ...refine the entire mathematical-statistical framework
- ...and use to develop and evaluate (“virtually”) potential adaptive treatment strategies
- Feedback control
- And design the next trial to study the most promising strategies...
Remarks:

- *Modeling and simulation* have a significant role to play in design of HIV treatment strategies and clinical trials to study them.

- *In principle* – could link HIV dynamic models with models for pharmacokinetics, etc.

- We envision cycles of smaller “learning trials” that provide richer information needed to develop more *refined adaptive strategies* that will then be evaluated in confirmatory trials.