

MA/ST 810

Mathematical-Statistical Modeling and Analysis of Complex Systems

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

Introduction

“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)...

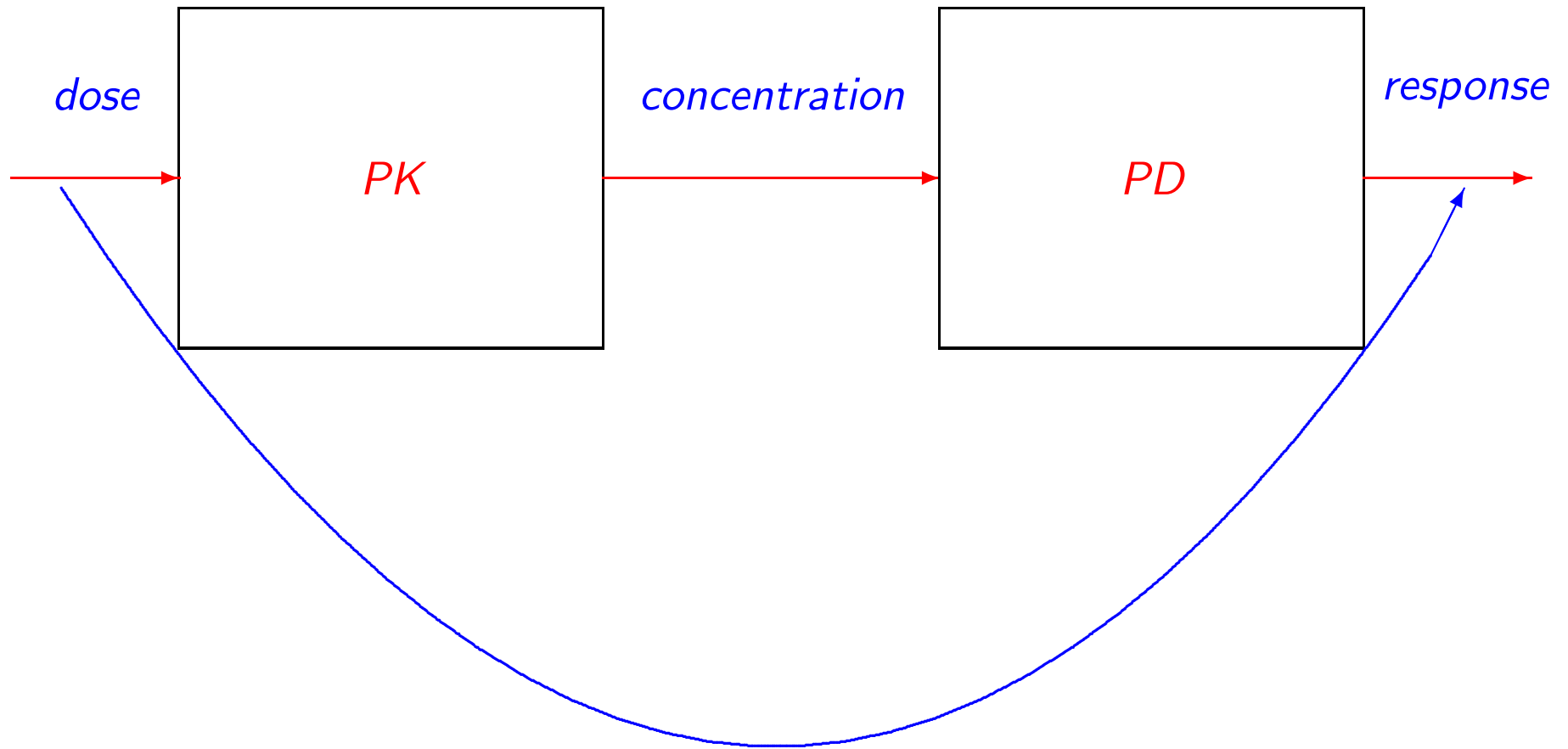
Pharmacokinetics and pharmacodynamics

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



Pharmacokinetics and pharmacodynamics

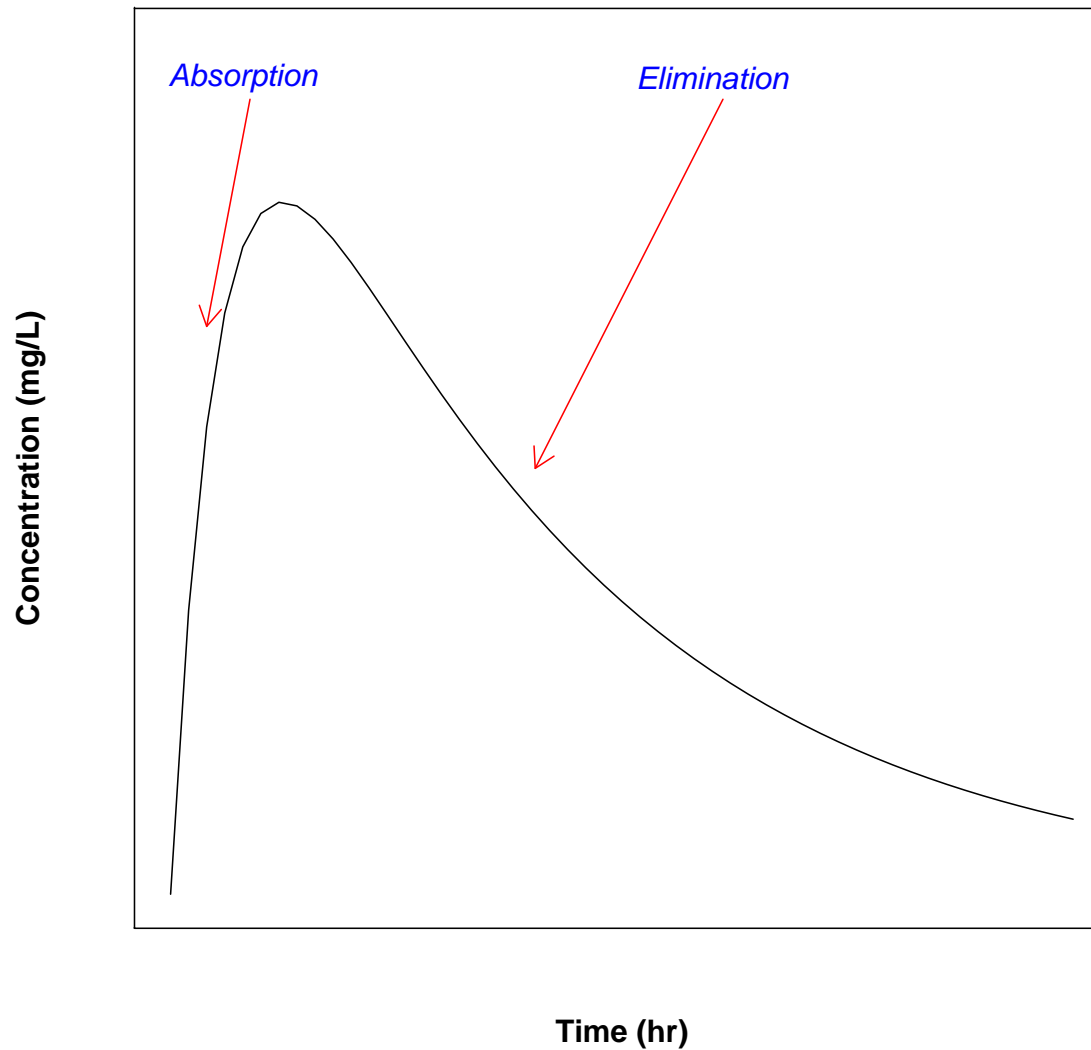
Basic assumptions and principles:

- 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

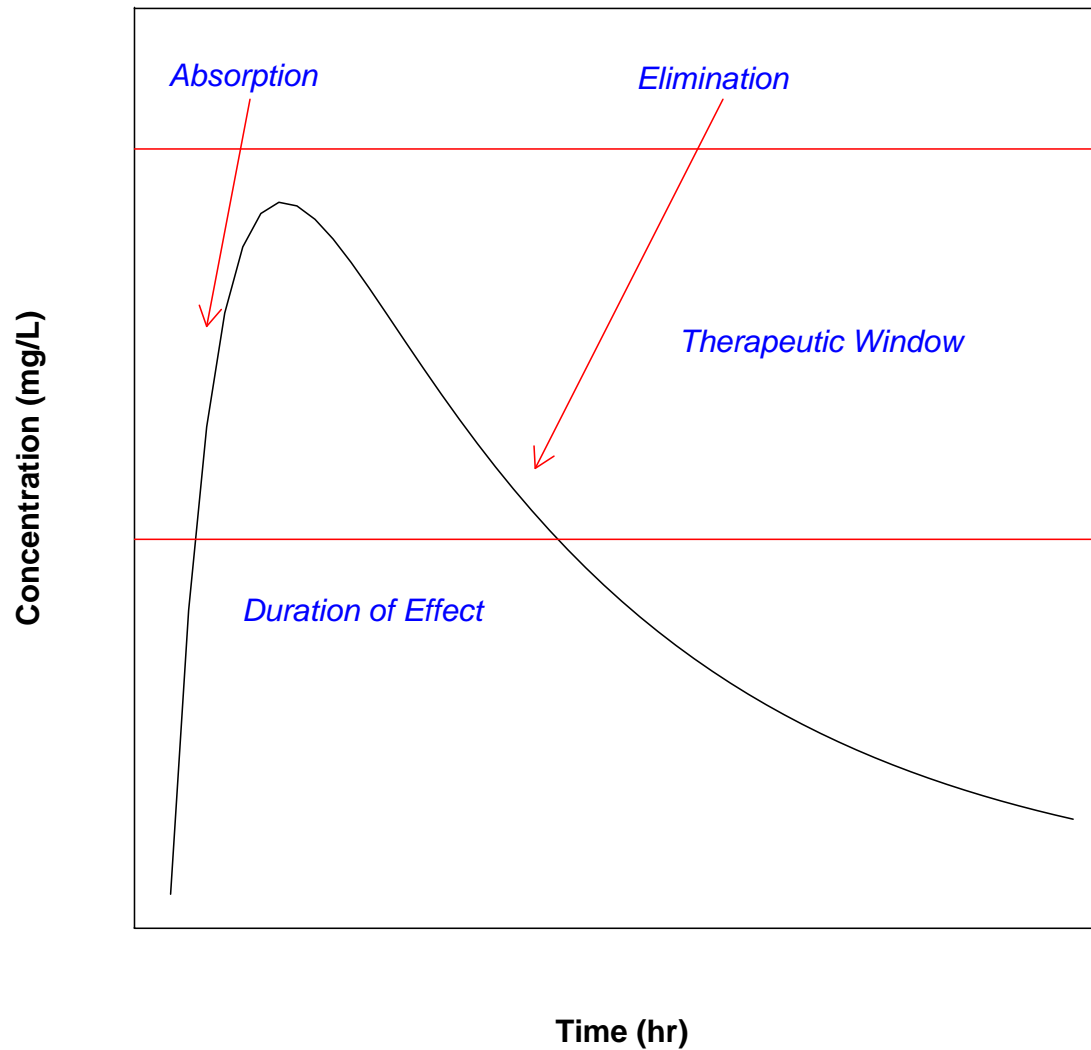
⇒ “*Therapeutic window*”

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

Pharmacokinetics and pharmacodynamics



Pharmacokinetics and pharmacodynamics



Pharmacokinetics and pharmacodynamics

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

- *Steady state*

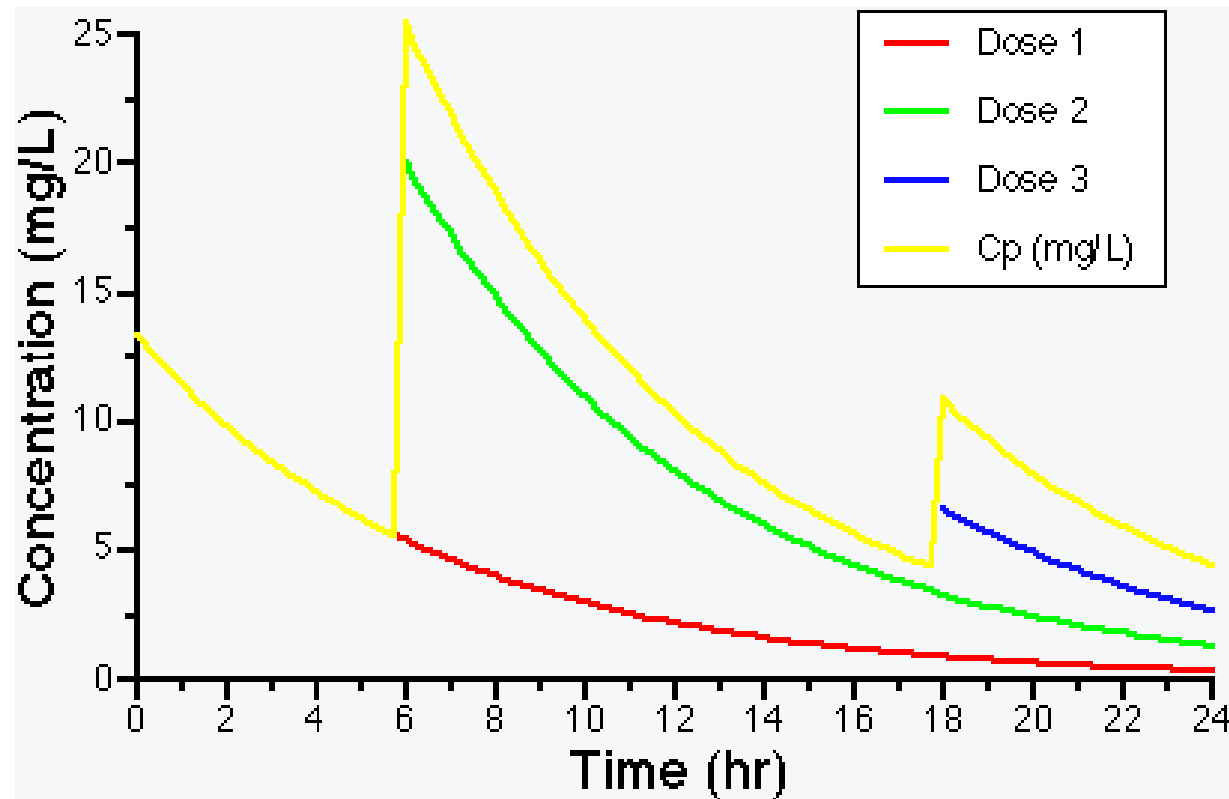
Frequency, amount for multiple-dose regimen governed by:

- *ADME*
- *Width* of therapeutic window

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

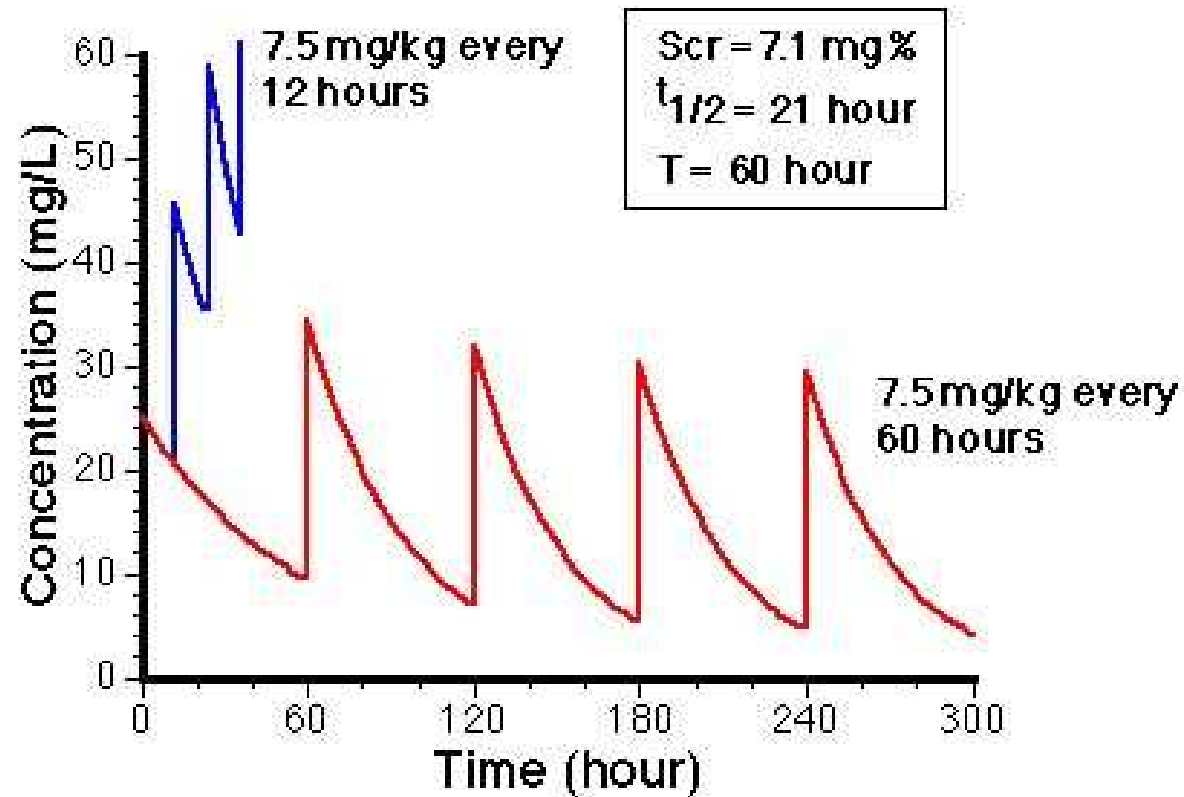
Pharmacokinetics and pharmacodynamics

Principle of superposition:



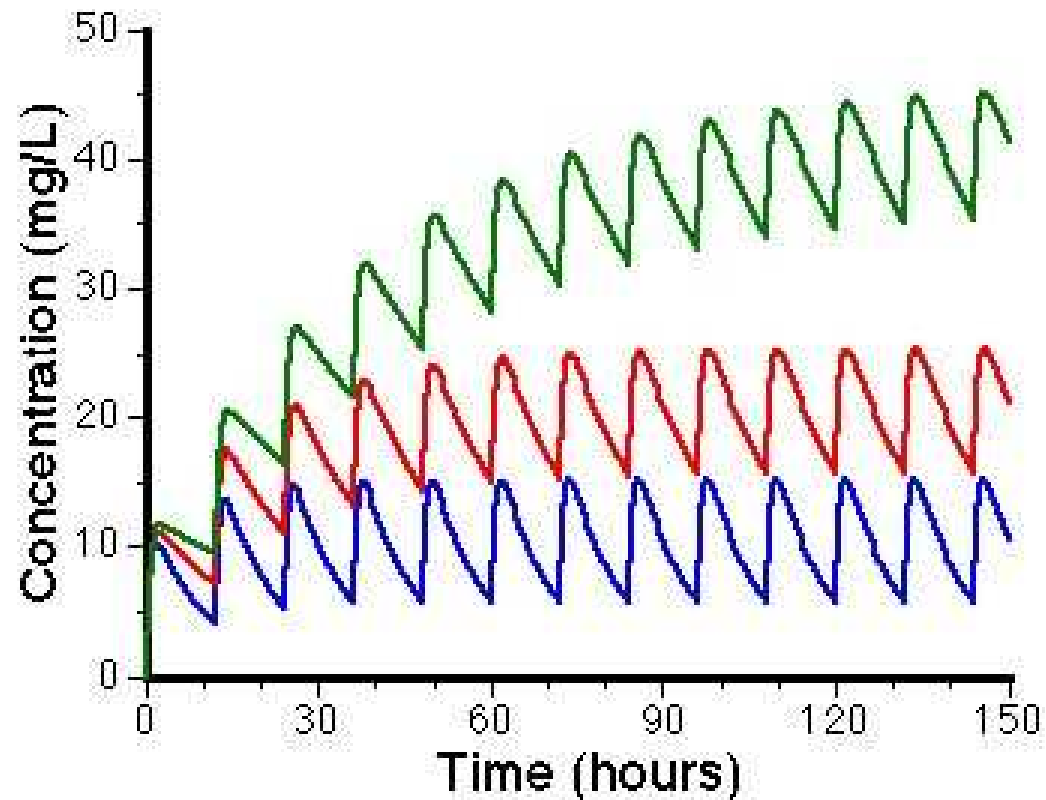
Pharmacokinetics and pharmacodynamics

Effect of different frequency: Same dose and ADME characteristics



Pharmacokinetics and pharmacodynamics

Effect of different elimination characteristics: Same dose and frequency



Pharmacokinetics and pharmacodynamics

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* \implies *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

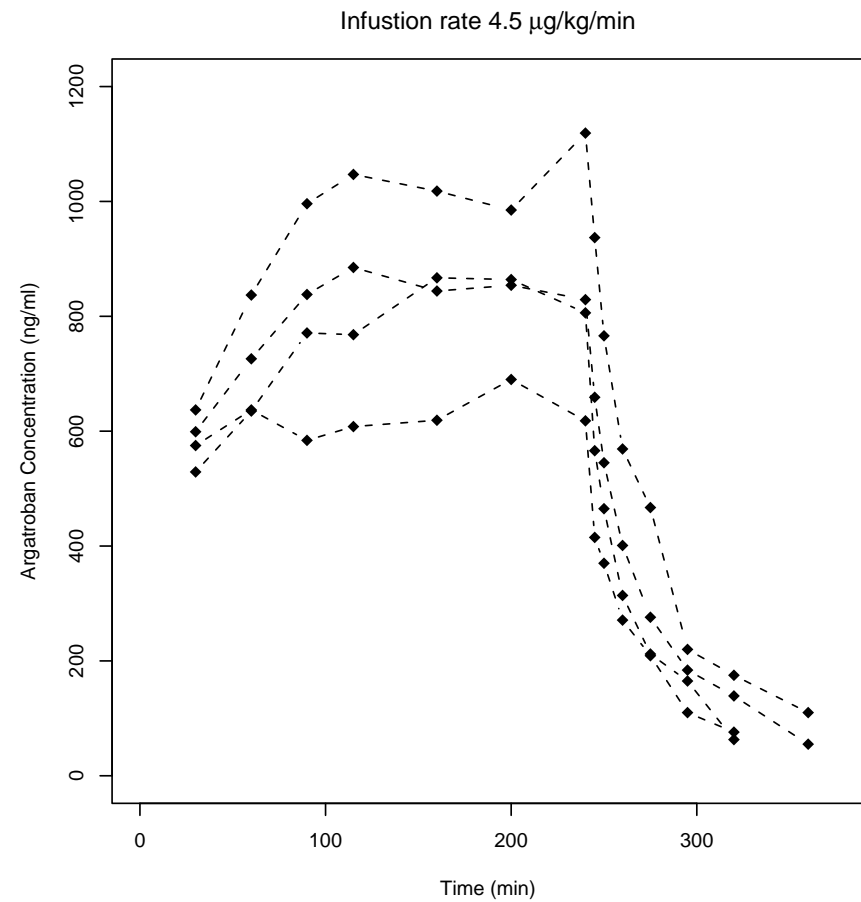
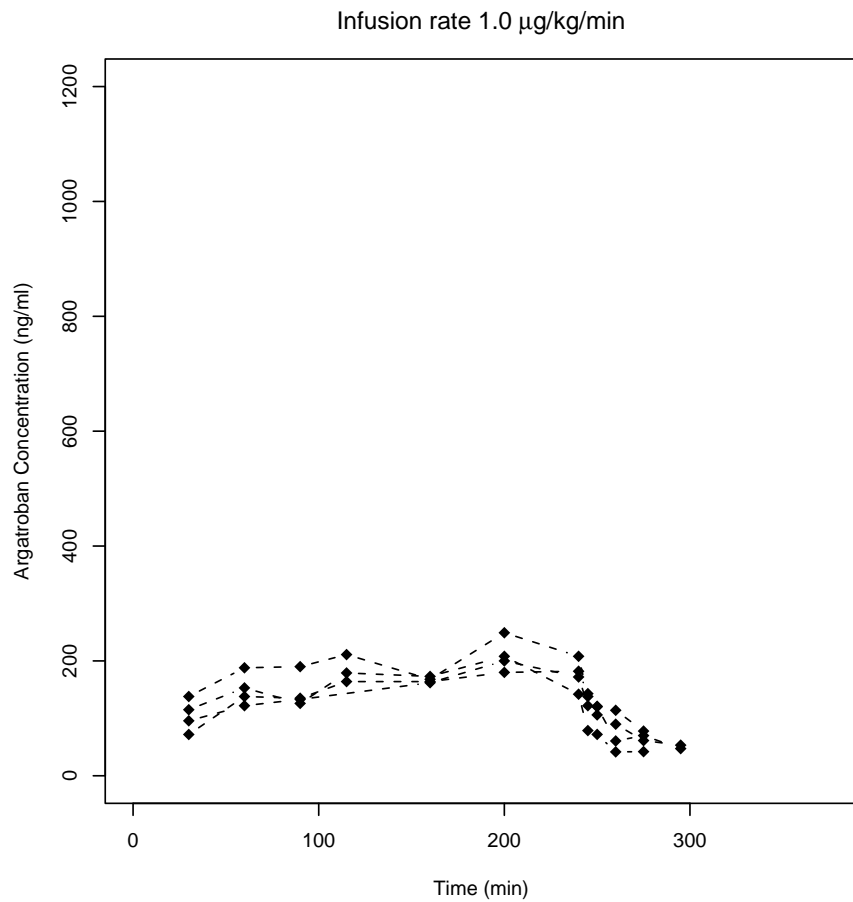
Example: PK/PD study of argatroban

- Anti-coagulant
- Early clinical study with $m = 37$ subjects receiving 4-hour IV infusion at rates (doses) of 1 to 5 $\mu/\text{kg}/\text{min}$ 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*)

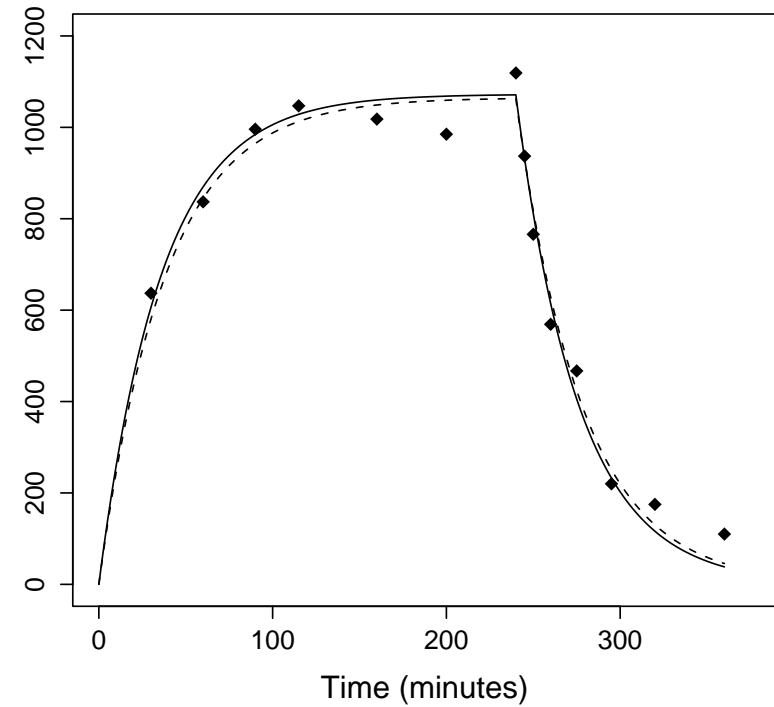
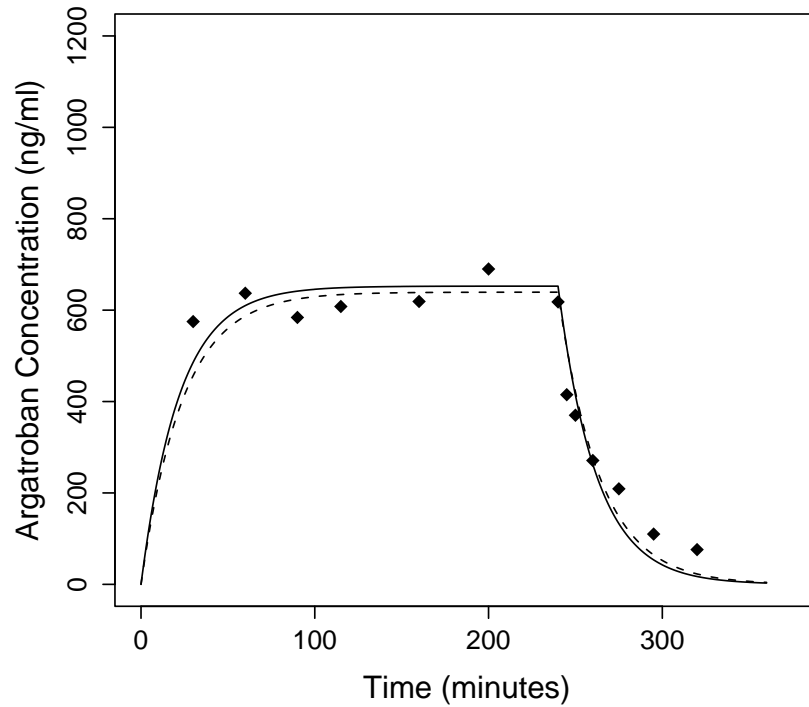
Objectives:

- 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

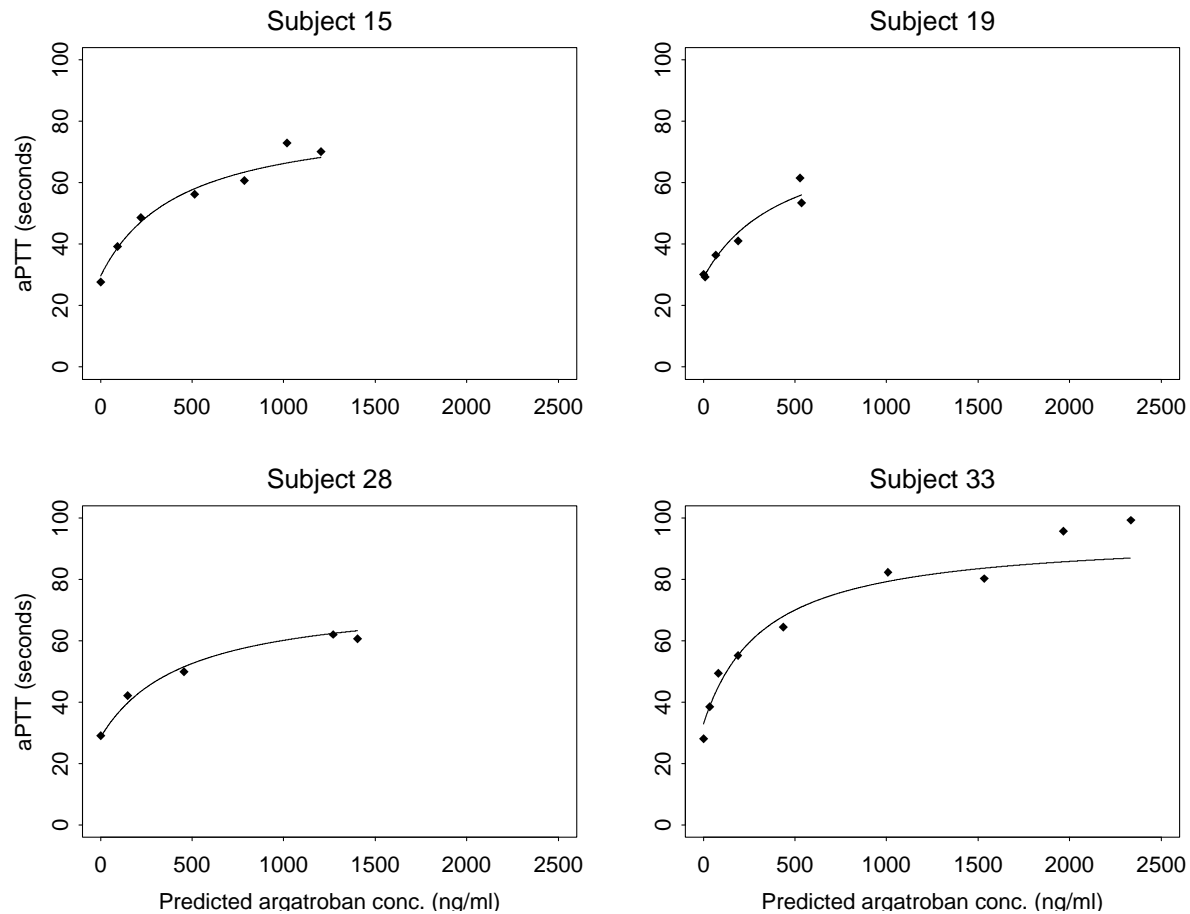


Pharmacokinetics and pharmacodynamics



Pharmacokinetics and pharmacodynamics

Response-concentration for 4 subjects:



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 $(Y_{i1}^{(1)}, \dots, Y_{in_i}^{(1)})^T$ at times $(t_{i1}, \dots, t_{in_i})^T$
- Subject i assigned to receive *intravenous infusion* at rate R_i ($\mu/\text{kg}/\text{min}$) for $t_{\text{inf}} = 240$ minutes
- *One-compartment IV infusion model*, $U_i = (R_i, t_{\text{inf}})$

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

$$\begin{aligned} t_{ij}^\dagger &= 0, & t_{ij} &\leq t_{\text{inf}}, & \theta_{PK,i} &= (\log Cl_i, \log V_i)^T \\ &= t_{ij} - t_{\text{inf}}, & t_{ij} &> t_{\text{inf}} \end{aligned}$$

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 $(Y_{i1}^{(2)}, \dots, Y_{ir_i}^{(2)})^T$ at times $(s_{i1}, \dots, s_{ir_i})^T$ (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*

- “*E_{max} model*”: A standard *empirical* representation of response-concentration relationships

$$f^{(2)}(s_{ij}, U_i, \theta_{PK,i}, \theta_{PD,i}) = E_{0i} + \frac{E_{\max i} - E_{0i}}{1 + EC_{50i}/c_{ij}}$$

$$\theta_{PD,i} = (E_{0i}, E_{\max i}, EC_{50i})^T, \quad c_{ij} = f^{(1)}(s_{ij}, U_i, \theta_{PK,i})$$

- *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: $Y_i = (Y_i^{(1)T}, Y_i^{(2)T})^T, i = 1, \dots, m$

- $Y_i^{(1)} = (Y_{i1}^{(1)}, \dots, Y_{in_i}^{(1)})^T$ at times $(t_{i1}, \dots, t_{in_i})^T$, *PK concentrations*
- $Y_i^{(2)} = (Y_{i1}^{(2)}, \dots, Y_{ir_i}^{(2)})^T$ at times $(s_{i1}, \dots, s_{ir_i})^T$, *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 $U_i, \theta_i \implies p(y_i | u_i, \theta_i)$
- E.g., do we expect *correlation* among elements of $\epsilon_i^{(1)}$ and $\epsilon_i^{(2)}$?

Pharmacokinetics and pharmacodynamics

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

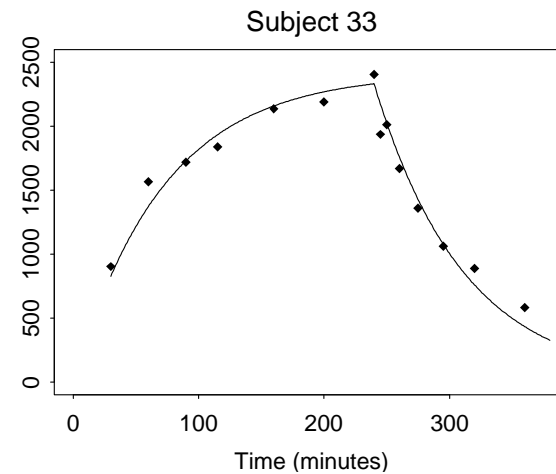
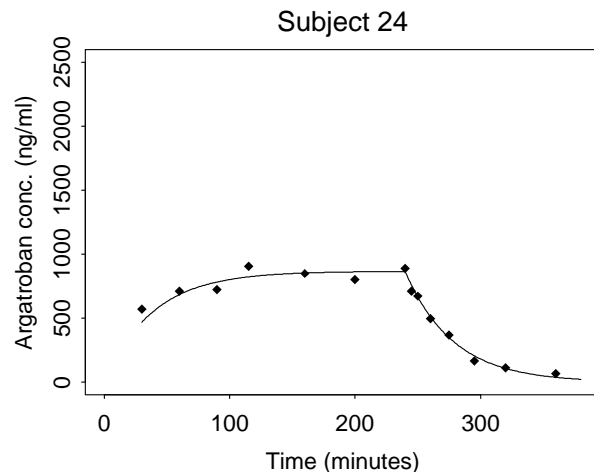
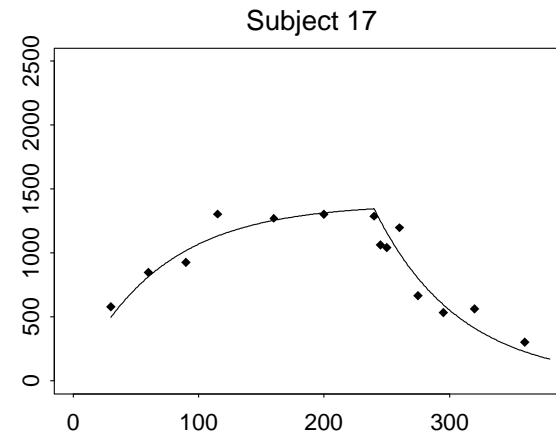
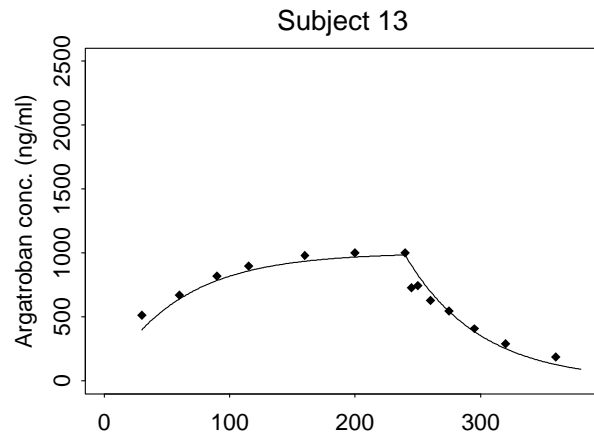
- *Among individual covariates* A_i , could be associated with *both* PK and PD parameters
- Assume $b_i = \mathcal{N}_p(0, D)$, $p = 5$ here
- $\theta = (\theta_{PK,i}^T, \theta_{PD,i}^T)^T \implies$ are elements of $\theta_{PK,i}$ and $\theta_{PD,i}$ *correlated?*

Implied hierarchical model:

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

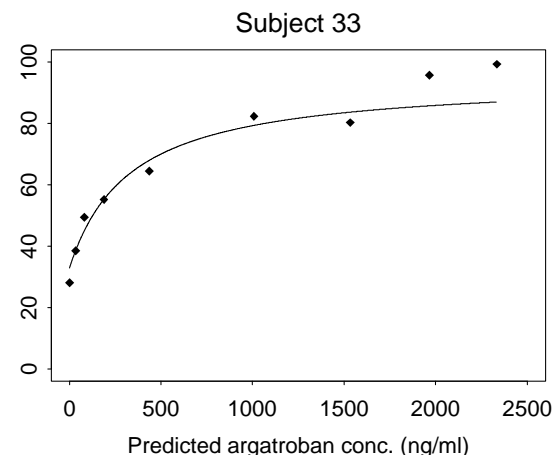
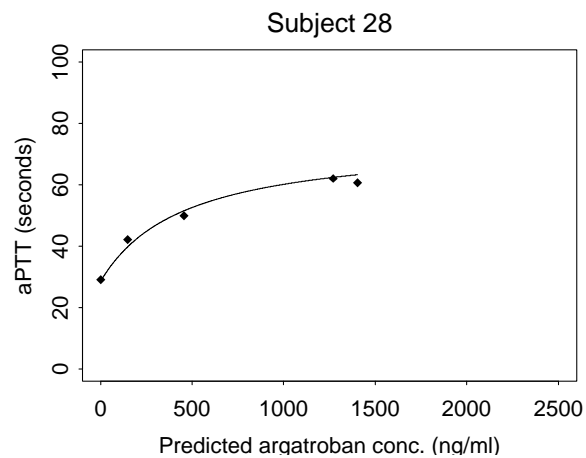
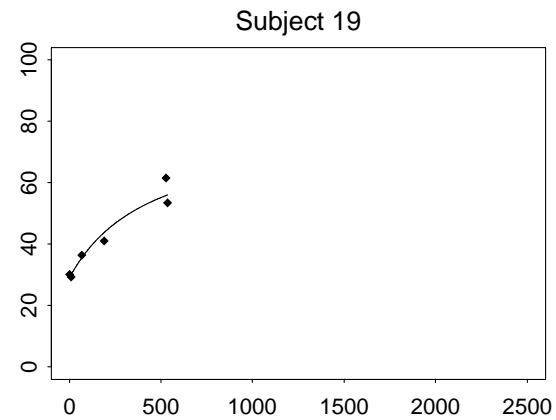
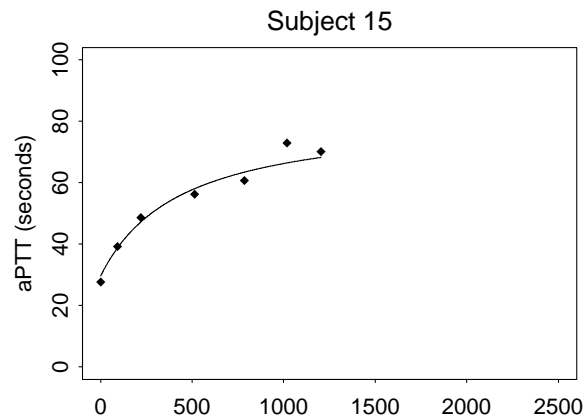
Pharmacokinetics and pharmacodynamics

Concentration-time for 4 subjects:



Pharmacokinetics and pharmacodynamics

Response-concentration for 4 subjects:



Pharmacokinetics and pharmacodynamics

Based on fit of hierarchical model: *Simulation*

- Estimates $\hat{\beta}$, $\hat{\alpha}$, $\hat{\zeta}$ and *standard errors*
- Can generate N_{sim} “*virtual subjects*” by generating θ_i and then Y_i from assumed *probability models* at each stage evaluated at a range of values β , α , ζ based on estimates and standard errors
- \implies choose different sets of values for (β, α, ζ)
- Different *infusion rates* R_i , *infusion lengths* t_{inf}
- N_{sim} “*large*” \implies effective *knowledge of the population* under different infusion strategies

Pharmacokinetics and pharmacodynamics

Simulation procedure: For $i = 1, \dots, N_{\text{sim}}$

- Generate b_i^{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^{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 α to obtain “*virtual data*” at intermittent *design points* \implies “*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 β, ζ

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
- \implies 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

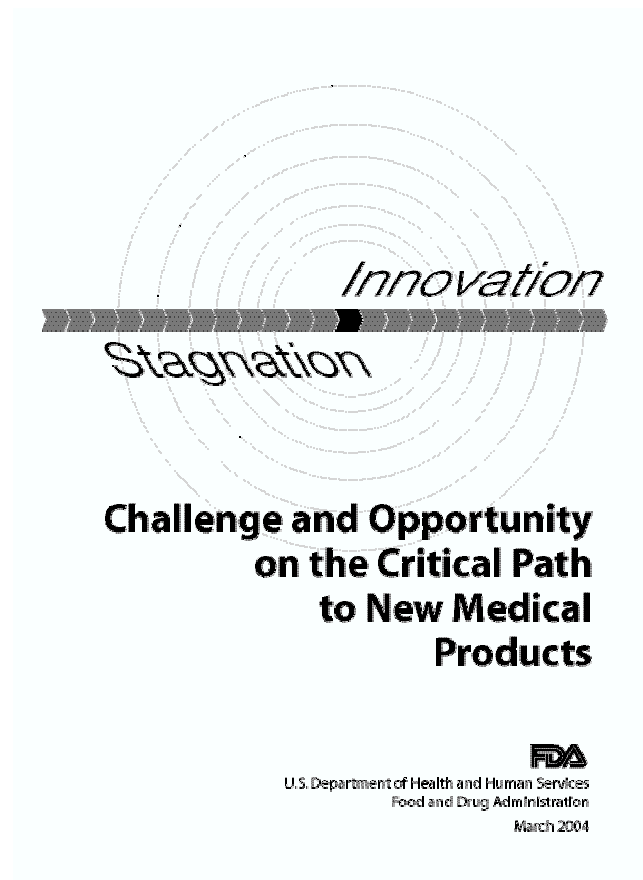
Traditional approach: *Which doses to study?*

- 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



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*

M&S in drug development

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*

M&S in drug development

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

M&S in drug development

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.,

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

$$\begin{aligned} \bar{f}_i^{(2)} &= \text{cumulative expected PD response over first 15 days} \\ &= \int_0^{15} f^{(2)}(s, U_i, \theta_i) ds \end{aligned}$$

M&S in drug development

Simulation of drug effects on population, continued:

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

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

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*)

M&S in drug development

Simulation of a single trial: For $i = 1, \dots, m$

- *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*

M&S in drug development

Simulation of a single trial: For $i = 1, \dots, m$

- *Non-compliance to regimen*: May depend on underlying θ_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 θ_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 θ_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

M&S in drug development

Simulation of a single trial: For $i = 1, \dots, m$

- *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* \implies incorporating methods/conventions for handling of *missing data*, *non-compliance*, *drop-out*

Result: Conduct N_{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*?

M&S in drug development

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* \implies more sophisticated strategies and trials

M&S in design of a clinical trial

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/ μ l

Diagnosis: *Acute HIV infection*

- Within *weeks* of initial infection

M&S in design of a clinical trial



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

Disadvantages

High cost, side effects, QoL
Unknown long term risks of ARV
Acquisition of drug resistance
Limitation of future ARV options

Advantages

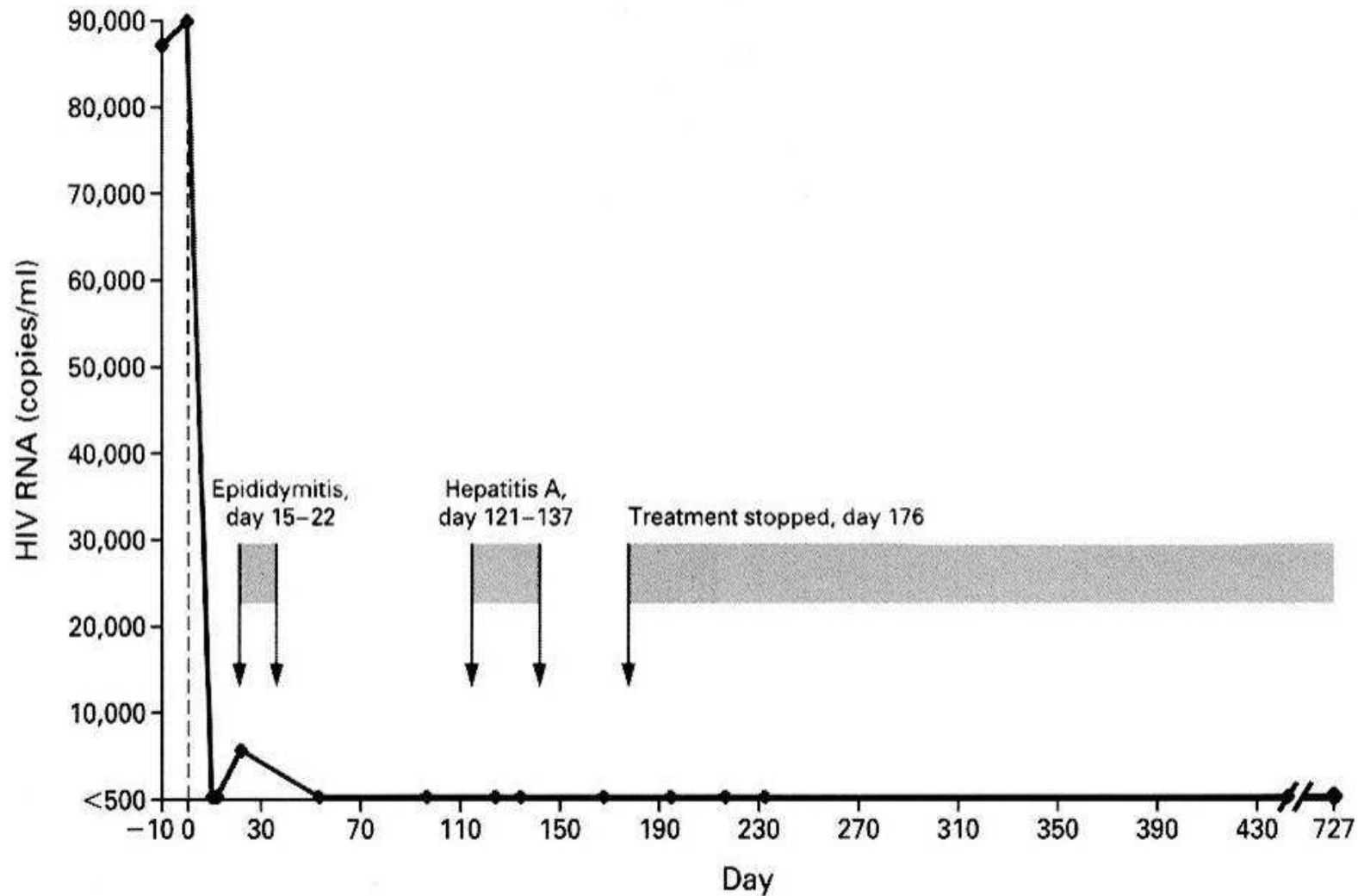
Delay of costs, side effects, risks
Delay of drug resistance
Preservation of HIV-specific immune response
Opportunity for treatment interruption

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”:



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*

M&S in design of a clinical trial

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)
- \implies 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*?

M&S in design of a clinical trial

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

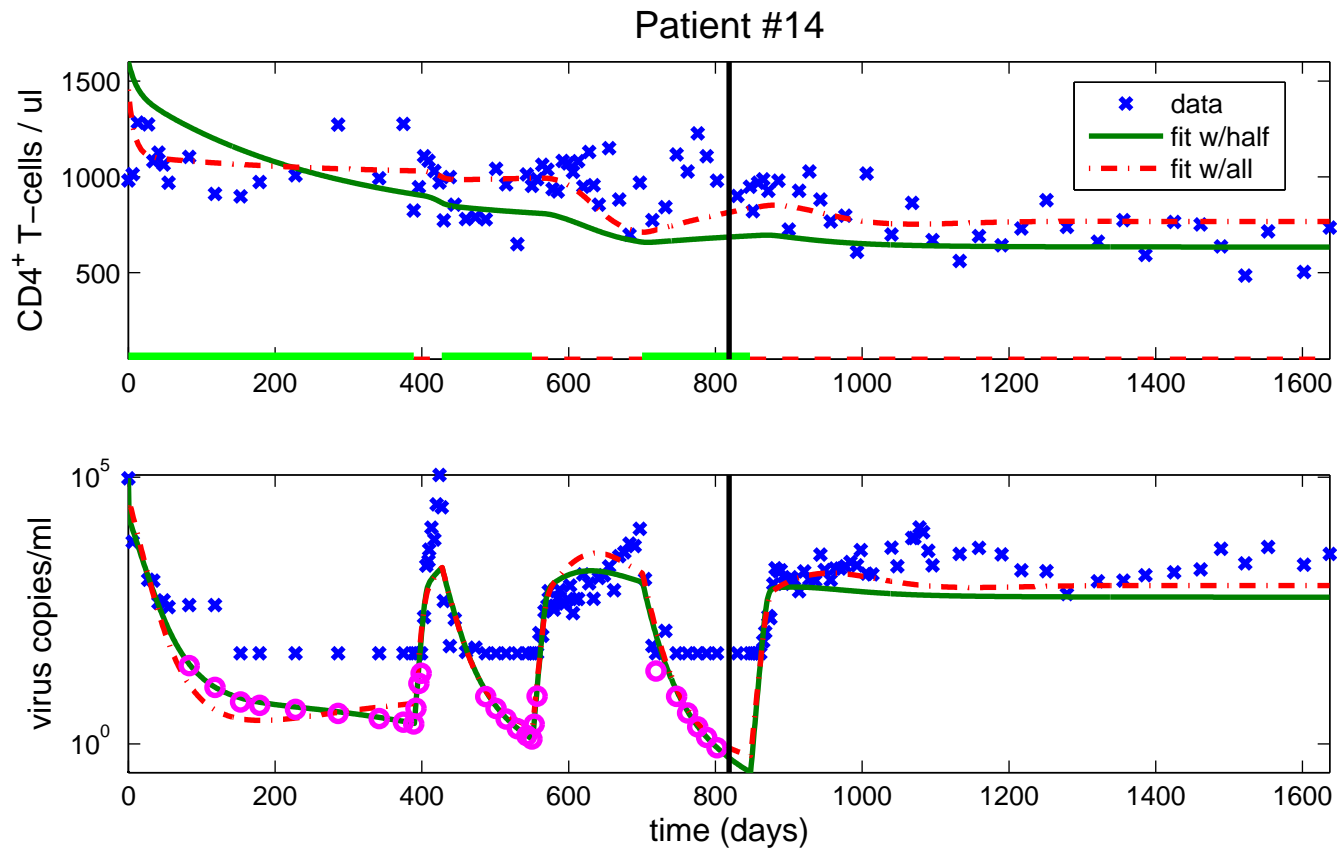
M&S in design of a clinical trial

Model for within-subject dynamics: $s = 7$ states

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

- $\theta = (\lambda_1, d_1, \epsilon_1, k_1, \dots)$ 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 = off, 1 = on)

M&S in design of a clinical trial



M&S in design of a clinical trial

Hierarchical model:

- $Y_{ij} = (Y_{ij}^{(1)}, Y_{ij}^{(2)})^T =$ 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 $u(t)$) \implies *mixture of normal distributions*

M&S in 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 *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

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

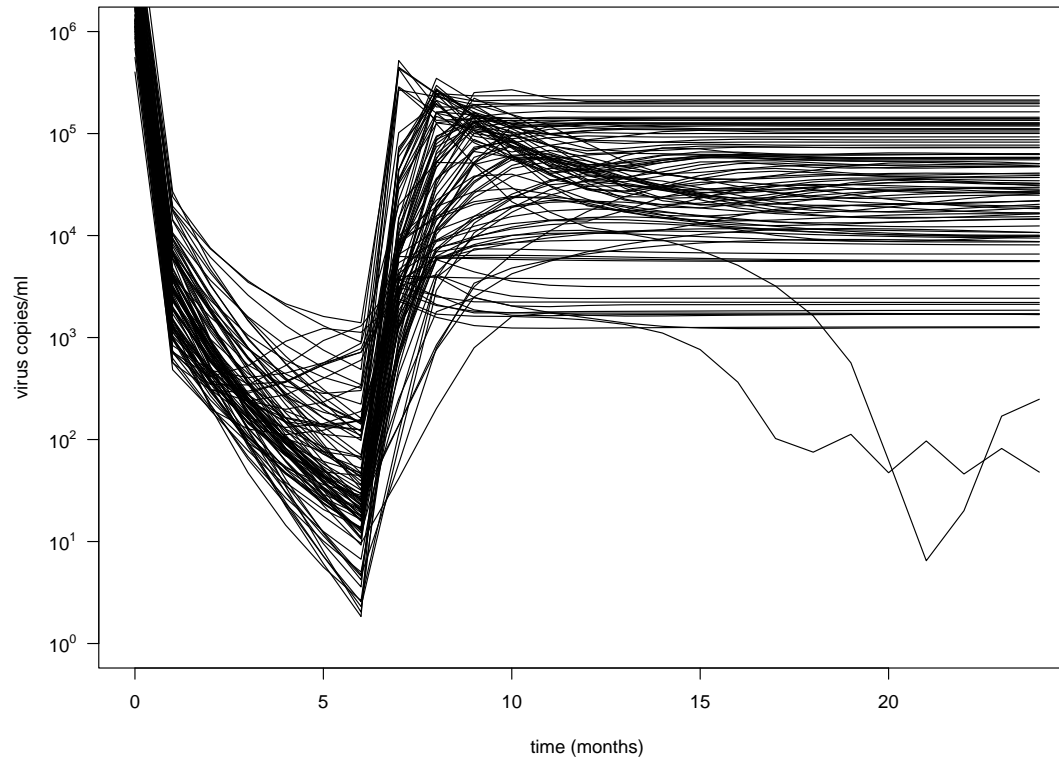
for *termination times* $\tau = 3, 4, \dots, 12$ months

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*

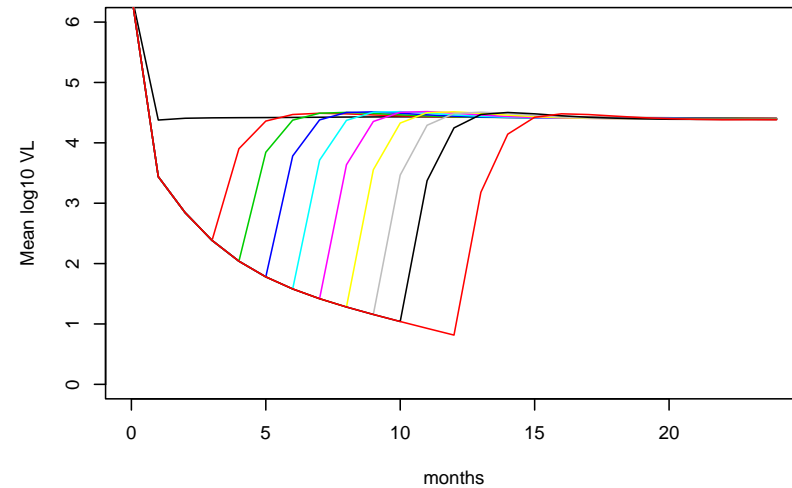
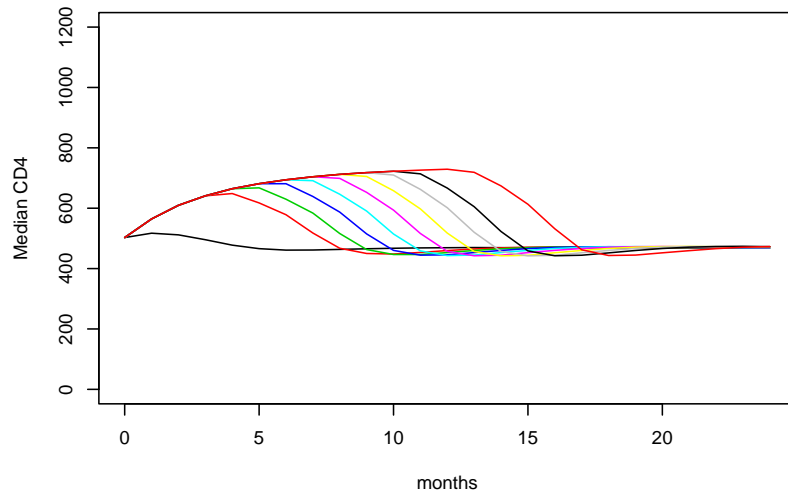
M&S in design of a clinical trial

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



M&S in design of a clinical trial

Different termination times τ : Means of 15,000 “*virtual*” CD4 and viral load data profiles with $u(t) = 1, 0 \leq t \leq \tau, u(t) = 0, t > \tau,$
 $\tau = 0, 3, 4, \dots, 12$ months



M&S in design of a clinical trial

Summary:

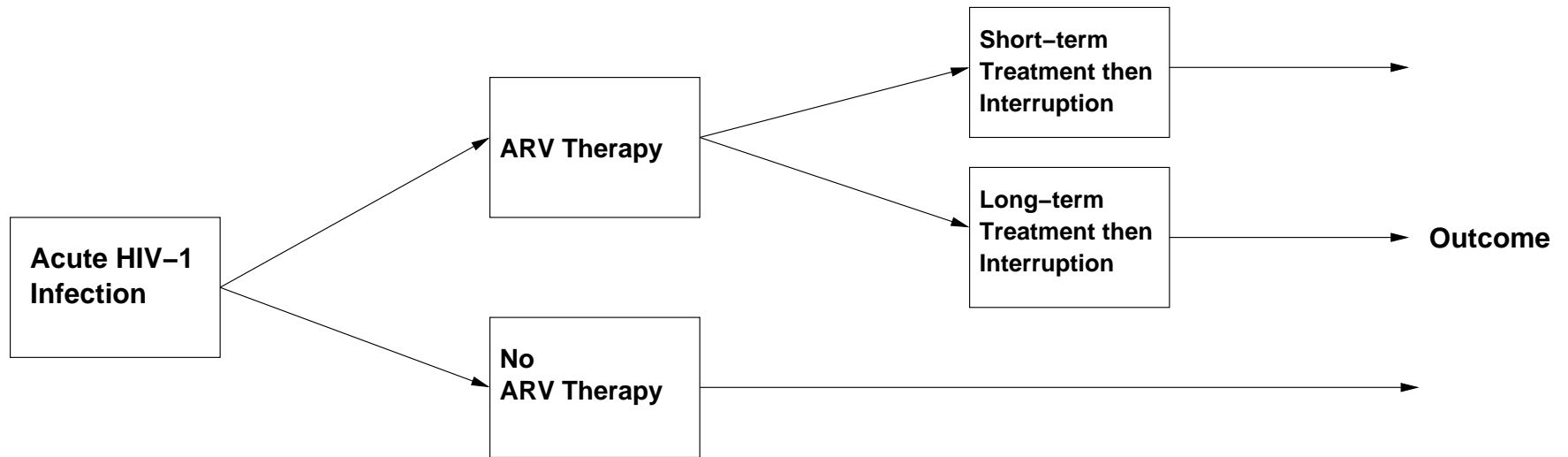
- Based on this (simple) HIV dynamic model, *no differences expected*
- Simple model does not represent adequately the *immune response*
- Since the grant was awarded, we have developed a *refined model*
- Simulations with the *refined model* show larger *subpopulations* with *lowered VL set point* for larger τ ...
- ... 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

M&S in design of a clinical trial

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 . . .

M&S in design of a clinical trial

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