Mathematical-Statistical Modeling to Inform the Design of HIV Treatment Strategies and Clinical Trials

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Modeling for Design of HIV Treatment and Trials
Overview

- **Multidisciplinary collaboration** supported by a grant from NIAID

- **Main players**: Imunologist/infectious disease clinician (Eric, MGH), statistician (Marie, NCSU), applied mathematician/control theorist (H.T. Banks, NCSU)

- **Big picture**: Use **mathematical-statistical modeling of disease progression** and **simulation** to design HIV treatment strategies and clinical trials to study them

- Develop better strategies for use of **existing antiretroviral therapies** (ART) to manage HIV infection over time

- Design and carry out a **clinical trial** in subjects with acute HIV infection assisted by modeling and simulation

- Collect **extensive data** to inform **refined modeling** $\Rightarrow$ more sophisticated strategies and trials
Overview

1. Eric will give background on HIV, acute HIV infection, HIV therapy, and structured treatment interruption (STI)

2. Marie will follow with descriptions of our mathematical-statistical modeling and simulation framework, our approach to design of treatment strategies and clinical trials to study them, and the clinical trial we will carry out
Marie will talk about:

- Recap: HIV therapy and STI
- HIV dynamic models and control
- Mathematical-statistical framework
- Design of a clinical trial in acute infection
- Next steps - design of STI strategies
- Closing remarks
Recap: HIV therapy and STI

Main points:

- **Continuous ART** is impossible for most patients
- This has inspired interest in the use of **structured treatment interruption (STI)**
- **Non-adaptive** (non-dynamic) strategies – planned **in advance**, e.g., cycles of 8-weeks-on/8-weeks-off
- **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**
Recap: HIV therapy and STI

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 ART to an adaptive STI strategy (“drug conservation”) – on-off ART dictated by CD4+ T cell count
  - Stopped early (∼5500 pts), drug conservation
    \[\Rightarrow\] 2x risk of primary endpoint (AIDS or death)
Recap: HIV therapy and STI

Drug conservation strategy in the SMART study:

OFF

CD4 > 250

OFF

CD4 <= 250

ON

CD4 > 350

OFF

CD4 <= 350

ON
Recap: HIV therapy and STI

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 among experts...
- ...and decision rules did not include viral load (or other info)
- \( \implies \) it is premature to dismiss STI and adaptive treatment strategies for managing HIV infection
- A formal, evidence-based approach combining biological knowledge, data in a principled way is needed to design and evaluate strategies
HIV dynamic models and control

HIV dynamic models:

- Represent mathematically known and hypothesized mechanisms involved in the virus-immune system interaction taking place within a single subject
- Series of “compartments” characterizing different populations of virus and constituents of the immune system
- Interactions among compartments described by a system of (deterministic) nonlinear ordinary differential equations
- The solution to the system of ODEs yields a mechanistic model characterizing the joint behavior of the compartments over time (the “dynamics”)
- Viral load, CD4+ T cell count, etc, at any time
Possible model for within-subject dynamics:
HIV dynamic models and control

Model for within-subject dynamics: \( s = 7 \) “states”

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

- \( \theta = (\lambda_1, d_1, \epsilon_1, k_1, \ldots)^T \) plus initial conditions
- Observable: **CD4 count** = \( T_1 + T_1^* \), **viral load** = \( V_I + V_{NI} \)
- \( u(t) \) = ART input at \( t \) (\( 0 \leq u(t) \leq 1 \), \( 0 \) = off, \( 1 \) = on)
In general: HIV dynamic model with $s$ states

$$\dot{x}(t, \theta) = g\{t, x(t, \theta), \theta\}, \text{ solution } x(t, \theta) \ (s \times 1)$$

- Embodies hypothesized mechanisms through model parameters $\theta$
- $\theta$ includes cell and virus production, death, clearance rates; treatment efficacy parameters; etc
- $\theta$ dictates pattern of progression over time (deterministic) under any treatment pattern $u(t)$

Control theory: Mathematical theory and techniques for modifying (controlling) the behavior of such systems

- Goal – Optimize some objective function, e.g., drive viral load set point below a threshold while keeping “cost of therapy” low
- i.e., determine $u(t)$ to achieve this objective
Our ultimate goal: Use HIV dynamic models and control along with simulation to design treatment strategies \( u(t) \) for acute HIV infection and to design clinical trials to study them

- Find strategies that “do well” for individuals and for the population
- Need evidence supporting HIV dynamic model \( \Rightarrow \) data (e.g., measured CD4, VL, other stuff over time on lots of subjects)
- Intra-subject variation due to assay error, realization error; left-censoring of viral loads due to assay lower limits of quantification
- Substantial inter-subject variation \( \iff \) heterogeneity in mechanisms \( \theta \) across the subject population

For both fitting to data and simulation: Must embed the (deterministic) mathematical model in a statistical framework that characterizes faithfully inter- and intra-subject variation
Data: Eric has been collecting intensive longitudinal viral loads, CD4 counts on a cohort of $\geq 150$ acutely-infected subjects for $> 7$ years.
Mathematical-statistical framework

**Mathematical model:** \( \dot{x}(t, \theta) = g\{t, x(t, \theta), \theta\}, \) solution \( x(t, \theta) \) \((s \times 1)\)

- Observations not available on all \( s \) states

- \( \bar{x} = \mathcal{O}x \) for observation operator \( \mathcal{O} \)

- E.g., CD4 and VL only

**Statistical framework:** Embed \( \bar{x} \) in a hierarchical statistical model

- For each subject \( i \) in the population, conceive of a bivariate (CD4, VL) subject-specific stochastic process under \( u(t) \)

\[
Y_i\{t, u(t)\} = [Y_i^{\text{CD4}}\{t, u(t)\}, Y_i^{\text{VL}}\{t, u(t)\}]^T
\]

- Depends on treatment strategy \( u(t) \) up through time \( t \)
Intra-subject model: Decompose into

\[ Y_i\{t, u(t)\} = \bar{x}\{t, u(t), \theta_i\} + e_i\{t, u(t)\} \]

- \( e_i\{t, u(t)\} \) is the deviation process – realizations, assay errors
- \( e_i\{t, u(t)\} \) average out to zero over all possible realizations, assay errors (conditional on \( \theta_i \) and the strategy imposed)
- Interpret \( \bar{x}\{t, u(t), \theta_i\} \) as average trajectories over all possible realizations we could see on subject \( i \) under strategy \( u(t) \)
- Also, assumptions on (conditional) correlation (across \( t \) and among elements of \( e_i\{t, u(t)\} \)), variances, probability distribution

Inter-subject model: \( \theta_i \) is an “inherent characteristic” of subject \( i \)

- Probability distribution \( p(\theta_i; \theta^*, D) \), e.g., \( \theta_i \sim \mathcal{N}(\theta^*, D) \)
- Could also be conditional on subject characteristics
Mathematical-statistical framework

**Result:** Full description of the hypothesized data-generation process in **continuous time**

- For **individual** subjects (randomly-chosen from the **population**)
- And thus for **samples of such subjects** drawn at random from the population
- For **large enough** sample $\Rightarrow$ effectively, knowledge of the **entire population**
- Basis for **simulation** of “**virtual**” subjects

**Needed:** Full characterization based on **data**
Mathematical-statistical framework

**Data:** For subject \( i, i = 1, \ldots, N \), observed at \( n_i \) times \( t_{i1}, \ldots, t_{in_i} \)

- \( U_i(t) = \) actual ART pattern over entire observation period (known)
- \( Y_{ij} = (Y_{ij}^{CD4}, Y_{ij}^{VL})^T \) at time \( t_{ij} \) \( \implies \) \( Y_i = (Y_{i1}, \ldots, Y_{in_i})^T \)
- Conceive \( Y_{ij} = Y_i \{t_{ij}, U_i(t_{ij})\} \) (similarly for \( e_i \))
- **Eric’s data** – \( N \approx 150, n_i \approx 30–60 \)
- \( A_i = \) possible subject characteristics

**Nonlinear mixed effects model (bivariate response):** Fit to data

\[
Y_{ij} = \bar{x}\{t_{ij}, U_i(t_{ij}), \theta_i\} + e_{ij}, \quad j = 1, \ldots, n_i \\
\theta_i \sim p(\theta_i; \theta^*, D), \quad i = 1, \ldots, N
\]
Mathematical-statistical framework

Challenges:

- **Left-censoring** of VL by lower assay limit
- \( \text{dim}(\theta) > 25 \) and not all **identifiable** from CD4, VL only
- Components of \( \bar{x} \) only calculable **numerically** by forward solution of ODEs

Two-stage approach:

- For each \( i \), estimate \( \theta_i \) via EM algorithm to handle censoring incorporating **regularization** to address **identifiability** and **dimensionality**
- Use resulting \( \hat{\theta}_i \) as “data” to obtain \( \hat{\theta}^*, \hat{D} \) using moment methods
Mathematical-statistical framework

Predictive capability:

Patient #14

CD4+ T-cells / ul

virus copies/ml

Modeling for Design of HIV Treatment and Trials
Mathematical-statistical framework

Simulation:

• Generate $N_{sim}$ “virtual subjects” by generating $\theta^*_i$, $i = 1, \ldots, N_{sim}$, from $p(\theta_i; \hat{\theta}^*, \hat{D})$

• Generate “inherent trajectories” $x\{t, u(t), \theta^*_i\}$ under a given $u(t)$ (continuous time)

• Add within-subject deviations according to intra-subject model to obtain “virtual data”

• Suitable $p(\theta_i; \hat{\theta}^*, \hat{D})$ determined by comparing “virtual profile” distributions (VL, CD4) to those from Multicenter AIDS Cohort Study (MACS, $u(t) \equiv 0$) and Eric’s data (various $u(t)$)

• Mixture of normals
Design of a clinical trial

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 addressing a question involving non-adaptive treatment strategies?

- Unresolved – Whether or not individuals acutely-infected with HIV should be treated with ART

- More precisely – Is it better to give ART for some period following acute infection (“train” the immune system, “self-vaccinate”) or is it better to give no treatment at all until later (delay drug resistance, etc)

- Primary endpoint – VL set point at 12 months
Design of a clinical trial

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

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

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
Design of a clinical trial

**Strategy** $u(t)$ with $\tau = 6$: 100 “virtual” “inherent” viral load trajectories with ART terminated at 6 months, i.e., $u(t) = 1$, $0 \leq t \leq 6$, $u(t) = 0$, $t > 6$
Design of a clinical trial

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.
- Simulations with a refined model showed larger subpopulations with lowered VL set point for larger $\tau$...
- ...but are less reliable (very little data on immune response).

Result: Study ART under more than one termination time.

- $\tau = 3$ ("short-term") and $\tau = 8$ months ("long-term").
**Trial schema:** 1/2 pts randomized to ART, 1/2 pts to no ART

Diagram:
- ACUTE HIV-1 INFECTION
  - ARV THERAPY
    - SHORT-TERM TREATMENT THEN INTERRUPTION
    - LONG-TERM TREATMENT THEN INTERRUPTION
  - NO THERAPY
- OUTCOME
Design of a clinical trial

Plan: 3 year accrual period (36 patients), 1 year follow-up

- Standard design 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 ART termination)
Design of STI strategies

Next step: Armed with more informative data (e.g., measurements reflecting aspects of immune response)

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

Input data:
Clinical, immunological and virological data

Individual Model

Population Model

Clinical Trial Design

Model Simulation & Robust Control Design

Clinical Data

Clinical Practice

Modeling for Design of HIV Treatment and Trials
Closing remarks

- **Modeling and simulation** have a significant role to play in design of HIV treatment strategies

- **In principle** – could link dynamic models with models for PK, 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

- We’ll see how this turns out!

**Slides at:**  [http://www.stat.ncsu.edu/~davidian](http://www.stat.ncsu.edu/~davidian)