MA/ST 810
Mathematical-Statistical Modeling and Analysis of Complex Systems

Integrating Mathematical and Statistical Models

- Recap of mathematical models
- Models and data
- Statistical models and sources of variation

Recap of mathematical models

Deterministic models: For the purposes of this discussion, we will consider *mathematical models* of the following form

- *System* $\dot{x}(t) = g\{t, x(t), \theta\}$
- *Solution* $y = x(t, \theta)$
- $x(t)$ is the vector whose elements correspond to *states* of a system of interest at time t
- $\dot{x}(t)$ is the vector of derivatives of the elements of $x(t)$ (ODEs)
- Often arise from a *compartmental model* of the system (a gross simplification)

Some examples. . .

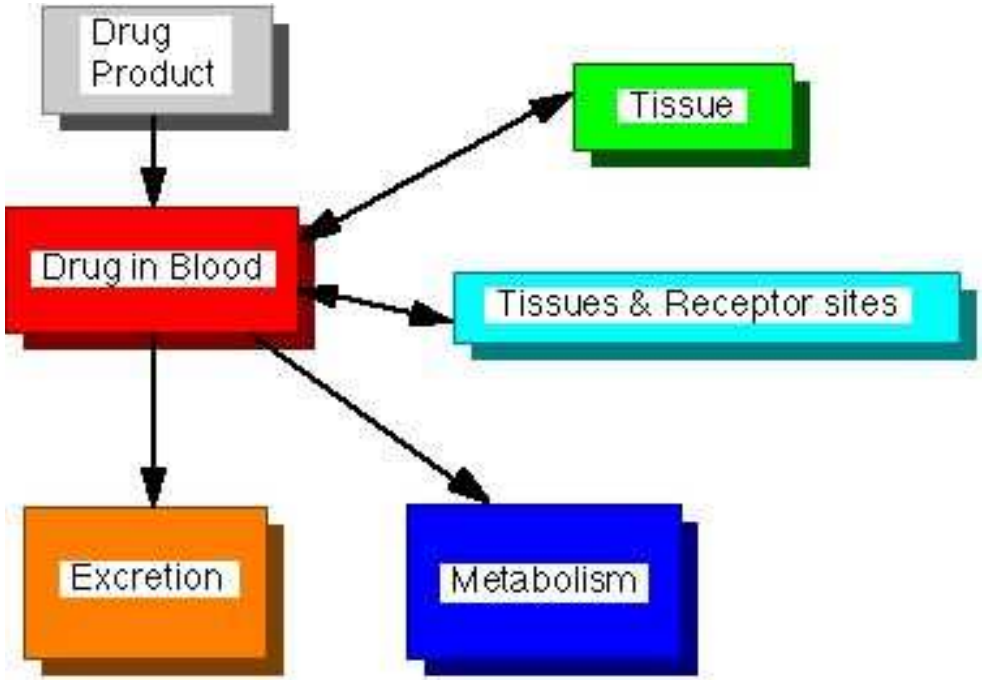
Recap of mathematical models

Example 1: *Pharmacokinetics* (*PK*) of a drug

- *Pharmacokinetics*: "What the body does to the drug"
- *ADME processes*: *absorption*, *distribution*, *metabolism*, *excretion* (metabolism + excretion = *elimination*) – dictate the *concentrations of drug* in the body
- Critical to understand (*quantify*) ADME processes in the development of *dosing recommendations*
- *Premise*: Measure concentrations of drug in the blood over time and use these to learn about ADME processes

Recap of mathematical models

ADME:

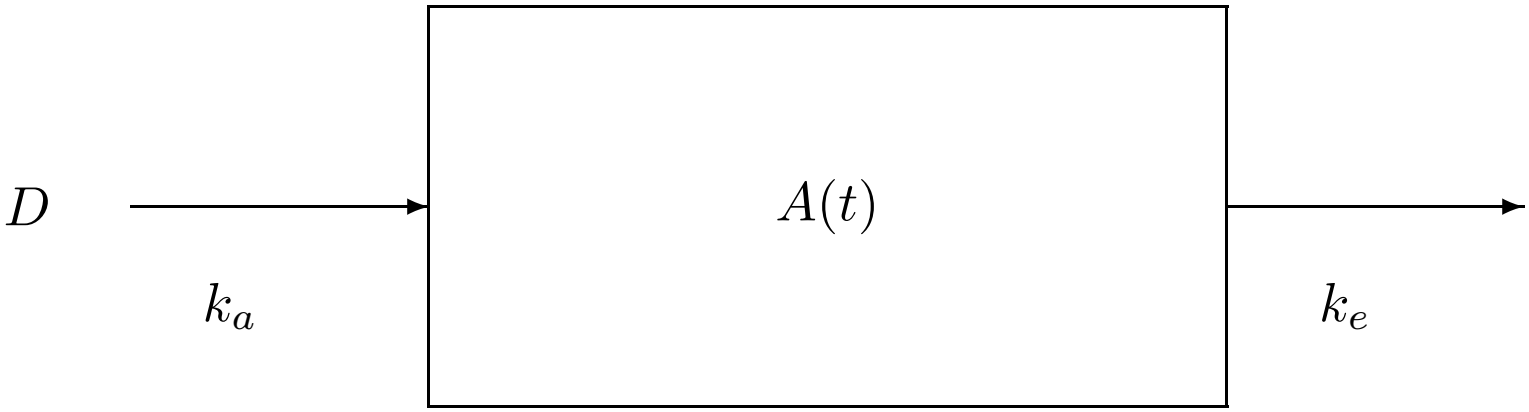


Routes of drug administration: *Intravenously*, *orally*, *intramuscularly*, *subcutaneously*,. . .

Recap of mathematical models

Pharmacokinetics of theophylline: Anti-asthmatic agent

- Common deterministic model: *One compartment model with first-order absorption and elimination* following *oral* dose D at $t = 0$
- $A(t) =$ amount of drug in the "*blood compartment*" at time t ("*well-mixed*")



- *Assumption*: $A(t) = VC(t)$ (constant relationship between drug concentration $C(t)$ and amount of drug in body $A(t)$ for all t)

Recap of mathematical models

System: Letting $A_a(t)$ be the amount of drug at the absorption site at time t

$$\begin{aligned} \dot{A}(t) &= k_a A_a(t) - k_e A(t) \\ \dot{A}_a(t) &= -k_a A_a(t) \end{aligned}$$

with initial conditions $A_a(0) = A_{a0} = FD$, $A(0) = A_0 = 0$, where F is the fraction available (take $F \equiv 1$ for simplicity)

- $x(t) = \{A(t), A_a(t)\}^T$, $\dot{x}(t) = \{\dot{A}(t), \dot{A}_a(t)\}^T = g\{t, x(t), \theta\}$

$$g\{t, x(t), \theta\} = \begin{pmatrix} k_a A_a(t) - k_e A(t) \\ -k_a A_a(t) \end{pmatrix}, \quad \theta = (k_a, k_e)^T$$

Solution: Expression for $A(t)$ [and $A_a(t)$] may be found analytically in a *closed form*

Recap of mathematical models

Laplace transform of $A(t)$: $\mathcal{L}\,A = \int_0^\infty e^{-st} A(t)\,dt$

$$s\mathcal{L}\,A - A_0 = k_a \mathcal{L}\,A_a - k_e \mathcal{L}\,A \quad (1)$$

$$s\mathcal{L}\,A_a - A_{a0} = -k_a \mathcal{L}\,A_a \quad (2)$$

- Solve (2) for $\mathcal{L}\,X_a$ and substitute in (1) to obtain

$$\mathcal{L}\,A = \frac{k_a F D}{(s + k_e)(s + k_a)}$$

- From a table of Laplace transforms, we find immediately that

$$A(t) = \frac{k_a F D}{k_a - k_e}\{e^{-k_e t} - e^{-k_a t}\}$$

so that (divide by V)

$$C(t) = \frac{k_a F D}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}$$

Recap of mathematical models

Result: If the model is *perfectly correct*, the relationship

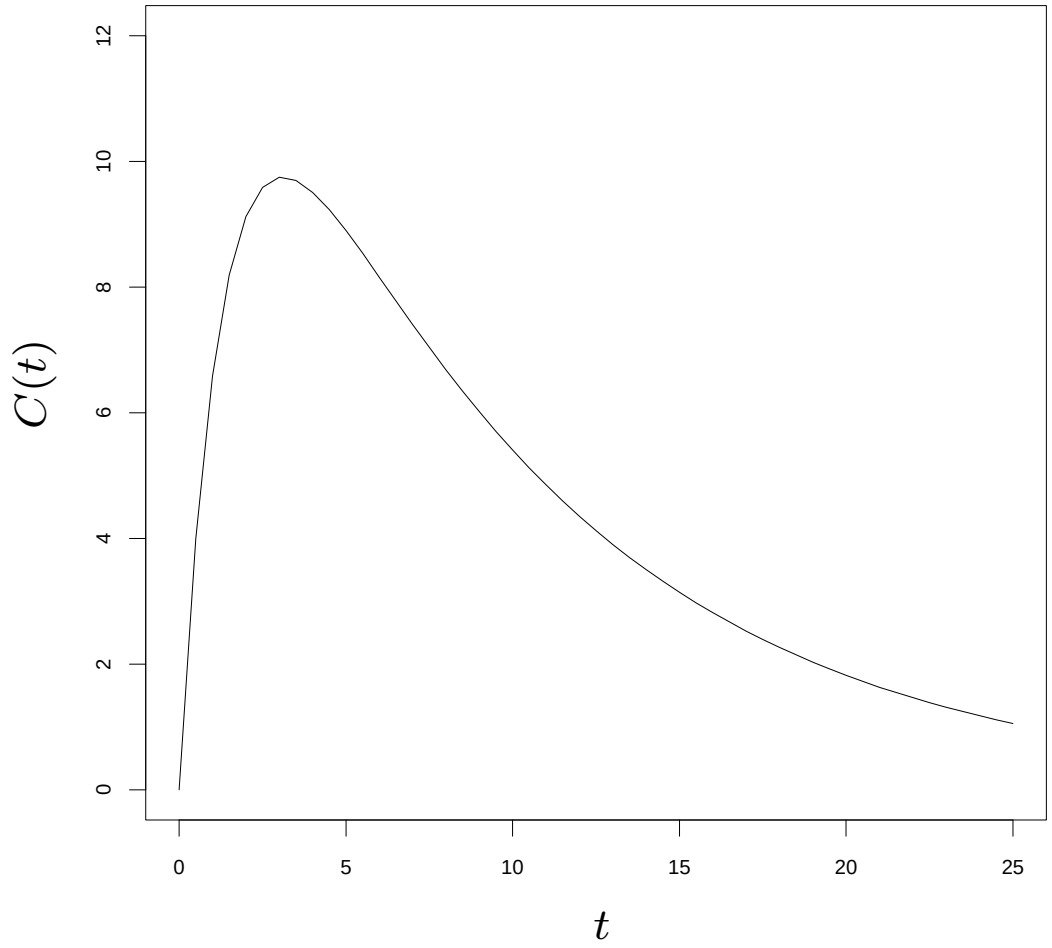
$$C(t) = \frac{k_a F D}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}$$

should describe concentration of drug at time t *within a single subject* to whom oral dose D was administered at time $t = 0$

- The expression for $C(t)$ involves three *parameters* $\theta = (k_a, k_e, V)^T$.
- If we *knew* θ, could predict concentration at any time t following any oral dose D for this subject (*dosing recommendations*)
- Based on *data* (concentrations over time), could learn about *unknown* θ for this subject
- More shortly...

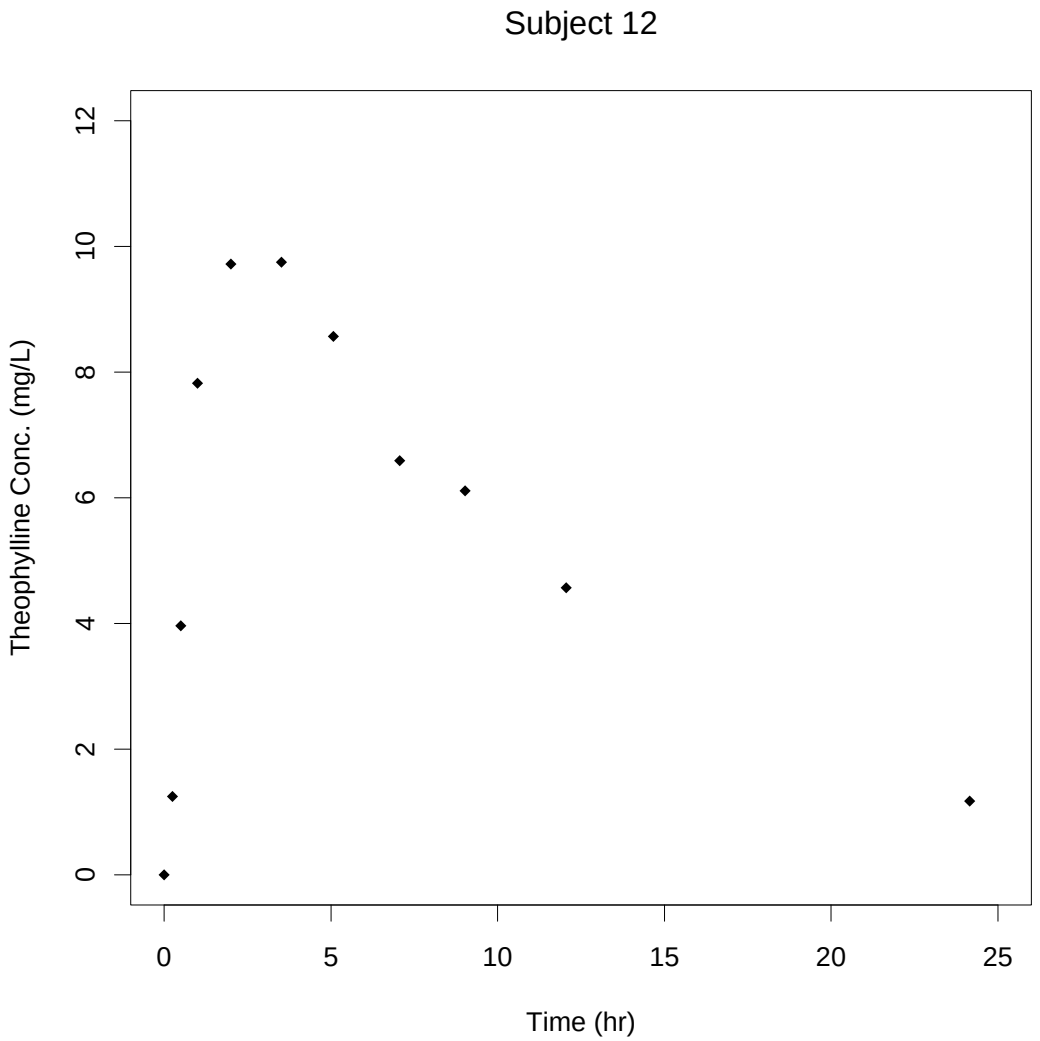
Recap of mathematical models

For example: With k_a =0.7, k_e =1.1, V =0.4



Recap of mathematical models

Data: From a single subject



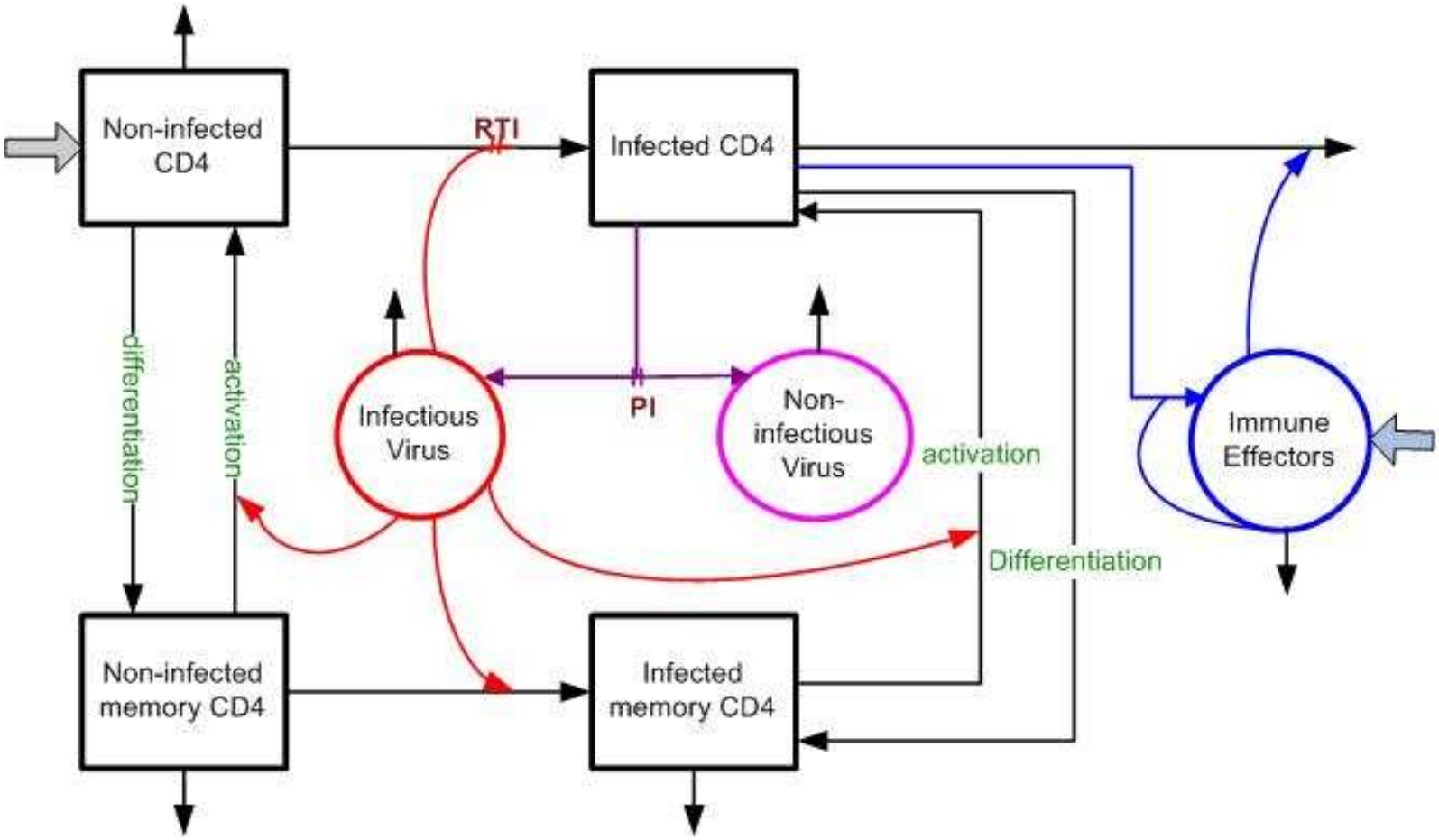
Recap of mathematical models

Example 2: Dynamics of HIV under *antiretroviral* therapy (ARV)

- HIV (*Human immunodeficiency virus*) infects *target cells* in the immune system and uses them to produce *more virus* (that then infects more cells. . .)
- The immune system *responds* to remove infected cells
- A model describes the *interplay* between HIV and immune system taking place *within* a single subject over time
- Can use to *predict* progression of infection under different ARV regimens
- *Reverse transcriptase inhibitor* (*RTI*) *blocks* infectious virus from infecting target cells
- *Protease inhibitor* (*PI*) causes infected cells to produce *non-infectious virus*

Recap of mathematical models

Possible model for within-subject dynamics:



Recap of mathematical models

Typical model components:

T_1, T_1^*	Type 1 target cells (e.g, CD4$^+$ T cells), uninfected, infected
T_2, T_2^*	Type 2 target cells (e.g., macrophages), uninfected, infected
V_I, V_{NI}	infectious and non-infectious free virus
E	cytotoxic T-lymphocytes

- Uninfected cells (T_j) become infected (T_j^*) via encounters with infectious virus (V_I); infection rates k_j
- Uninfected cell source rates λ_j and natural death rates d_j
- Infected cell death rate δ; each cell produces N_T virions
- Virus natural death rate c
- ϵ_1, $f\epsilon_2$ govern efficacy of *RTI* in blocking new infections of T_1, T_2
- ϵ_2, $f\epsilon_2$ govern efficacy of *PI* in causing T_1^*, T_2^* to produce non-infectious virus

Recap of mathematical models

Mathematical model: 7 compartments (states)

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

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

$$\{T_1(0), T_2(0), T_1^*(0), T_2^*(0), V_I(0), V_{NI}(0), E(0)\}$$

- $u(t)$ = ARV input at t ($0 \leq u(t) \leq 1$, 0 = off, 1 = on)

Recap of mathematical models

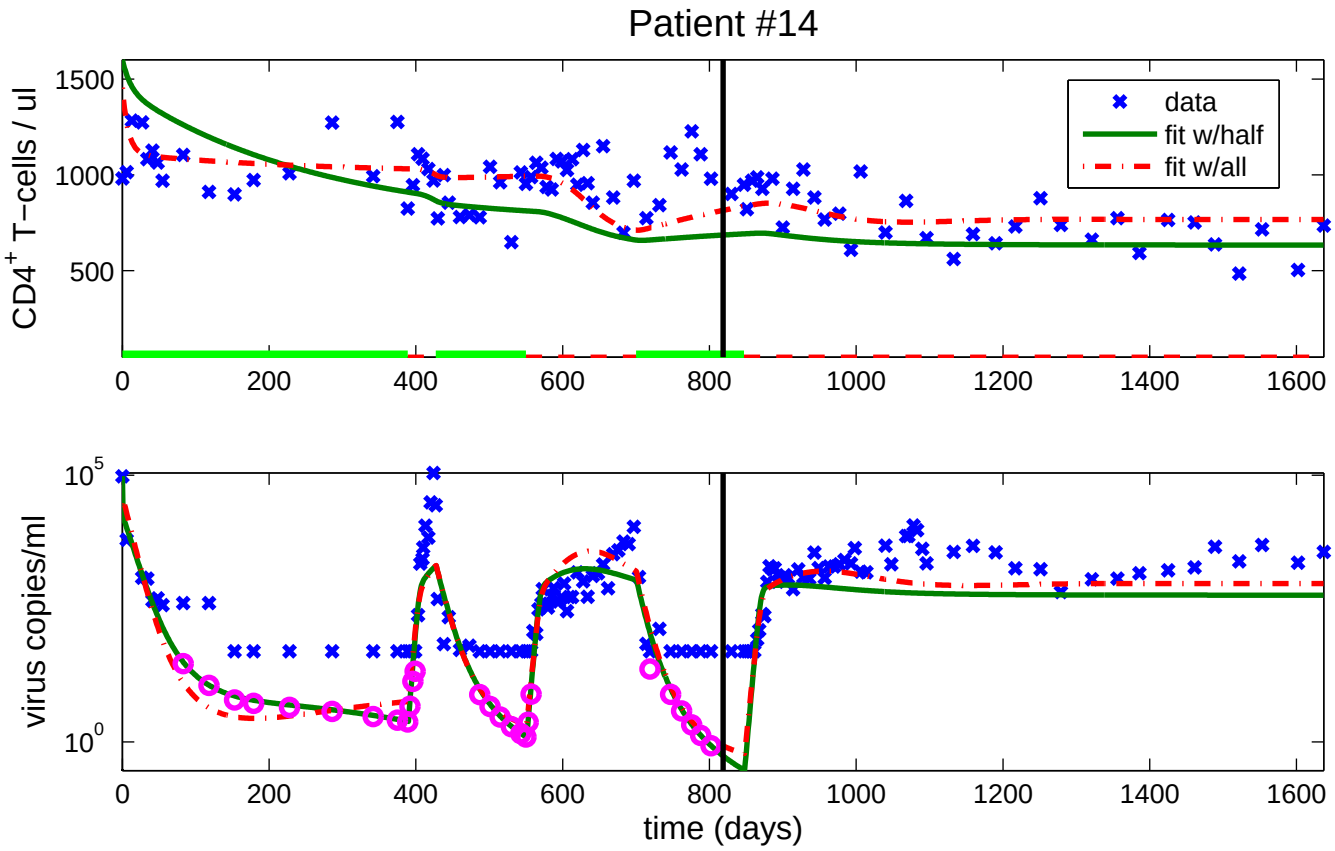
Thus:

$$x(t) = \{T_1(t), T_2(t), T_1^*(t), T_2^*(t), V_I(t), V_{NI}(t), E(t)\}^T$$

$$\dot{x}(t) = g\{t, x(t), \theta\} \quad \text{as on previous slide}$$

- Usual data: *CD4$^+$ T cell count* $= T_1 + T_1^*$, *viral load* $= V_I + V_{NI}$
- So only *observe* some of the *states* (and do not observe any state explicitly)
- More later. . .

Recap of mathematical models



Recap of mathematical models

Again:

- If we knew θ, could predict *viral load*, *CD4 count*, etc, at any time t under different ARV regimens
- If we had *data* on CD4 counts, viral load under a known regimen followed by the subject, could learn about *unknown* θ for this subject (we hope)
- Could use this framework to *design* ARV regimens
- In particular, *adaptive regimens* that use what is known about the subject so far to dictate the best thing to do next
- More later in the course...

Models and data

Goals of (mathematical) modeling:

- Describe (*quantitatively*) known and hypothesized mechanisms governing behavior of a system of interest...
- ...recognizing that the model is a *simplified depiction* of the *real system* that we would like to understand
- Use the models with *data* (i.e., observations on the real system) to learn about underlying mechanisms

Forward solution: Given θ, predict observations on the system over time

- Need to *solve* to obtain expressions for the states at any time t
- *Simple models*: A *closed form* expression available for all states at any t
- *More complex models*: Solution at any time t must be obtained *numerically*

Models and data

Inverse problem: Given observations on the system over time, determine the (*unknown*) θ governing them

- I.e., observe *data* on the system over time: record $y_1, \ldots, y_n$ at times $0 \leq t_1 < \cdots < t_n$ on $x(t_1), \ldots, x(t_n)$
- Statisticians call this *parameter estimation*
- Primary focus in much of this course is the *inverse problem*
- *Ideally*: Observe *all states* over time, as above (y_j are *vectors*)
- *In reality*: Observe only some states (PK example) or functions of some states (HIV example)

For now: Will start with simplest case of PK example, where $y_1, \ldots, y_n$ are *scalar* observations on a single state, then *generalize*

Models and data

Critical issue: *Data* are subject to *variation* and *uncertainty*

- Indeed, observations usually *do not* track exactly on $y = x(t, \theta)$
- Must recognize this and take it into appropriate account
- *Statistical inference*

Notation:

- Solution to the entire system $= x(t, \theta)$ (all states)
- Solution for the part of the system that is observed is denoted $f(t, \theta)$, defined as

$$f(t, \theta) = \mathcal{O}x(t, \theta)$$

  for "*observation matrix*" $\mathcal{O}$ with # columns = # states

- E.g., for the *PK example* (2 states) $\mathcal{O} = (1, 0)^T$ (1×2) (and divide by V)

Models and data

Theophylline study: PK in *humans* following oral dose

- 12 "*healthy volunteers*" each given dose D (mg/kg) at time $t = 0$
- Blood samples drawn at 10 subsequent time points over the next 25 hours for each subject
- Samples *assayed* for theophylline concentration
- *Observe* $y_1, \ldots, y_{10}$ at times $t_1, \ldots, t_{10}$ on each subject

Objectives:

- For a *specific subject*, learn about absorption, distribution, and elimination by determining k_a, k_e, V $\Rightarrow$ dosing recommendations for this subject – we tackle this first
- Learn about how absorption, distribution, and elimination differ from subject to subject $\Rightarrow$ dosing recommendations for the *population* of likely subjects – later in the course

Models and data

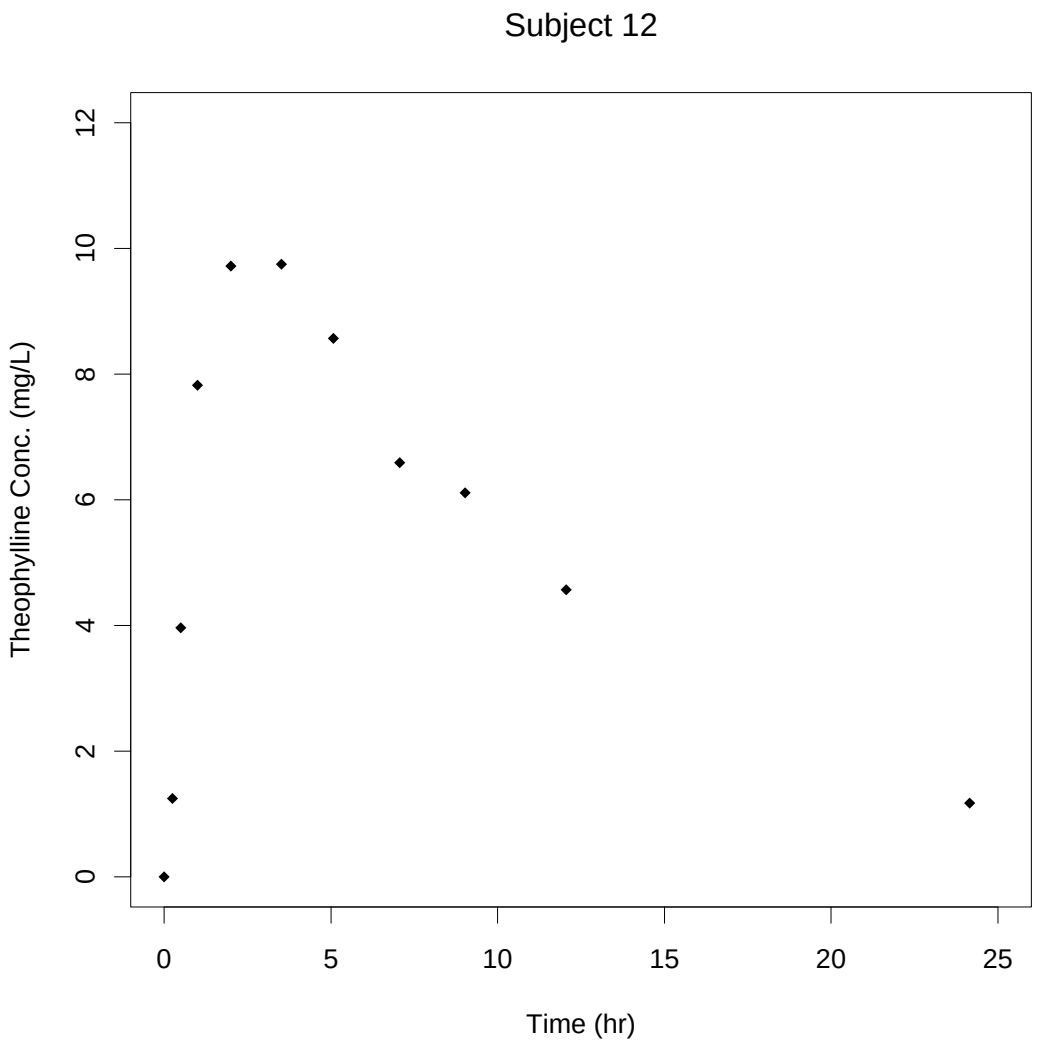
Model-based expression for theophylline concentration $C(t)$ at time t for a single subject:

$$f(t,\theta) = \frac{k_a F D}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}, \quad \theta = (k_a, k_e, V)^T$$

- We take $F \equiv 1$
- Note that $f(t,\theta)$ *also* depends on the dose D; we suppress this dependence in the notation for now

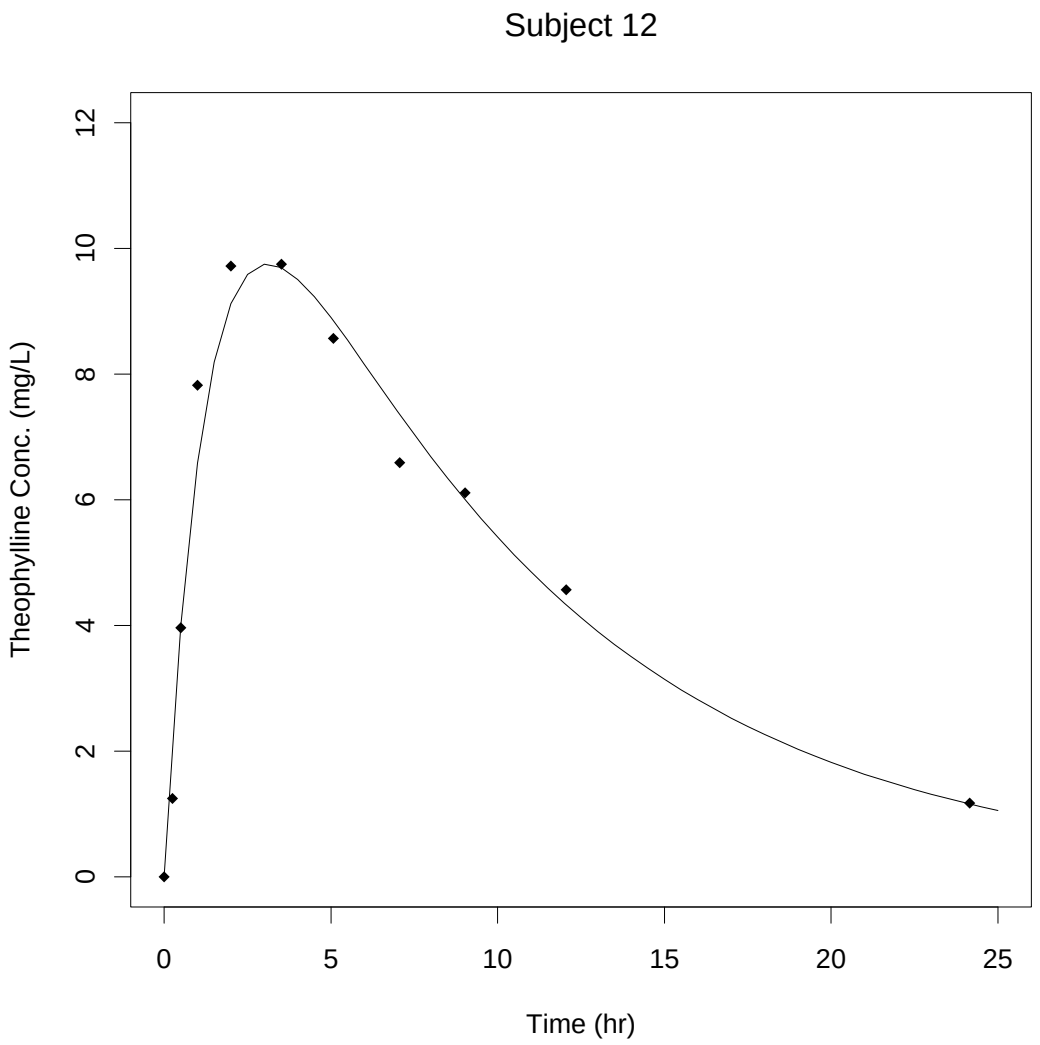
Models and data

Data for subject 12: Plot of concentration vs. time



Models and data

Data for subject 12: With "fitted model" superimposed



Models and data

Remarks:

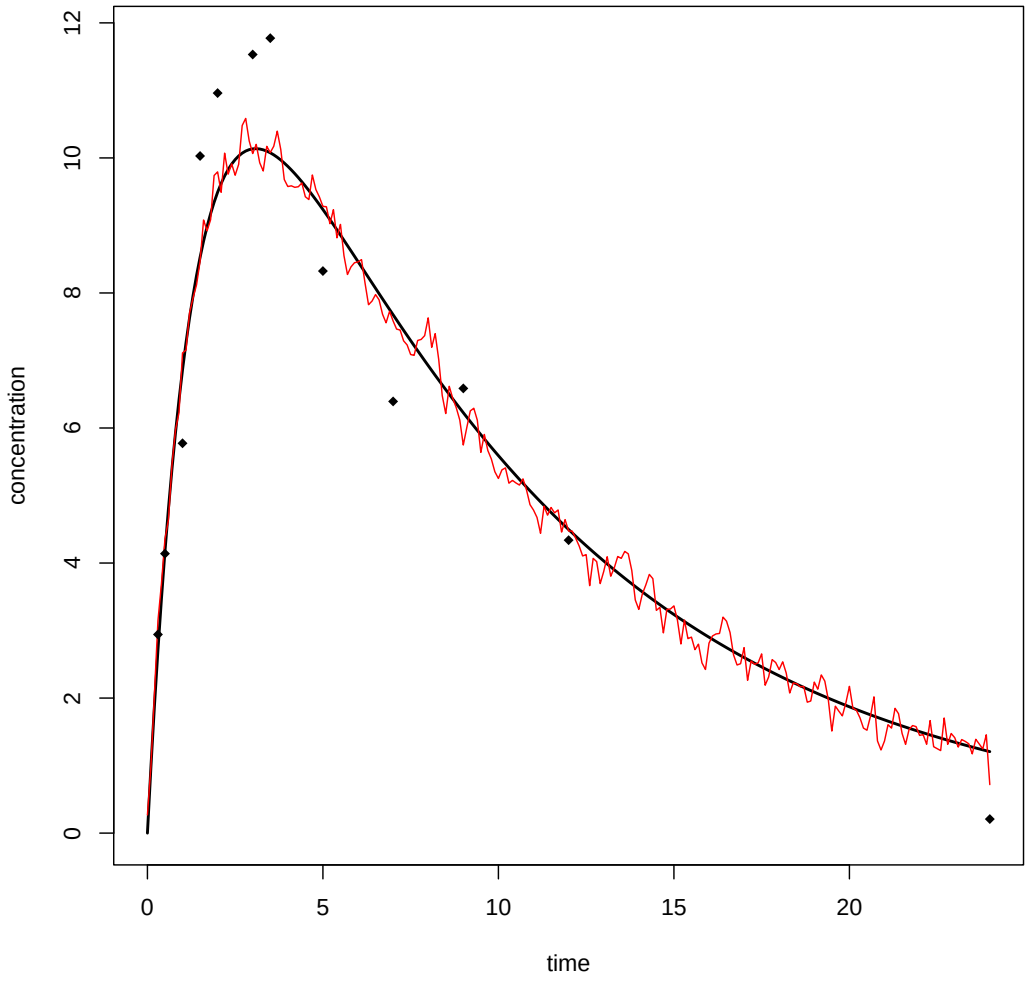
- Observed concentrations appear to trace out a pattern over time quite similar to that dictated by the one compartment model
- But they do not lie *exactly* on a smooth trajectory
- "*Observation error*"

Why?

- One obvious reason: Assay is not perfect, cannot measure concentration *exactly* (measurement error)
- Other reasons?

Models and data

Approximation: Model is an *idealized* representation of a more complicated biological process

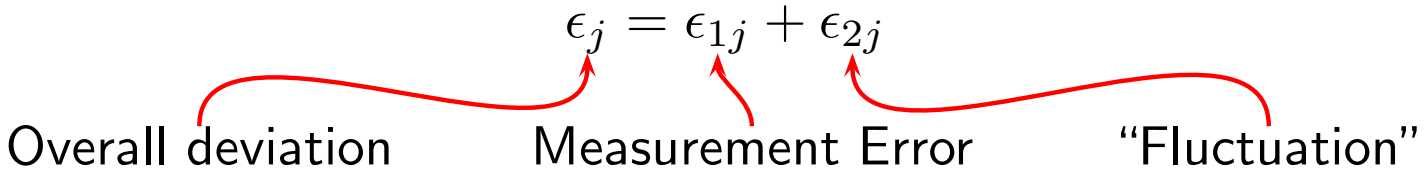


Models and data

Standard conceptualization: Think of what we *observe* as

$$y_j = f(t_j, \theta) + \epsilon_j$$

- $f(t, \theta) = C(t)$, a function of $\theta = (k_a, k_e, V)^T$
- ϵ_j is the *deviation* between what the (deterministic) model dictates we would see at t_j and what we actually observe
- Here, ϵ_j represents deviations from $f(t_j, \theta)$ due to *measurement error*, "*biological fluctuations*"



Models and data

Thought experiment: Consider measurement error

- A particular blood sample has a "*true*" concentration of theophylline
- When we measure this concentration, an error is committed, which causes "*observed*" to deviate from "*true*" by an amount that is negative or positive
- Suppose we were to measure the same sample *over and over* (zillions of times) – each time, a possibly different error is committed
- So all such observations would turn out *differently*, even though, *ideally*, they should be all the *same* (measuring the *same thing*)

Models and data

Result: Measurement error is a *source of variation* that leads to *uncertainty* in what we *observe*

- In actuality, we measure the concentration only *once*
- The error that results may be thought of as drawn from a "*population*" of *all possible errors* that could be committed when measuring concentration
- $\Rightarrow$ *UNCERTAINTY* – the observation could have turned out *differently*
- Errors, and hence, observations, are *variable*

Models and data

Recall: Would like to determine θ from the pairs (y_j, t_j), $j = 1, \ldots, n$

- Any determination of θ we try to make from these observations will be subject to *uncertainty*
- That is, if we *estimate* θ from data subject to measurement error (and *other sources of variation*), the estimate *could have turned out differently*

We will see:

- Failure to acknowledge this can lead to *erroneous conclusions*
- Acknowledging this requires a *formal* way to describe and assess uncertainty, and thus limitations of what can be learned from *data*

Models and data

Deterministic models: Representation of the "ideal relationship" between model states and time

Statistical models: Representation of the "actual relationship" between *observations* on model states and time

- Incorporate sources of *uncertainty* (variation)
- Framework for *formalizing* assumptions about the effects of variation
- Main tool: *probability*

Statistical model for observed theophylline concentrations:

$$Y_j = f(t_j, \theta) + \epsilon_j, \quad j = 1, \ldots, n$$

- Think of ϵ_j as a *random variable* with a *probability distribution* that characterizes "*populations*" of possible values of phenomena like measurement errors, fluctuations that might occur at t_j

Models and data

Statistical model for observed theophylline concentrations:

$$Y_j = f(t_j, \theta) + \epsilon_j, \quad j = 1, \ldots, n$$

- If ϵ_j is a random variable, then so is what we observe
- $\Rightarrow Y_j$ is a random variable with a *probability distribution* that characterizes how observations at t_j on this subject may vary because of measurement error, fluctuations, etc.
- The model describes pairs (Y_j, t_j), $j = 1, \ldots, n$, we might see; i.e, the model describes the *mechanism* by which data are thought to arise
- *Data* we observe are realizations of Y_j, $j = 1, \ldots, n$: $y_1, \ldots, y_n$
- The *mechanism* is characterized by assumptions on the *probability distribution* of ϵ_j (so, equivalently, on that of Y_j)

Statistical models and sources of variation

In general: *Random variables* and *probability distributions* are the building blocks of *statistical models*

- A *statistical model* is a representation of the *mechanism* by which *data* are assumed to arise
- Phenomena that are *subject to variation* and hence give rise to *uncertainty* in the way data may "*turn out*" are represented by *random variables*
- Assumptions on the nature of *probability distributions* for random variables in statistical models represent assumptions on the nature and extent of such variation
- *Mathematical models* that describe the "idealized" relationship need to be *embedded* in such a model in an appropriate way and given an appropriate interpretation
- Continue with the *theophylline example* for a demonstration. . .

Statistical models and sources of variation

Recap: Theophylline PK on a single subject

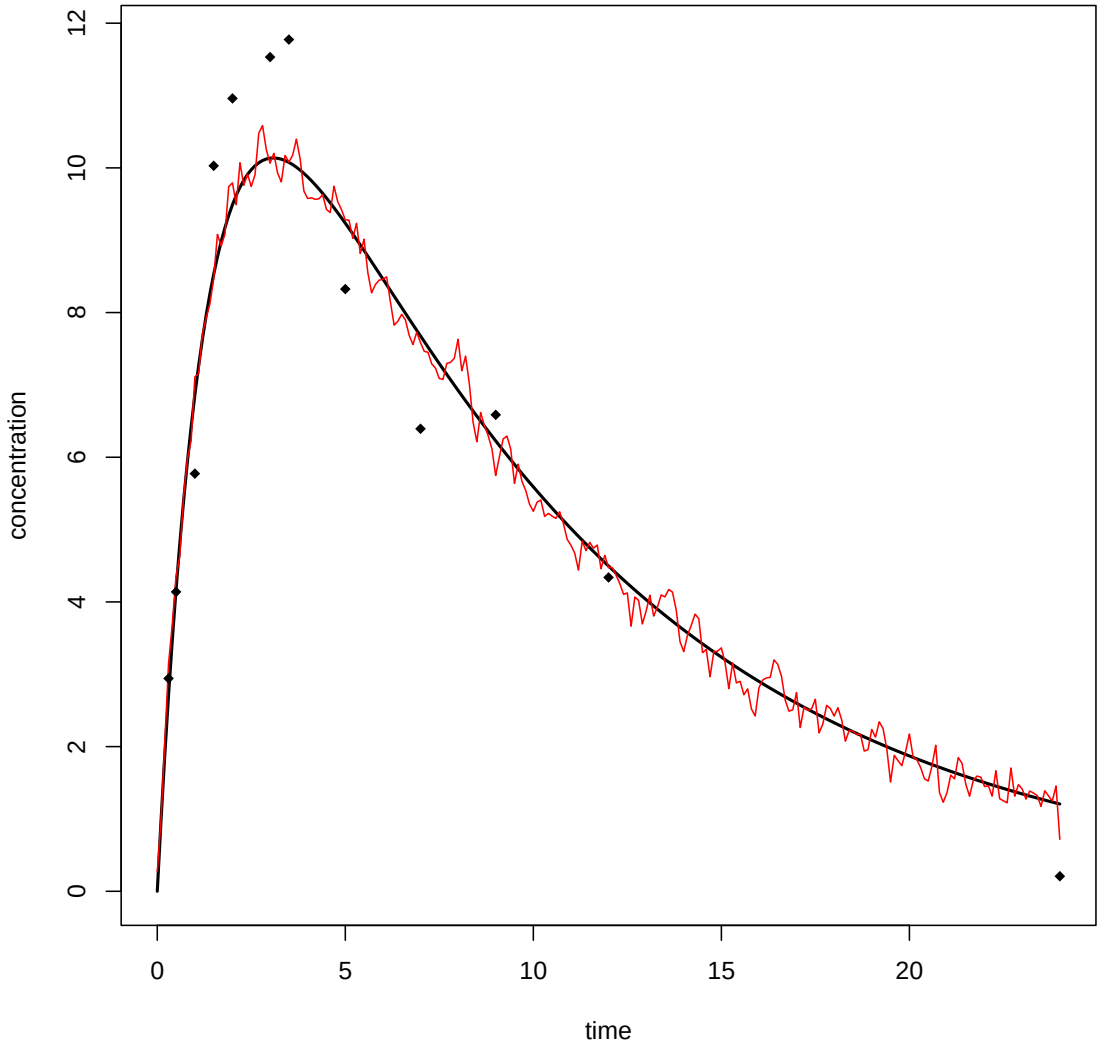
$$Y_j = f(t_j, \theta) + \epsilon_j, \quad j = 1, \ldots, n$$

$$f(t, \theta) = \frac{k_a F D}{V(k_a - k_e)}\{e^{-k_e t} - e^{-k_a t}\}, \quad \theta = (k_a, k_e, V)^T$$

- $f(t, \theta)$ derived from the *deterministic* compartment model; also depends on other stuff (*dose* D at $t = 0$)
- ϵ_j represents *deviation* that causes observations to not fall exactly on the smooth path $f(t, \theta)$
- Aggregate effects of *measurement error*, "*biological fluctuations*," other phenomena
- $\Rightarrow$ ϵ_j is a *random variable* whose *probability distribution* reflects assumed features of these phenomena
- And Y_j is also a *random variable* (transformation of ϵ_j)

Statistical models and sources of variation

Conceptual representation:



Statistical models and sources of variation

More formal: In principle, the PK *process* could be observed at *any time*

- $Y(t)$ is observed concentration that would be seen at time t and $\epsilon(t)$ is the corresponding deviation under conditions U (U = dose D at $t = 0$)

$$Y(t) = f(t, U, \theta) + \epsilon(t), \quad t \geq 0$$

- Could have $U = U(t)$ (e.g., HIV example); suppress for now
- Represents the assumed data generating mechanism at *any* time t
- $Y(t)$, $\epsilon(t)$ are *stochastic processes* – *random function* of time with sample space of possible values (functions); e.g., $y(t)$, $t \geq 0$ (*sample paths*)
- For a *fixed set* of times $t_1 < \cdots < t_n$ write

$$Y(t_j) = f(t_j, U, \theta) + \epsilon(t_j)$$

  to represent observations that would be seen at these times under conditions U

- $Y_j = Y(t_j)$, $\epsilon_j = \epsilon(t_j)$

Statistical models and sources of variation

$$Y(t_j) = f(t_j, U, \theta) + \epsilon(t_j)$$

Thus:

- $\{\epsilon(t_1), \epsilon(t_2), \ldots, \epsilon(t_n)\}^T = (\epsilon_1, \epsilon_2, \ldots, \epsilon_n)^T$ and $\{Y(t_1), Y(t_2), \ldots, Y(t_n)\}^T = (Y_1, Y_2, \ldots, Y_n)^T$ are *random vectors*
- Can consider the *joint probability distribution* of $(\epsilon_1, \epsilon_2, \ldots, \epsilon_n)^T$ [and thus of $(Y_1, Y_2, \ldots, Y_n)^T$]
- *Technical point 1*: Probability distribution for a stochastic process arises from thinking of *all possible* such vectors and their joint distributions for all n (infinitely many)
- *Technical point 2*: Probability distributions here depend on conditions U and are hence *conditional probability distributions* (conditional on U)

Statistical models and sources of variation

$$Y(t_j) = f(t_j, U, \theta) + \epsilon(t_j)$$

Nature of $\epsilon(t)$: "*Biological fluctuations*," *measurement error*

$$\epsilon(t) = \epsilon_1(t) + \epsilon_2(t)$$

- $\epsilon_1(t_j) = \epsilon_{1j}$ represents *measurement error* that could be committed at fixed time t_j
- $\epsilon_2(t_j) = \epsilon_{2j}$ represents "*fluctuation*" that might occur at t_j
- These random variables are *continuous* – concentrations *in principle* can take on *any value* (although we may be limited in what we may actually observe due to limits on resolution of measurement)
- Write $\{\epsilon_1(t_1), \ldots, \epsilon_1(t_n)\}^T = (\epsilon_{11}, \ldots, \epsilon_{1n})^T$ and $\{\epsilon_2(t_1), \ldots, \epsilon_2(t_n)\}^T = (\epsilon_{21}, \ldots, \epsilon_{2n})^T$ – *random vectors*

Statistical models and sources of variation

Measurement error: "*Reasonable*" assumptions on $\epsilon_1(t)$ and hence on aspects of the *joint probability distribution* of $(\epsilon_{11}, \ldots, \epsilon_{1n})^T$ (conditional on U)

- Measuring device is *unbiased* – does not systematically err in one direction

$$E\{\epsilon_1(t)|U\} = 0 \ \forall t \ \Rightarrow \ E(\epsilon_{1j}|U) = 0 \quad \text{for each } j = 1 \ldots, n$$

  (All possible errors for measuring concentration for the sample taken at any t_j "average out" to zero)

- In fact, negative or positive errors are *equally likely* $\Rightarrow$ the *marginal conditional probability density* of ϵ_{1j} is *symmetric* for each j

- Measurement errors at any two times are "*unrelated*"

$$\epsilon_1(t) \perp\!\!\!\perp \epsilon_1(s)|U \ \forall t, s \ \Rightarrow \ \epsilon_{1j} \perp\!\!\!\perp \epsilon_{1j'}|U \ \Rightarrow \ \text{cov}(\epsilon_{1j}, \epsilon_{1j'}|U) = 0$$

Statistical models and sources of variation

Measurement error: "*Reasonable*" assumptions on $\epsilon_1(t)$ and hence on aspects of the *joint probability distribution* of $(\epsilon_{11}, \ldots, \epsilon_{1n})^T$ (conditional on U)

- *Variation* among all errors that might occur at any time is of the *same* magnitude

$$\text{var}\{\epsilon_1(t)|U\} = \sigma_1^2 \ \forall t \ \Rightarrow \ \text{var}(\epsilon_{1j}|U) = \sigma_1^2$$

  for all j (unaffected by time or "actual concentration" in the sample at t_j) – *is this realistic?*

- In many cases, *NO* – measurement error variance tends to *increase* with increasing magnitude of the true concentration being measured – approximate by

$$\text{var}\{\epsilon_1(t)|U\} \ \text{ is a function of } \ f(t, U, \theta)$$

Statistical models and sources of variation

"Biological fluctuations": "*Reasonable*" assumptions on aspects of the *joint probability distribution* of $(\epsilon_{21}, \ldots, \epsilon_{2n})^T$ (conditional on U)

- Fluctuations tend to "track" the smooth trajectory $f(t, U, \theta)$ over time (sample path) but can be "above" or "below" at any time

$$E\{\epsilon_2(t)|U\} = 0 \ \forall t \ \Rightarrow \ E(\epsilon_{2j}|U) = 0$$

  (All possible fluctuations at any time "average out" to zero)

- In fact, negative or positive fluctuations at a particular time are *equally likely* $\Rightarrow$ the *marginal conditional probability density* of ϵ_{2j} is *symmetric* for each j

- *Variation* among fluctuations that might occur at any time is *same* at all times

$$\text{var}\{\epsilon_2(t)|U\} = \sigma_2^2 \ \forall t \ \Rightarrow \ \text{var}(\epsilon_{2j}|U) = \sigma_2^2 \ \forall j$$

Statistical models and sources of variation

"Biological fluctuations": "*Reasonable*" assumptions on aspects of the *joint probability distribution* of $(\epsilon_{21}, \ldots, \epsilon_{2n})^T$ (conditional on U)

- Fluctuations "*close together*" in time tend to behave "*similarly*," with extent of "*similarity*" decreasing are the times grow more apart

$$\text{cov}\{\epsilon_2(t), \epsilon_2(s)|U\} = C(|t-s|) \quad \text{and} \quad \text{corr}\{\epsilon_2(t), \epsilon_2(s)|U\} = c|t-s|) \ \ \forall t, s$$

for decreasing functions $C(\,\cdot\,)$, $c(\,\cdot\,)$ with with $C(0) = \sigma_2^2$ and $c(0) = 1$

- Hence at times t_j, $t_{j'}$

$$\text{cov}(\epsilon_{2j}, \epsilon_{2j'}|U) = C(|t_j - t_{j'}|) \ \text{ and } \ \text{corr}(\epsilon_{2j}, \epsilon_{2j'}|U) = c(|t_j - t_{j'}|).$$

Statistical models and sources of variation

"Biological fluctuations," continued:

- E.g., for $\text{corr}(\epsilon_{2j}, \epsilon_{2j'}) = c(|t_j - t_{j'}|)$,

$$c(u) = \exp(-\phi u^2)$$

(so correlation between fluctuations at two times is *nonnegative*, reflecting "*similarity*")

- Extent and direction of measurement error at any time t is *unrelated* to fluctuations at t or any other time

$$\epsilon_1(t) \perp\!\!\!\perp \epsilon_2(s) | U \ \ \forall t, s \ \ \Rightarrow \ \ \epsilon_{1j} \perp\!\!\!\perp \epsilon_{2j'}$$

for any t_j, $t_{j'}$, $j, j' = 1, \ldots, n$

Statistical models and sources of variation

Remarks:

- The foregoing assumptions are not the *only* assumptions one could make, but exemplify the considerations involved
- The *normal probability distribution* is a natural choice to represent the assumption of *symmetry*

Statistical models and sources of variation

Recapping the assumptions: $\epsilon_j = \epsilon_{1j} + \epsilon_{2j}$

- $E(\epsilon_{1j}|U) = 0$, $E(\epsilon_{2j}|U) = 0 \Rightarrow E(\epsilon_j|U) = 0$
- $\text{var}(\epsilon_{1j}|U) = \sigma_1^2$, $\text{var}(\epsilon_{2j}|U) = \sigma_2^2$, and $\epsilon_{1j} \perp\!\!\!\perp \epsilon_{2j}|U$ for all j

$$\Rightarrow \quad \text{var}(\epsilon_j|U) = \sigma_1^2 + \sigma_2^2$$

- $\text{cov}(\epsilon_{1j}, \epsilon_{1j'}|U) = 0$, $\text{cov}(\epsilon_{2j}, \epsilon_{2j'}|U) = \sigma_2^2 c(|t_j - t_{j'}|) = \sigma_2^2 e^{-\phi(t_j - t_{j'})^2}$
- Conditional on U, $(\epsilon_{11}, \ldots, \epsilon_{1n})^T$ has *mean vector 0* and *covariance matrix*

$$\begin{pmatrix} \sigma_1^2 & 0 & \cdots & 0 \\ 0 & \sigma_1^2 & \ddots & \vdots \\ \vdots & \ddots & \ddots & 0 \\ 0 & \cdots & 0 & \sigma_1^2 \end{pmatrix} = \sigma_1^2 I_n$$

and has a *multivariate normal distribution*

Statistical models and sources of variation

Recapping the assumptions: $\epsilon_j = \epsilon_{1j} + \epsilon_{2j}$

- Conditional on U, $(\epsilon_{21}, \ldots, \epsilon_{2n})^T$ has *mean vector 0* and *covariance matrix*

$$\sigma_2^2 \begin{pmatrix} 1 & e^{-\phi(t_1-t_2)^2} & \cdots & e^{-\phi(t_1-t_n)^2} \\ e^{-\phi(t_1-t_2)^2} & 1 & \ddots & \vdots \\ \vdots & \ddots & \ddots & e^{-\phi(t_{n-1}-t_n)^2} \\ e^{-\phi(t_1-t_n)^2} & \cdots & e^{-\phi(t_{n-1}-t_n)^2} & 1 \end{pmatrix} = \sigma_2^2 \Gamma$$

  and has a *multivariate normal distribution*

- So, conditional on U,
  $(\epsilon_1, \ldots, \epsilon_n)^T = (\epsilon_{11}, \ldots, \epsilon_{1n})^T + (\epsilon_{21}, \ldots, \epsilon_{2n})^T$ has mean vector 0 and covariance matrix

$$\sigma_1^2 I_n + \sigma_2^2 \Gamma$$

Statistical models and sources of variation

Thus: Implications for $Y = (Y_1, \ldots, Y_n)^T$

- $E(Y_j|U) = f(t_j, U, \theta) + E(\epsilon_j|U) = f(t_j, U, \theta)$
- Thus, may think of $f(t, U, \theta)$ as the result of averaging across all possible *sample paths of the fluctuation process* and *measurement errors*, so representing the "*inherent trajectory*" for subject 12
- $\text{var}(Y_j|U) = \text{var}(\epsilon_j|U) = \sigma_1^2 + \sigma_2^2$
- $\text{cov}(Y_j, Y_{j'}|U) = \text{cov}(\epsilon_j, \epsilon_{j'}|U) = \sigma_2^2 \exp\{-\phi(t_j - t_{j'})^2\}$
- Y_j is normally distributed (conditional on U)
- The *random vector* $Y = (Y_1, \ldots, Y_n)^T$ has a (conditional on U) *multivariate normal distribution* with *mean vector* and *covariance matrix*

$$f(U, \theta) = \{f(t_1, U, \theta), \ldots, f(t_n, U, \theta)\}^T \quad \text{and} \quad \sigma_1^2 I_n + \sigma_2^2 \Gamma$$

Statistical models and sources of variation

More succinctly: We have the *statistical model*

$$Y|U \sim \mathcal{N}_n\{f(U,\theta), \sigma_1^2 I_n + \sigma_2^2 \Gamma\} \tag{3}$$

- Each *marginal* is a normal density, e.g. $Y_j|U \sim \mathcal{N}\{f(t_j, U, \theta), \sigma_1^2 + \sigma_2^2\}$

Simplifications: We may be willing to make *simplifying assumptions*

- If the t_j are *far apart*, $|t_j - t_{j'}|$ may be *large*, and hence $\exp\{-\phi(t_j - t_{j'})^2\}$ *close to zero* $\Rightarrow$ "correlation among fluctuations at $t_1, \ldots, t_n$ is *negligible*"
- *Approximate* by assuming $\epsilon_{2j} \perp\!\!\!\perp \epsilon_{2j'}|U \Rightarrow \text{cov}(\epsilon_{2j}, \epsilon_{2j'}|U) = 0$ and thus $\Gamma = I_n$, which implies

$$Y_j \perp\!\!\!\perp Y_{j'}|U \;\Rightarrow\; \text{cov}(Y_j, Y_{j'}|U) = 0,$$

and $\text{var}(Y_j|U) = \sigma^2 = \sigma_1^2 + \sigma_2^2$

Statistical models and sources of variation

Summarizing: The *statistical model* becomes

$$Y|U \sim \mathcal{N}_n\{f(U,\theta), \sigma^2 I_n\}, \quad \psi = (\theta^T, \sigma^2)^T \tag{4}$$

- The *statistical model* (4) is the standard one that is typically assumed
- The foregoing development shows the considerations involved in *justifying* this model
- These considerations are almost *never* mentioned in the literature on *inverse problems*; indeed, no reference to a statistical model is typically even made
- *Important*: Just because we assume this statistical model holds doesn't mean we're *correct*
- We might proceed as if the model is correct, but need to worry about the implications if it is *not*; more later

Statistical models and sources of variation

So far: For simplicity, we have restricted attention to the situation where Y_j are *scalars*

- Y_j is theophylline concentration at time t_j
- The data observed at each t_j may be *multivariate*; i.e., Y_j is a *random vector*
- In the *HIV example*, the data observed are *bivariate*; i.e.

$$Y_j = (Y_j^{(1)}, Y_j^{(2)})^T = (\text{CD4 count at } t_j, \text{viral load at } t_j)^T$$

- In terms of the *mathematical model* on slide 14, with the 7 states

$$x(t) = \{T_1(t), T_2(t), T_1^*(t), T_2^*(t), V_I(t), V_{NI}(t), E(t)\}^T$$

we have observations on

$$T_1(t) + T_1^*(t) = \text{CD4 count} \quad \text{and} \quad V_I(t) + V_{NI}(t) = \text{viral load} \quad \text{at } t_1, \ldots, t_n$$

Statistical models and sources of variation

Multivariate observations:

- As on slide 20, a model $f(t, U, \theta)$ (2×1) can be derived from the solution $x(t, U, \theta)$ to the system $\dot{x} = g\{t, x(t), \theta\}$ as

$$f(t, U, \theta) = \mathcal{O}x(t, U, \theta),$$

  where $\mathcal{O}$ is the (2×7) *observation matrix*

$$\mathcal{O} = \begin{pmatrix} 1 & 0 & 1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 1 & 1 & 0 \end{pmatrix}$$

- Thus, we have the bivariate model

$$f(t, U, \theta) = \begin{pmatrix} f^{(1)}(t, U, \theta) \\ f^{(2)}(t, U, \theta) \end{pmatrix}.$$

- *All data*: $Y = (Y_1^T, \ldots, Y_n^T)^T$ $(2n \times 1)$

Statistical models and sources of variation

Bivariate stochastic process:

$$Y(t) = \begin{pmatrix} Y^{(1)}(t) \\ Y^{(2)}(t) \end{pmatrix} = f(t, U, \theta) + \epsilon(t), \quad t \geq 0$$

$$\epsilon(t) = \epsilon_1(t) + \epsilon_2(t) = \begin{pmatrix} \epsilon_1^{(1)}(t) \\ \epsilon_1^{(2)}(t) \end{pmatrix} + \begin{pmatrix} \epsilon_2^{(1)}(t) \\ \epsilon_2^{(2)}(t) \end{pmatrix}$$

- Observations

$$Y_j = \{Y^{(1)}(t_j), Y^{(2)}(t_j)\}^T = (Y_j^{(1)}, Y_j^{(2)})^T, \quad j = 1, \ldots, n$$

- *Measurement error* deviations

$$\epsilon_{1j} = \{\epsilon_1^{(1)}(t_j), \epsilon_1^{(2)}(t_j)\}^T = (\epsilon_{1j}^{(1)}, \epsilon_{1j}^{(2)})^T$$

- "*Fluctuation*" deviations

$$\epsilon_{2j} = \{\epsilon_2^{(1)}(t_j), \epsilon_2^{(2)}(t_j)\}^T = (\epsilon_{2j}^{(1)}, \epsilon_{2j}^{(2)})^T$$

Statistical models and sources of variation

In fact: Observations on each component of $Y(t)$ need not even be at the *same times*; for simplicity, we assume that they are here

Statistical model: Considerations for *each component* of $\epsilon(t)$ and hence $\epsilon_j = \epsilon_{1j} + \epsilon_{2j}$ and $Y_j = (Y_j^{(1)}, Y_j^{(2)})^T$ are as before

- We might still assume $\epsilon_{1j} \perp\!\!\!\perp \epsilon_{2j} | U$ and believe

$$E(\epsilon_{1j}|U) = 0, \;\; E(\epsilon_{2j}|U) = 0 \;\Rightarrow\; E(\epsilon_j|U) = 0$$

  based on the same rationale as before, applied to each component *separately*

- We now have to consider our beliefs about *variance and correlation* for *each component* in

$$\epsilon_j = \epsilon_{1j} + \epsilon_{2j} = (\epsilon_{1j}^{(1)}, \epsilon_{1j}^{(2)})^T + (\epsilon_{2j}^{(1)}, \epsilon_{2j}^{(2)})^T$$

- *AND* correlations between $\epsilon_{kj}^{(1)}$ and $\epsilon_{kj'}^{(2)}$ for $k = 1, 2$ at times j, j'

Statistical models and sources of variation

Statistical model, continued: For example, *variances*

- *Measurement error variances*

$$\text{var}(\epsilon_{1j}^{(1)}|U) = \sigma_1^{(1)2}, \quad \text{var}(\epsilon_{1j}^{(2)}|U) = \sigma_1^{(2)2}$$

- "*Fluctuation*" variances

$$\text{var}(\epsilon_{2j}^{(1)}|U) = \sigma_2^{(1)2}, \quad \text{var}(\epsilon_{2j}^{(2))}|U) = \sigma_2^{(2)2}$$

- Thus under the foregoing *independence assumption*

$$\text{var}(\epsilon_j^{(1)}|U) = \sigma_1^{(1)2} + \sigma_2^{(1)2}, \quad \text{var}(\epsilon_j^{(2)}|U) = \sigma_1^{(2)2} + \sigma_2^{(2)2}$$

Statistical models and sources of variation

Statistical model, continued: For example, *covariances*

- Between "*fluctuations*" for each $k = 1, 2$

$$\text{cov}(\epsilon_{2j}^{(k)}, \epsilon_{2j'}^{(k)}|U) = \sigma_2^{(k)2} c^{(k)}(|t_j - t_{j'}|) = \sigma_2^{(k)2} e^{-\phi_k (t_j - t_{j'})^2}$$

  (*separate* correlation functions depending on ϕ_k for each $k = 1, 2$)

- Between *measurement errors* in the same or different components at *different times*

$$\text{cov}(\epsilon_{1j}^{(k)}, \epsilon_{1j'}^{(k')}|U) = 0, \quad j \neq j', \ k, k' = 1, 2$$

- Between *measurement errors* in different components at the *same time*

$$\text{cov}(\epsilon_{1j}^{(1)}, \epsilon_{1j}^{(2)}|U) = 0$$

  Is this *reasonable*?

Statistical models and sources of variation

Statistical model, continued: For example, *covariances*

- Between "*fluctuations*" in "*true*" CD4 counts and viral loads

$$\text{cov}(\epsilon_{2j}^{(1)}, \epsilon_{2j'}^{(2)}|U) = ???$$

Do we believe that the fluctuations in "*true*" CD4 counts and viral loads are *independent*?

Statistical models and sources of variation

Distributional assumption: As before

- Could assume $Y_j|U$ has a *multivariate normal* distribution with whatever *covariance structure* is implied by the assumptions made
- I.e., the *marginal density* for each Y_j is *bivariate normal*

$$Y_j|U \sim \mathcal{N}_2\{f(t, U, \theta), \mathcal{V}\},$$

  where $\mathcal{V}$ is a (2×2) covariance matrix
- $\psi = (\theta^T, \xi^T)^T$, where ξ is the set of all *covariance parameters* in $\mathcal{V}$
- Implied distributional model for *all data* Y

Statistical models and sources of variation

Summarizing: *Lots* to think about and *make assumptions about* here...

Common practice in inverse problems: Amounts to assuming a statistical model with *all possible correlations negligible*

- E.g., t_j are far apart, each component operates *independently* of the other, etc.
- Implies $Y_j \perp\!\!\!\perp Y_{j'}|U$, $Y_j^{(1)} \perp\!\!\!\perp Y_j^{(2)}|U$ for all j, j', and thus

$$\text{var}(Y_j|U) = \mathcal{V} = \begin{pmatrix} \sigma^{(1)2} & 0 \\ 0 & \sigma^{(2)2} \end{pmatrix},$$

$$\text{var}(Y_j^{(1)}|U) = \sigma^{(1)2} = \sigma_1^{(1)2} + \sigma_2^{(1)2}, \quad \text{var}(Y_j^{(2)}|U) = \sigma^{(2)2} = \sigma_1^{(2)2} + \sigma_2^{(2)2}$$

- *Is this reasonable*?

Statistical models and sources of variation

Implied statistical model: The statistical model tacitly assumed in inverse problems is

$$Y_j|U \sim \mathcal{N}_2\{f(t, U, \theta), \mathcal{V}\}, \quad j = 1, \ldots, n \tag{5}$$

$$\mathcal{V} = \begin{pmatrix} \sigma^{(1)2} & 0 \\ 0 & \sigma^{(2)2} \end{pmatrix}.$$

- *In fact*, sometimes, the even more restrictive assumption that $\sigma^{(1)2} = \sigma^{(2)2} = \sigma^2$ is imposed, so that $\mathcal{V} = \sigma^2 I_2$!
- Does this make any sense? At the very least, it implies that errors in measurement are of *similar magnitude* for all components of Y_j, *regardless* of *different scales of measurement*...

Clearly: All of this of course generalizes to observation vectors with ≥ 2 components in the obvious way (*even more complicated*)

Statistical models and sources of variation

Key point: A *statistical model* like (3), (4), or (5) thus describes *all possible probability distributions* for *random vector* Y representing the *data generating mechanism* for observations we might see at $t_1, \ldots, t_n$ under conditions U

- E.g., for (3), *possible probability distributions* are specified by different values of the *parameter* $\psi = (\theta^T, \sigma_1^2, \sigma_2^2, \phi)^T \in \Psi$
- *The big question*: Which value of ψ truly governs the mechanism?
- We are interested in θ (the other components of ψ are required to describe the model fully, but are a *nuisance* . . . more later)

Objective: If we *collect data* (so observe *a single realization* of Y) under conditions U, what can we learn about ψ?

- . . . and how can we account for the fact that things could have turned out *differently* (i.e., a *different realization*)?