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**
  - “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

PK

Disease

PD

Drug Concentration

Drug Effect

Disease Status

Time

Drug Concentration

Time
Hierarchical Variability

Residual Unknown Variation

within-individual (what the model does not explain – e.g. measurement error)
Hierarchical Variability

Between-Subject Variation

between-individual
(physiological variability)
Hierarchical Variability
Simultaneously Present Between-Subject and Residual Unknown Variation

*Biological sources?*
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

\[
\frac{\partial c(x, y, z, t)}{\partial x}, \quad \frac{\partial c(x, y, z, t)}{\partial y}, \quad \frac{\partial c(x, y, z, t)}{\partial z}, \quad \frac{\partial c(x, y, z, t)}{\partial t}
\]
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

INPUT

SOURCE

AP

SYSTEM

MEASURE

ELIMINATION
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

INPUT  SOURCE  MEASURE

SYSTEM  AP

ELIMINATION
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

INPUT

SOURCE

SYSTEM

MEASURE

ELIMINATION
Recirculation-exchange Assumptions

Recirculation/Exchange

AP
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

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

Concentration time-curve
center of mass

Time

Drug
Areas Under The Curve

- **AUMC**
  - Area Under the Moment Curve

- **AUC**
  - Area Under the Curve

- **MRT**
  - “Normalized” AUMC (units = time)

\[
MRT = \frac{\int_{0}^{+\infty} tC(t)dt}{\int_{0}^{+\infty} C(t)dt} = \frac{\text{AUMC}}{\text{AUC}}
\]
What Is Needed For MRT?

- Estimates for AUC and AUMC.
What Is Needed For MRT?

- Estimates for AUC and AUMC.
  
  \[
  \text{AUC} = \int_0^\infty C(t)dt = \int_0^{t_1} C(t)dt + \int_{t_1}^{t_n} C(t)dt + \int_{t_n}^\infty C(t)dt
  \]

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

- 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

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

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

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

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

\[
\text{AUMC} = \int_0^\infty t \cdot C(t)dt = \int_0^{t_1} t \cdot C(t)dt + \int_{t_1}^{t_n} t \cdot C(t)dt + \int_{t_n}^\infty t \cdot C(t)dt
\]
Trapezoidal Rule

- For every time \( t_i, i = 1, \ldots, n \)

\[
\text{AUC}_{i-1}^i = \frac{1}{2} \left[ y_{\text{obs}}(t_i) + y_{\text{obs}}(t_{i-1}) \right] (t_i - t_{i-1})
\]

\[
\text{AUMC}_{i-1}^i = \frac{1}{2} \left[ t_i \cdot y_{\text{obs}}(t_i) + t_{i-1} \cdot y_{\text{obs}}(t_{i-1}) \right] (t_i - t_{i-1})
\]
Log-trapezoidal Rule

- For every time $t_i$, $i = 1, \ldots, n$

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

$AUMC_{i-1}^i = \frac{1}{\ln\left(\frac{y_{obs}(t_i)}{y_{obs}(t_{i-1})}\right)} \left[t_i \cdot y_{obs}(t_i) + t_{i-1} \cdot y_{obs}(t_{i-1})\right](t_i - t_{i-1})$
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 $\lambda_z$.
- Half-life of terminal decay can be calculated:
  $$t_{z/2} = \frac{\ln(2)}{\lambda_z}$$
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

\[ CL = \frac{\text{DrugDose}}{\text{AUC}} \]
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

INPUT

SOURCE

MEASURE

SYSTEM

ELIMINATION
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**

\[
\frac{\partial}{\partial x}, \frac{\partial}{\partial y}, \frac{\partial}{\partial z}, \frac{\partial}{\partial t}
\]

\[\rightarrow X(x, y, z, t)\]

- **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*:

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

- 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

- 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.

\[
\frac{dq_1(t)}{dt} = -k(0,1)q_1(t)
\]
The rate of change of the amount in the compartment, \( q_1(t) \), is equal to what enters the compartment (Dose), minus what leaves the compartment, a quantity proportional to \( q(t) \).

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

Dose(t) can be any function of time.
Experiment Design
Modeling Measurement Sites

- The measurement (sample) $s_1$ does not subtract mass or perturb the system.
- The measurement equation $s_1$ 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).

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

$V = \text{volume of distribution of compartment 1}$
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 $q_i$

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

Fractional input from $q_j$

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

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

- Rate of change of $Q_i$
- Fractional loss of $Q_i$
- Fractional input from $Q_j$
- Input from "outside" (production rates)
The Compartmental Matrix

\[ k_{ii} = - \left( \sum_{j=0}^{n} k_{ji} \right) \]

\[ K = \begin{bmatrix} k_{11} & k_{12} & \cdots & k_{1n} \\ k_{21} & k_{22} & \cdots & k_{2n} \\ \vdots & \vdots & \ddots & \vdots \\ k_{n1} & k_{n2} & \cdots & k_{nn} \end{bmatrix} \]
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
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 \(\Rightarrow\) 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

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

\[ \Theta = -K^{-1} = \begin{bmatrix}
  \theta_{11} & \theta_{12} & \cdots & \theta_{1n} \\
  \theta_{21} & \theta_{22} & \cdots & \theta_{2n} \\
  \vdots & \vdots & \ddots & \vdots \\
  \theta_{n1} & \theta_{n2} & \cdots & \theta_{nn}
\end{bmatrix} \]

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

\( \vartheta_{ij} \)  

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
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
SAAM II software system, http://depts.washington.edu/saam2
SAAM II software system, http://depts.washington.edu/saam2
## Results

<table>
<thead>
<tr>
<th></th>
<th>Trapezoidal Analysis</th>
<th>Sum of Exponentials</th>
<th>Compartmental Model</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Volume</strong></td>
<td></td>
<td>10.2 (9%)</td>
<td>10.2 (3%)</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>1.02</td>
<td>1.02 (2%)</td>
<td>1.02 (1%)</td>
</tr>
<tr>
<td><strong>MRT</strong></td>
<td>19.5</td>
<td>20.1 (2%)</td>
<td>20.1 (1%)</td>
</tr>
<tr>
<td>$\lambda_z$</td>
<td>0.0504</td>
<td>0.0458 (3%)</td>
<td>0.0458 (1%)</td>
</tr>
<tr>
<td><strong>AUC</strong></td>
<td>97.8</td>
<td>97.9 (2%)</td>
<td>97.9 (1%)</td>
</tr>
<tr>
<td><strong>AUMC</strong></td>
<td>1908</td>
<td>1964 (3%)</td>
<td>1964 (1%)</td>
</tr>
</tbody>
</table>
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