

Noncompartmental vs. Compartmental Approaches to Pharmacokinetic Data Analysis

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Questions To Be Asked

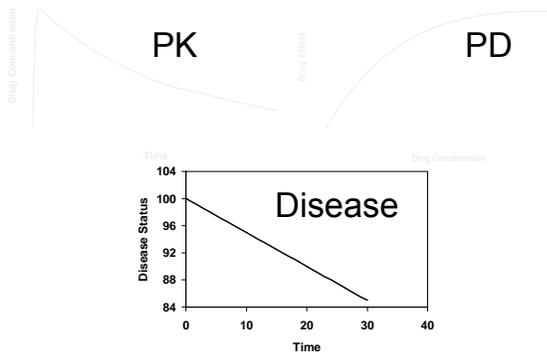
- Pharmacokinetics
 - What the body does to the drug
- Pharmacodynamics
 - What the drug does to the body
- Disease progression
 - Measurable therapeutic effect
- Variability
 - Sources of error and biological variation

Pharmacokinetics / Pharmacodynamics



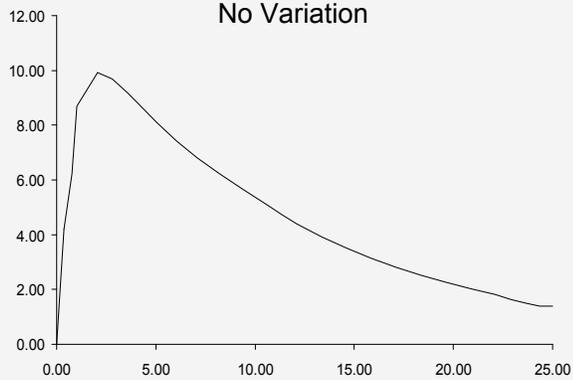
- | | |
|------------------------------------|------------------------------------|
| ➤ Pharmacokinetics | ➤ Pharmacodynamics |
| ➤ “What the body does to the drug” | ➤ “What the drug does to the body” |
| ➤ Fairly well known | ➤ Largely unknown |
| ➤ Useful to get to the PD | ➤ Has clinical relevance |

PK/PD/Disease Processes



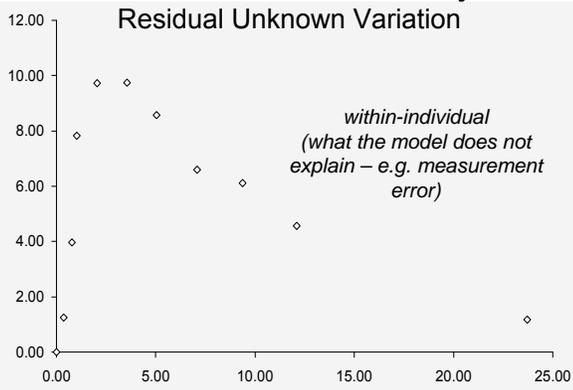
Hierarchical Variability

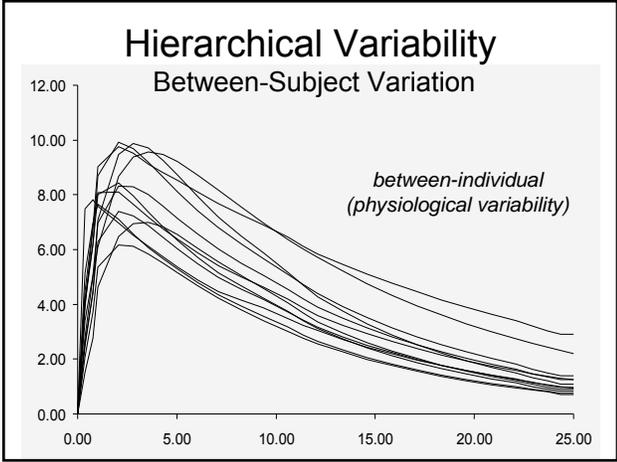
No Variation

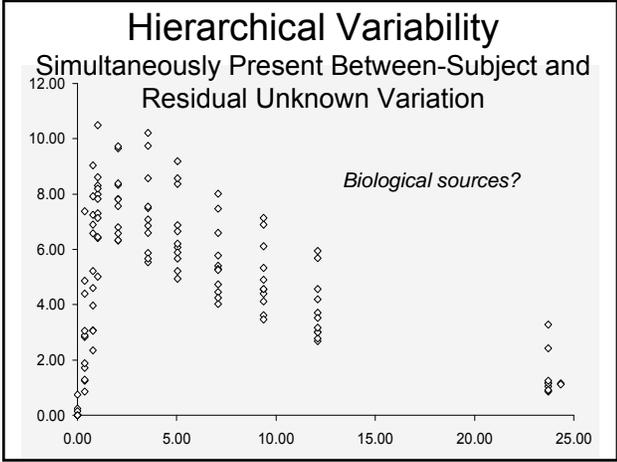


Hierarchical Variability

Residual Unknown Variation







Pharmacokinetic Parameters

- Definition of pharmacokinetic parameters
 - Descriptive or observational
 - Quantitative (requiring a formula and a means to estimate using the formula)
- Formulas for the pharmacokinetic parameters
- Methods to estimate the parameters from the formulas using measured data

Models For Estimation

Noncompartmental
Compartmental

Goals Of This Lecture

- Description of the parameters of interest
- Underlying assumptions of noncompartmental and compartmental models
- Parameter estimation methods
- What to expect from the analysis

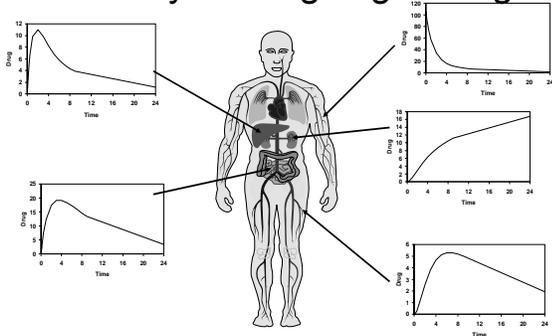
Goals Of This Lecture

- What this lecture is about
 - What are the assumptions, and how can these affect the conclusions
 - Make an intelligent choice of methods depending upon what information is required from the data
- What this lecture is not about
 - To conclude that one method is “better” than another

A Drug In The Body: Constantly Undergoing Change

- Absorption
 - Transport in the circulation
 - Transport across membranes
 - Biochemical transformation
 - Elimination
- ADME
- Absorption, Distribution, Metabolism, Excretion

A Drug In The Body: Constantly Undergoing Change



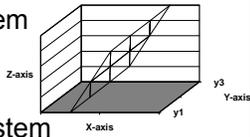
Kinetics And Pharmacokinetics

- Kinetics
 - The temporal and spatial distribution of a substance in a system.
- Pharmacokinetics
 - The temporal and spatial distribution of a drug (or drugs) in a system.

Definition Of Kinetics: Consequences

➤ Spatial: *Where* in the system

- Spatial coordinates
- Key variables: (x, y, z)

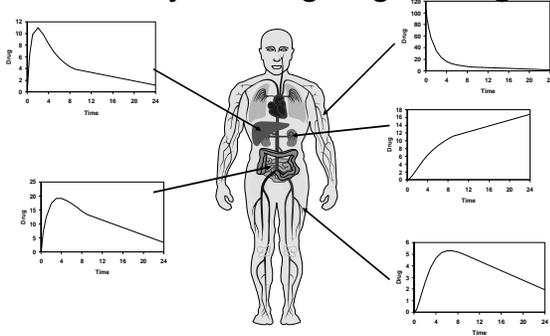


➤ Temporal: *When* in the system

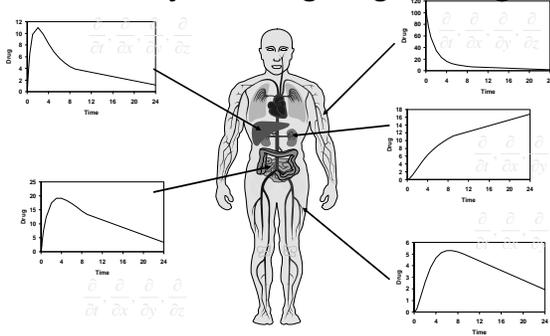
- Temporal coordinates
- Key variable: t

$$\frac{\partial c(x, y, z, t)}{\partial x}, \frac{\partial c(x, y, z, t)}{\partial y}, \frac{\partial c(x, y, z, t)}{\partial z}, \frac{\partial c(x, y, z, t)}{\partial t}$$

A Drug In The Body: Constantly Undergoing Change



A Drug In The Body: Constantly Undergoing Change



Spatially Distributed Models

- Spatially realistic models:
 - Require a knowledge of physical chemistry, irreversible thermodynamics and circulatory dynamics.
 - Are difficult to solve.
 - It is difficult to design an experiment to estimate their parameter values.
- While desirable, normally not practical.
- Question: What can one do?

Resolving The Problem

- Reducing the system to a finite number of components
- Lumping processes together based upon time, location or a combination of the two
- Space is not taken directly into account: rather, spatial heterogeneity is modeled through changes that occur in time

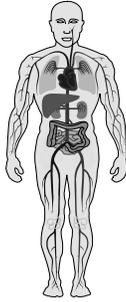
Lumped Parameter Models

- Models which make the system discrete through a lumping process thus eliminating the need to deal with partial differential equations.
- Classes of such models:
 - Noncompartmental models
 - Based on algebraic equations
 - Compartmental models
 - Based on linear or nonlinear differential equations

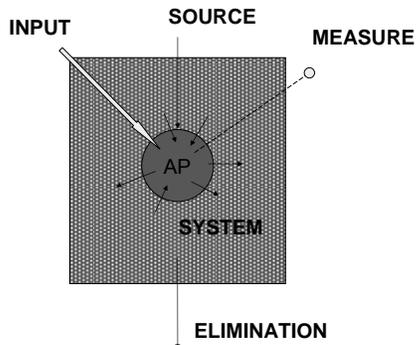
Probing The System

➤ **Accessible pools:** These are system spaces that are available to the experimentalist for test input and/or measurement.

➤ **Nonaccessible pools:** These are spaces comprising the rest of the system which are not available for test input and/or measurement.



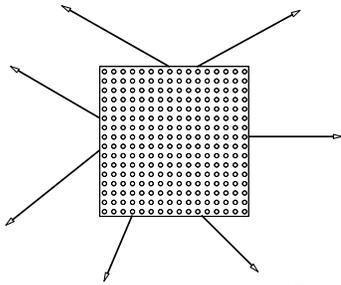
Focus On The Accessible Pool



Characteristics Of The Accessible Pool

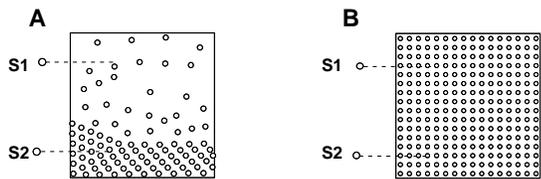
Kinetically Homogeneous
Instantaneously Well-mixed

Accessible Pool Kinetically Homogeneous



(ref: see e.g. Cobelli et al.)

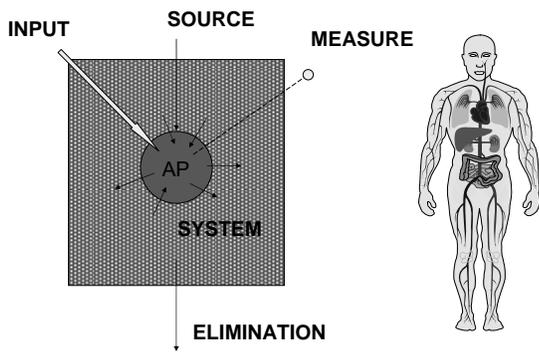
Accessible Pool Instantaneously Well-Mixed



- A = not mixed
- B = well mixed

(ref: see e.g. Cobelli et al.)

Probing The Accessible Pool



The Pharmacokinetic Parameters

- Which pharmacokinetic parameters can we estimate based on measurements in the accessible pool?
- Estimation requires a model
 - Conceptualization of how the system works
- Depending on assumptions:
 - Noncompartmental approaches
 - Compartmental approaches

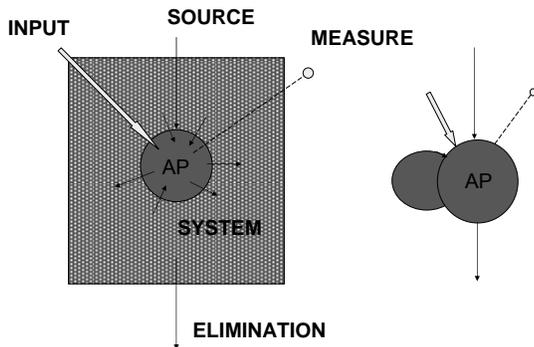
Accessible Pool & System Assumptions → Information

- Accessible pool
 - Initial volume of distribution
 - Clearance rate
 - Elimination rate constant
 - Mean residence time
- System
 - Equivalent volume of distribution
 - System mean residence time
 - Bioavailability
 - Absorption rate constant

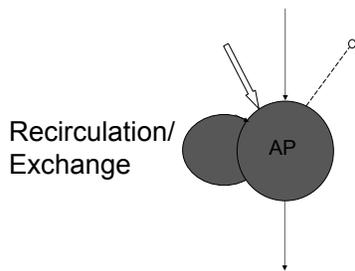
Compartmental and Noncompartmental Analysis

The only difference between the two methods is in how the nonaccessible portion of the system is described

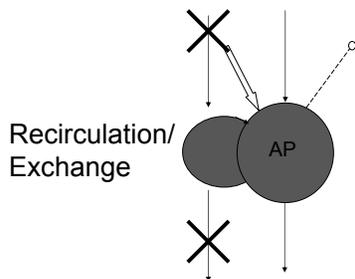
The Noncompartmental Model



Recirculation-exchange Assumptions



Recirculation-exchange Assumptions

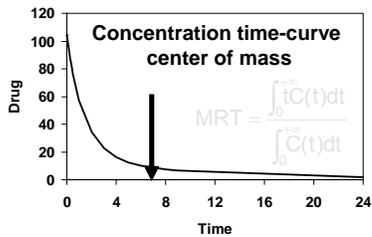


Single Accessible Pool Noncompartmental Model

- Parameters (IV bolus and infusion)
 - Mean residence time
 - Clearance rate
 - Volume of distribution
- Estimating the parameters from data
- Additional assumption:
 - Constancy of kinetic distribution parameters

Mean Residence Time

- The average time that a molecule of drug spends in the system



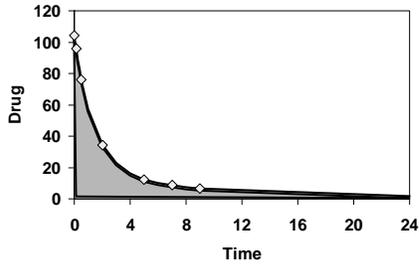
Areas Under The Curve

- AUMC
 - Area Under the Moment Curve
- AUC
 - Area Under the Curve
- MRT
 - “Normalized” AUMC (units = time)

$$MRT = \frac{\int_0^{+\infty} tC(t)dt}{\int_0^{+\infty} C(t)dt} = \frac{AUMC}{AUC}$$

What Is Needed For MRT?

- Estimates for AUC and AUMC.



What Is Needed For MRT?

- Estimates for AUC and AUMC.

$$AUC = \int_0^{\infty} C(t) dt = \int_0^{t_1} C(t) dt + \int_{t_1}^{t_n} C(t) dt + \int_{t_n}^{\infty} C(t) dt$$

$$AUMC = \int_0^{\infty} t \cdot C(t) dt = \int_0^{t_1} t \cdot C(t) dt + \int_{t_1}^{t_n} t \cdot C(t) dt + \int_{t_n}^{\infty} t \cdot C(t) dt$$

- They require extrapolations beyond the time frame of the experiment
- Thus, this method is not model independent as often claimed.

Estimating AUC And AUMC Using Sums Of Exponentials

$$AUC = \int_0^{\infty} C(t) dt = \int_0^{t_1} C(t) dt + \int_{t_1}^{t_n} C(t) dt + \int_{t_n}^{\infty} C(t) dt$$

$$AUMC = \int_0^{\infty} t \cdot C(t) dt = \int_0^{t_1} t \cdot C(t) dt + \int_{t_1}^{t_n} t \cdot C(t) dt + \int_{t_n}^{\infty} t \cdot C(t) dt$$

$$C(t) = A_1 e^{-\lambda_1 t} + \dots + A_n e^{-\lambda_n t}$$

Bolus IV Injection

Formulas can be extended to other administration modes

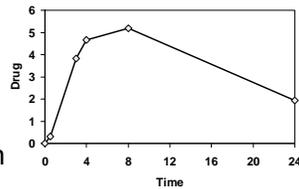
$$AUC = \int_0^{\infty} C(t)dt = \frac{A_1}{\lambda_1} + \dots + \frac{A_n}{\lambda_n}$$

$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \frac{A_1}{\lambda_1^2} + \dots + \frac{A_n}{\lambda_n^2}$$

$$C(0) = A_1 + \dots + A_n$$

Estimating AUC And AUMC Using Other Methods

- Trapezoidal
- Log-trapezoidal
- Combinations
- Other
- Role of extrapolation



The Integrals

- These other methods provide formulas for the integrals between t_1 and t_n leaving it up to the researcher to extrapolate to time zero and time infinity.

$$AUC = \int_0^{\infty} C(t)dt = \int_0^{t_1} C(t)dt + \int_{t_1}^{t_n} C(t)dt + \int_{t_n}^{\infty} C(t)dt$$

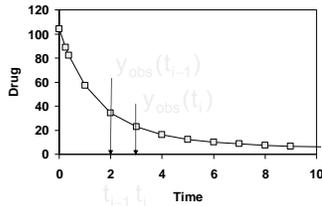
$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^{\infty} t \cdot C(t)dt$$

Trapezoidal Rule

➤ For every time $t_i, i = 1, \dots, n$

$$AUC_{i-1}^i = \frac{1}{2} [y_{\text{obs}}(t_i) + y_{\text{obs}}(t_{i-1})](t_i - t_{i-1})$$

$$AUMC_{i-1}^i = \frac{1}{2} [t_i \cdot y_{\text{obs}}(t_i) + t_{i-1} \cdot y_{\text{obs}}(t_{i-1})](t_i - t_{i-1})$$



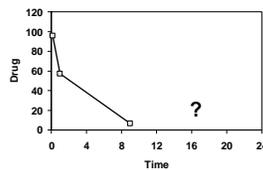
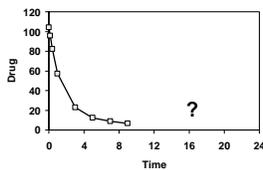
Log-trapezoidal Rule

➤ For every time $t_i, i = 1, \dots, n$

$$AUC_{i-1}^i = \frac{1}{\ln\left(\frac{y_{\text{obs}}(t_i)}{y_{\text{obs}}(t_{i-1})}\right)} [y_{\text{obs}}(t_i) + y_{\text{obs}}(t_{i-1})](t_i - t_{i-1})$$

$$AUMC_{i-1}^i = \frac{1}{\ln\left(\frac{y_{\text{obs}}(t_i)}{y_{\text{obs}}(t_{i-1})}\right)} [t_i \cdot y_{\text{obs}}(t_i) + t_{i-1} \cdot y_{\text{obs}}(t_{i-1})](t_i - t_{i-1})$$

Trapezoidal Rule Potential Pitfalls



- As the number of samples decreases, the interpolation may not be accurate (depends on the shape of the curve)
- Extrapolation from last measurement necessary

Extrapolating From t_n To Infinity

- Terminal decay is assumed to be a monoexponential
- The corresponding exponent is often called λ_z .
- Half-life of terminal decay can be calculated:

$$t_{z/2} = \ln(2) / \lambda_z$$

Extrapolating From t_n To Infinity

From last data point:

$$AUC_{\text{extrap-dat}} = \int_{t_n}^{\infty} C(t) dt = \frac{y_{\text{obs}}(t_n)}{\lambda_z}$$

$$AUMC_{\text{extrap-dat}} = \int_{t_n}^{\infty} t \cdot C(t) dt = \frac{t_n \cdot y_{\text{obs}}(t_n)}{\lambda_z} + \frac{y_{\text{obs}}(t_n)}{\lambda_z^2}$$

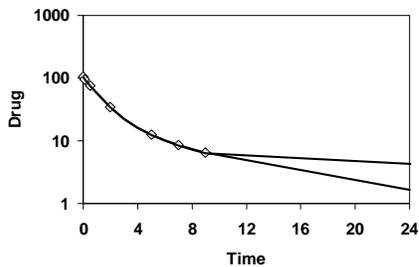
From last calculated value:

$$AUC_{\text{extrap-calc}} = \int_{t_n}^{\infty} C(t) dt = \frac{A_z e^{-\lambda_z t_n}}{\lambda_z}$$

$$AUMC_{\text{extrap-calc}} = \int_{t_n}^{\infty} t \cdot C(t) dt = \frac{t_n \cdot A_z e^{-\lambda_z t_n}}{\lambda_z} + \frac{A_z e^{-\lambda_z t_n}}{\lambda_z^2}$$

Extrapolating From t_n To Infinity

- Extrapolating function crucial



Estimating The Integrals

- To estimate the integrals, one sums up the individual components.

$$AUC = \int_0^{\infty} C(t) dt = \int_0^{t_1} C(t) dt + \int_{t_1}^{t_n} C(t) dt + \int_{t_n}^{\infty} C(t) dt$$

$$AUMC = \int_0^{\infty} t \cdot C(t) dt = \int_0^{t_1} t \cdot C(t) dt + \int_{t_1}^{t_n} t \cdot C(t) dt + \int_{t_n}^{\infty} t \cdot C(t) dt$$

Advantages Of Using Function Extrapolation (Exponentials)

- Extrapolation is automatically done as part of the data fitting
- Statistical information for all parameters (e.g. their standard errors) calculated
- There is a natural connection with the solution of linear, constant coefficient compartmental models
- Software is available

Clearance Rate

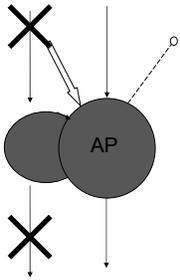
- The volume of blood cleared per unit time, relative to the drug

$$CL = \frac{\text{Elimination rate}}{\text{Concentration in blood}}$$

- It can be shown that

$$CL = \frac{\text{DrugDose}}{AUC}$$

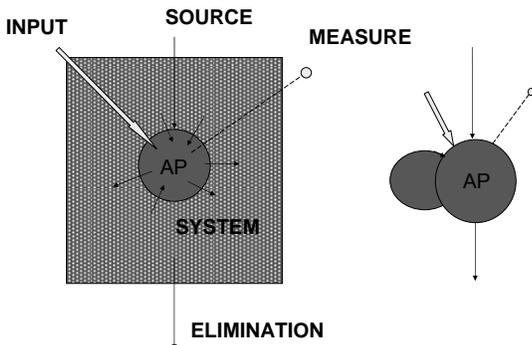
Remember Our Assumptions



- If these are not verified the estimates will be incorrect
- In addition, this approach cannot straightforwardly handle nonlinearities in the data (time-varying rates, saturation processes, etc.)

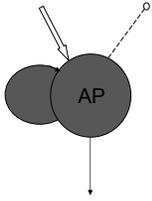
The Compartmental Model

Single Accessible Pool

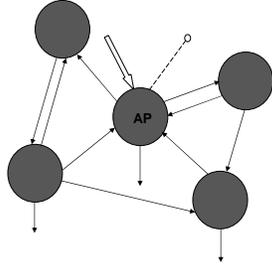


Single Accessible Pool Models

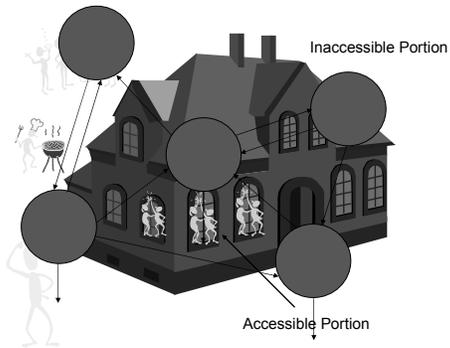
➤ Noncompartmental



➤ Compartmental



A Model Of The System



Compartmental Model

➤ Compartment

- Instantaneously well-mixed
- Kinetically homogeneous

➤ Compartmental model

- Finite number of compartments
- Specifically connected
- Specific input and output

Kinetics And The Compartmental Model

➤ Time and space

$$\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}, \frac{\partial}{\partial t}$$

→ $X(x, y, z, t)$

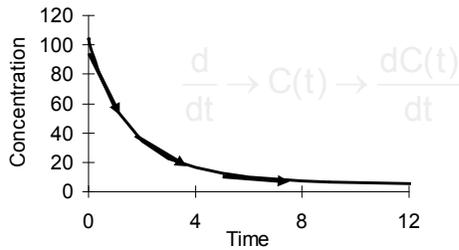
$$\rightarrow \frac{\partial X(x, y, z, t)}{\partial x}, \frac{\partial X(x, y, z, t)}{\partial y}, \frac{\partial X(x, y, z, t)}{\partial z}, \frac{\partial X(x, y, z, t)}{\partial t}$$

➤ Time

$$\frac{d}{dt} \rightarrow X(t) \rightarrow \frac{dX(t)}{dt}$$

Demystifying Differential Equations

➤ It is all about modeling *rates of change*, i.e. *slopes*, or *derivatives*:



➤ Rates of change may be constant or not

Ingredients Of Model Building

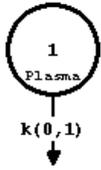
➤ Model of the system

- Independent of experiment design
- Principal components of the biological system

➤ Experimental design

- Two parts:
 - Input function (dose, shape, protocol)
 - Measurement function (sampling, location)

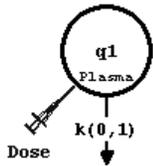
Single Compartment Model



$$\frac{dq_1(t)}{dt} = -k(0,1)q_1(t)$$

- > The *rate of change* of the amount in the compartment, $q_1(t)$, is equal to what enters the compartment (inputs or initial conditions), minus what leaves the compartment, a quantity proportional to $q_1(t)$
- > $k(0,1)$ is a *rate constant*

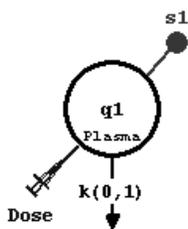
Experiment Design Modeling Input Sites



$$\frac{dq_1(t)}{dt} = -k(0,1)q_1(t) + \text{Dose}(t)$$

- > The *rate of change* of the amount in the compartment, $q_1(t)$, is equal to what enters the compartment (Dose), minus what leaves the compartment, a quantity proportional to $q_1(t)$
- > $\text{Dose}(t)$ can be any function of time

Experiment Design Modeling Measurement Sites

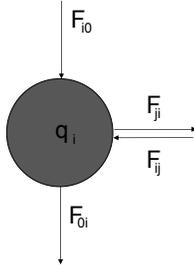


$$s1(t) = \frac{q_1(t)}{V}$$

- > The measurement (sample) $s1$ does not subtract mass or perturb the system
- > The measurement equation $s1$ links q_1 with the experiment, thus preserving the units of differential equations and data (e.g. q_1 is mass, the measurement is concentration)
 $\Rightarrow s1 = q_1 / V$
- > V = volume of distribution of compartment 1

Notation

- The fluxes F_{ij} (from j to i) describe material transport in units of mass per unit time



The Compartmental Fluxes (F_{ij})

- Describe movement among, into or out of a compartment
- A composite of metabolic activity
 - transport
 - biochemical transformation
 - both
- Similar (compatible) time frame

A Proportional Model For The Compartmental Fluxes

- q = compartmental masses
- p = (unknown) system parameters
- k_{ji} = a (nonlinear) function specific to the transfer from i to j

$$F_{ji}(q, p, t) = k_{ji}(q, p, t) \cdot q_i(t)$$

(ref: see Jacquez and Simon)

The Fractional Coefficients (k_{ij})

- The fractional coefficients k_{ij} are called fractional transfer functions
- If k_{ij} does not depend on the compartmental masses, then the k_{ij} is called a fractional transfer (or rate) constant.

$$k_{ij}(q, p, t) = k_{ij}$$

Compartmental Models And Systems Of Ordinary Differential Equations

- Good mixing
 - permits writing $q_i(t)$ for the i^{th} compartment.
- Kinetic homogeneity
 - permits connecting compartments via the k_{ij} .

The i^{th} Compartment

Rate of change of q_i

Fractional input from q_j

$$\frac{dq_i}{dt} = - \left(\sum_{j=1}^n k_{ij}(q, p, t) \right) q_i(t) + \sum_{j=1}^n k_{ji}(q, p, t) q_j(t) + F_{i0}$$

Fractional loss of q_i

Input from "outside" (production rates)

Linear, Constant Coefficient Compartmental Models

- All transfer rates k_{ij} are constant.
 - This facilitates the required computations greatly
- Assume “steady state” conditions.
 - Changes in compartmental mass do not affect the values for the transfer rates

The i^{th} Compartment

Rate of change of Q_i

Fractional input from Q_j

$$\frac{dq_i}{dt} = - \left(\sum_{j=1}^n k_{ji} \right) q_i(t) + \sum_{j=1}^n k_{ij} q_j(t) + F_{i0}$$

Fractional loss of Q_i

Input from “outside” (production rates)

The Compartmental Matrix

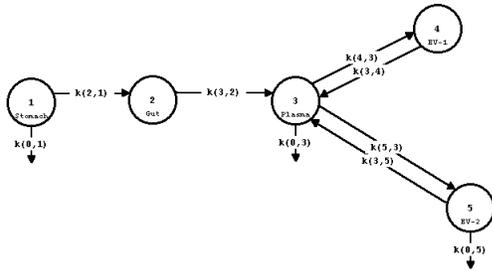
$$k_{ji} = - \left(\sum_{j=1}^n k_{ji} \right)$$

$$K = \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1n} \\ k_{21} & k_{22} & \cdots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \cdots & k_{nn} \end{bmatrix}$$

Compartmental Model

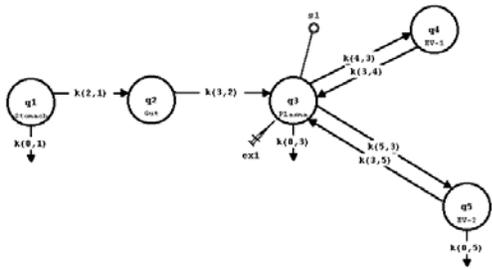
- A detailed postulation of how one believes a system functions.
- The need to perform the same experiment on the model as one did in the laboratory.

Underlying System Model



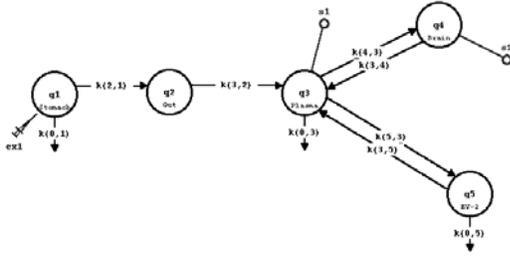
SAAM II software system, <http://depts.washington.edu/saam2>

System Model with Experiment



SAAM II software system, <http://depts.washington.edu/saam2>

System Model with Experiment



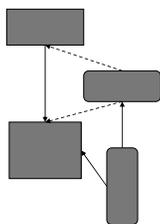
SAAM II software system, <http://depts.washington.edu/saam2>

Experiments

- Need to recreate the laboratory experiment on the model.
- Need to specify input and measurements
- Key: UNITS
 - Input usually in mass, or mass/time
 - Measurement usually concentration
 - Mass per unit volume

Model Of The System?

Reality (Data) Conceptualization (Model) Data Analysis and Simulation

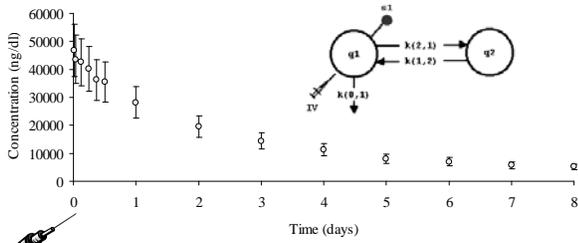


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program optimize
begin model
...
end
    
```



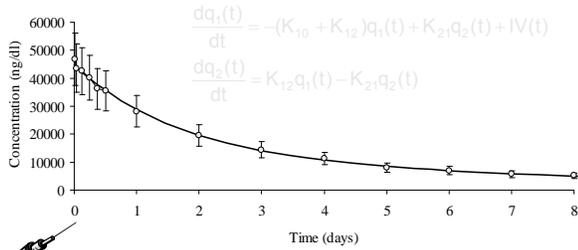
Pharmacokinetic Experiment Collecting System Knowledge



The model starts as a qualitative construct, based on known physiology and further assumptions

Data Analysis

Distilling Parameters From Data



- Qualitative model \Rightarrow quantitative differential equations with parameters of physiological interest
- Parameter estimation (nonlinear regression)

Parameter Estimates

- Model parameters: k_{ij} and volumes
- Pharmacokinetic parameters: volumes, clearance, residence times, etc.
- Reparameterization - changing the parameters from k_{ij} to the PK parameters.

Recovering The PK Parameters From Compartmental Models

- Parameters can be based upon
 - The model primary parameters
 - Differential equation parameters
 - Measurement parameters
 - The compartmental matrix
 - Aggregates of model parameters

Compartmental Model \Rightarrow Exponential

$$\frac{dq_1(t)}{dt} = -k(0,1)q_1(t) + \text{Dose}\delta(t)$$

$$s_1(t) = \frac{q_1(t)}{V}$$

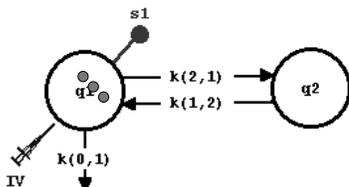
For a pulse input $\delta(t)$

$$q_1(t) = \text{Dose} \cdot e^{-k(0,1)t}$$

$$s_1(t) = \frac{q_1(t)}{V} = \frac{\text{Dose}}{V} e^{-k(0,1)t}$$

$$CL = k(0,1) \times V$$

Compartmental Residence Times



- Rate constants
- Residence times
- Intercompartmental clearances

Parameters Based Upon The Compartmental Matrix

$$K = \begin{bmatrix} k_{11} & k_{12} & \dots & k_{1n} \\ k_{21} & k_{22} & \dots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \dots & k_{nn} \end{bmatrix}$$

Theta, the negative of the inverse of the compartmental matrix, is called the mean residence time matrix.

Parameters Based Upon The Compartmental Matrix

Generalization of Mean Residence Time

θ_{ij} The average time the drug entering compartment j for the first time spends in compartment i before leaving the system.

$\frac{\theta_{ij}}{\theta_{jj}}$, $i \neq j$ The probability that a drug particle in compartment j will eventually pass through compartment i before leaving the system.

Compartmental Models: Advantages

- Can handle nonlinearities
- Provide hypotheses about system structure
- Can aid in experimental design, for example to design dosing regimens
- Can support translational research

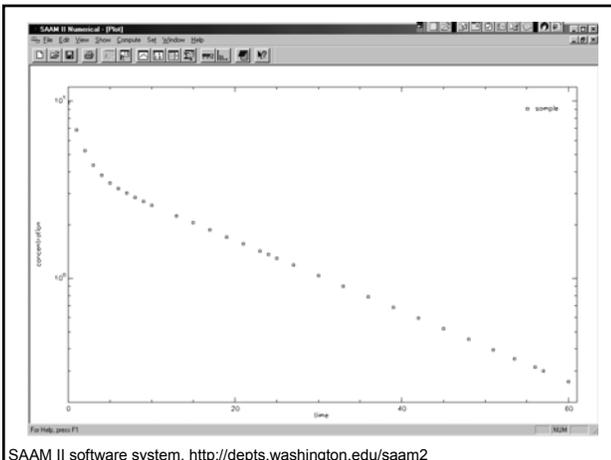
Bias That Can Be Introduced By Noncompartmental Analysis

- Not a single sink
 - = Clearance rate
 - ↓ Mean residence time
 - ↓ Volume of distribution
 - ↑ Fractional clearance
- Not a single sink / not a single source
 - ↓ Clearance rate
 - ↓ Mean residence time
 - ↓ Volume of distribution
 - ↑ Fractional clearance

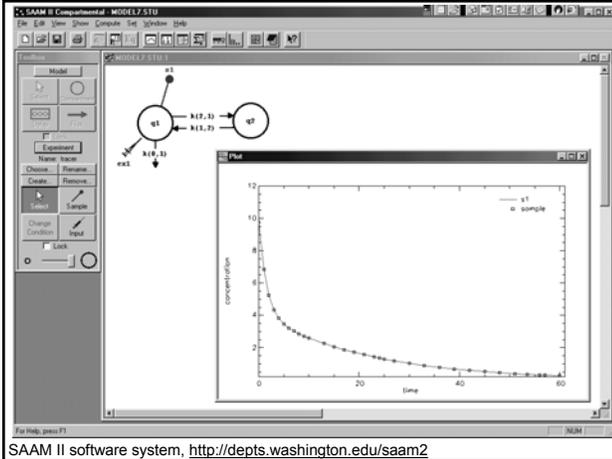
JJ DiStefano III.
Noncompartmental vs compartmental analysis: some bases for choice.
Am J. Physiol. 1982;243:R1-R6

Noncompartmental Versus Compartmental Approaches To PK Analysis: An Example

- Experiment design
 - Bolus injection of 100 mg of a drug into plasma
 - Serial plasma samples taken for 60 hours
- Analysis using:
 - Trapezoidal integration
 - Sums of exponentials
 - Linear compartmental model



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Results

	Trapezoidal Analysis	Sum of Exponentials	Compartmental Model
Volume		10.2 (9%)	10.2 (3%)
Clearance	1.02	1.02 (2%)	1.02 (1%)
MRT	19.5	20.1 (2%)	20.1 (1%)
λ_z	0.0504	0.0458 (3%)	0.0458 (1%)
AUC	97.8	97.9 (2%)	97.9 (1%)
AUMC	1908	1964 (3%)	1964 (1%)

Take Home Message

- To estimate traditional pharmacokinetic parameters, either model is probably adequate when the sampling schedule is dense, provided all assumptions required for noncompartmental analysis are met
- Sparse sampling schedule and nonlinearities may be an issue for noncompartmental analysis
- Noncompartmental models are not predictive
- Best strategy is probably a blend: but, careful about assumptions!

Some References

- JJ DiStefano III. Noncompartmental vs compartmental analysis: some bases for choice. *Am J. Physiol.* 1982;243:R1-R6
- DG Covell et. al. Mean Residence Time. *Math. Biosci.* 1984;72:213-2444
- Jacquez, JA and SP Simon. Qualitative theory of compartmental analysis. *SIAM Review* 1993;35:43-79
- Jacquez, JA. Compartmental Analysis in Biology and Medicine. BioMedware 1996. Ann Arbor, MI.
- Cobelli, C, D Foster and G Toffolo. Tracer Kinetics in Biomedical Research. Kluwer Academic/Plenum Publishers. 2000, New York.
