Noncompartmental vs. Compartmental Approaches to Pharmacokinetic Data Analysis

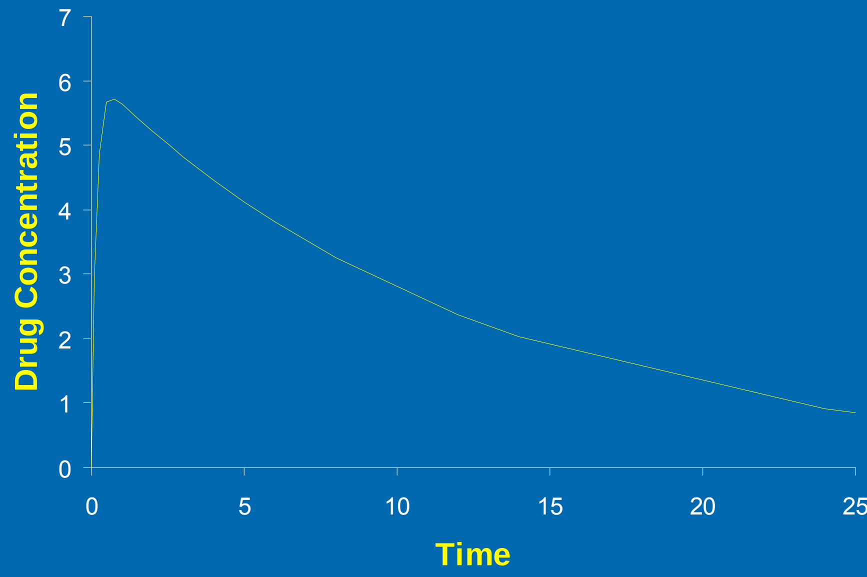
Paolo Vicini, Ph.D.
Pfizer Global Research and Development

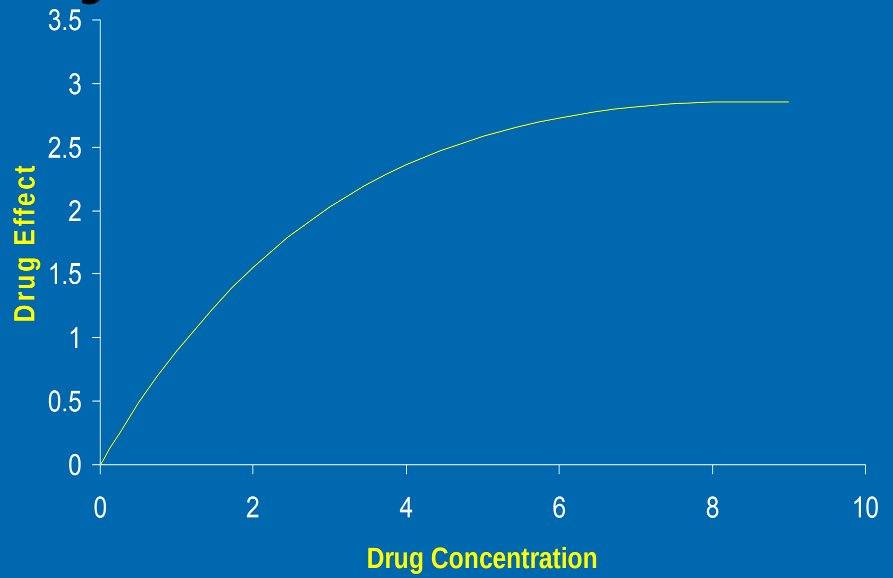
David M. Foster., Ph.D.
University of Washington

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

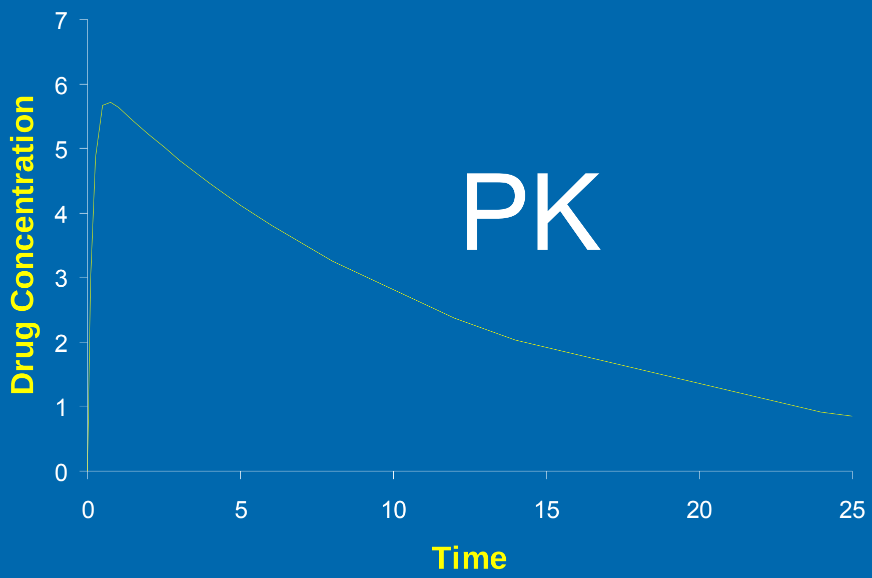


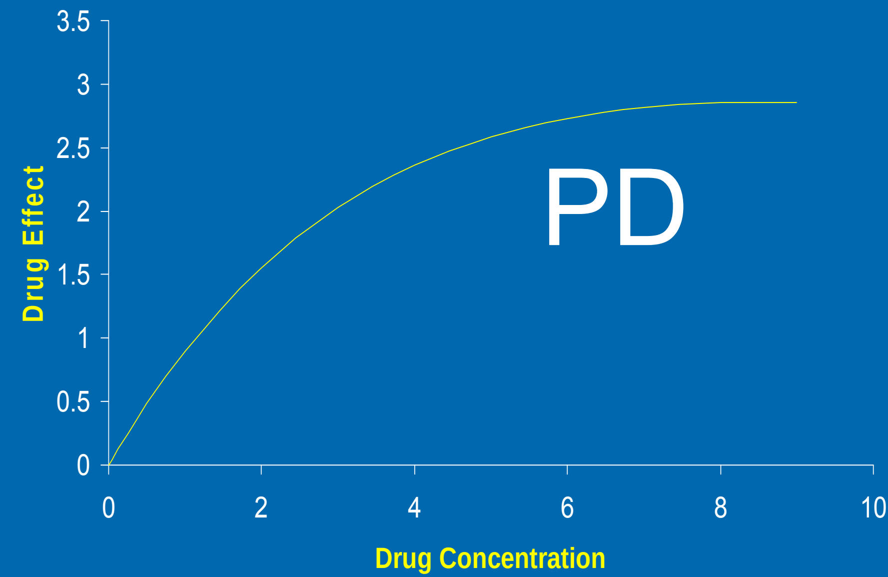


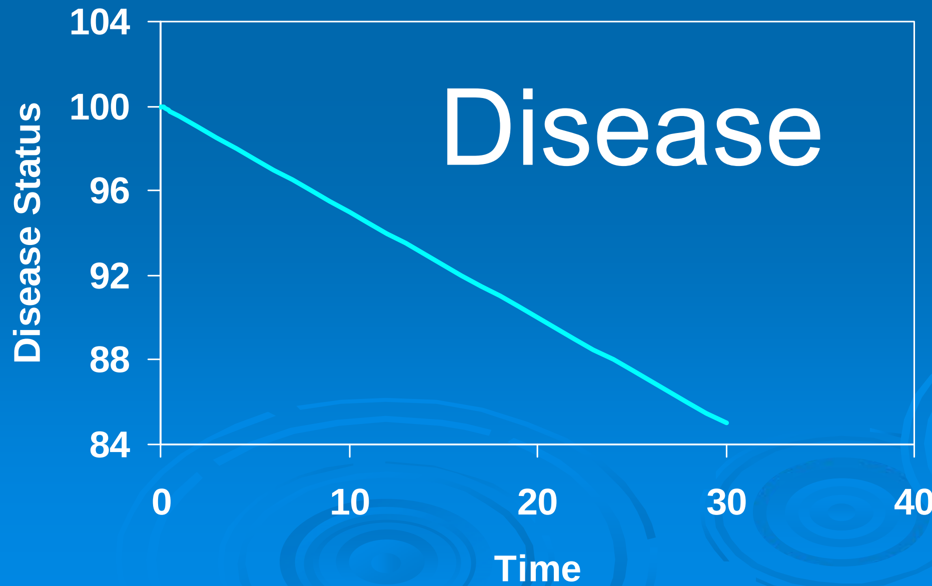
- Pharmacokinetics
- "What the body does to the drug"
- Fairly well known
- Useful to get to the PD

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

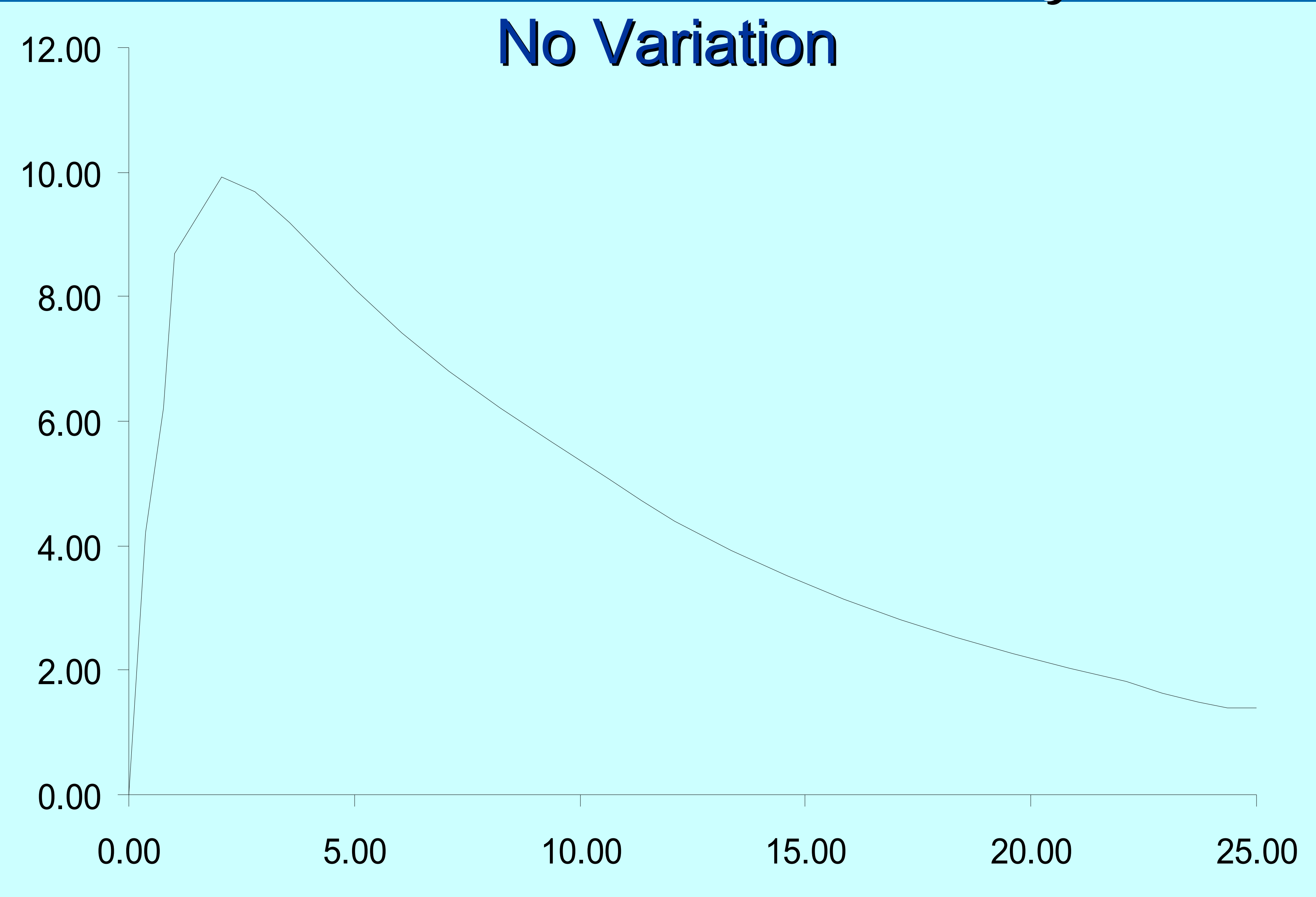
PK/PD/Disease Processes



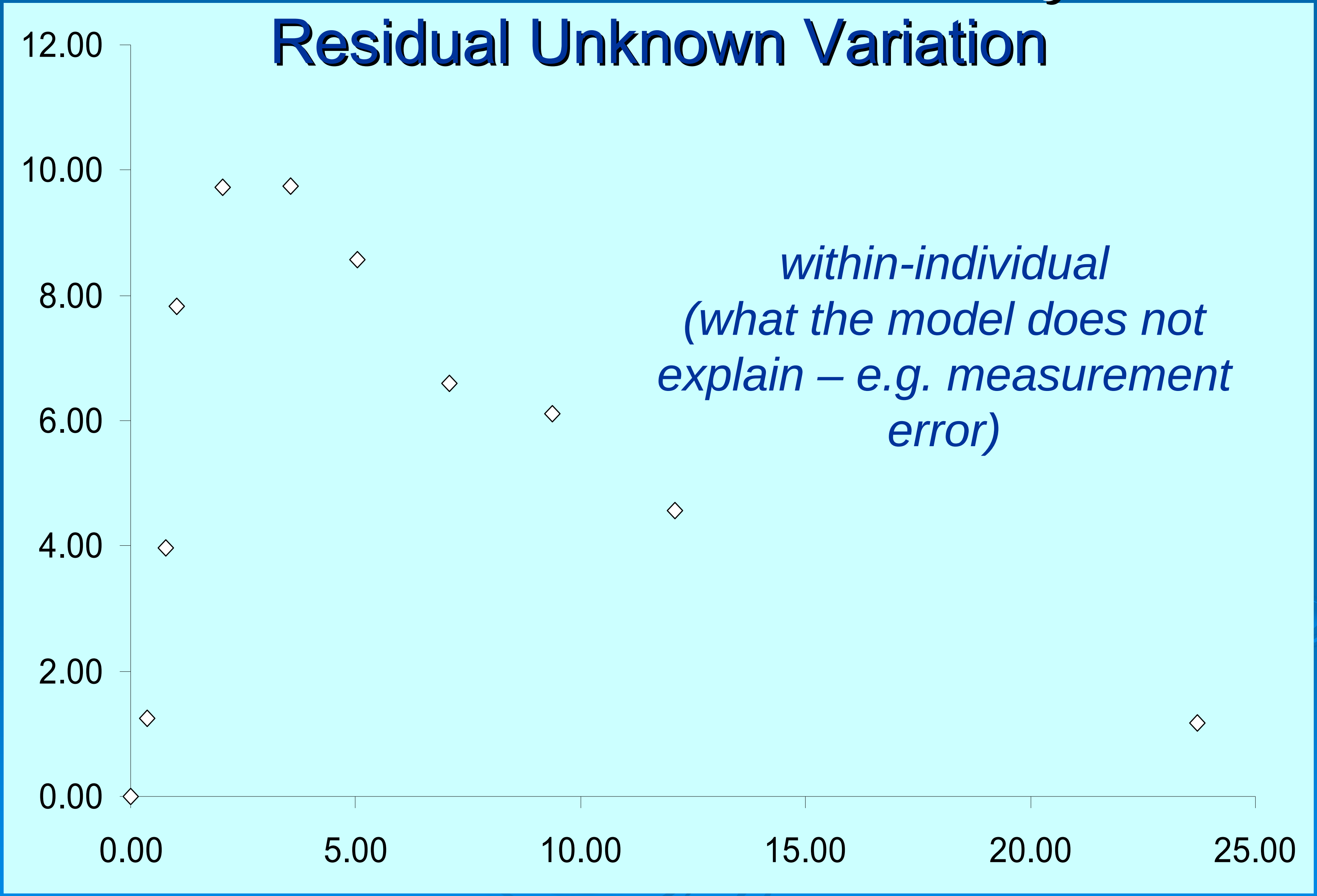




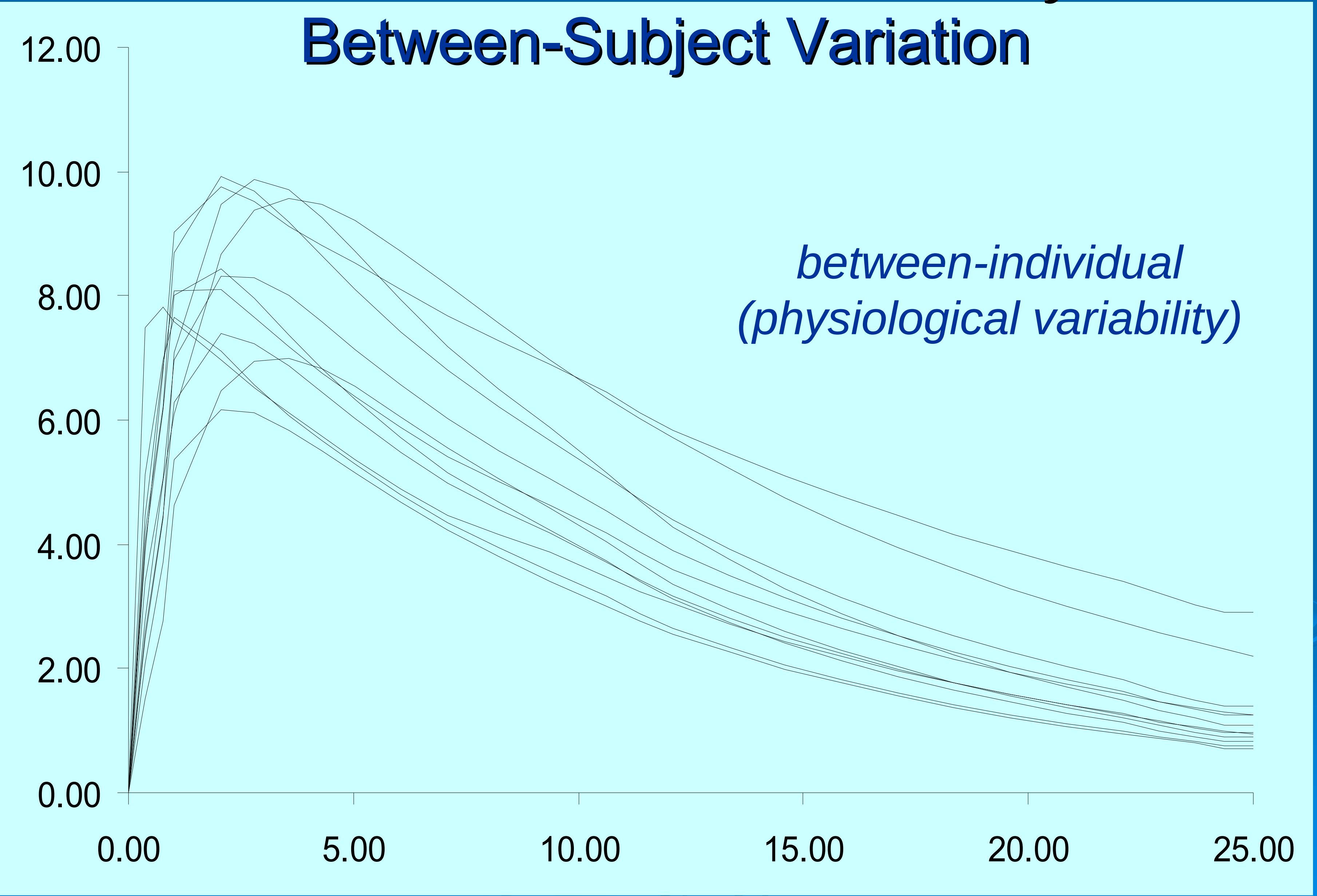
Hierarchical Variability



Hierarchical Variability

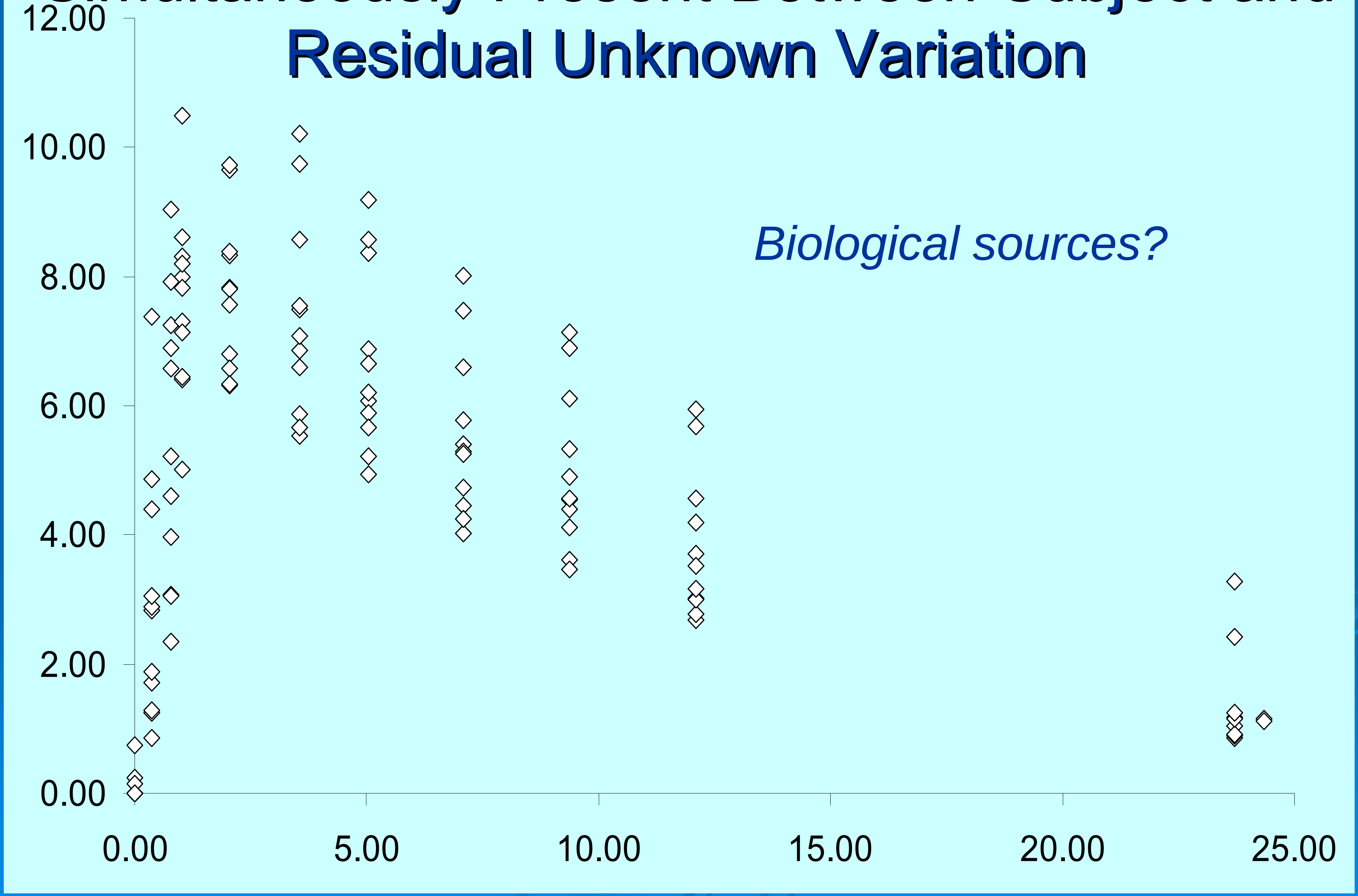


Hierarchical Variability



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

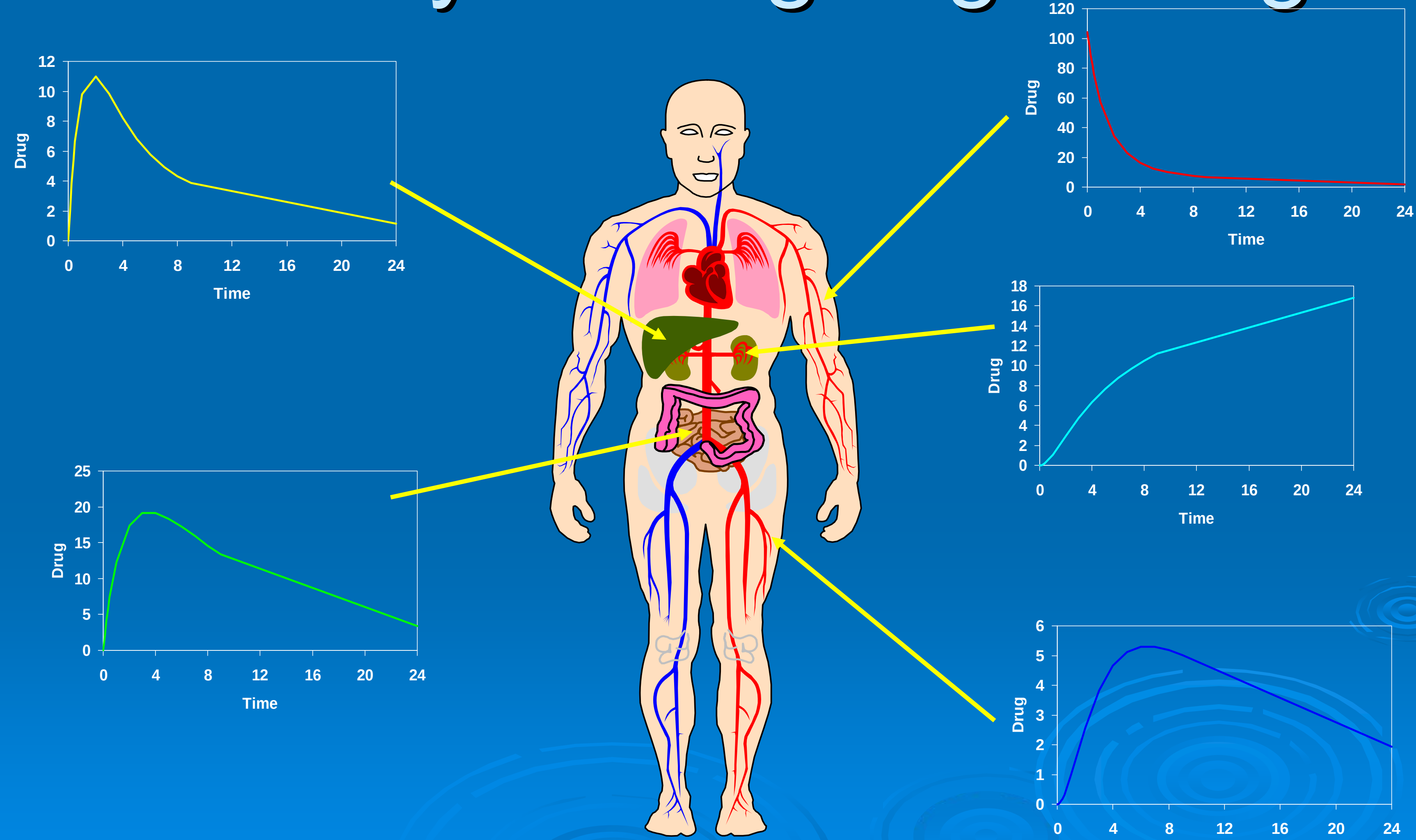
Goals Of This Lecture

- 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

A Drug In The Body: Constantly Undergoing Change

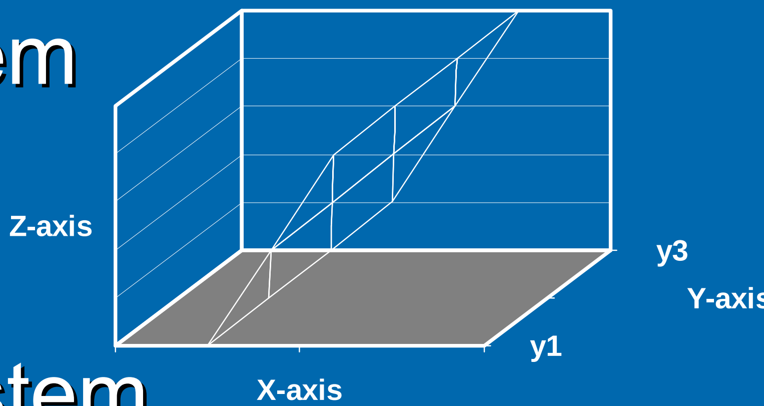


Kinetics And Pharmacokinetics

- 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

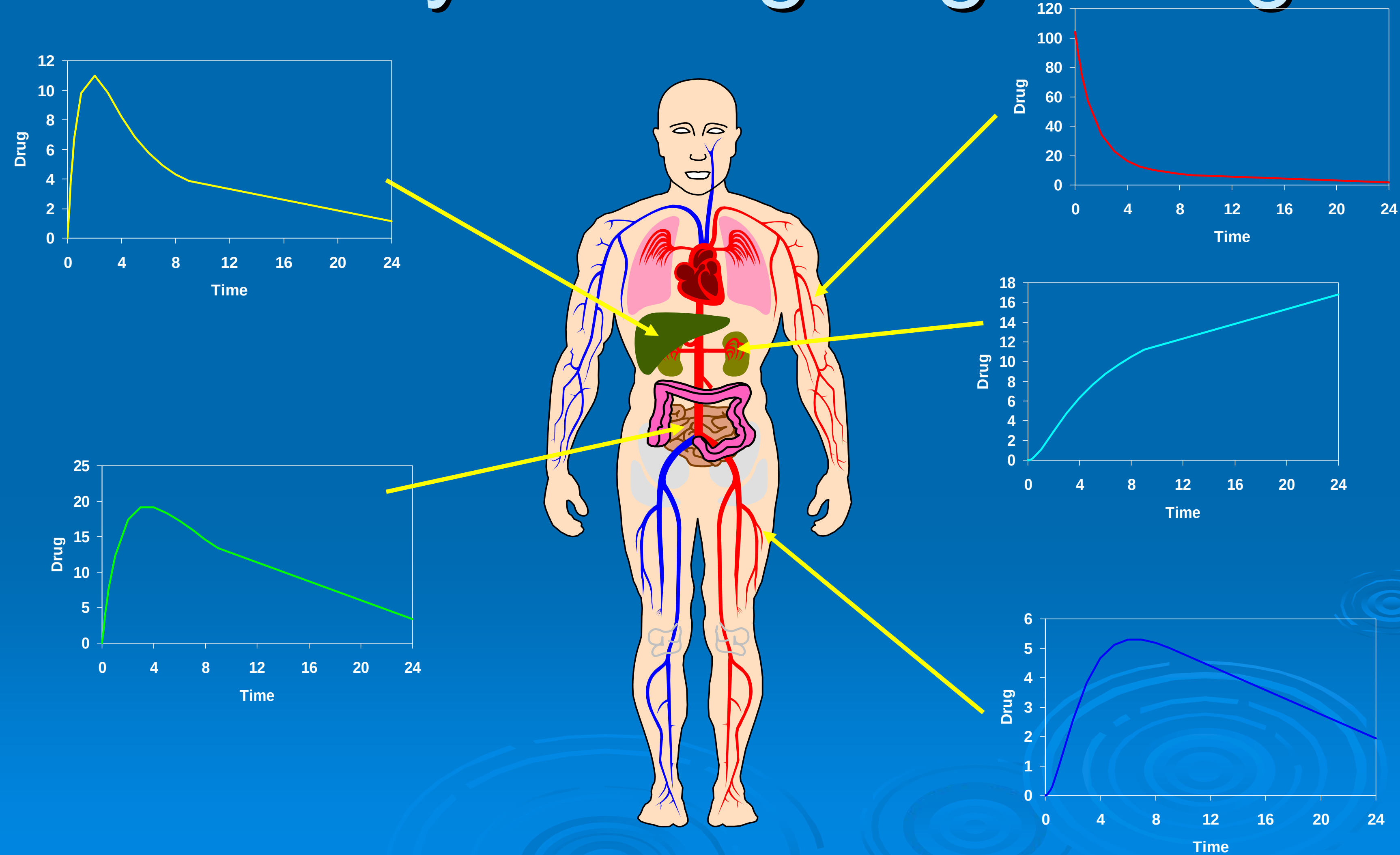
- <u>Spatial</u>: *Where* in the system
  - Spatial coordinates
  - Key variable: s = (x, y, z)



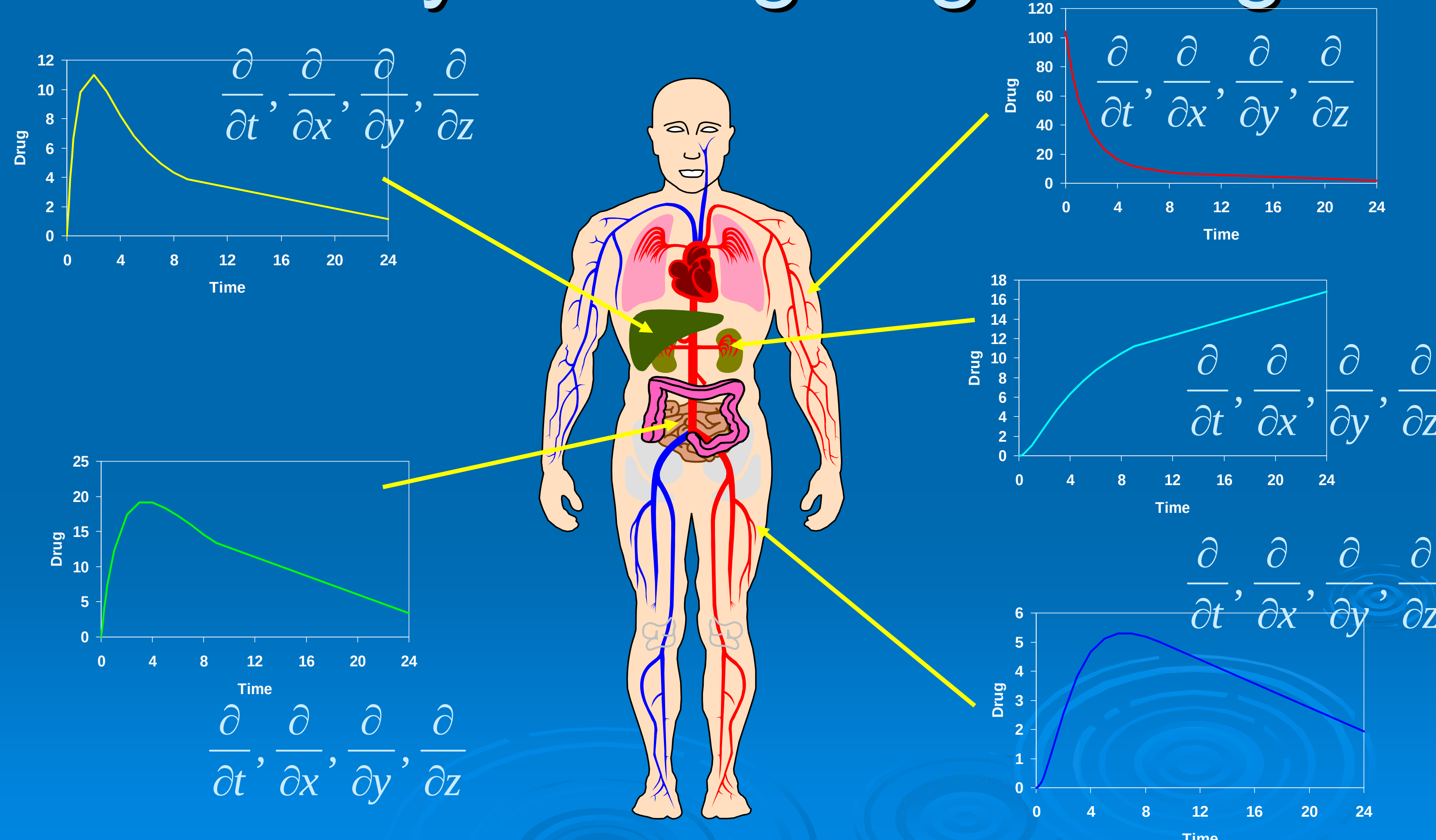
- <u>Temporal</u>: *When* in the system
  - Temporal coordinates
  - Key variable: t

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

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

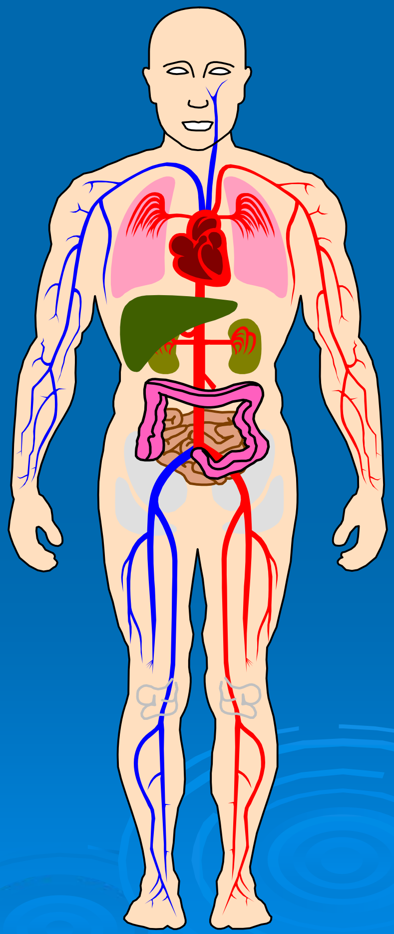
- Reducing the system to a finite number of components
- Lumping processes together based upon time, location or a combination of the two
- Space is not taken directly into account: rather, spatial heterogeneity is modeled through changes that occur in time

Lumped Parameter Models

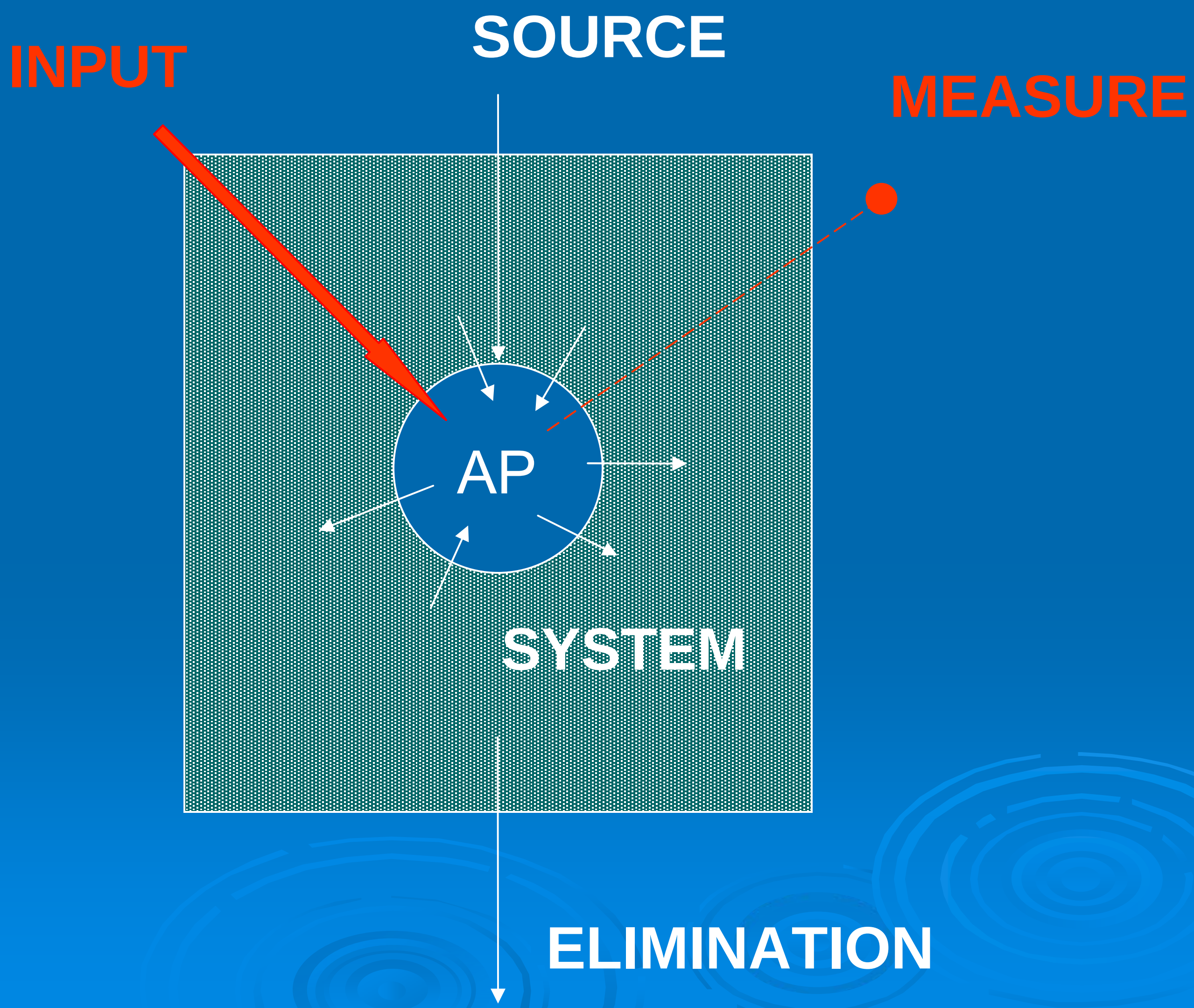
- Models which make the system discrete through a lumping process thus eliminating the need to deal with partial differential equations.
- Classes of such models:
  - Noncompartmental models
    - Based on algebraic equations
  - Compartmental models
    - Based on linear or nonlinear differential equations

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

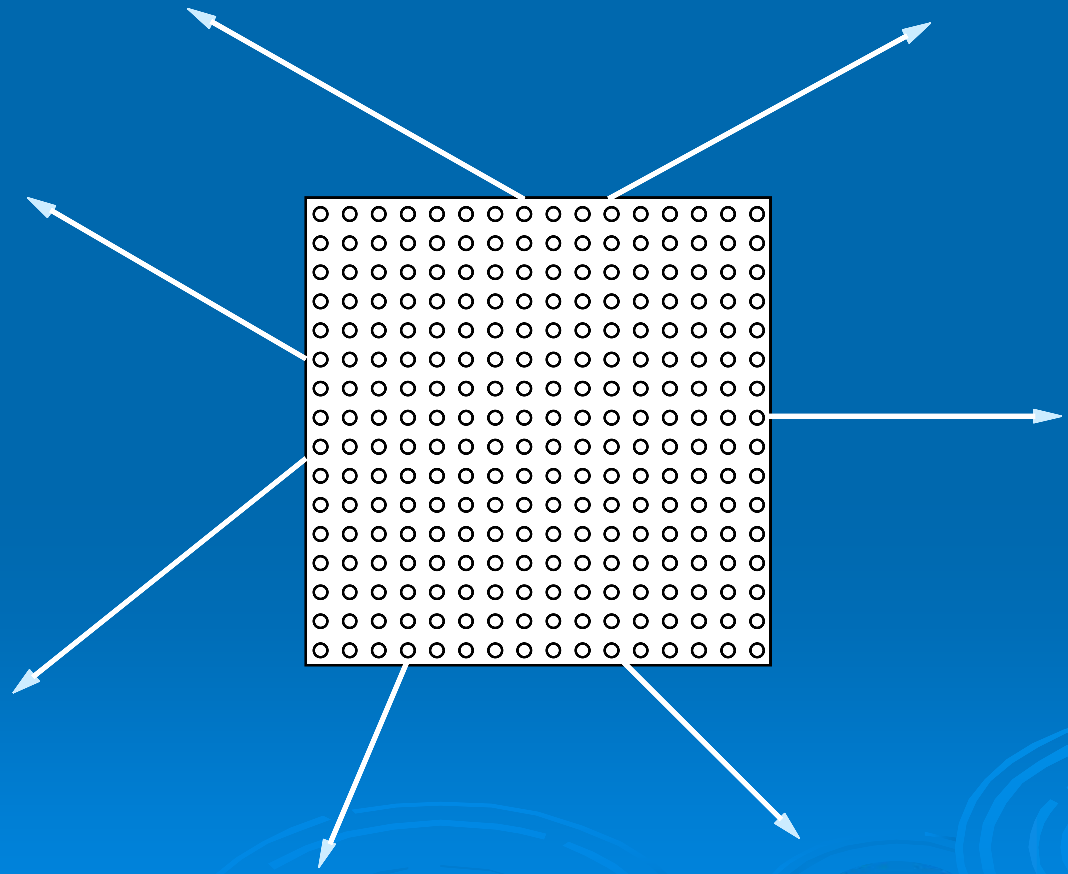


Characteristics Of The Accessible Pool

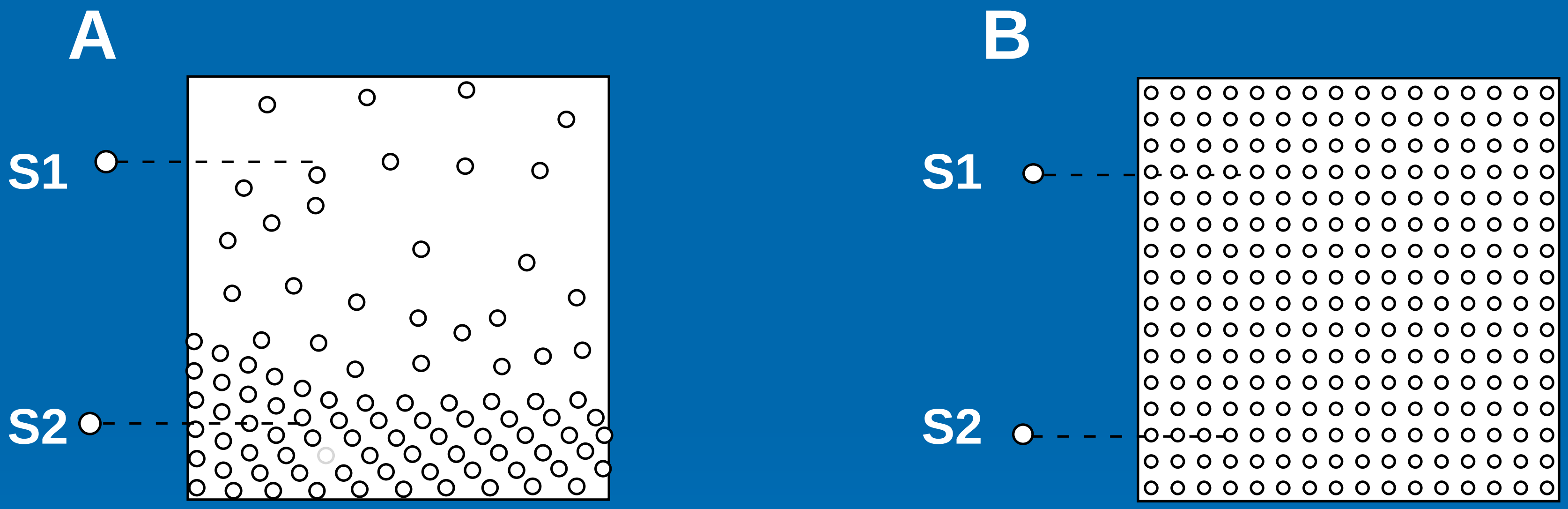
Kinetically Homogeneous

Instantaneously Well-mixed

Accessible Pool
Kinetically Homogeneous

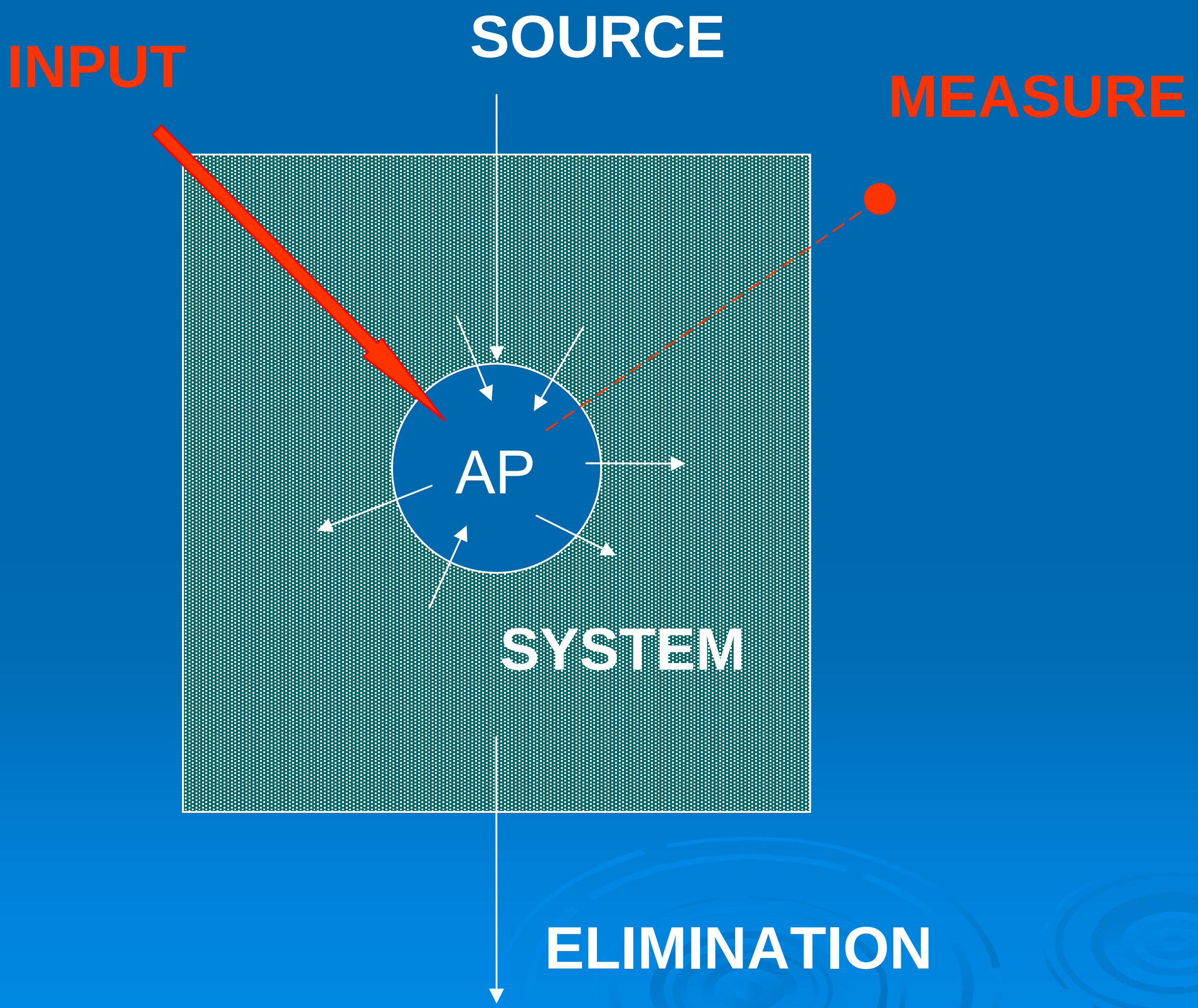


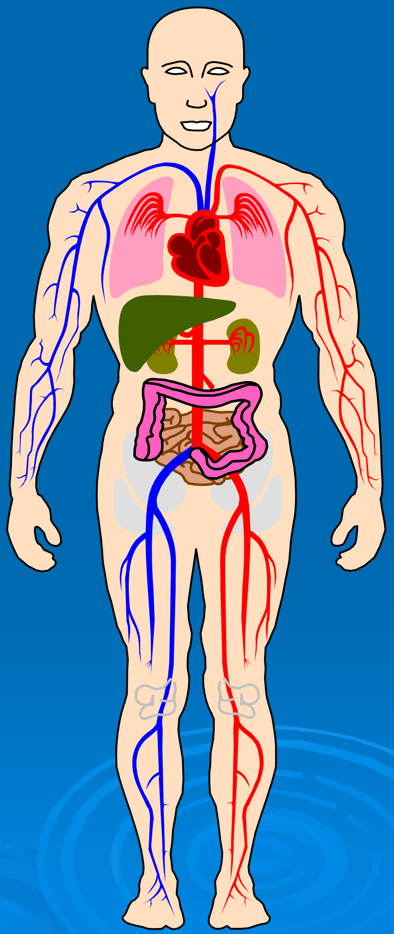
Accessible Pool Instantaneously Well-Mixed



- A = not mixed
- B = well mixed

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

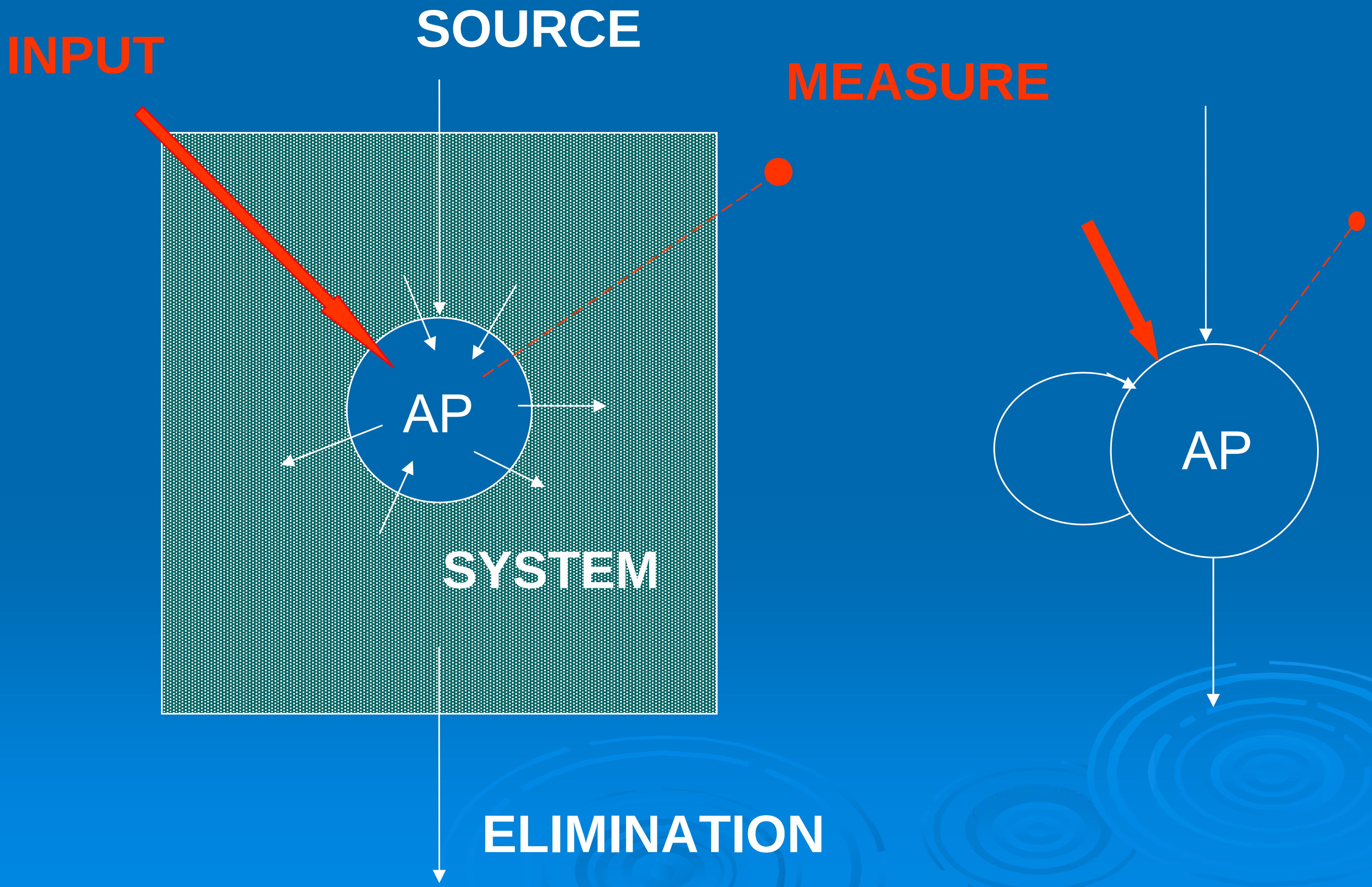
Accessible Pool & System Assumptions → Information

- 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

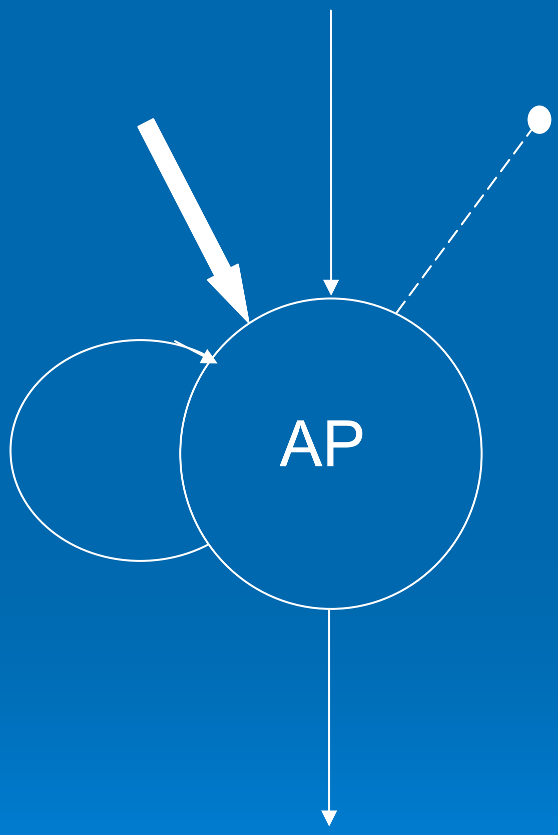
The only difference between the two methods is in how the nonaccessible portion of the system is described

The Noncompartmental Model



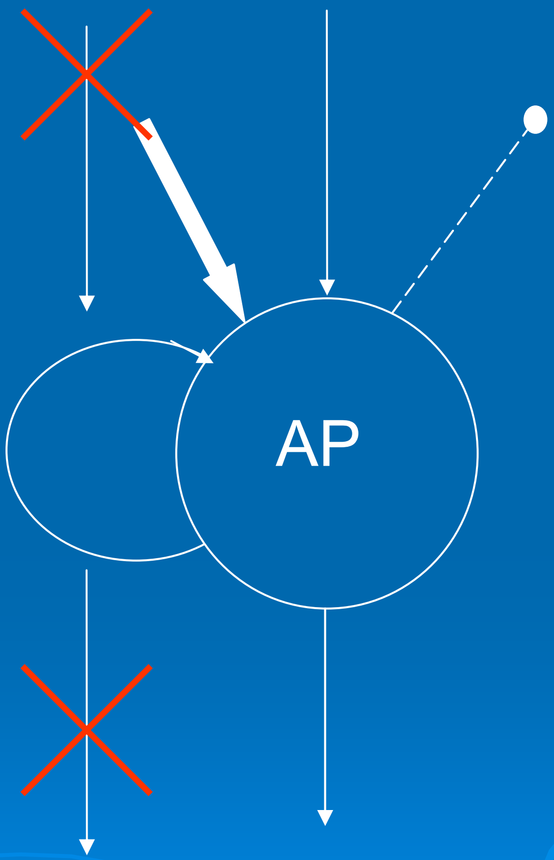
Recirculation-exchange Assumptions

Recirculation/ Exchange



Recirculation-exchange Assumptions

Recirculation/
Exchange

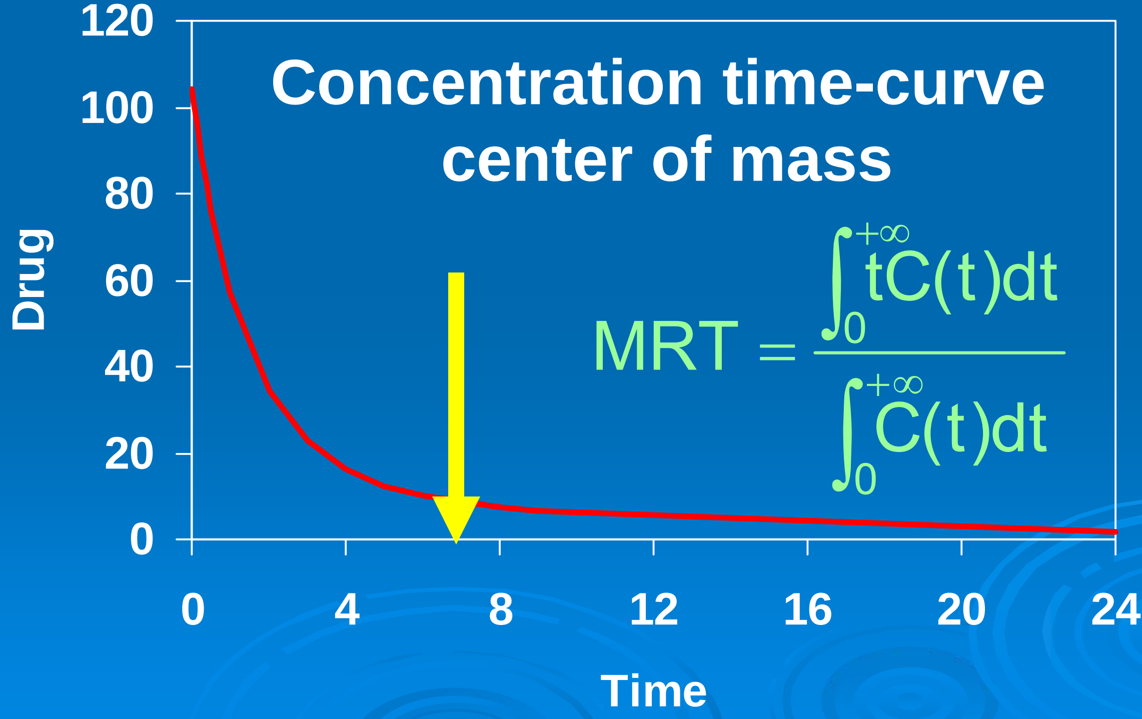


Single Accessible Pool Noncompartmental Model

- 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



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

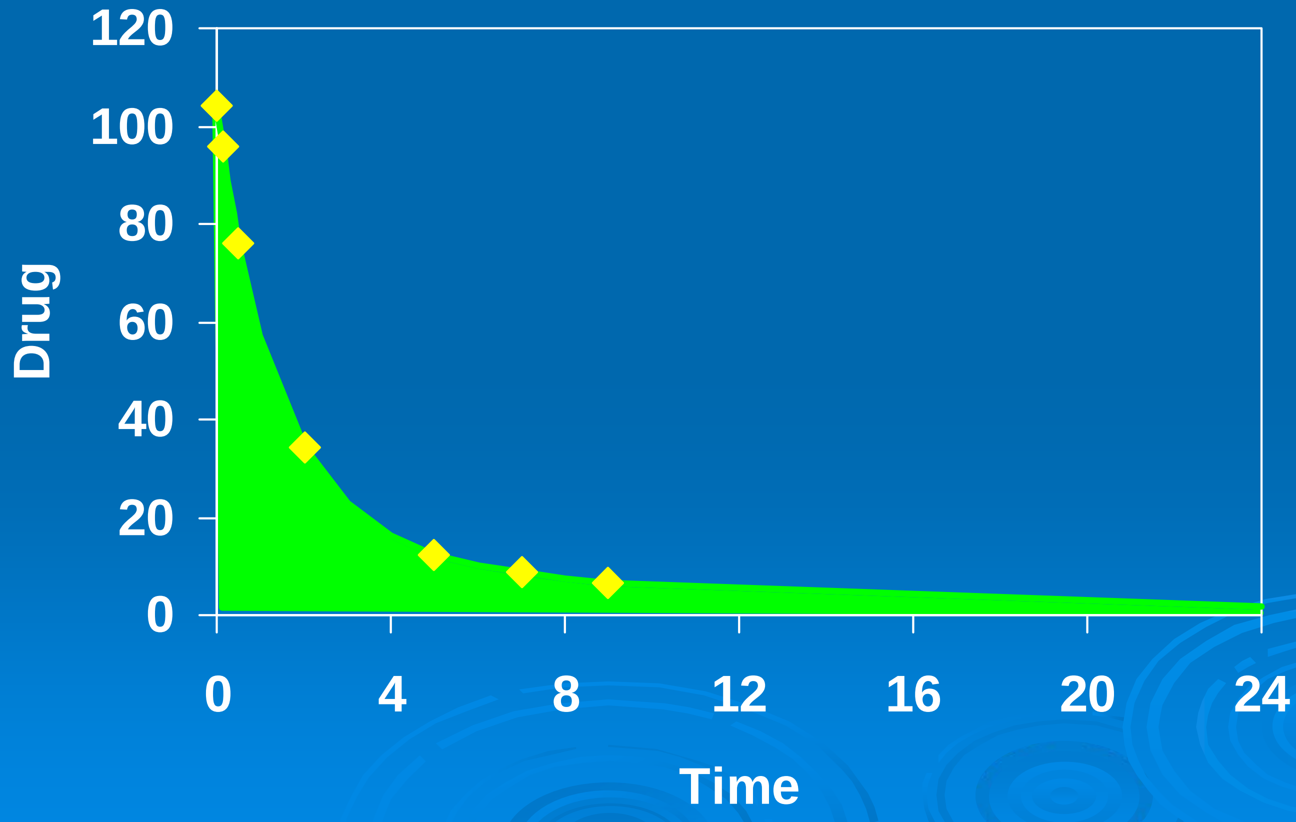
Areas Under The Curve

- 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 sites

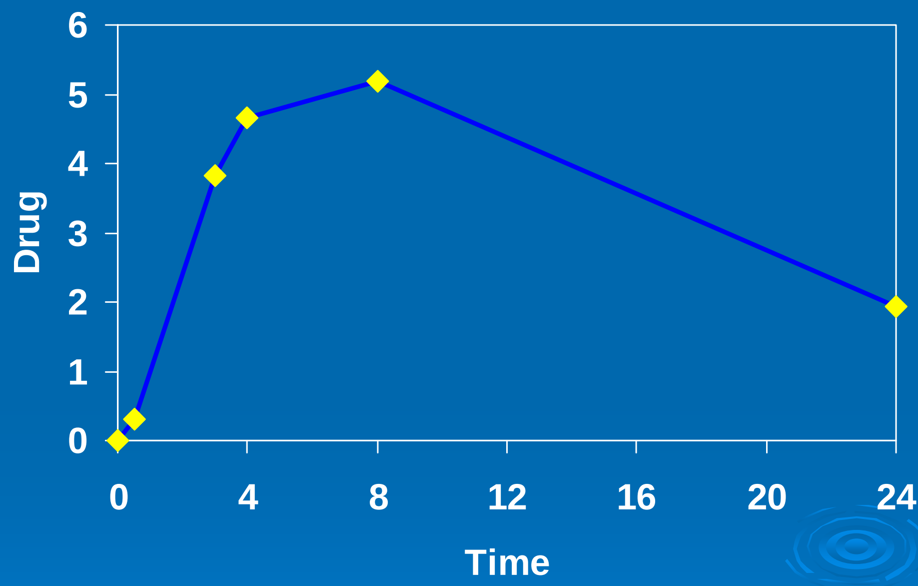
$$AUC = \int_0^\infty C(t)dt = \frac{A_1}{\lambda_1} + \cdots + \frac{A_n}{\lambda_n}$$

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

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

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.

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

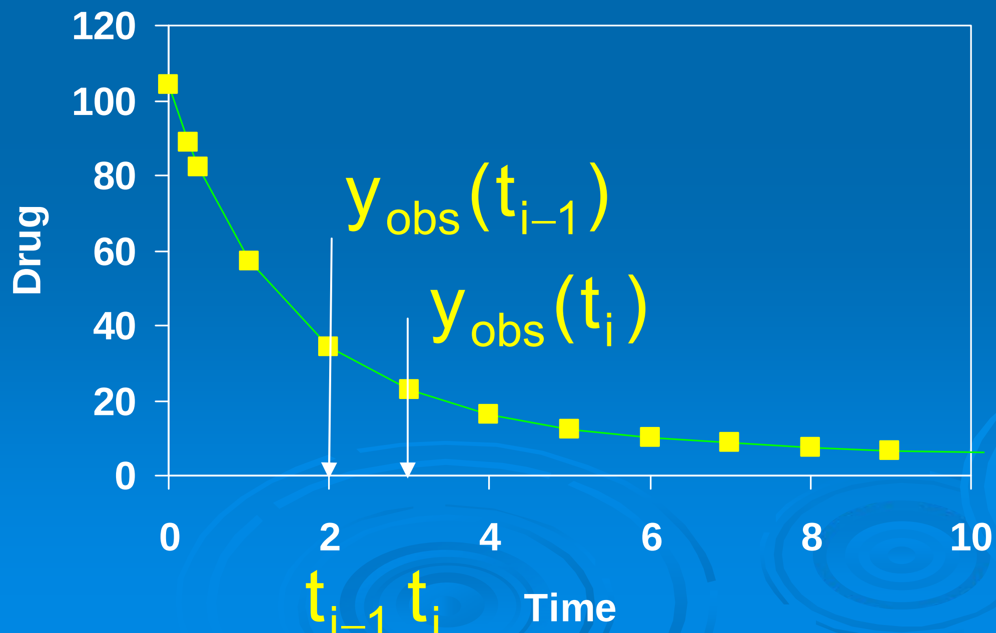
$$AUMC = \int_0^\infty t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^\infty t \cdot C(t)dt$$

Trapezoidal Rule

- For every time t_i, i = 1, …, n

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

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



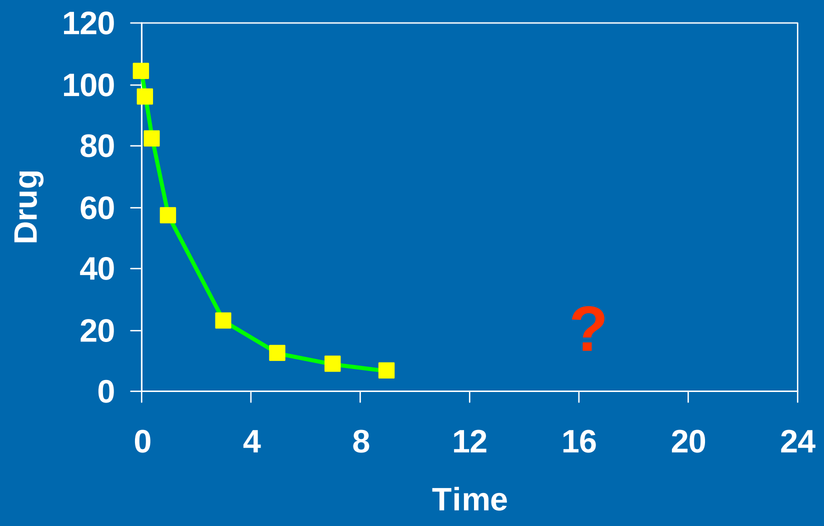
Log-trapezoidal Rule

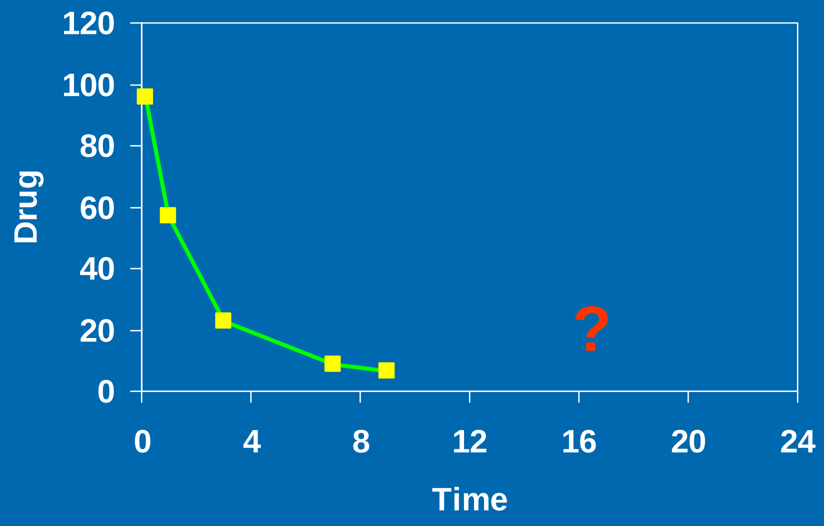
- For every time t_i, i = 1, …, n

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

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

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:

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

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

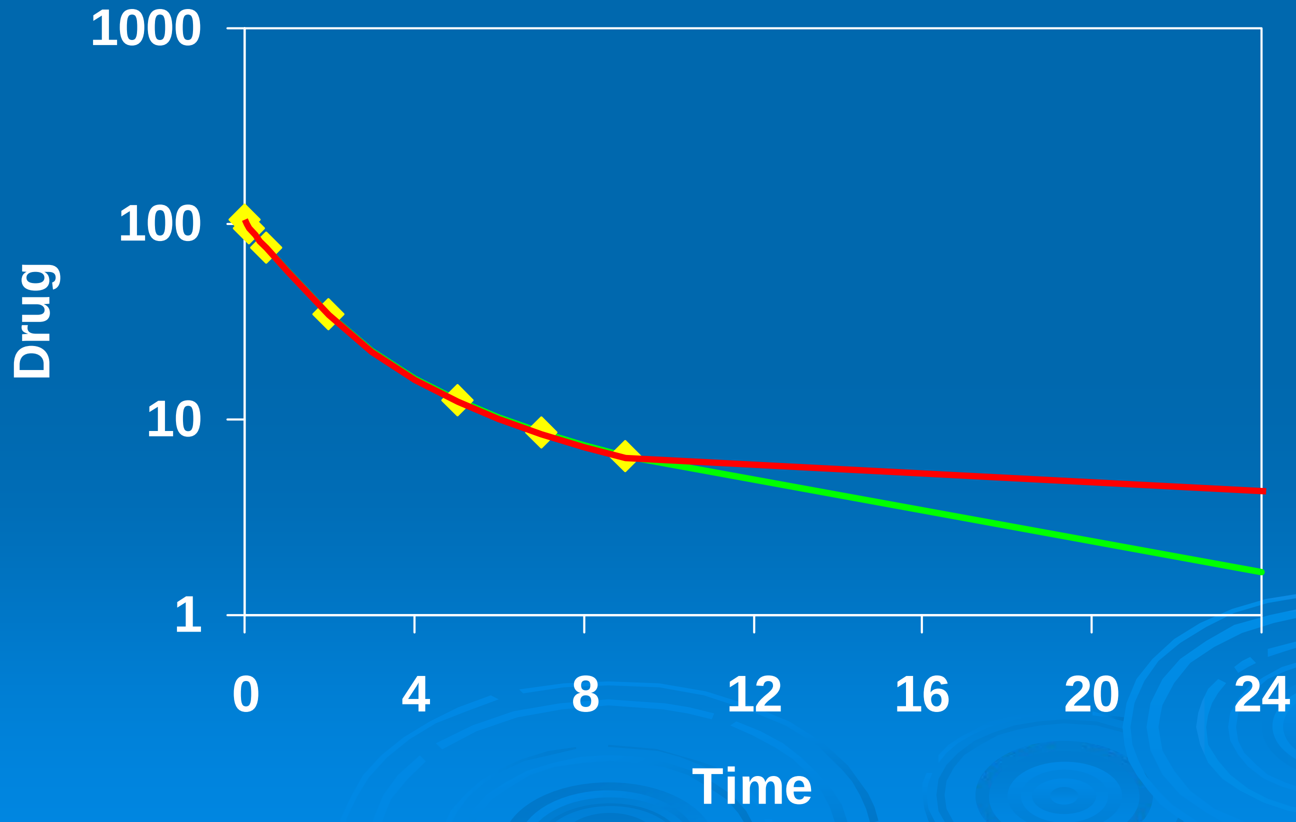
From last calculated value:

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

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

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 Sums Of Exponentials

- Extrapolation done as part of the data fitting
- Statistical information of all parameters calculated
- Natural connection with the solution of linear, constant coefficient compartmental models
- Software available

Clearance Rate

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

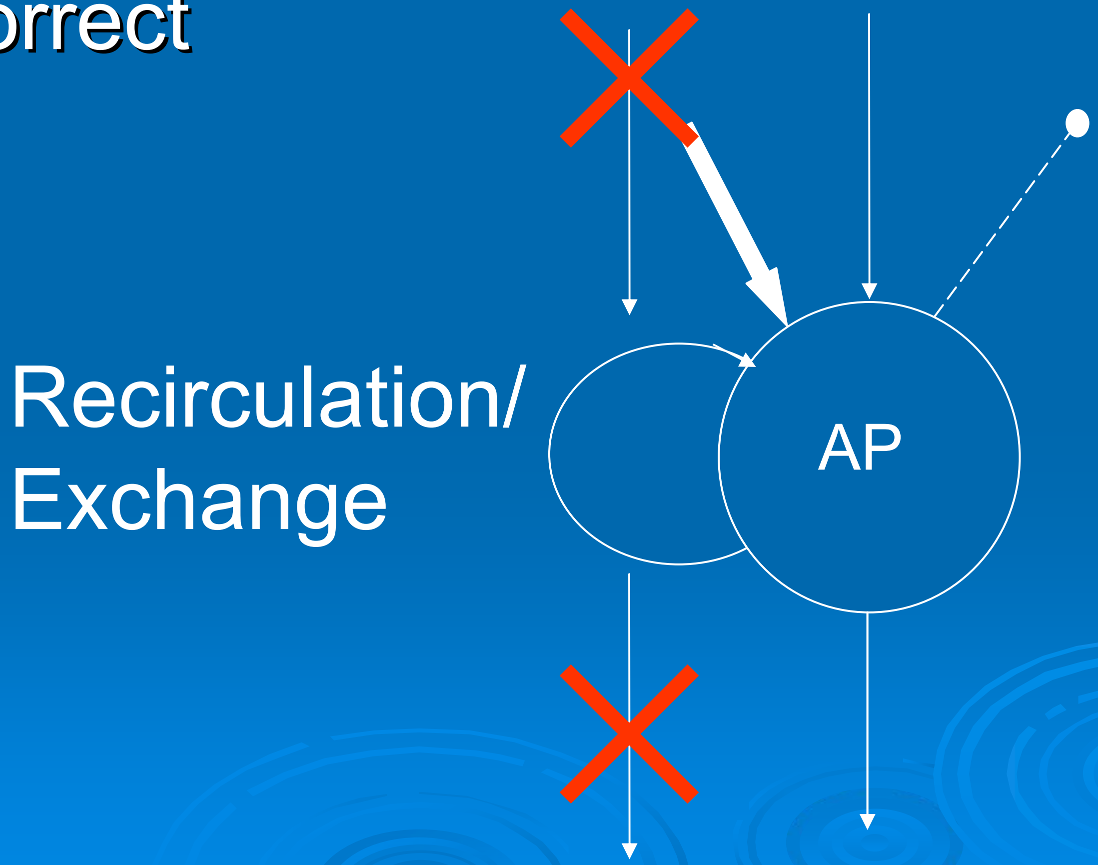
$$CL = \frac{\text{Elimination rate}}{\text{Concentration in blood}}$$

- It can be shown that

$$CL = \frac{\text{Drug Dose}}{\text{AUC}}$$

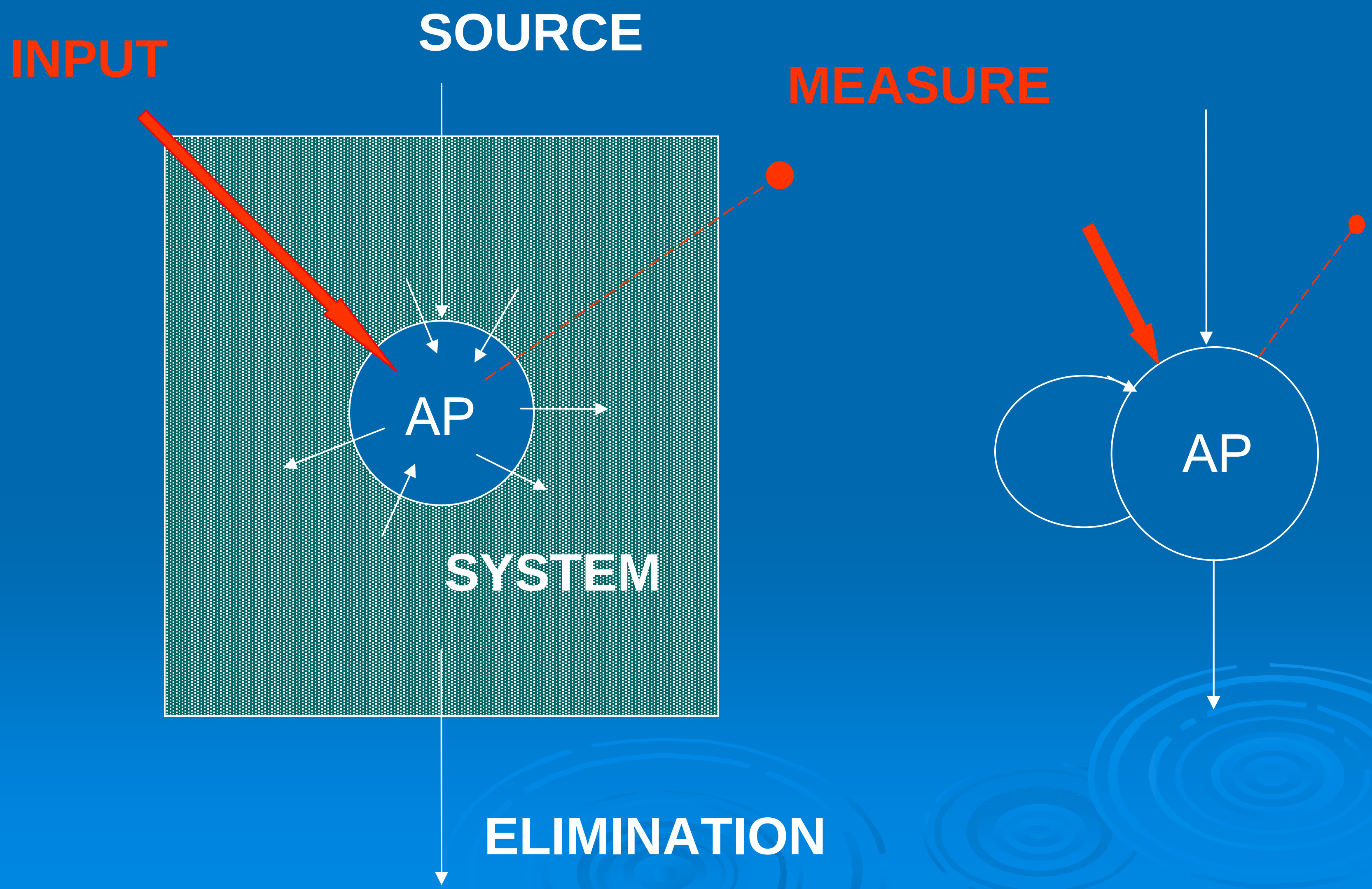
Remember Our Assumptions

- If these are not verified the estimates will be incorrect



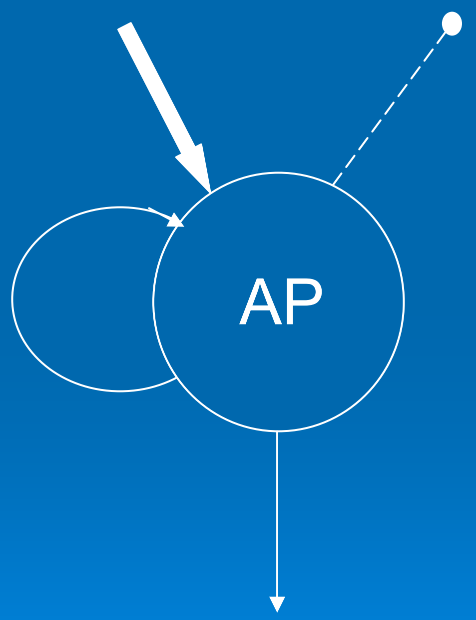
The Compartmental Model

Single Accessible Pool

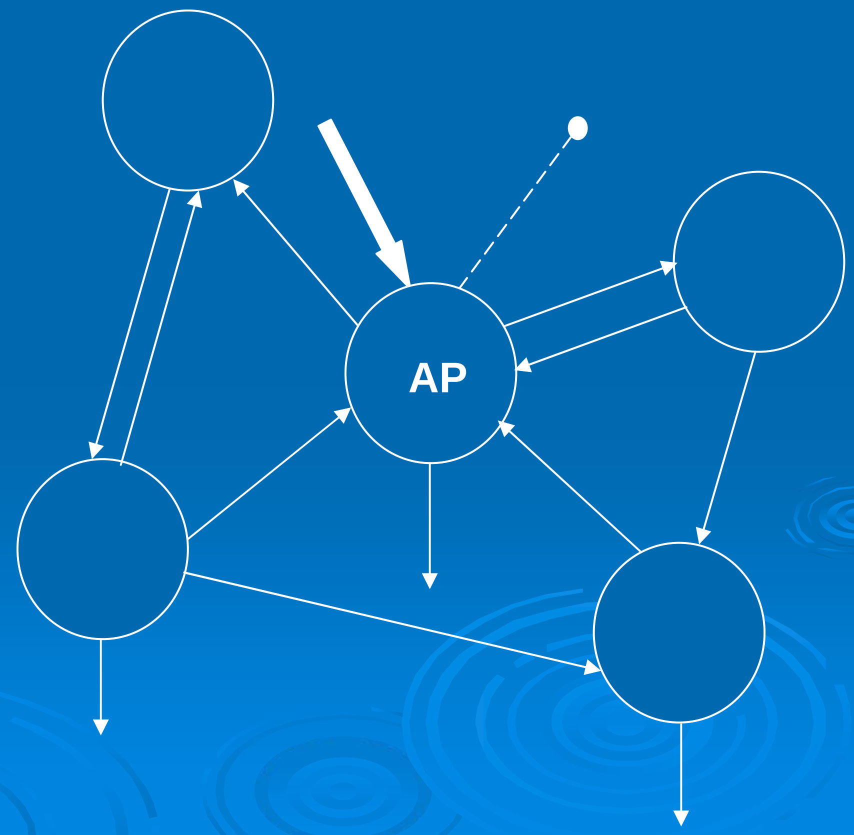


Single Accessible Pool Models

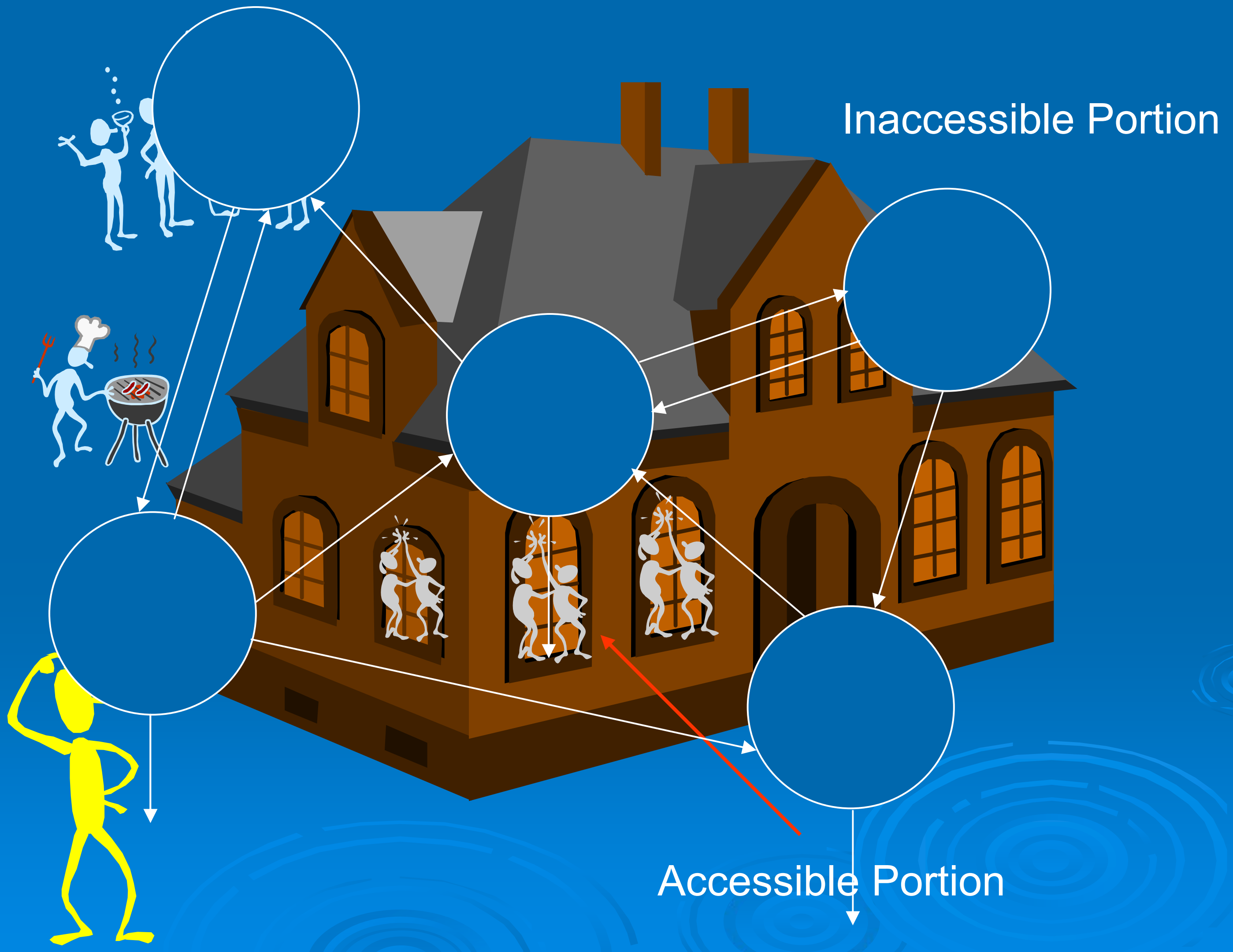
- Noncompartmental



- 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

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

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

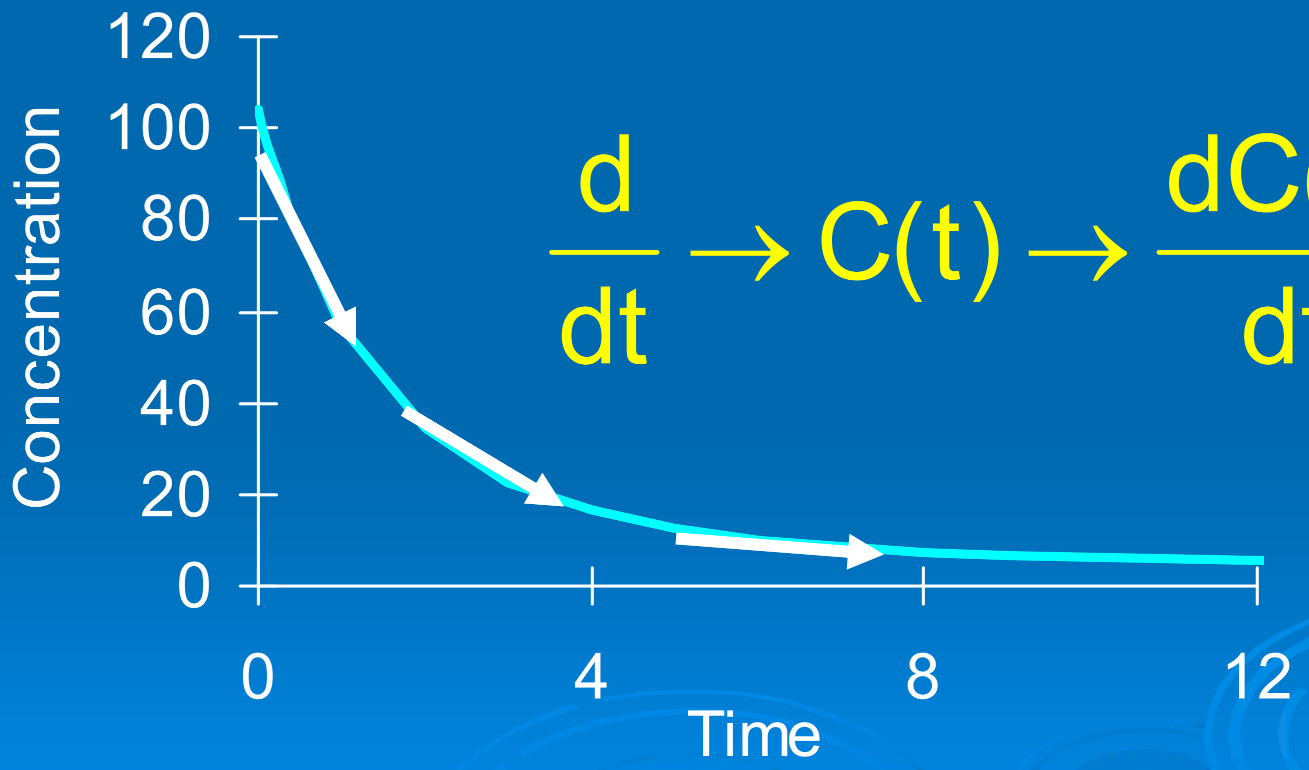
$$\rightarrow \frac{\partial X(x, y, z, t)}{\partial x}, \frac{\partial X(x, y, z, t)}{\partial y}, \frac{\partial X(x, y, z, t)}{\partial z}, \frac{\partial X(x, y, z, t)}{\partial t}$$

- 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*:



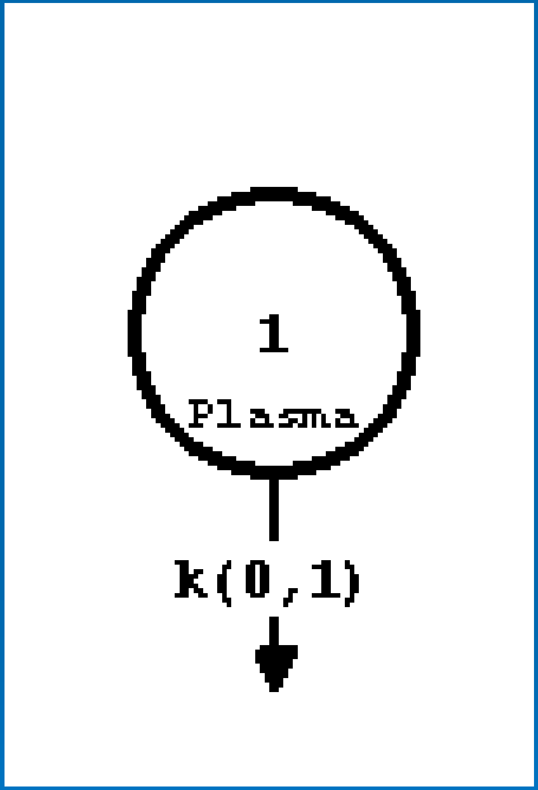
$$\frac{d}{dt} \rightarrow C(t) \rightarrow \frac{dC(t)}{dt}$$

- 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)

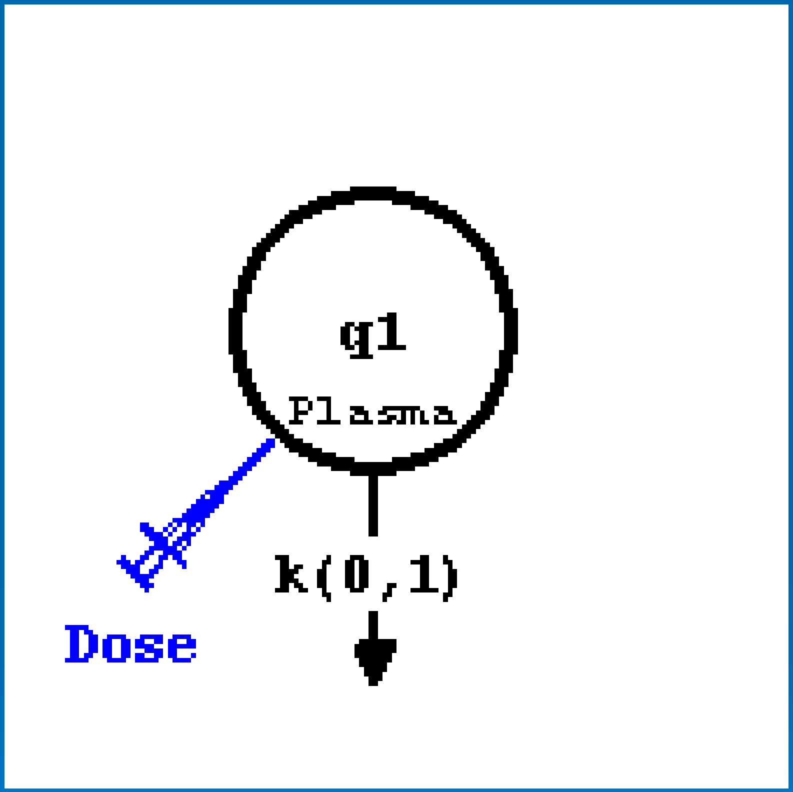
Single Compartment Model



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

- 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*

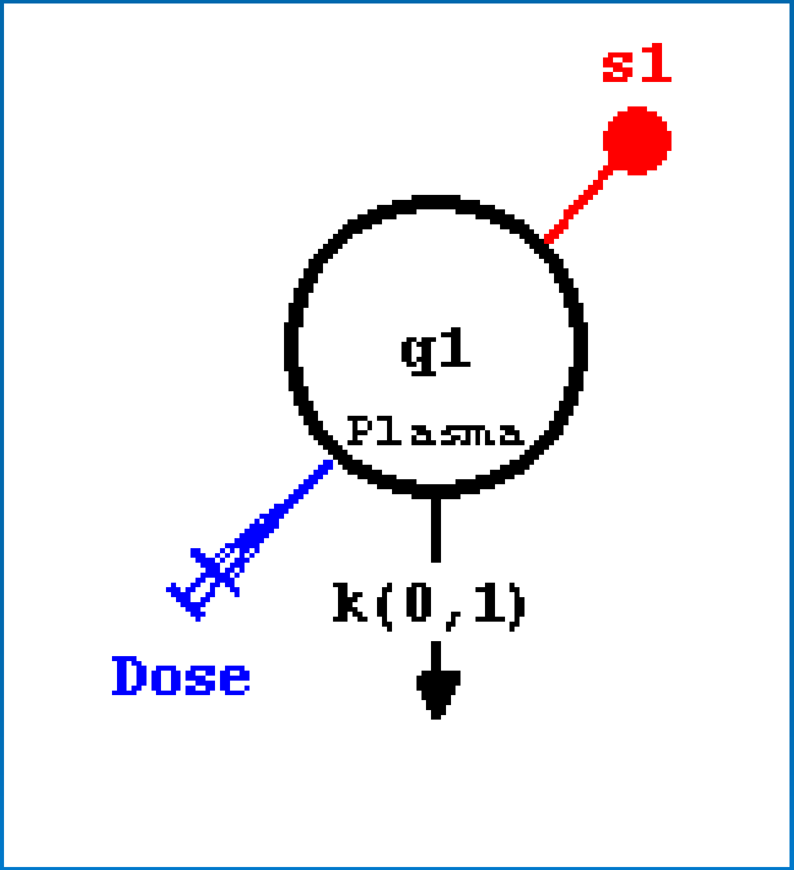
Experiment Design
Modeling Input Sites



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

- 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



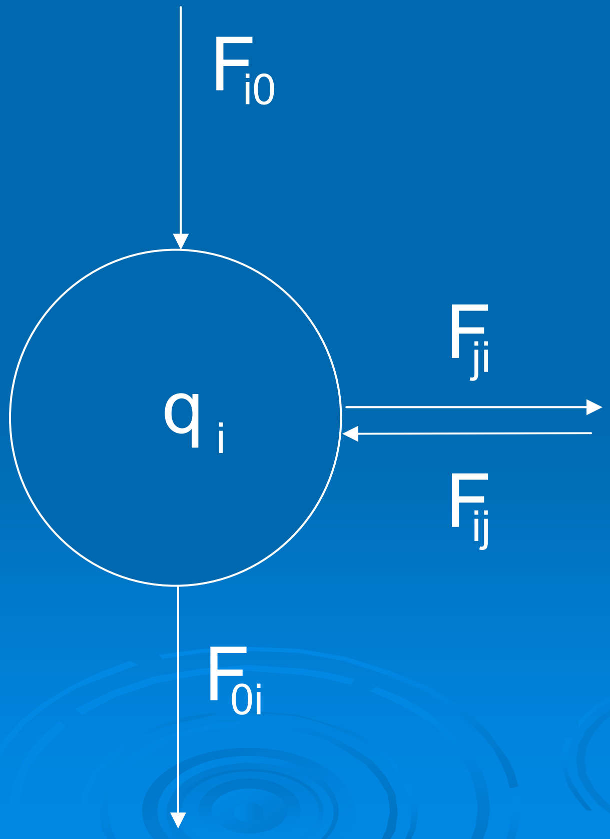
$$s1(t) = \frac{q_1(t)}{V}$$

- 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 <u>mass</u>, the measurement is <u>concentration</u>

  $\Rightarrow s1 = q_1 / V$
- V = volume of distribution of compartment 1

Notation

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



The 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 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

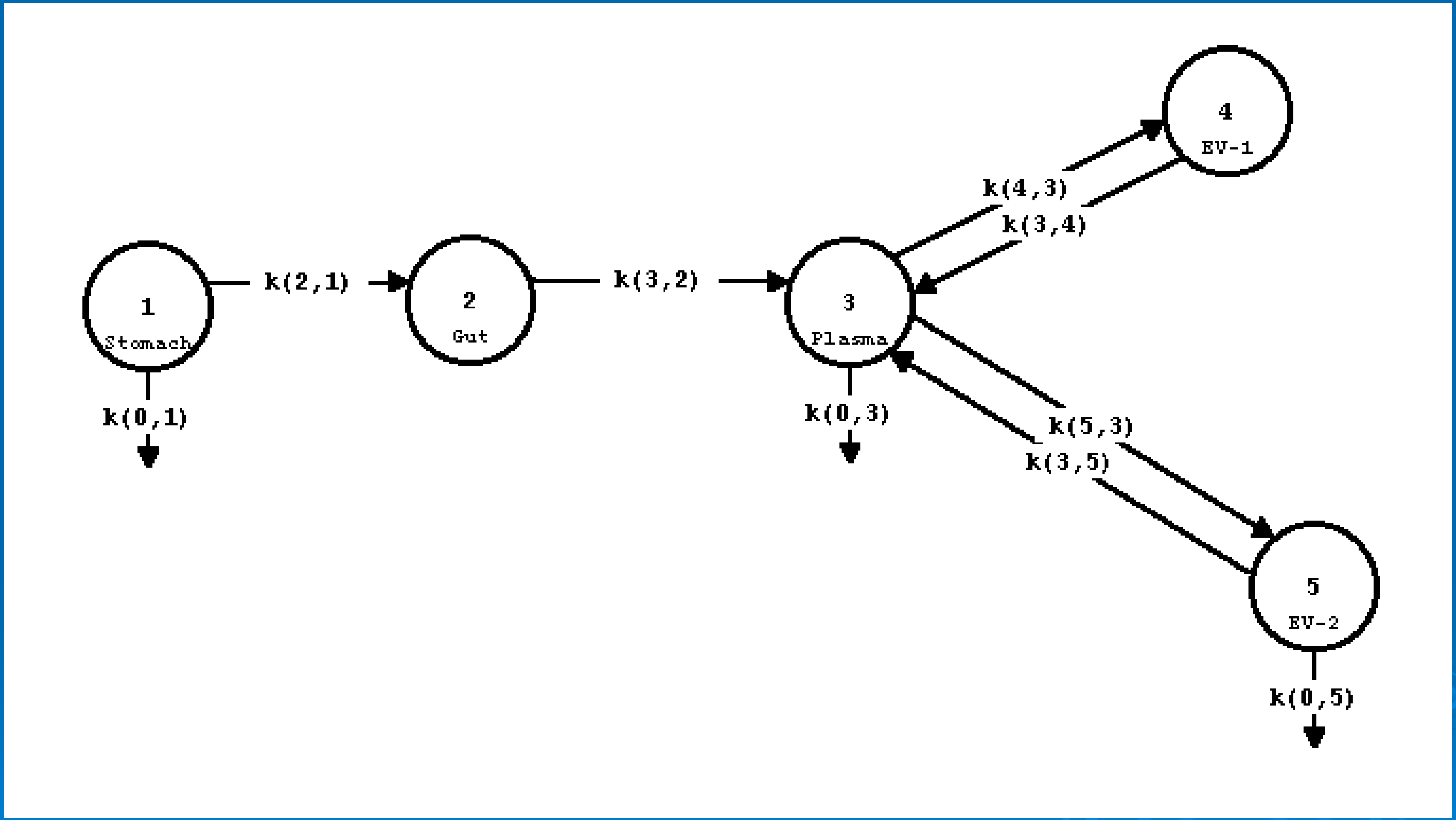
$$k_{ii} = -\left(\sum_{\substack{j=0 \\ j \neq i}}^{n} k_{ji} \right)$$

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

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



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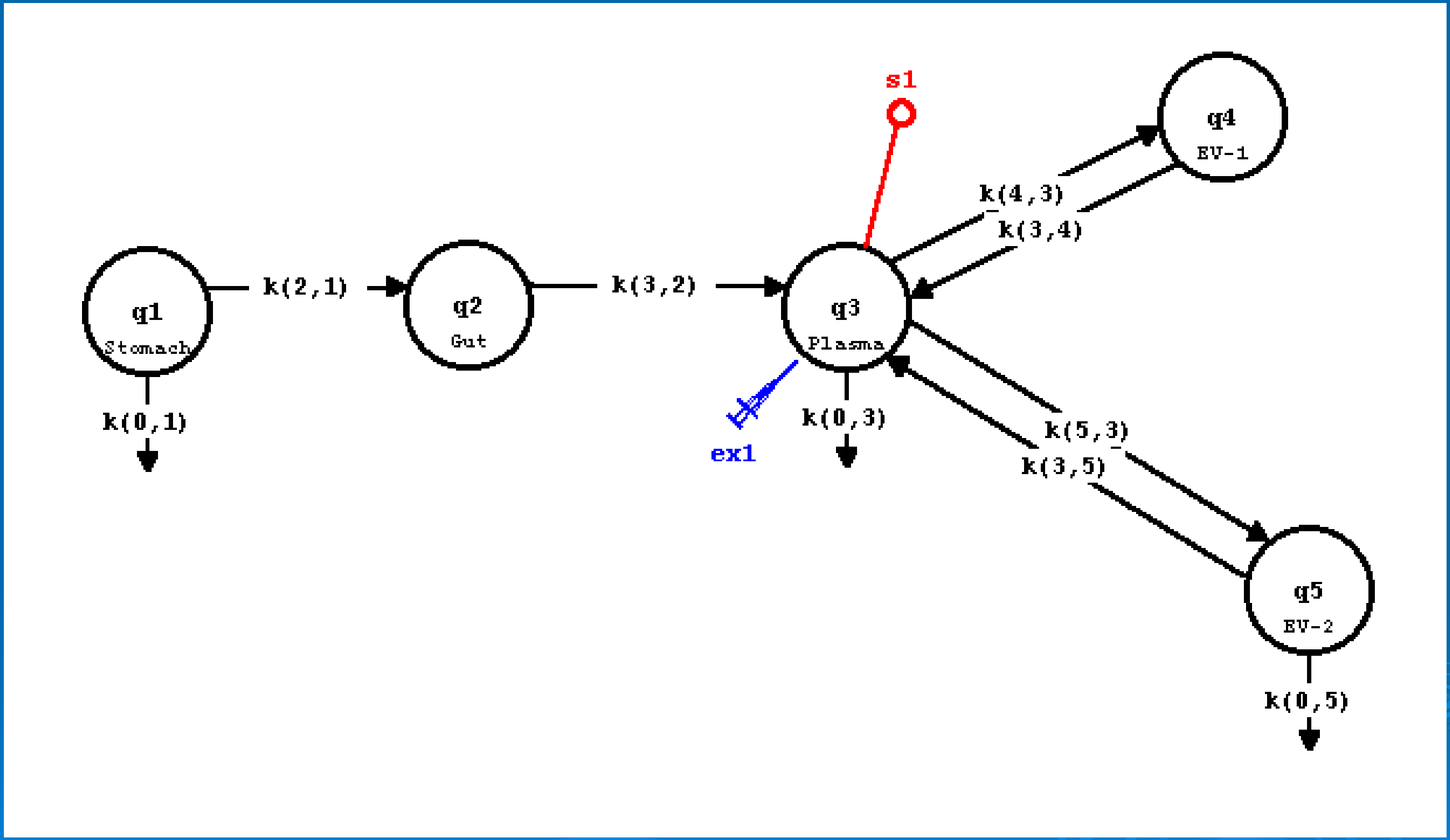
System Model with Experiment



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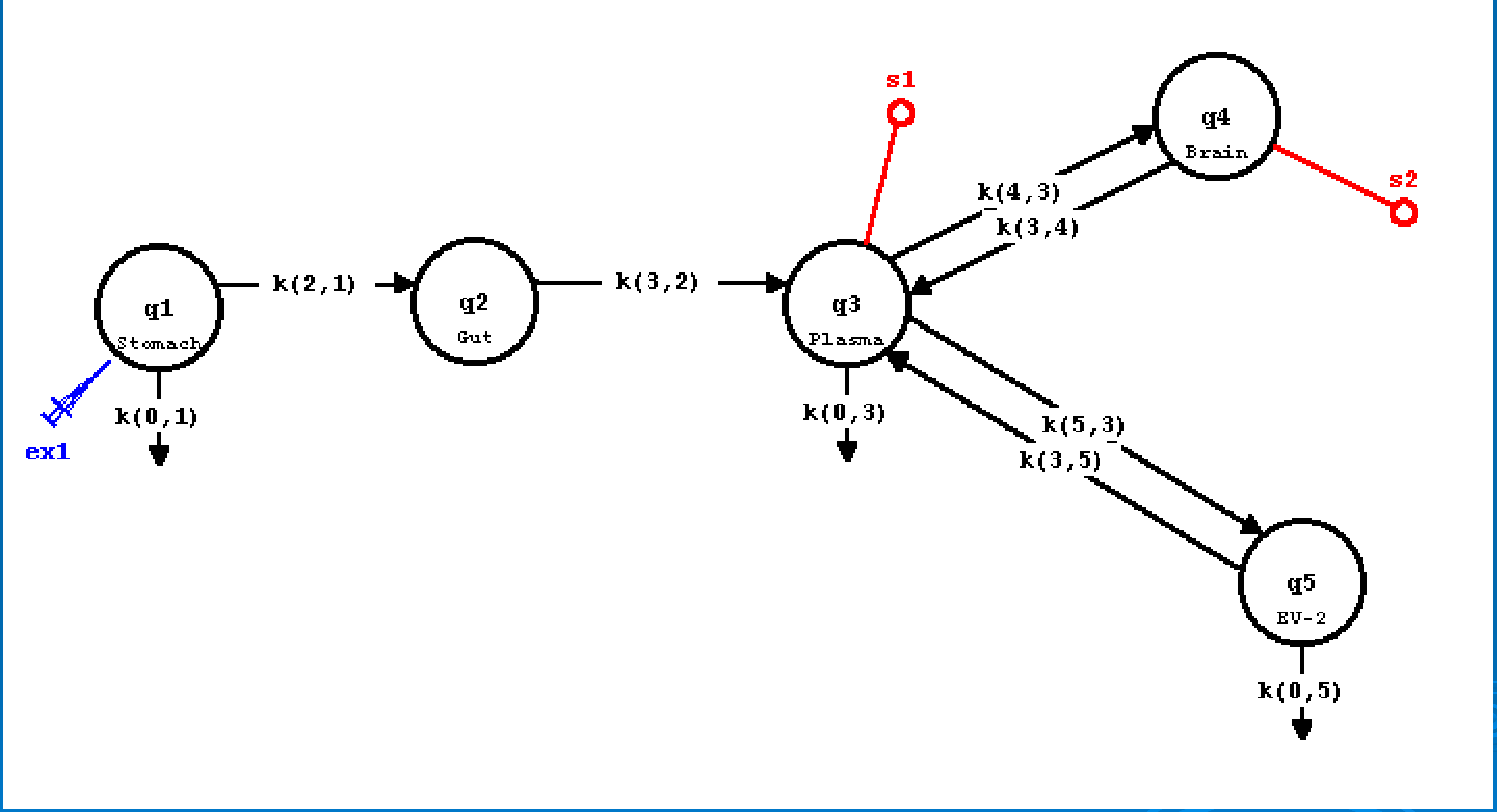
System Model with Experiment



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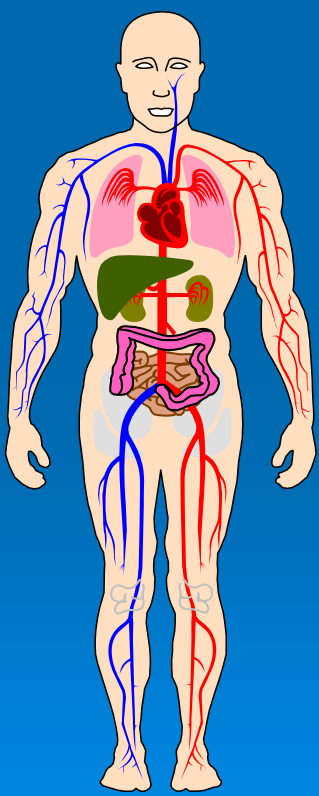
Experiments

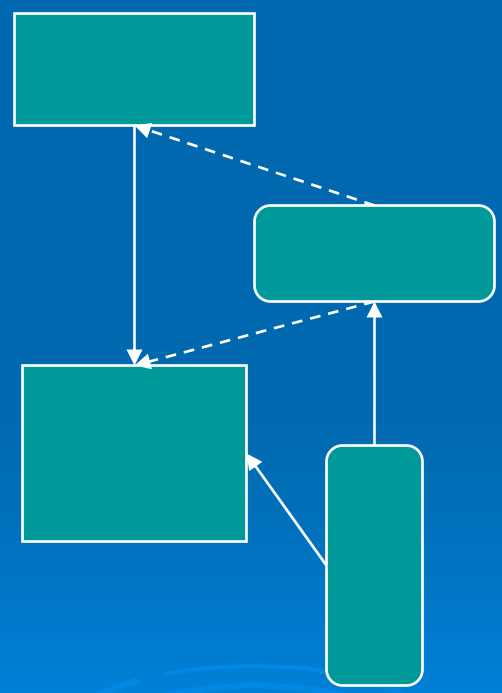
- Need to recreate the laboratory experiment on the model.
- Need to specify input and measurements
- Key: UNITS
  - Input usually in mass, or mass/time
  - Measurement usually concentration
    - Mass per unit volume

Model Of The System?

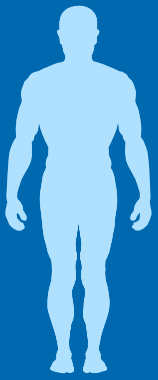
Reality (Data)



Conceptualization (Model)

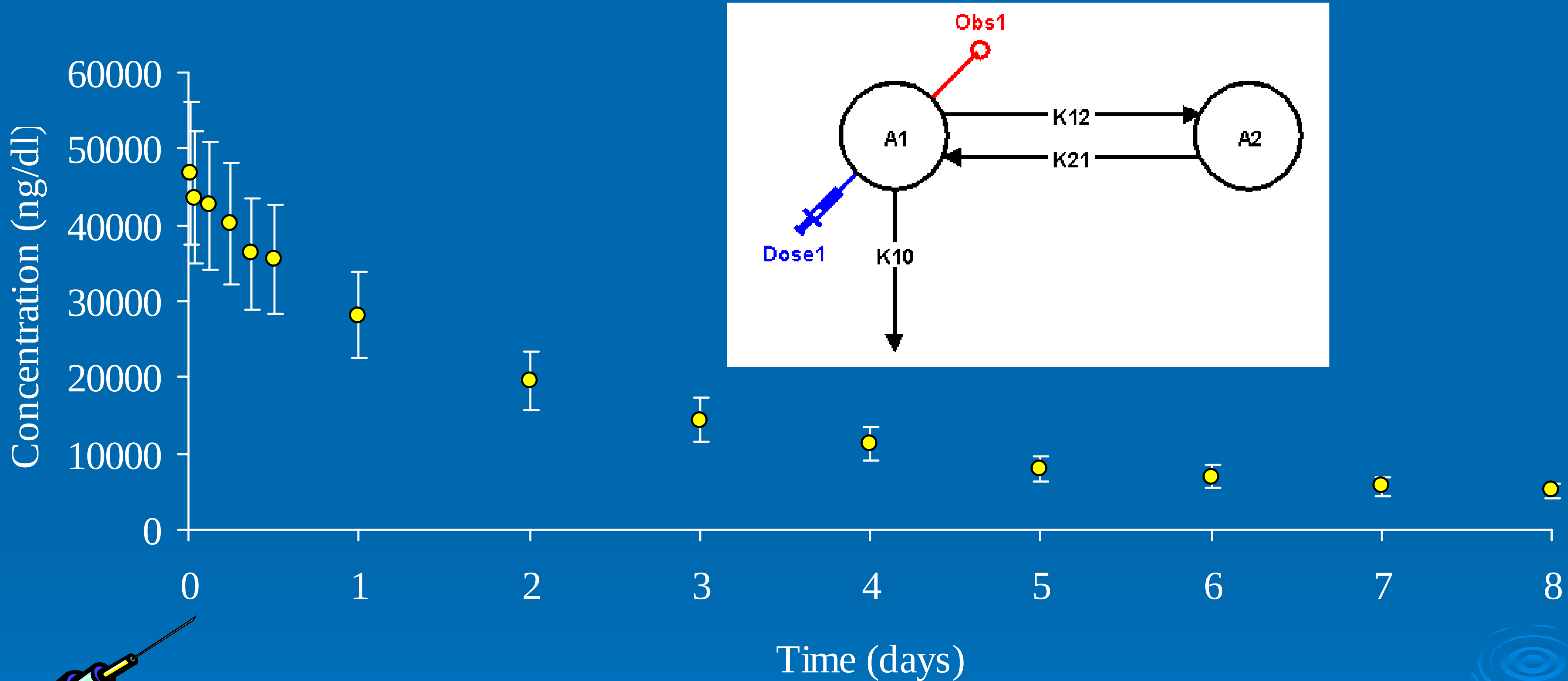


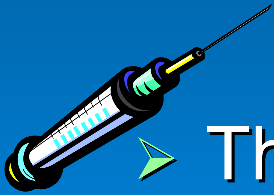
Data Analysis and Simulation



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

Pharmacokinetic Experiment
Collecting System Knowledge





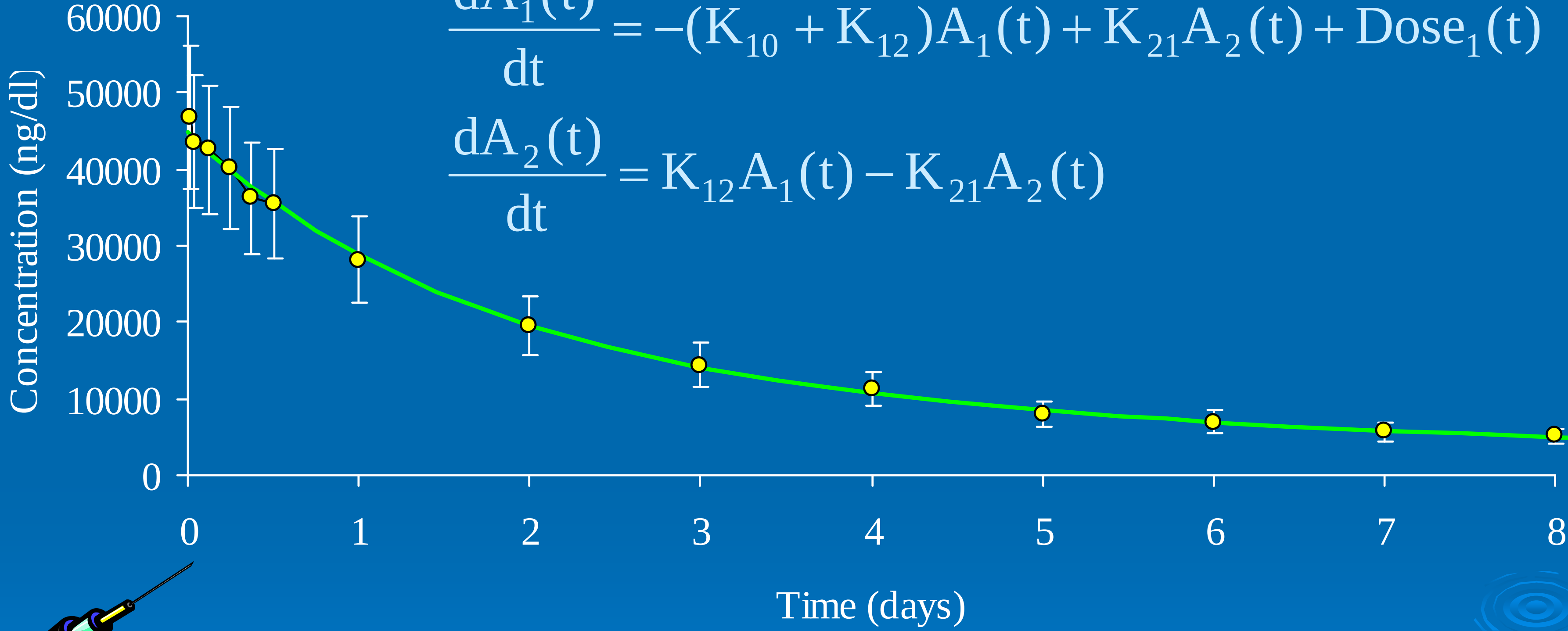
- The model starts as a qualitative construct, based on known physiology and further assumptions

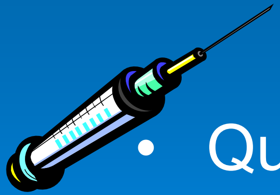
Data Analysis

Distilling Parameters From Data

$$\frac{dA_1(t)}{dt} = -(K_{10} + K_{12})A_1(t) + K_{21}A_2(t) + Dose_1(t)$$

$$\frac{dA_2(t)}{dt} = K_{12}A_1(t) - K_{21}A_2(t)$$





- 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 ⇒ Exponential

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

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

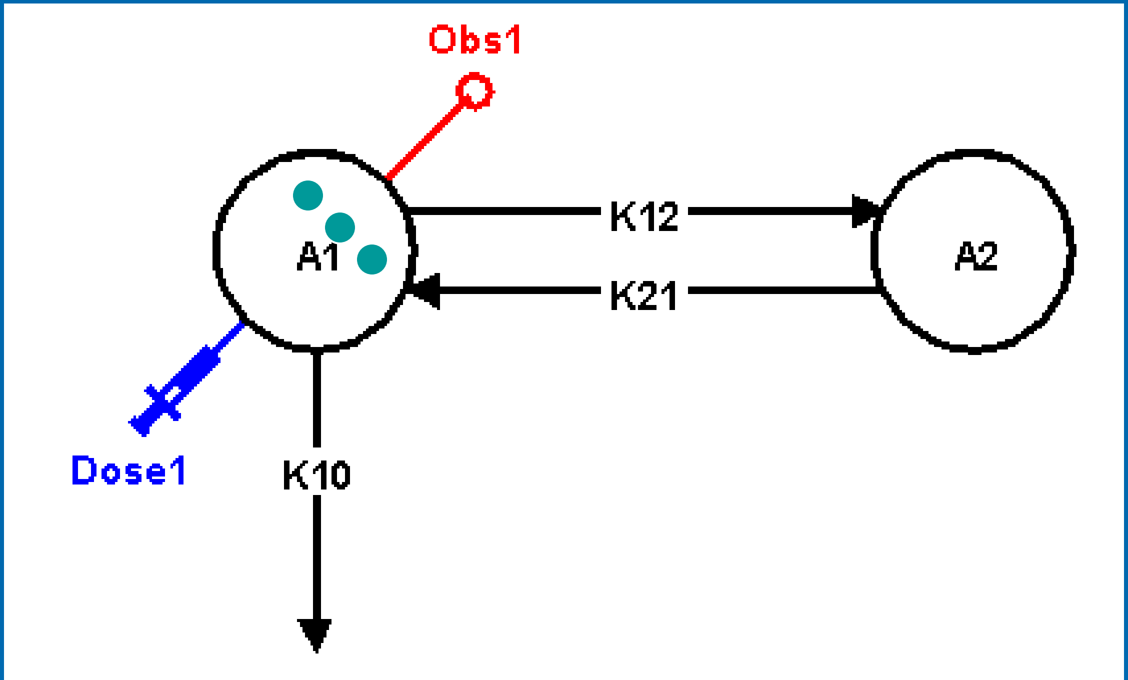
For a pulse input $\delta(t)$

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

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

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

Compartmental Residence Times



- Rate constants
- Residence times
- Intercompartmental clearances

Parameters Based Upon The Compartmental Matrix

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

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

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.

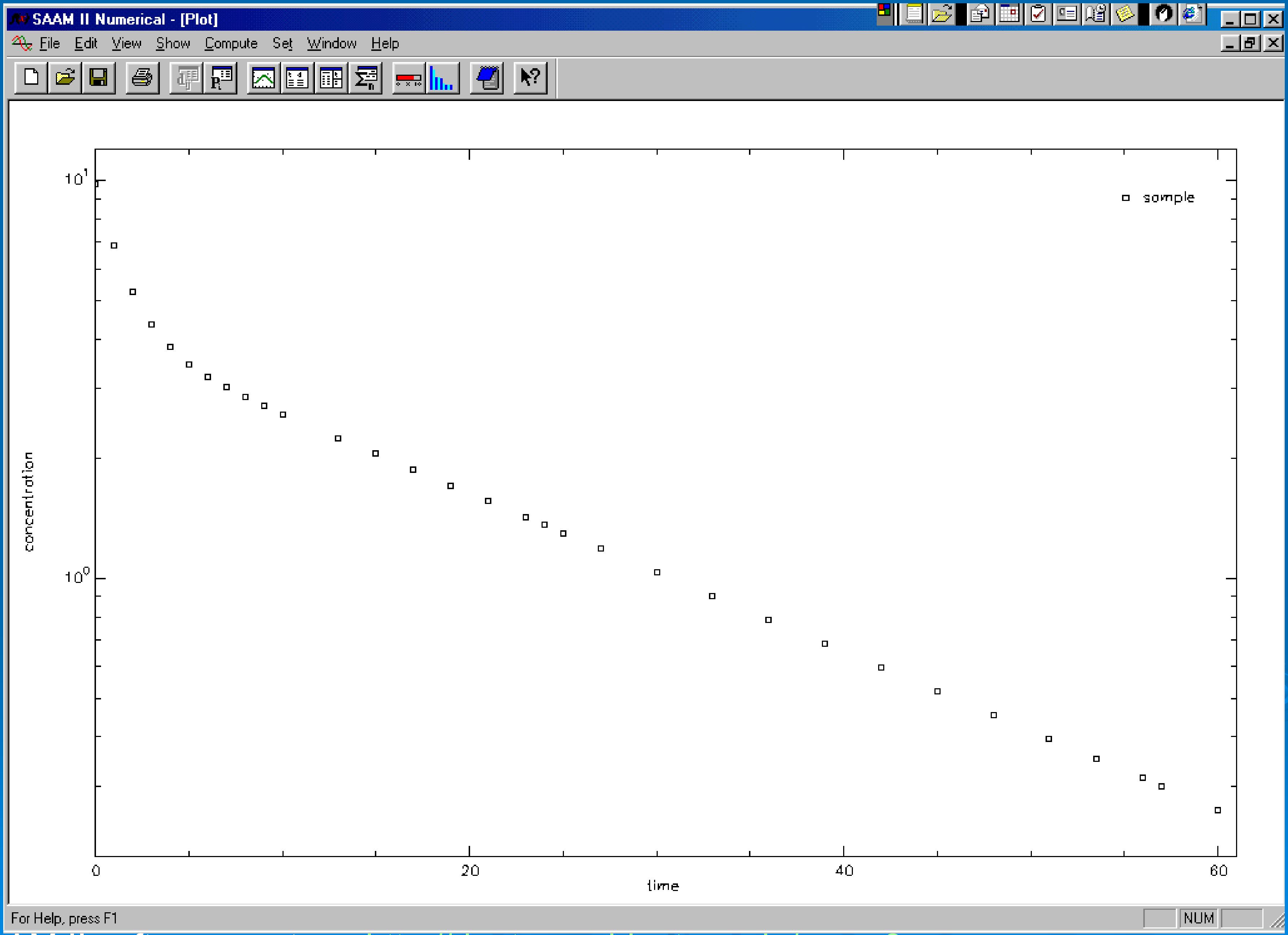
$\dfrac{\vartheta_{ij}}{\vartheta_{ii}}, \quad i \neq j$ The probability that a drug particle in compartment j will eventually pass through compartment i before leaving the system.

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

Noncompartmental Versus Compartmental Approaches To PK Analysis: A Example

- 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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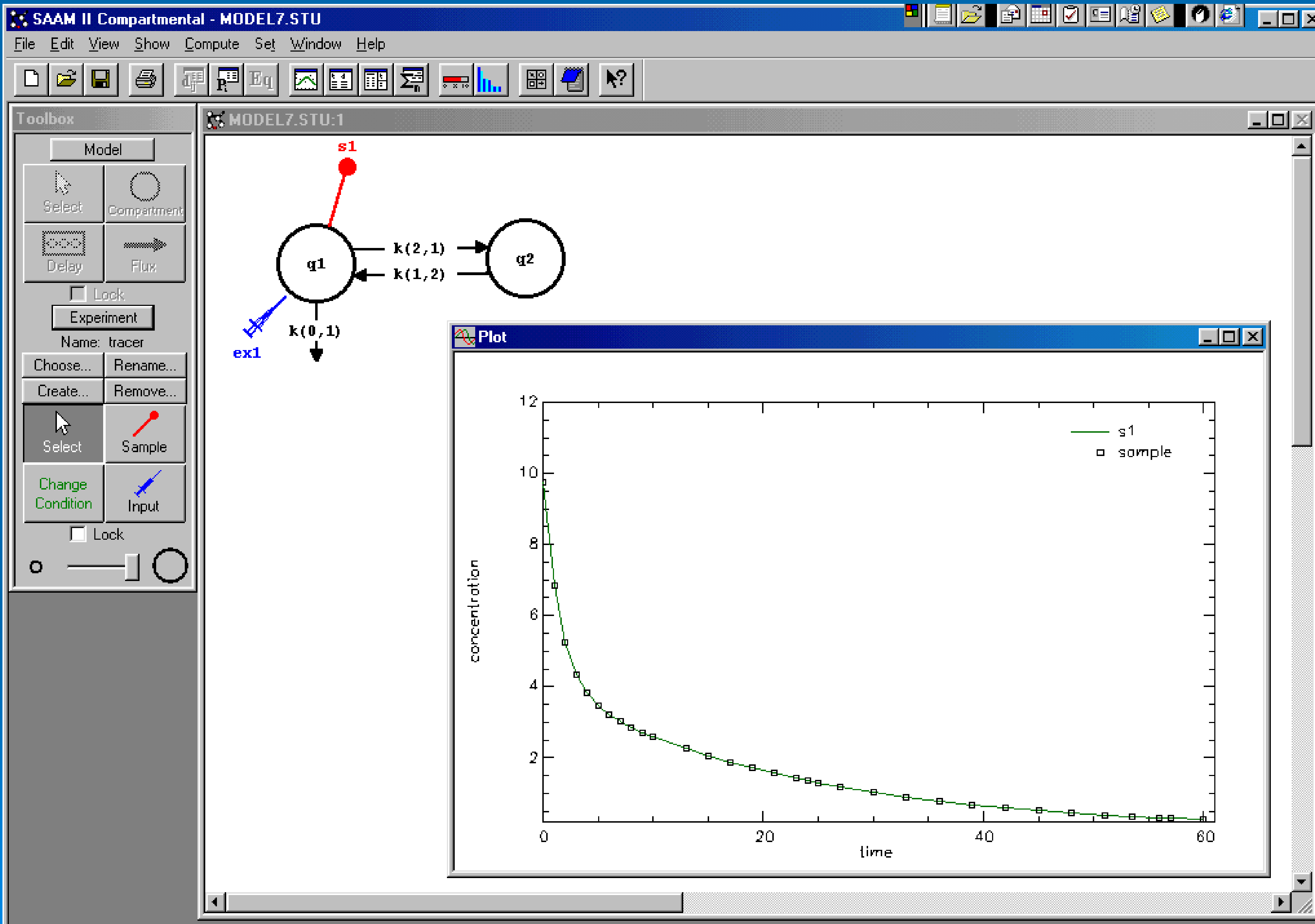

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Results

	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 okay when the sampling schedule is dense
- Sparse sampling schedule may be an issue for noncompartmental analysis
- Noncompartmental models are not predictive
- Best strategy is probably a blend: but, careful about assumptions!

Some References

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