Noncompartmental vs. Compartmental Approaches to Pharmacokinetic Data Analysis

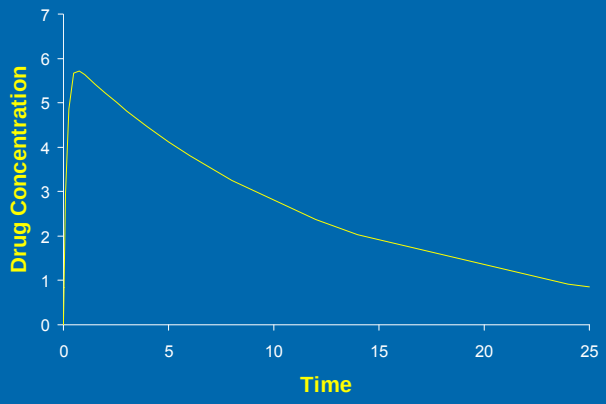
Paolo Vicini, Ph.D.
Pfizer Global Research and Development

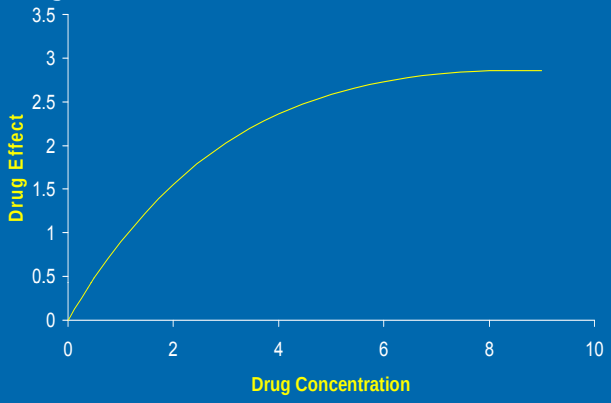
David M. Foster., Ph.D.
University of Washington

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

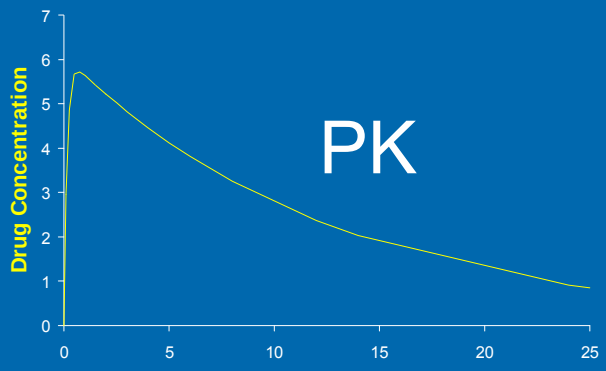


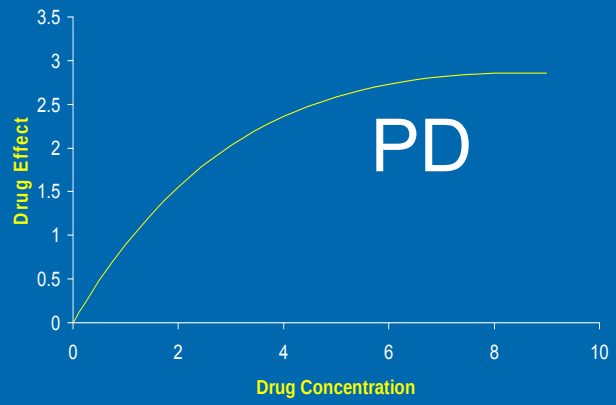


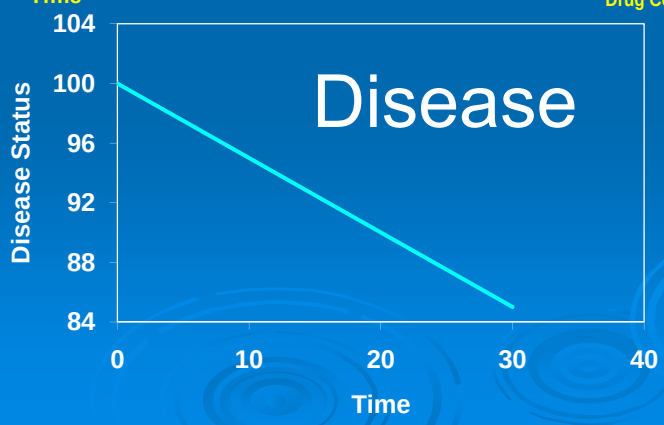
- Pharmacokinetics
- "What the body does to the drug"
- Fairly well known
- Useful to get to the PD

- Pharmacodynamics
- "What the drug does to the body"
- Largely unknown
- Has clinical relevance

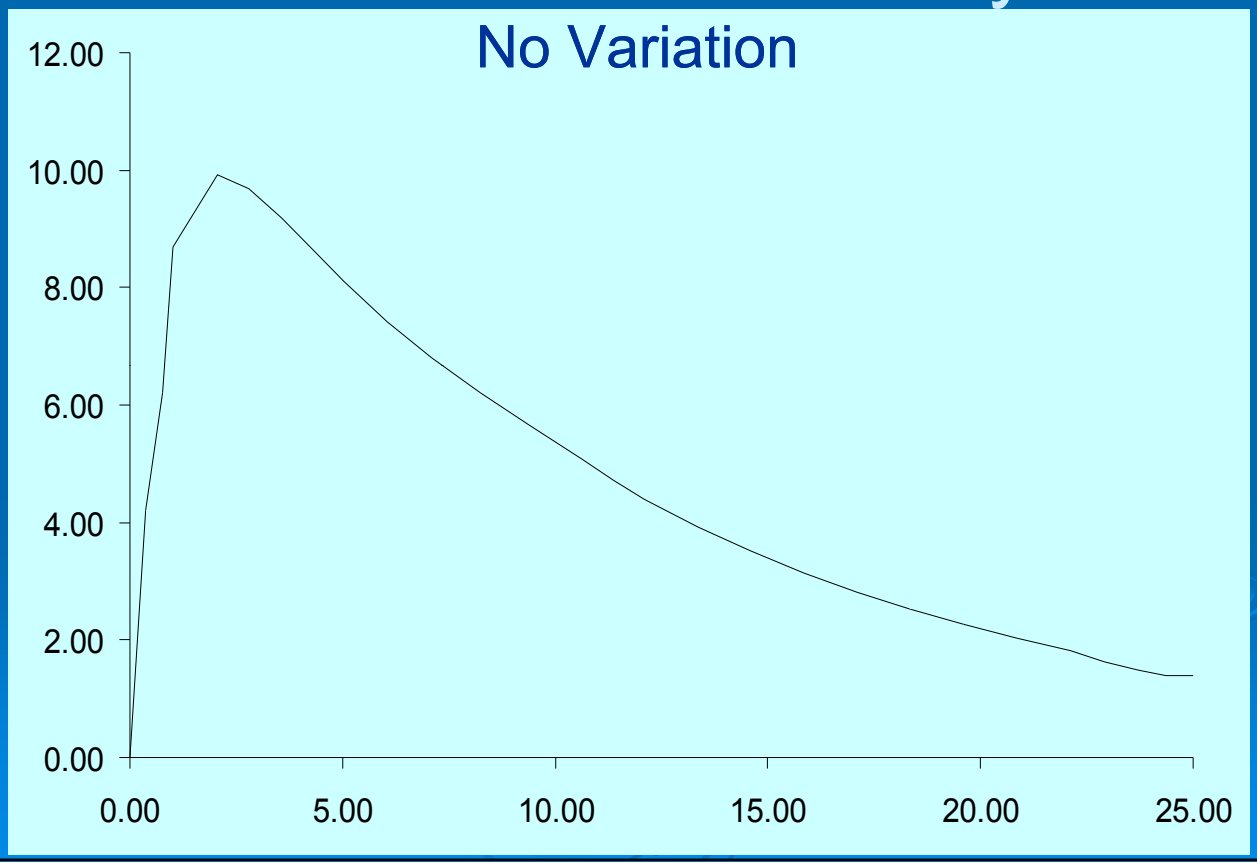
PK/PD/Disease Processes







Hierarchical Variability



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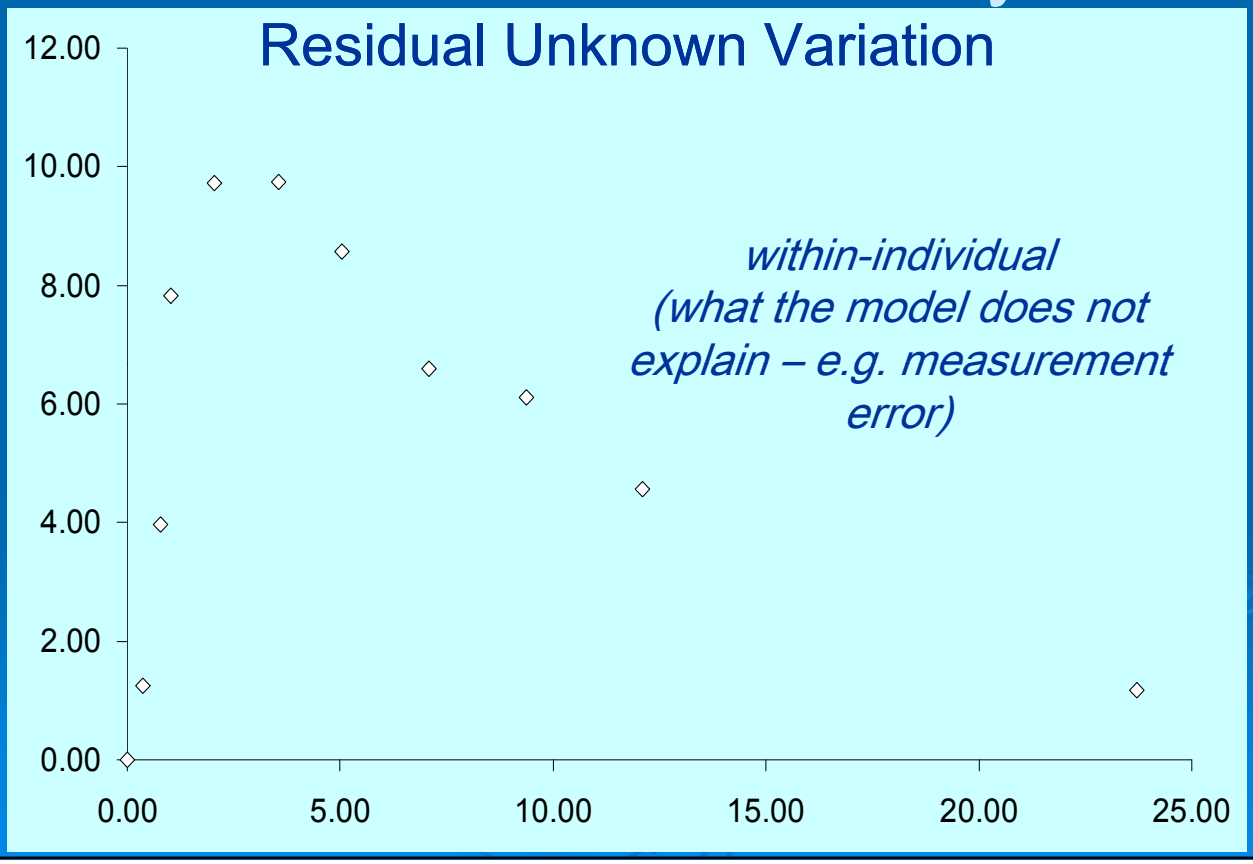
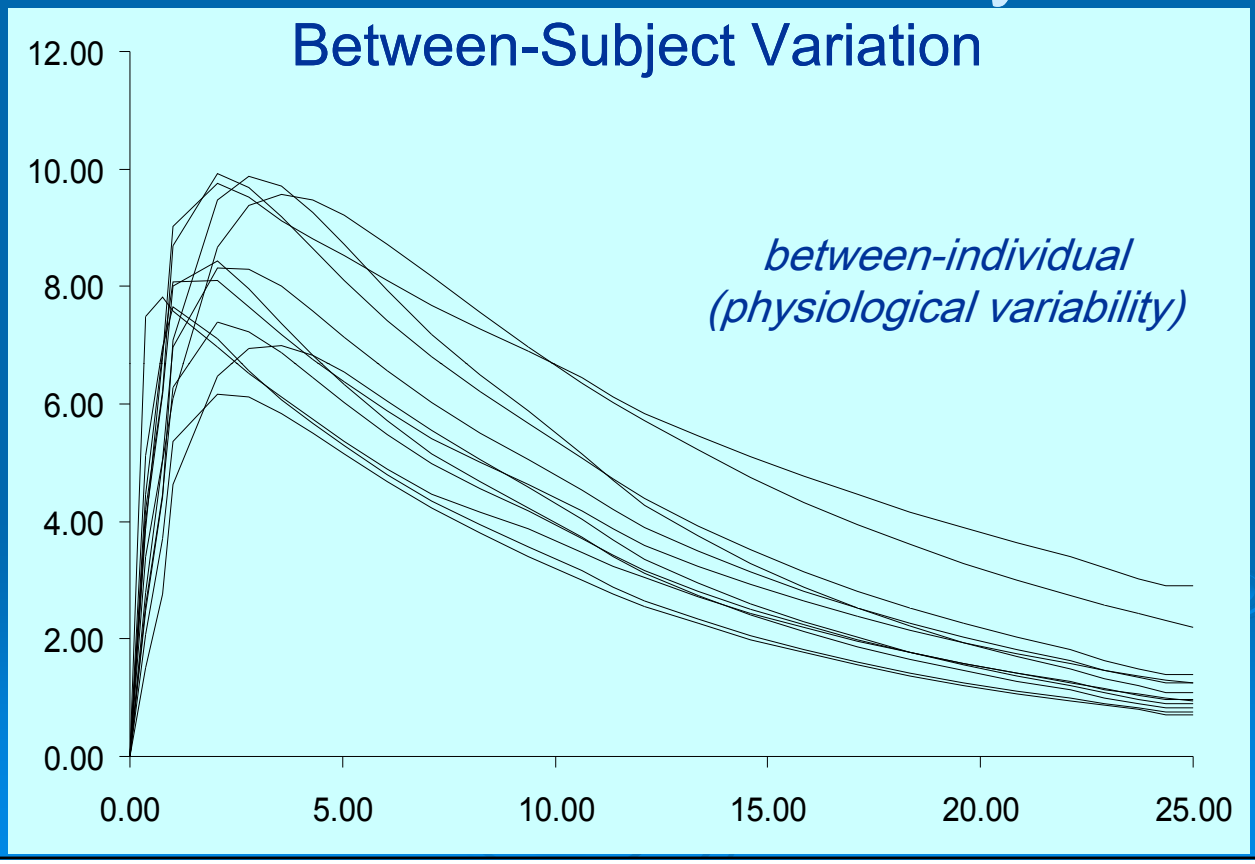
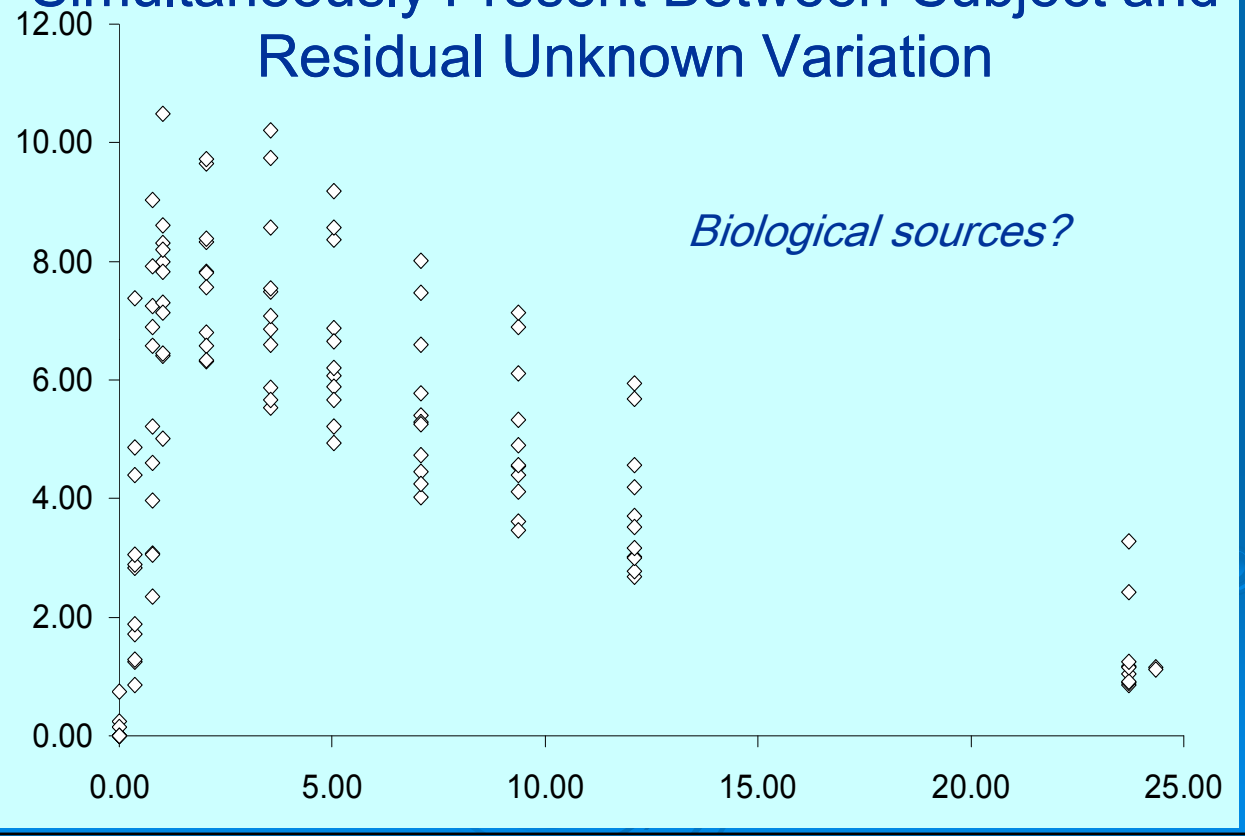


Hierarchical Variability



Hierarchical Variability

Simultaneously Present Between-Subject and 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

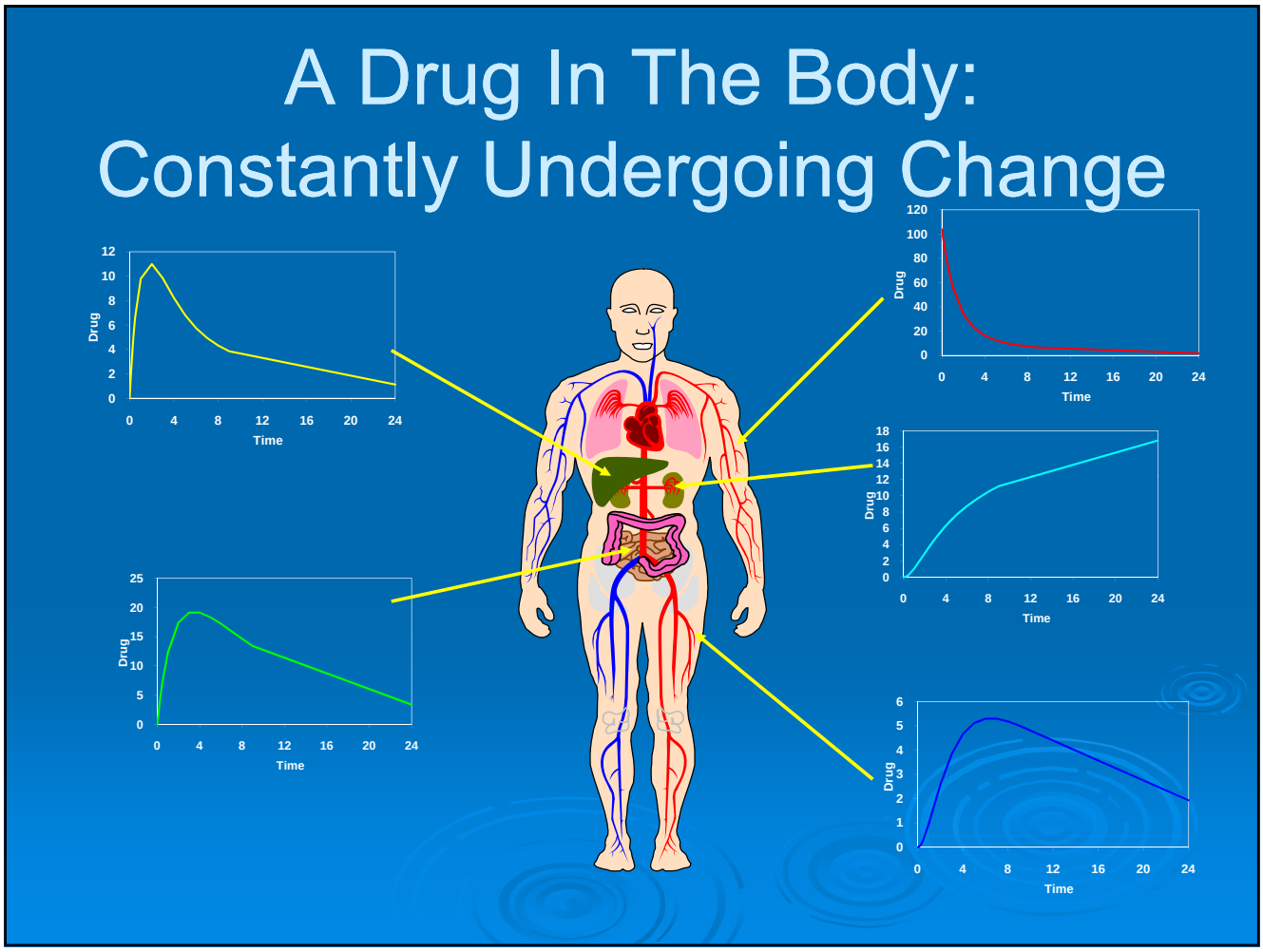
A Drug In The Body: Constantly Undergoing Change

- Absorption
- Transport in the circulation
- Transport across membranes
- Biochemical transformation
- Elimination

→ADME

  - Absorption, Distribution, Metabolism, Excretion

A Drug In The Body: Constantly Undergoing Change

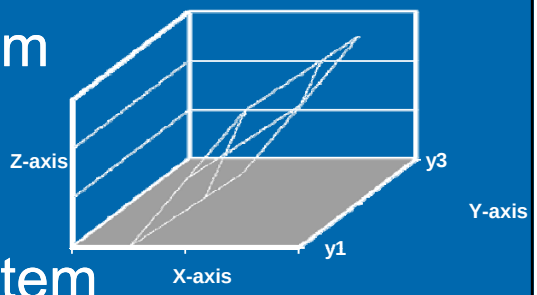


Kinetics
And Pharmacokinetics

- 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.

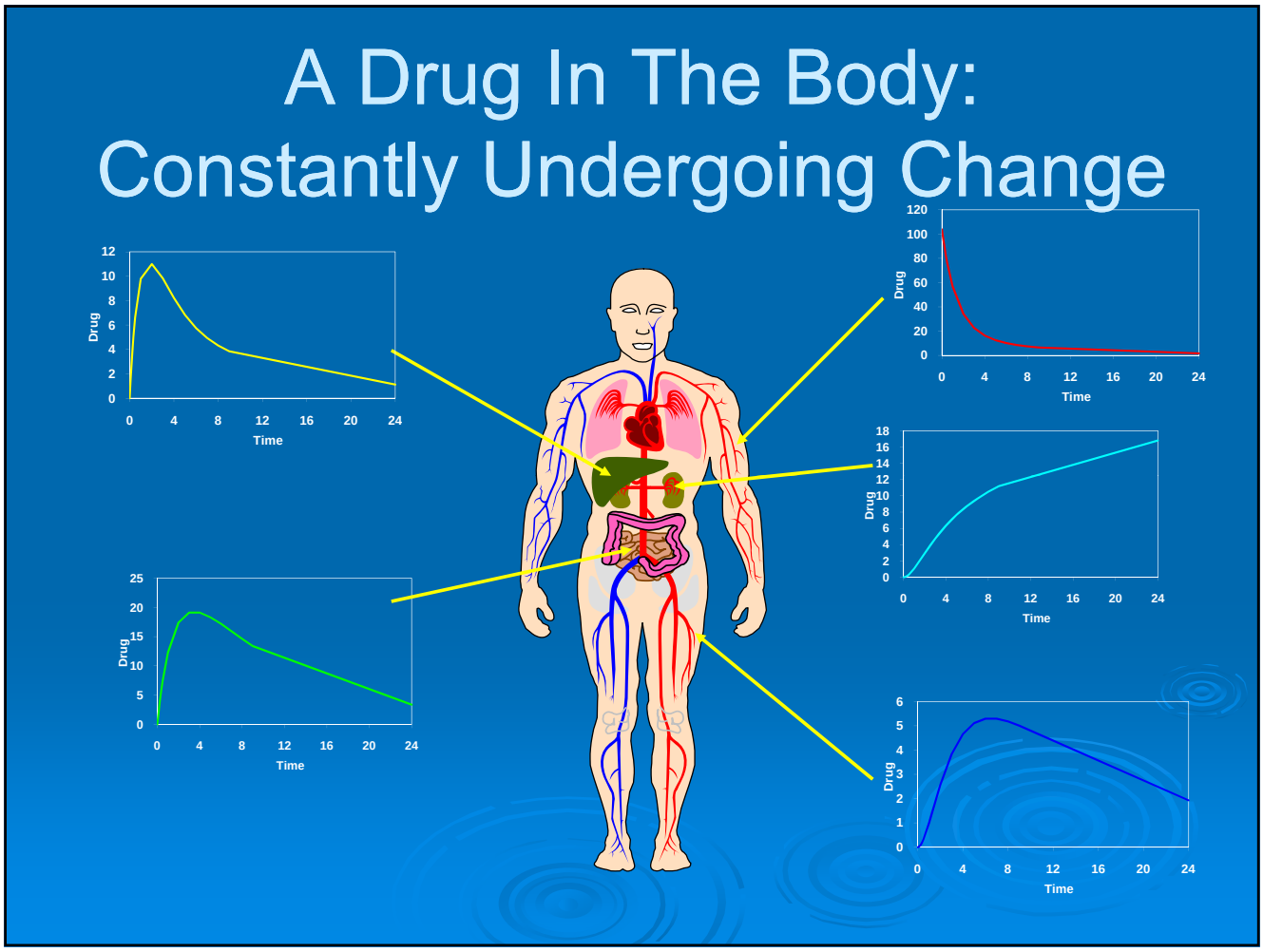
Definition Of Kinetics: Consequences

- Spatial: *Where* in the system
  - Spatial coordinates
  - Key variables: (x, y, z)
- Temporal: *When* in the system
  - Temporal coordinates
  - Key variable: t

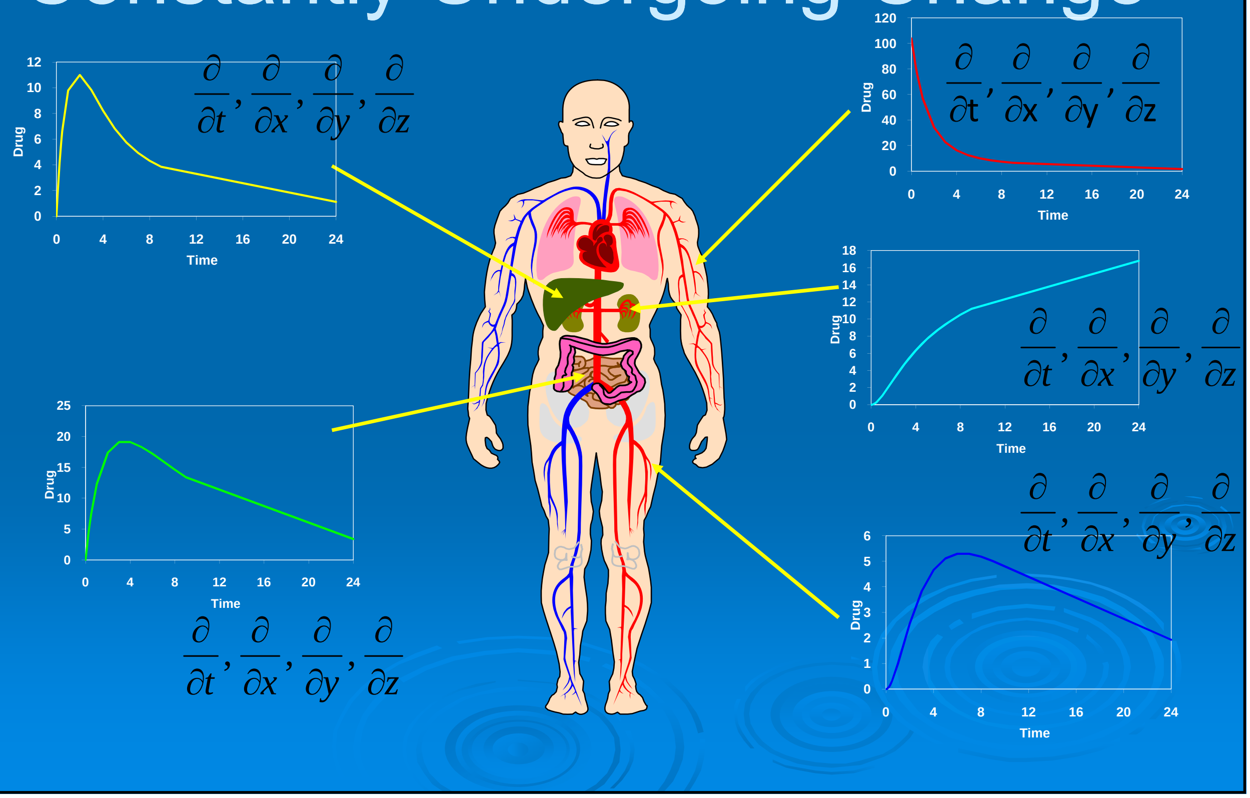


$$\frac{\partial c(x,y,z,t)}{\partial x}, \frac{\partial c(x,y,z,t)}{\partial y}, \frac{\partial c(x,y,z,t)}{\partial z}, \frac{\partial c(x,y,z,t)}{\partial t}$$

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

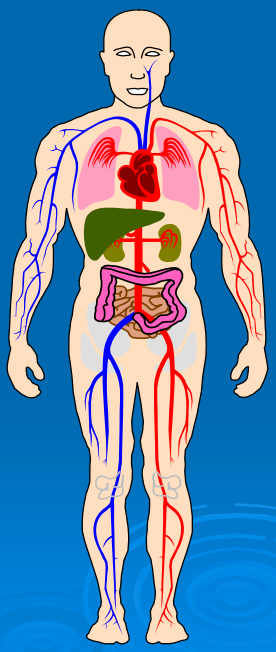
- Reducing the system to a finite number of components
- Lumping processes together based upon time, location or a combination of the two
- Space is not taken directly into account: rather, spatial heterogeneity is modeled through changes that occur in time

Lumped Parameter Models

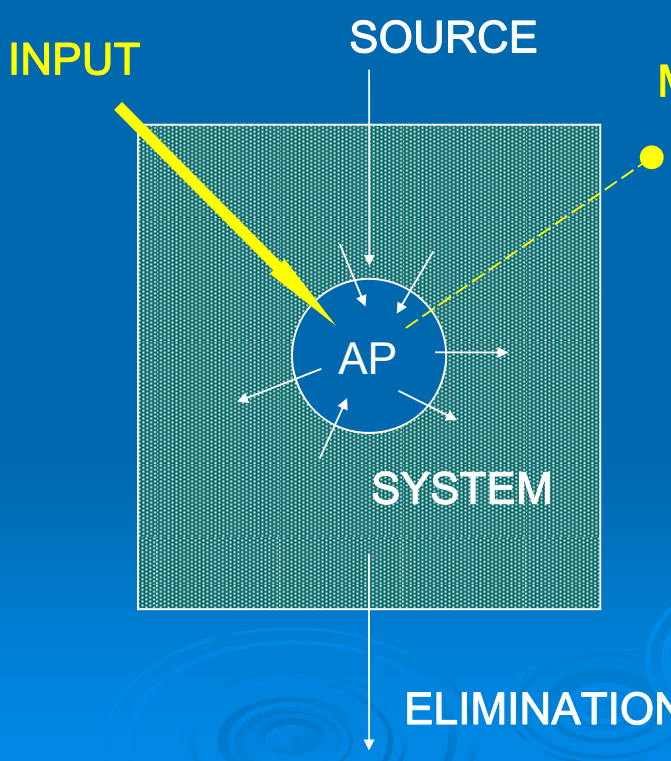
- Models which make the system discrete through a lumping process thus eliminating the need to deal with partial differential equations.
- Classes of such models:
  - Noncompartmental models
    - Based on algebraic equations
  - Compartmental models
    - Based on linear or nonlinear differential equations

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

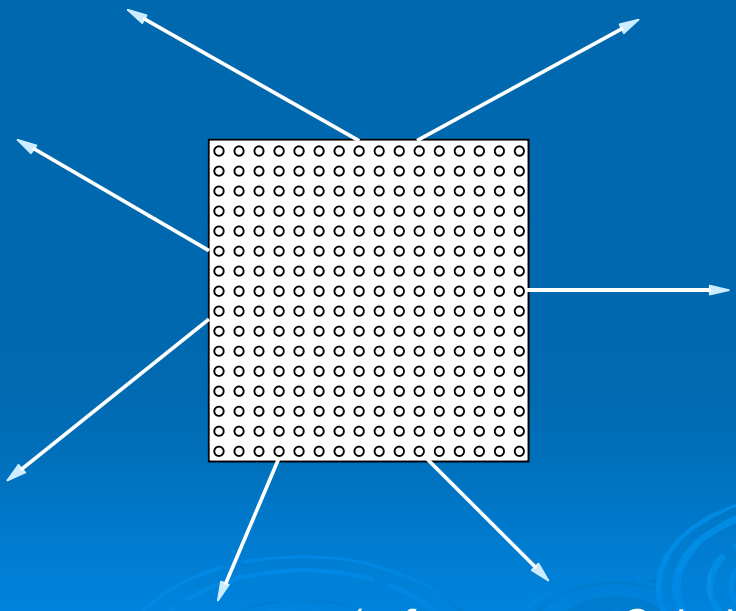


Characteristics Of The Accessible Pool

Kinetically Homogeneous

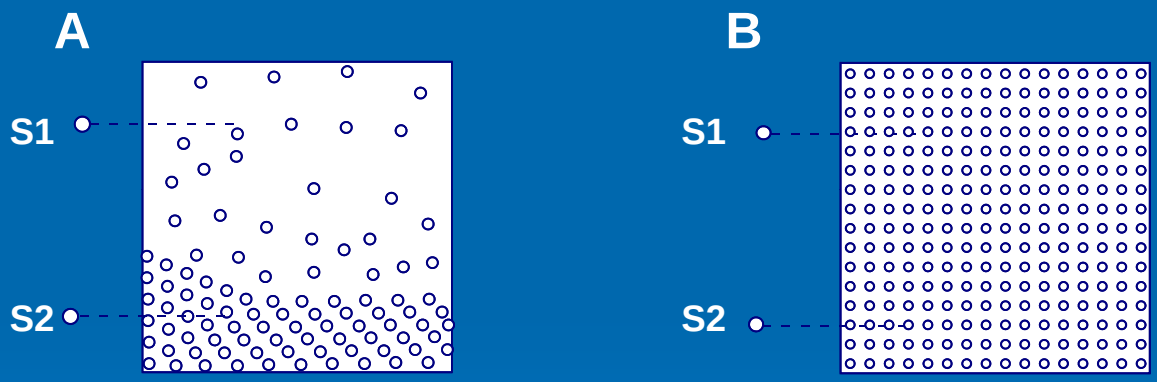
Instantaneously Well-mixed

Accessible Pool
Kinetically Homogeneous



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

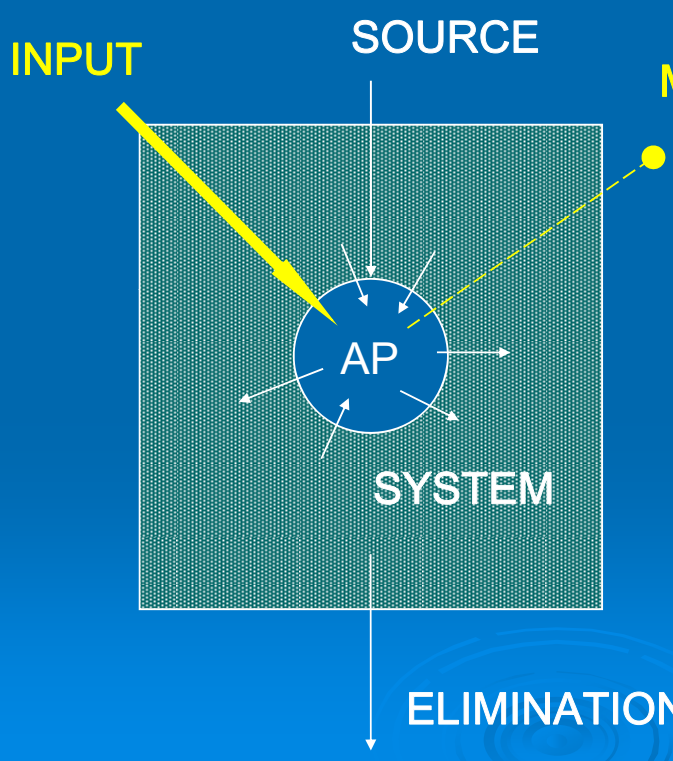
Accessible Pool Instantaneously Well-Mixed

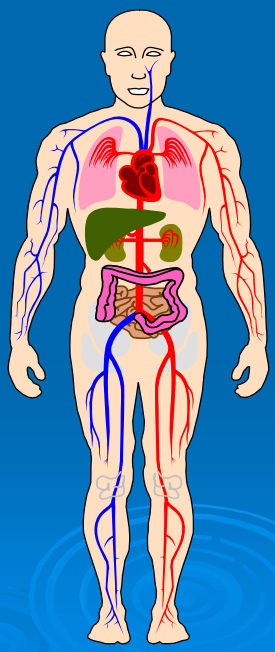


- A = not mixed
- B = well mixed

(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

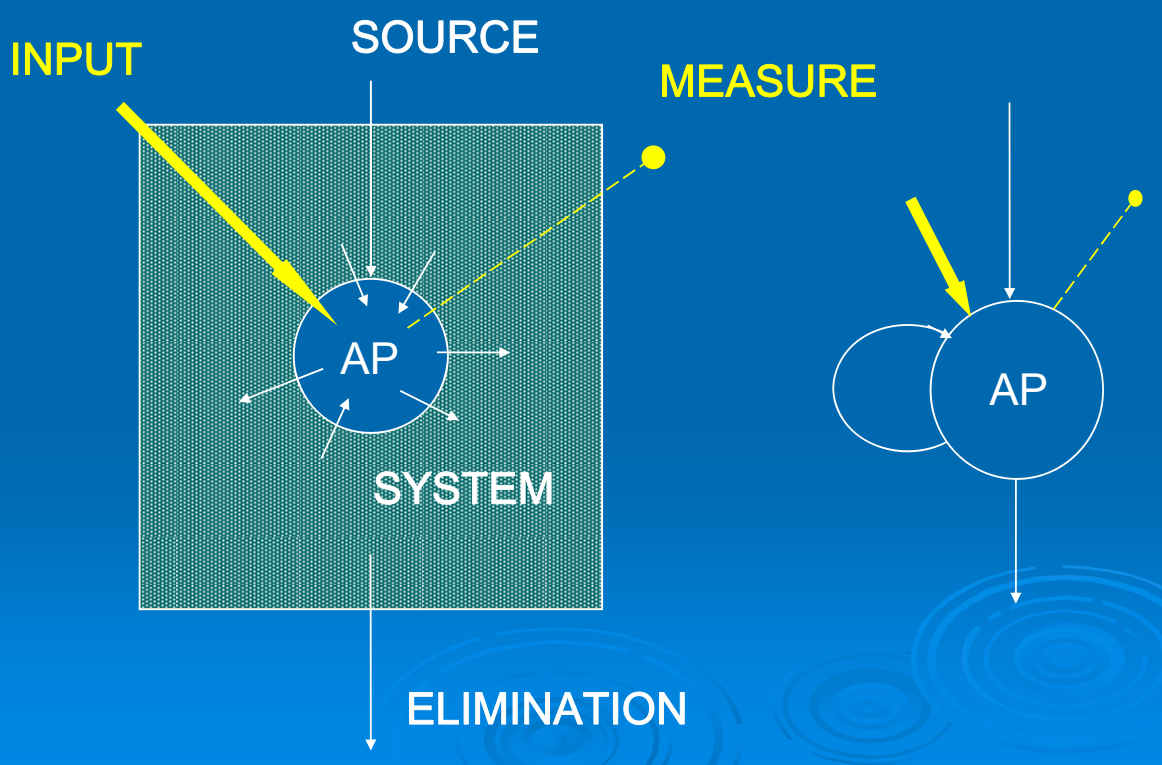
Accessible Pool & System Assumptions → Information

- 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

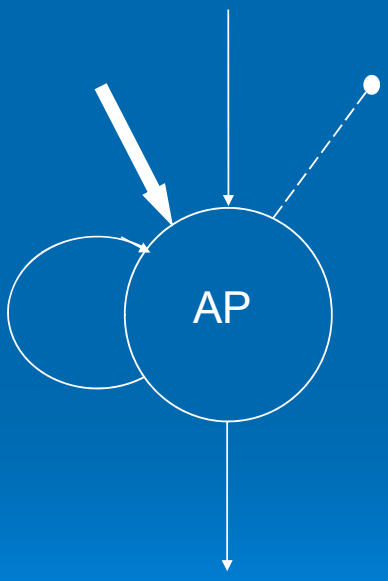
The only difference between the two methods is in how the nonaccessible portion of the system is described

The Noncompartmental Model

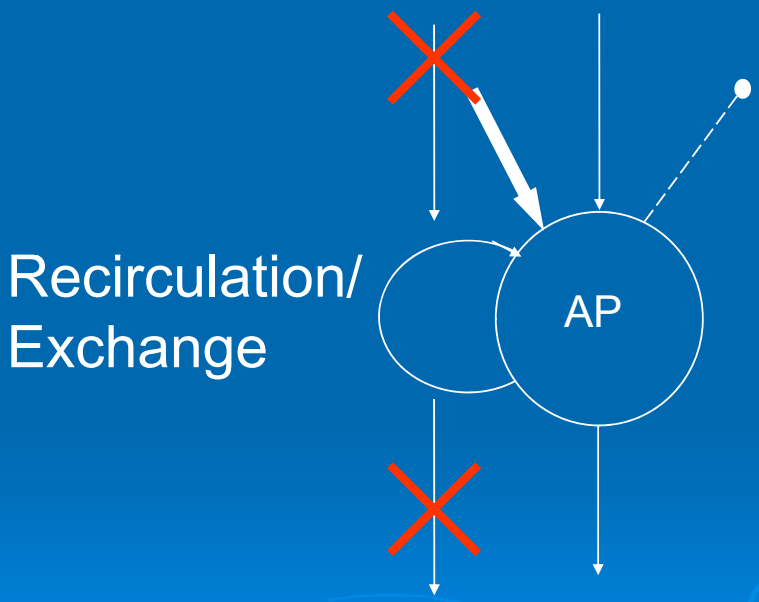


Recirculation-exchange Assumptions

Recirculation/
Exchange



Recirculation-exchange Assumptions

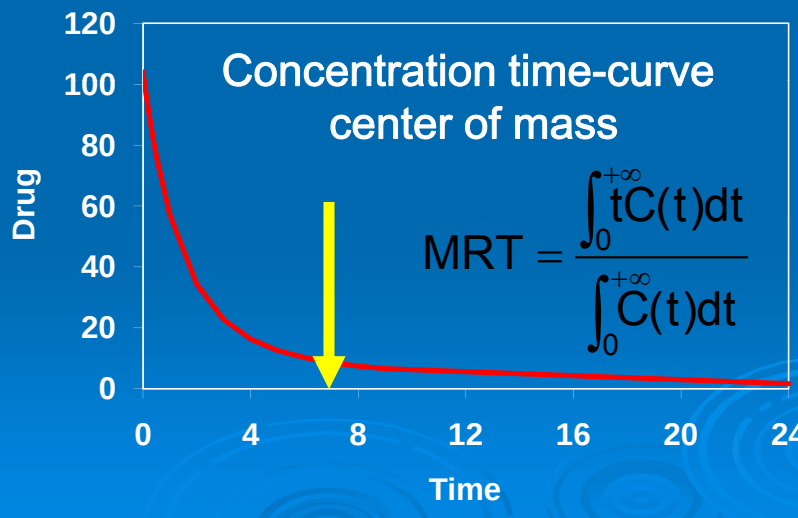


Single Accessible Pool Noncompartmental Model

- 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



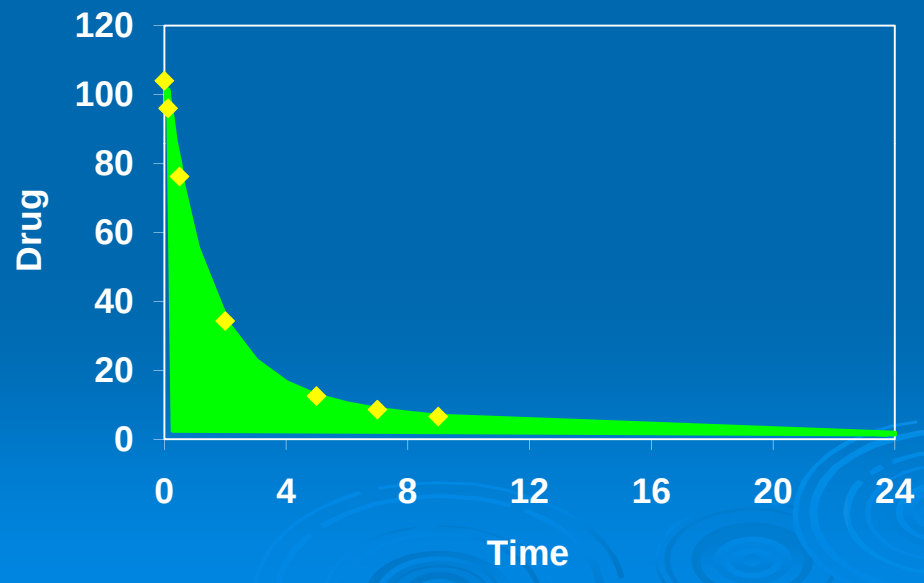
Areas Under The Curve

- 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

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

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

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

Bolus IV Injection

Formulas can be extended to other administration modes

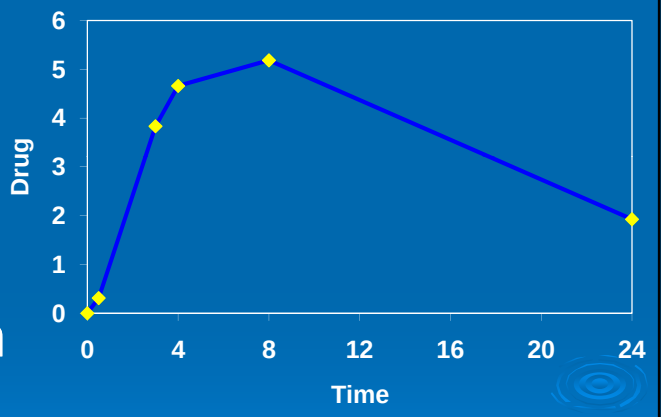
$$AUC = \int_0^\infty C(t)dt = \frac{A_1}{\lambda_1} + \cdots + \frac{A_n}{\lambda_n}$$

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

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

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.

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

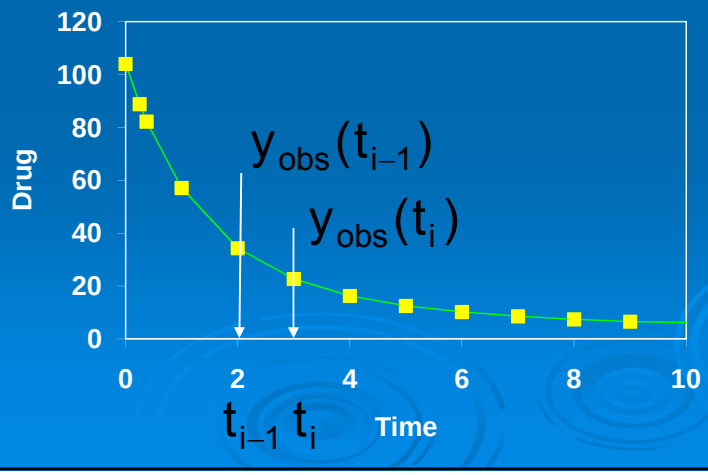
$$AUMC = \int_0^{\infty} t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^{\infty} t \cdot C(t)dt$$

Trapezoidal Rule

- For every time t_i, i = 1, …, n

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

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



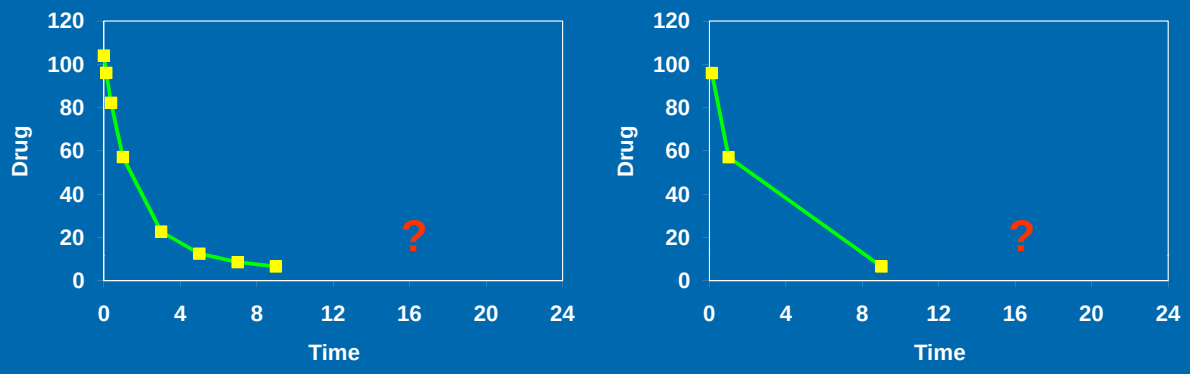
Log-trapezoidal Rule

- For every time t_i, i = 1, …, n

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

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

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:

$$t_{z/1/2} = \ln(2)/ \lambda_z$$

Extrapolating From t_n To Infinity

From last data point:

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

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

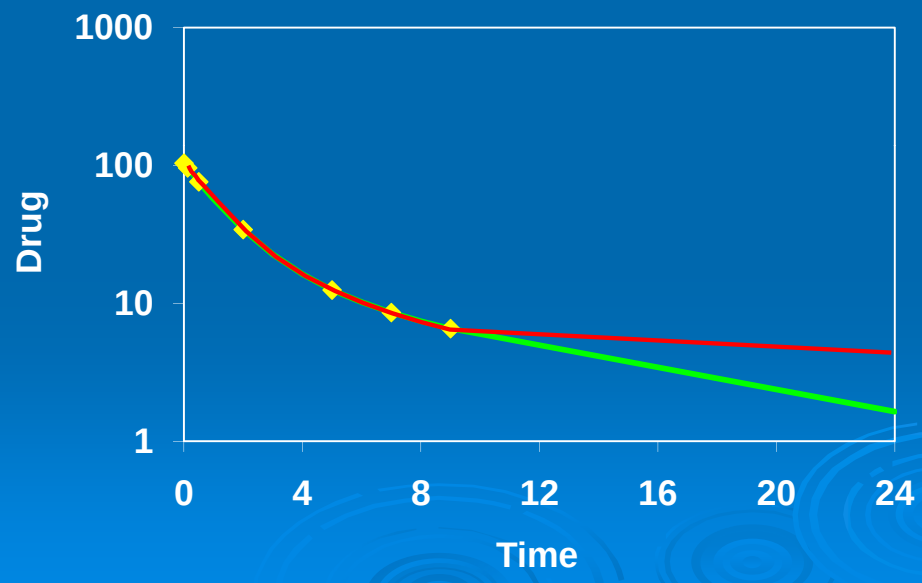
From last calculated value:

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

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

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

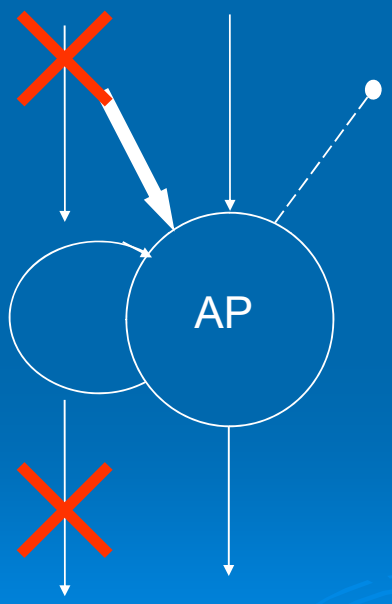
- The volume of blood cleared per unit time, relative to the drug

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

- It can be shown that

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

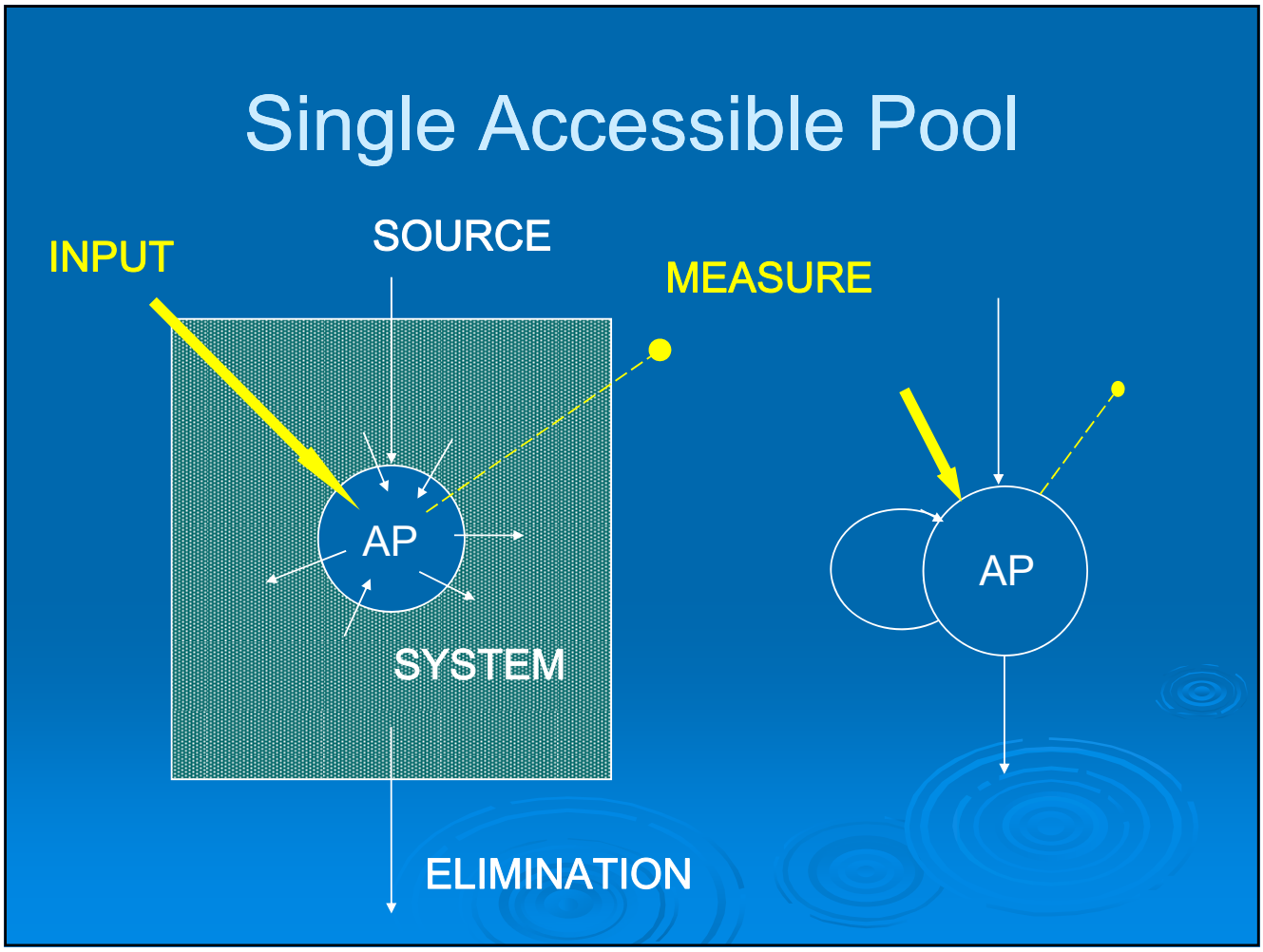
Remember Our Assumptions



- 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.)

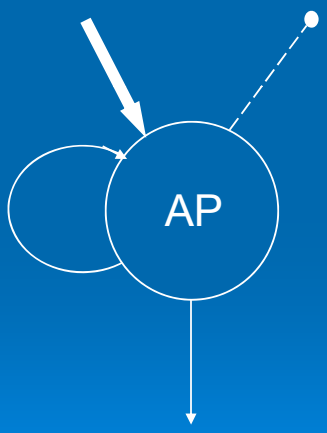
The Compartmental Model

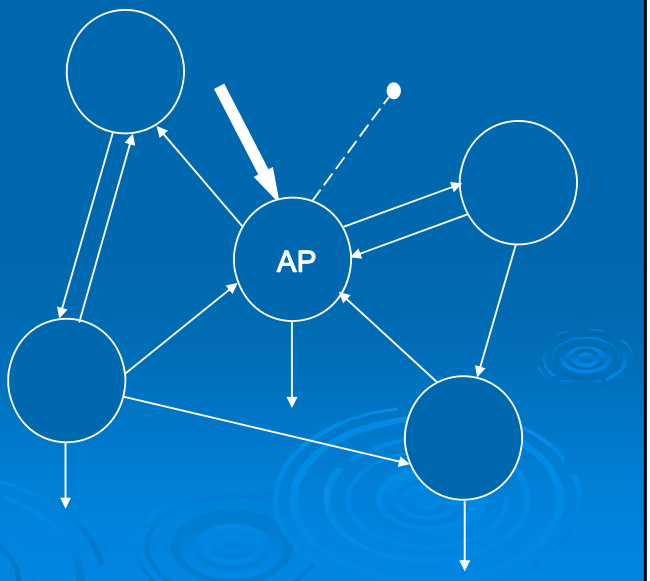
Single Accessible Pool



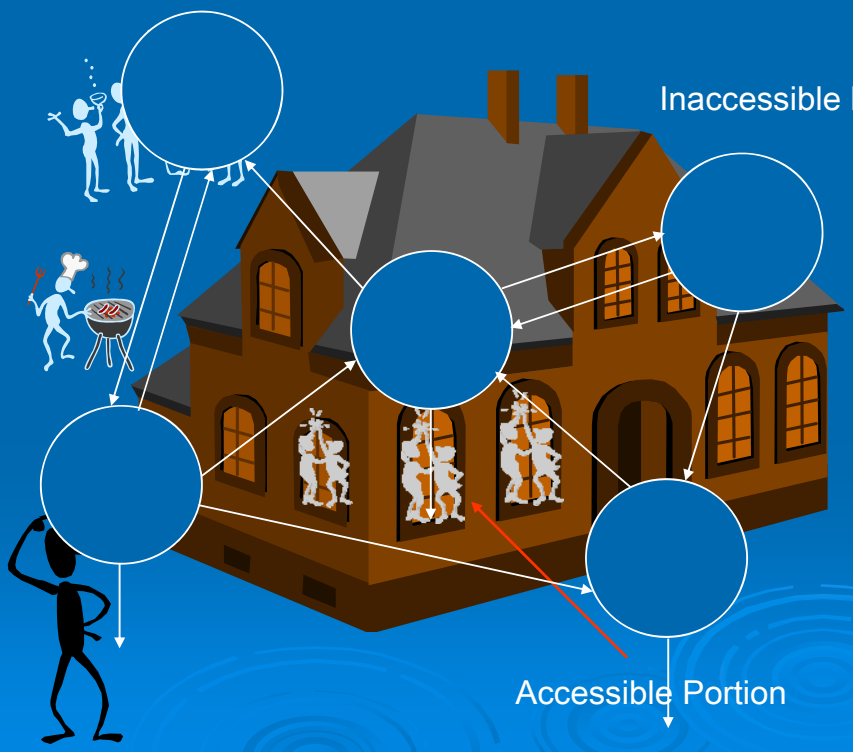
Single Accessible Pool Models

- 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

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

$$\rightarrow X(x, y, z, t)$$

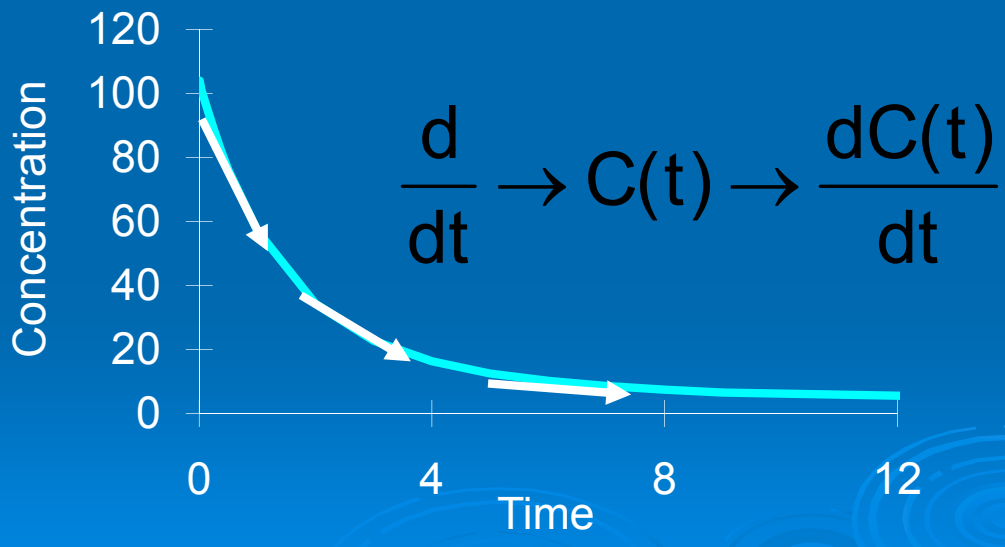
$$\rightarrow \frac{\partial X(x, y, z, t)}{\partial x}, \frac{\partial X(x, y, z, t)}{\partial y}, \frac{\partial X(x, y, z, t)}{\partial z}, \frac{\partial X(x, y, z, t)}{\partial t}$$

- 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*:



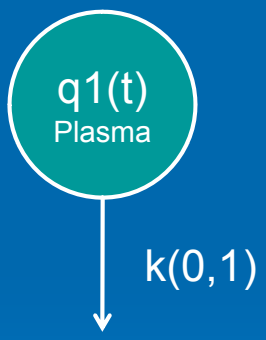
$$\frac{d}{dt} \rightarrow C(t) \rightarrow \frac{dC(t)}{dt}$$

- 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

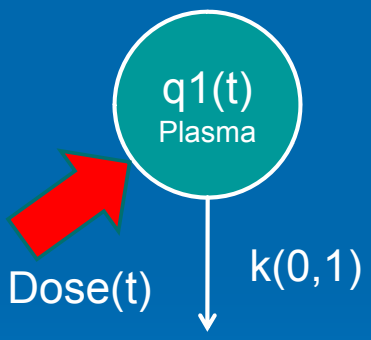


$$\frac{dq_1(t)}{dt} = -k(0,1)q_1(t)$$

- 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

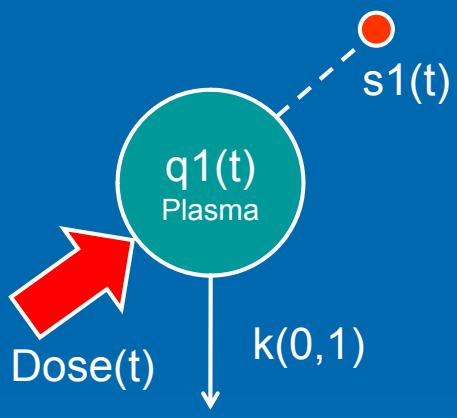


$$\frac{dq_1(t)}{dt} = -k(0,1)q_1(t) + Dose(t)$$

- 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(t)
- Dose(t) can be any function of time

Experiment Design

Modeling Measurement Sites



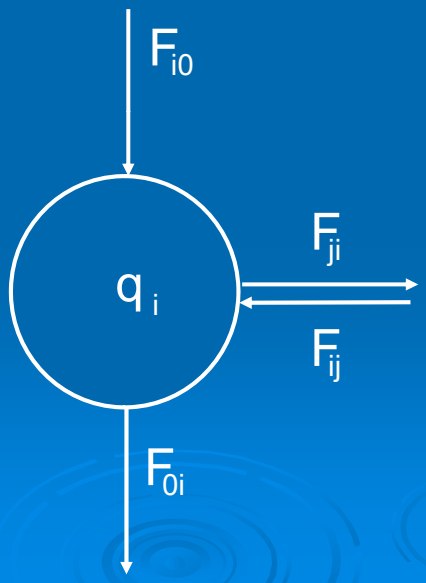
$$s1(t) = \frac{q_1(t)}{V}$$

- 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 $F_{ij\ (\text{from j to i})}$ 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)

Nonlinear Kinetics Example

- Remember the one-compartment model:

$$\frac{dq1(t)}{dt} = -k(0,1)q1(t) + Dose(t)$$

$$s1(t) = \frac{q1(t)}{V}$$

- What if we had a concentration-dependent drug elimination rate?

Nonlinear Kinetics: Michaelis-Menten

- Michaelis-Menten kinetics:

$$\frac{dq1(t)}{dt} = -\frac{Vm}{Km + c(t)} q1(t) + Dose(t)$$

$$s1(t) = \frac{q1(t)}{V}$$

- Vm = maximal metabolic rate
- Km = Michaelis-Menten constant

Linear vs. Nonlinear Kinetics

- If Km >> c(t) then:

$$\frac{dq1(t)}{dt} \cong -\frac{Vm}{Km} q1(t) + Dose(t)$$

$$s1(t) = \frac{q1(t)}{V}$$

- The concentration declines at a rate proportional to it (*first-order kinetics*)
- This is true at *low* concentrations (w.r.t. Km)

Linear vs. Nonlinear Kinetics

- If Km << c(t) then:

$$\frac{dq1(t)}{dt} \cong -\frac{Vm}{c(t)} q1(t) + D\delta(t) = -Vm \times v1 + Dose(t)$$

$$s1(t) = \frac{q1(t)}{V}$$

- The concentration declines at a constant rate (*zero-order kinetics*)
- This is true at *high* concentrations (w.r.t. Km)

Tracking Nonlinearities

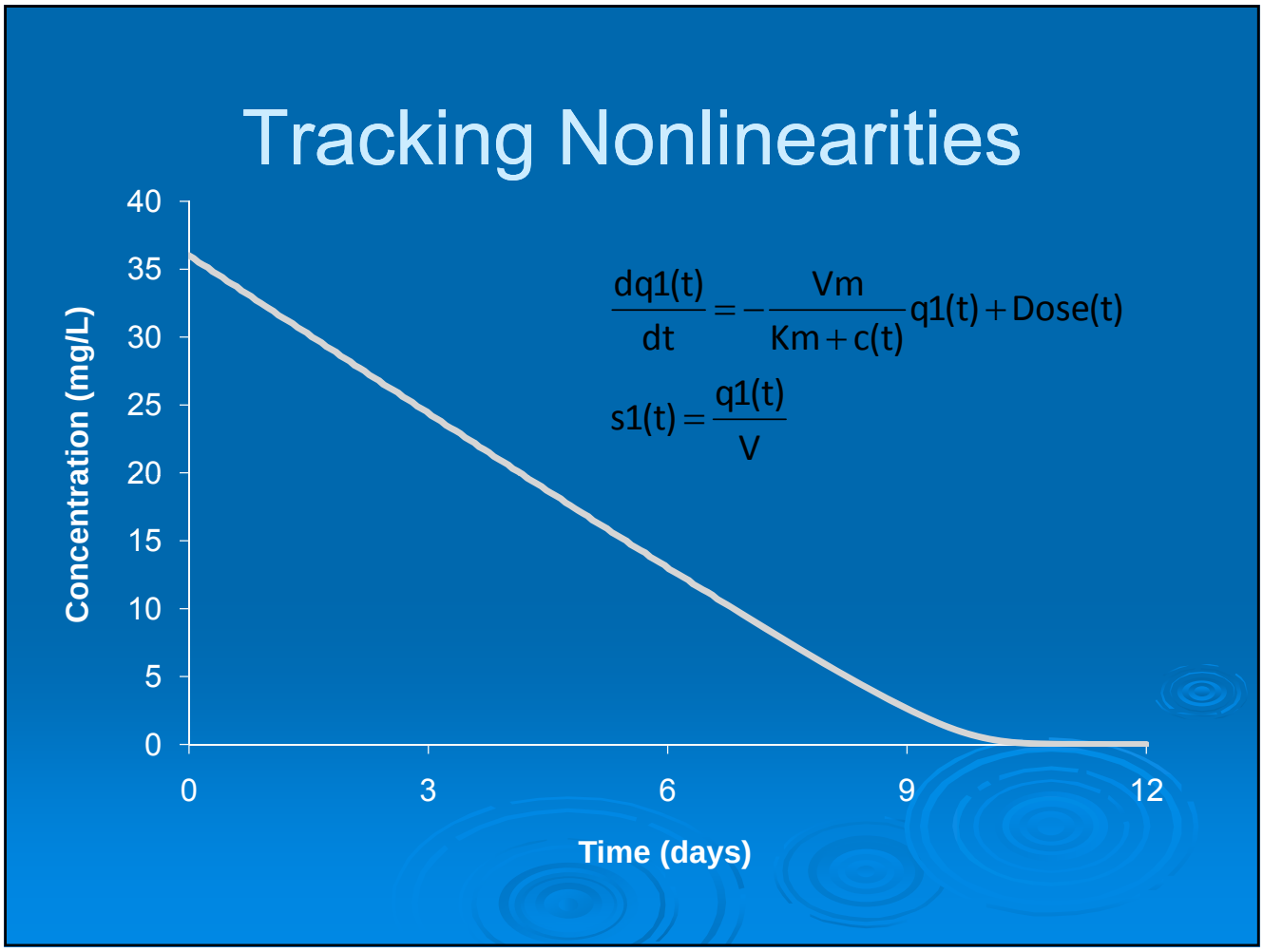
- How to find nonlinear behavior?

$$\frac{dq1(t)}{dt} = -\frac{Vm}{Km + c(t)} q1(t) + Dose(t)$$

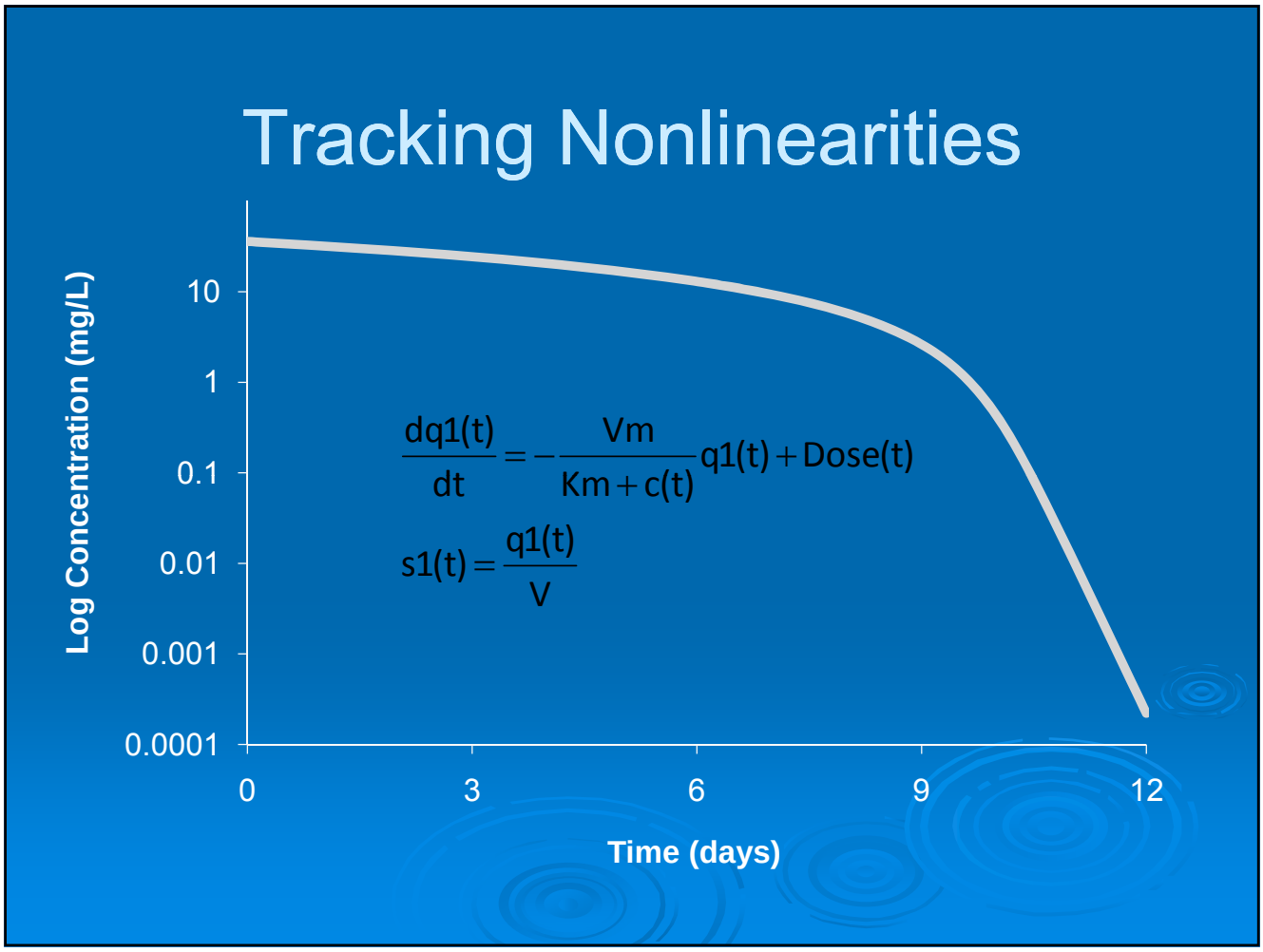
$$s1(t) = \frac{q1(t)}{V}$$

- **Watch**: Simulated concentration time profile for D = 180 mg, Vm = 20 mg/L/hr, Km = 1 mg/L, v1 = 5 L

Tracking Nonlinearities



Tracking Nonlinearities



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 kij 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

$$\frac{dq_i}{dt} = -\left(\sum_{\substack{j=0 \\ j\neq i}}^{n} k_{ji}(q,p,t)\right) q_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}(q,p,t)\, q_j(t) + F_{i0}$$

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

$$\frac{dq_i}{dt} = -\left(\sum_{\substack{j=0 \\ j\neq i}}^{n} k_{ji}\right) q_i(t) + \sum_{\substack{j=1 \\ j\neq i}}^{n} k_{ij}\, q_j(t) + F_{i0}$$

Fractional loss of Q_i

Input from "outside" (production rates)

The Compartmental Matrix

$$k_{ii} = -\left(\sum_{\substack{j=0 \\ j \neq i}}^{n} k_{ji} \right)$$

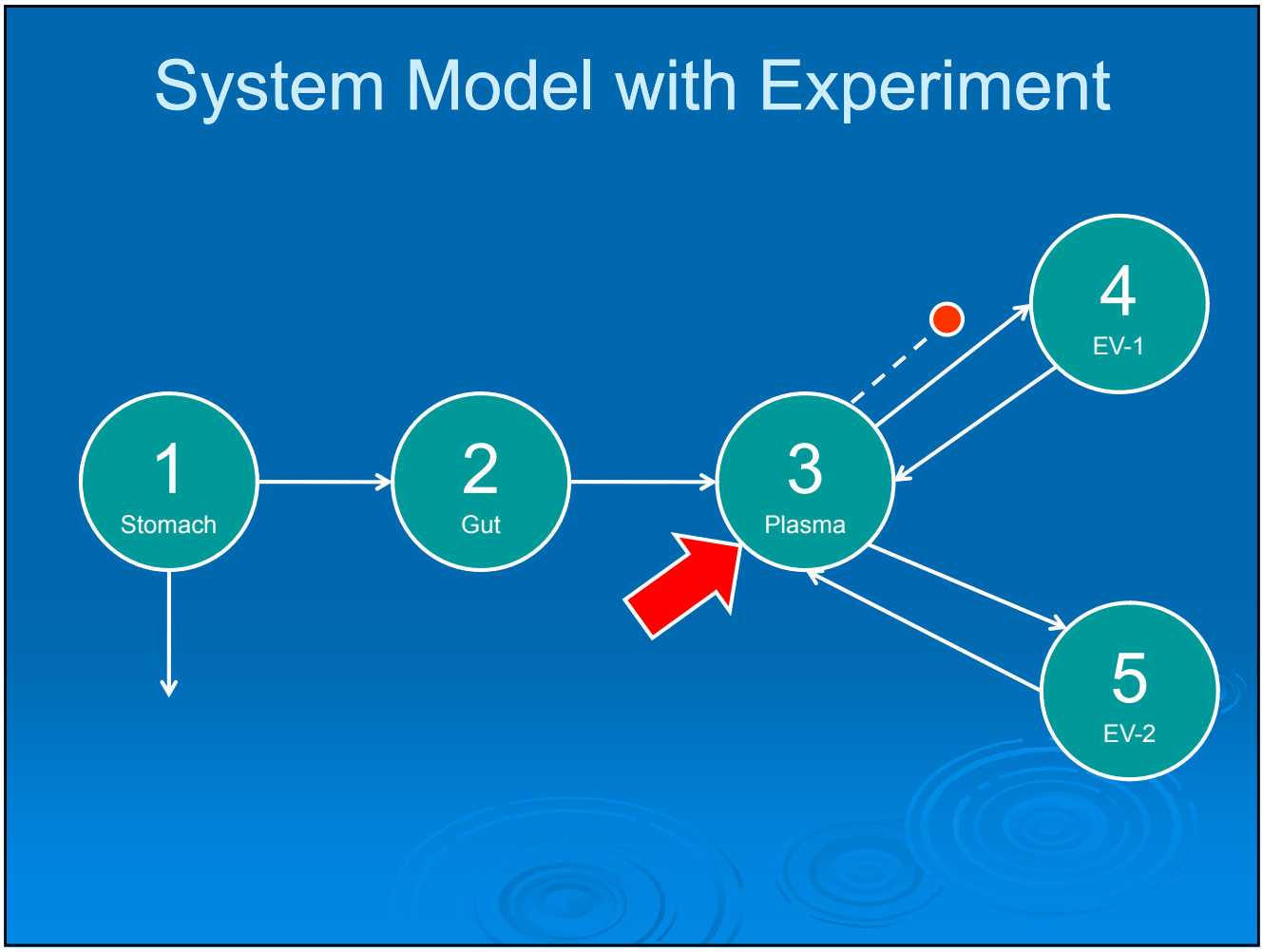
$$K = \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1n} \\ k_{21} & k_{22} & \cdots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \cdots & k_{nn} \end{bmatrix}$$

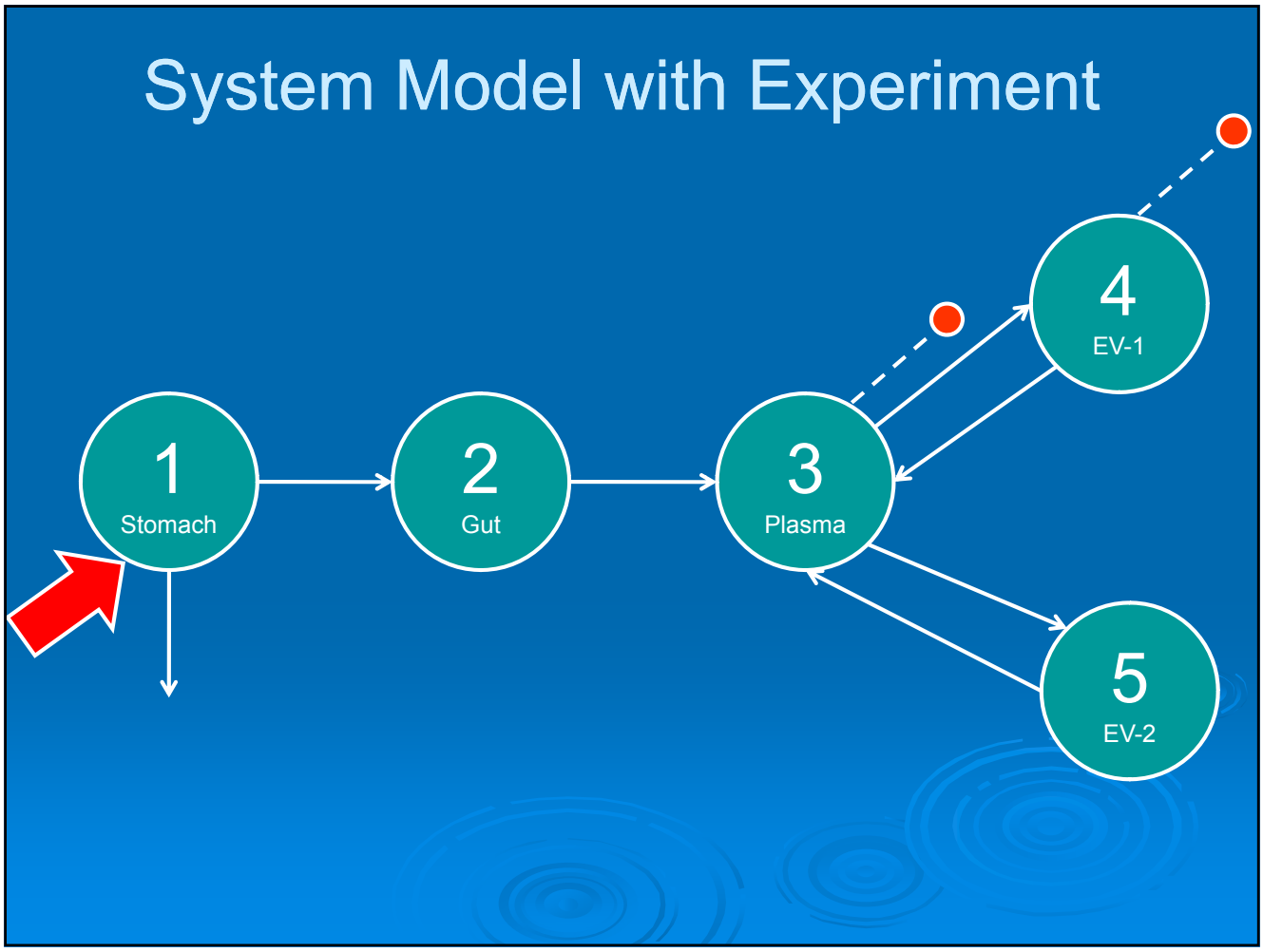
Compartmental Model

- 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

System Model with Experiment



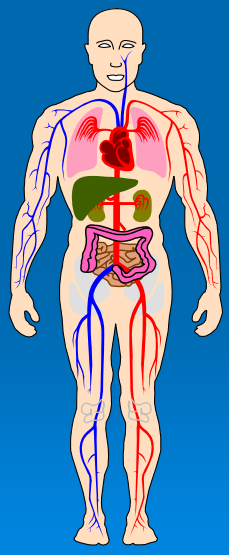

System Model with Experiment
1
Stomach
2
Gut
3
Plasma
4
EV-1
5
EV-2

Experiments

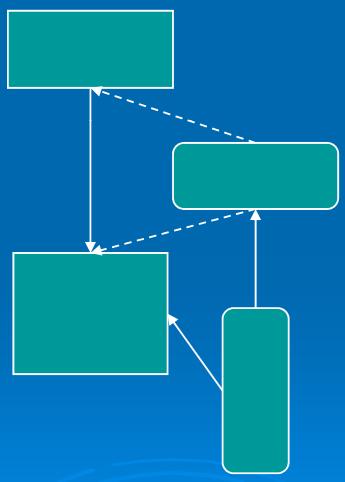
- Need to recreate the laboratory experiment on the model.
- Need to specify input and measurements
- Key: UNITS
  - Input usually in mass, or mass/time
  - Measurement usually concentration
    - Mass per unit volume

Model Of The System?

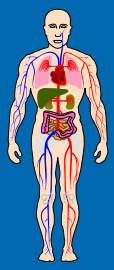
Reality (Data)



Conceptualization (Model)



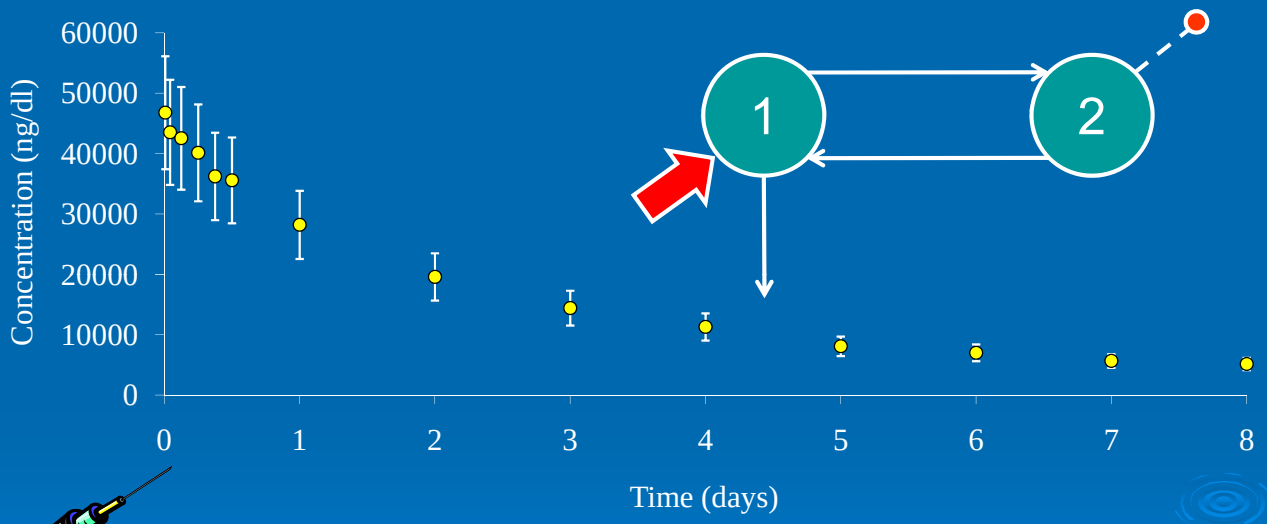
Data Analysis and Simulation

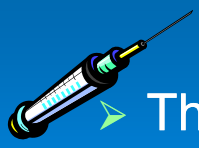


```
program optimize
  begin model
  …
  end
```

Pharmacokinetic Experiment

Collecting System Knowledge





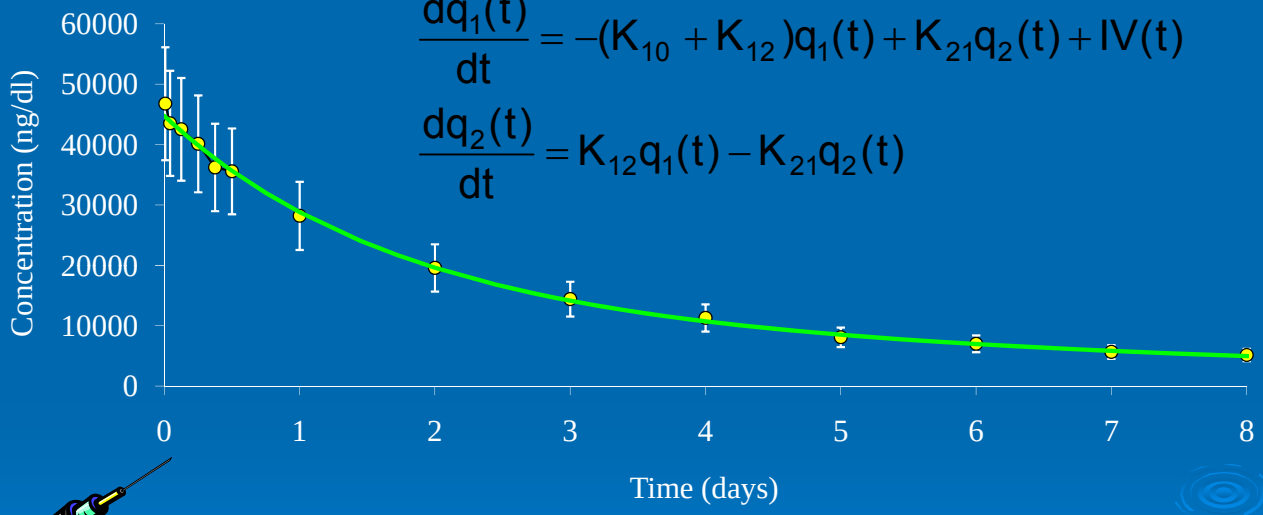
- The model starts as a qualitative construct, based on known physiology and further assumptions

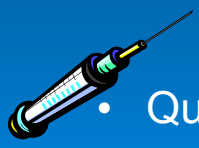
Data Analysis

Distilling Parameters From Data

$$\frac{dq_1(t)}{dt} = -(K_{10} + K_{12})q_1(t) + K_{21}q_2(t) + IV(t)$$

$$\frac{dq_2(t)}{dt} = K_{12}q_1(t) - K_{21}q_2(t)$$





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

Parameter Estimates

- Principles of model building
  - Model definition: structure, error model
  - Model selection: parsimony criteria
  - Estimation methods: maximum likelihood
- 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

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

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

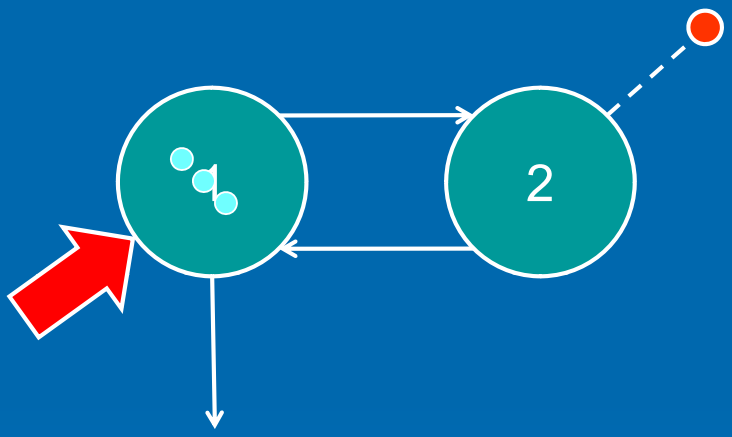
For a pulse input $\delta(t)$

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

$$s1(t) = \frac{q_1(t)}{V} = \frac{Dose}{V} e^{-k(0,1)t}$$

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

Compartmental Residence Times



- Rate constants
- Residence times
- Intercompartmental clearances

Parameters Based Upon The Compartmental Matrix

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

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.

$\frac{\vartheta_{ij}}{\vartheta_{ii}}, \quad i \neq j$ 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

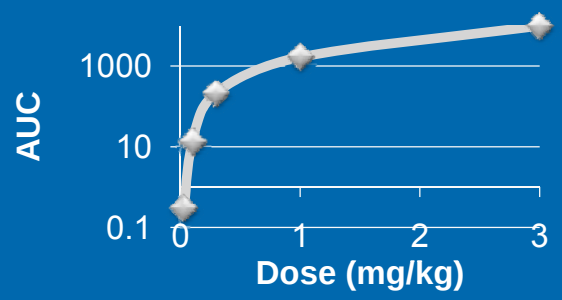
Nonlinear Pharmacokinetics

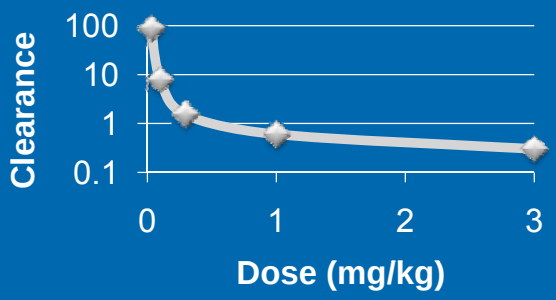
- Example: antibody pharmacokinetics
- Often, antibodies exhibit target-mediated disposition, and thus their elimination may occur at sites remote from plasma due to binding and internalization processes
- This is one of many possible biological processes causing nonlinear (capacity-limited) pharmacokinetic behaviors

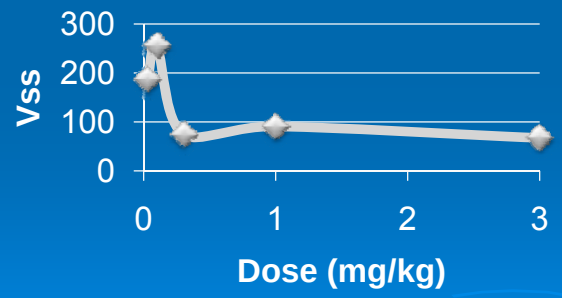
Impact of Noncompartmental Analysis Assumptions

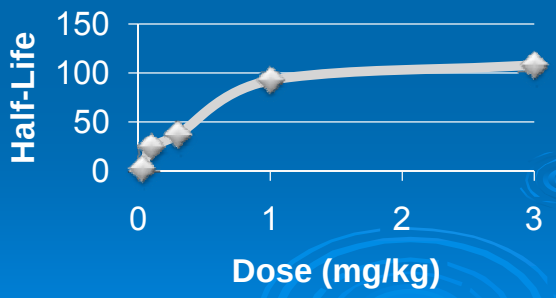
- When drug elimination is influenced by binding to its pharmacological target, the assumptions of noncompartmental analysis may not be met to a varying degree and parameter estimates may be misleading
- Noncompartmental analysis always requires linearity and time invariance, but it can be useful to explore nonlinearities

Example of Dose Nonlinearities

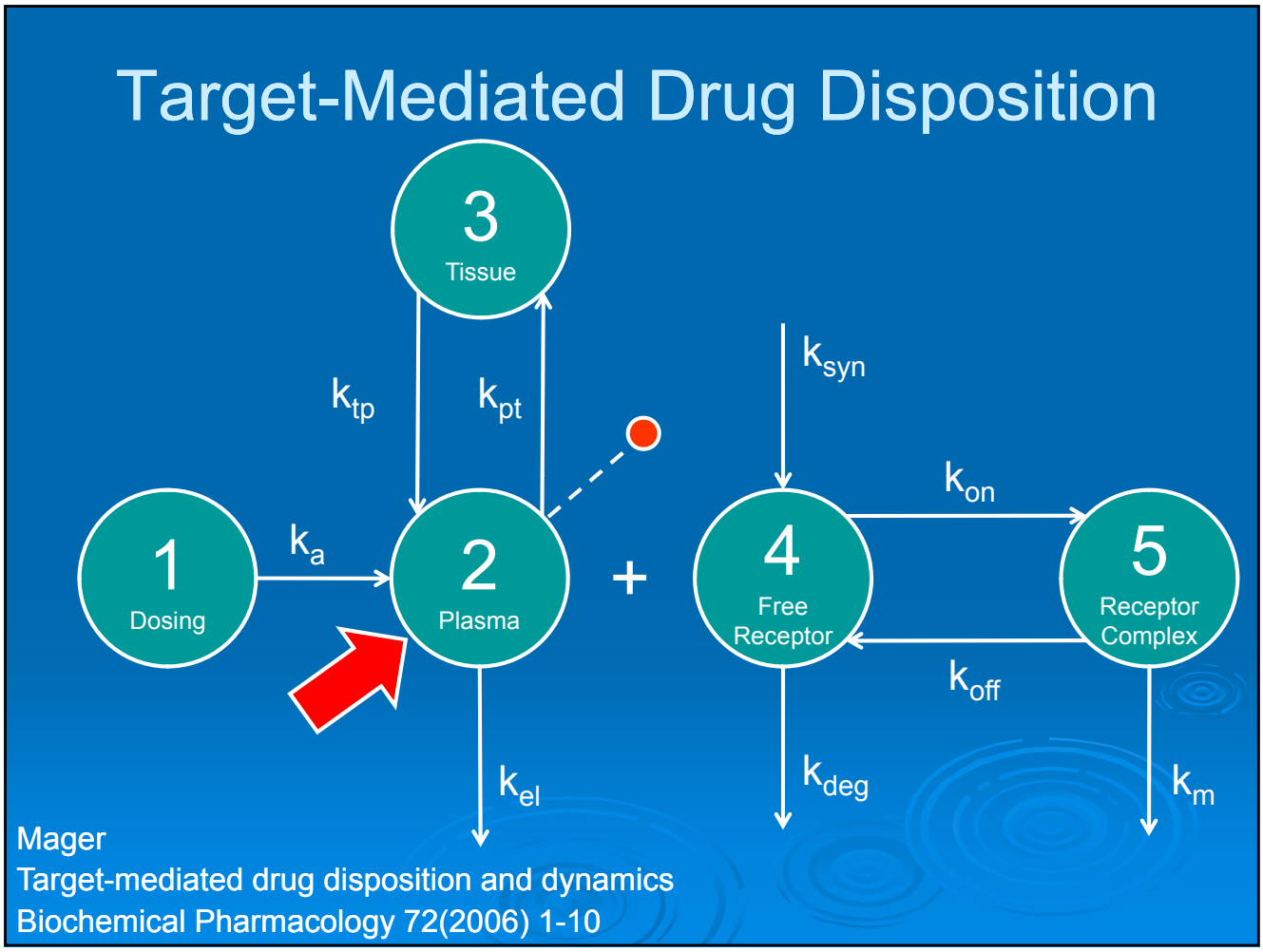








PK example from Sheremata et al. (1999)as reported in Mager (2006)
Target-mediated drug disposition and dynamics
Biochemical Pharmacology 72(2006) 1-10


Target-Mediated Drug Disposition
3
Tissue
k_{tp}
k_{pt}
1
Dosing
k_a
2
Plasma
+
k_{el}
k_{syn}
k_{on}
4
Free
Receptor
5
Receptor
Complex
k_{off}
k_{deg}
k_m
Mager
Target-mediated drug disposition and dynamics
Biochemical Pharmacology 72(2006) 1-10

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!

Selected References

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  - Mager DE. Target-mediated drug disposition and dynamics. Biochem Pharmacol. 2006 Jun 28;72(1):1-10.
  - Lobo ED, Hansen RJ, Balthasar JP. Antibody pharmacokinetics and pharmacodynamics. J Pharm Sci. 2004 Nov;93(11):2645-68.

- Thanks: Kenneth Luu (PGRD)