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

Chart showing drug concentration over time. Another chart showing drug effect and drug concentration.

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

Three charts showing drug concentration over time (PK), drug effect by drug concentration (PD), and disease status over time (Disease).

Hierarchical Variability

No Variation

Graphical example

Hierarchical Variability
Residual Unknown Variation

Graph illustrating within-individual variability (what the model does not explain – e.g., measurement error).

Hierarchical Variability

Between-Subject Variation (physiological variability)

Graph illustrating between-individual variability.

Hierarchical Variability
Simultaneously Present Between-Subject and Residual Unknown Variation

Graph illustrating this concept.

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

Drawing of a man showing internal organs and systems relating to information in graphs of drug concentration versus time.

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 variable: s = (x, y, z)

Temporal: *When* in the system

- Temporal coordinates
- Key variable: t

Drawing of a box showing the Z-axis, the X-axis and the Y-axis.

A Drug In The Body:
Constantly Undergoing Change

Drawing of a man showing internal organs and systems relating to information in graphs of drug concentration versus time.

A Drug In The Body:
Constantly Undergoing Change

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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.

Drawing of a man showing internal organs and systems

Focus On The Accessible Pool

Diagram of system, input source, accessible pool and elimination pathway.

Characteristics Of The Accessible Pool

Kinetically Homogeneous
Instantaneously Well-mixed

Accessible Pool
Kinetically Homogeneous

Illustration of homogeneous distribution of drug molecules.

Accessible Pool
Instantaneously Well-Mixed

Two illustrations (A and B) for the accessible pool.

A = not mixed
B = well mixed

Probing The Accessible Pool

Diagram of accessible pool.

Drawing of a man showing internal organs and systems.

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

Two illustrations: System and model.

Recirculation-exchange Assumptions

Illustration of recirculation/exchange features in non-compartmental model.

Recirculation-exchange Assumptions

Illustration of recirculation/exchange features. Neither input nor output can occur through this component of the model.

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

Chart showing drug over time – concentration time-curve center of mass.

Areas Under The Curve

AUMC
- Area Under the Moment Curve

AUC
- Area Under the Curve

MRT
- "Normalized" AUMC (units = time)

Equation

What Is Needed For MRT?

- Estimates for AUC and AUMC.

Illustration of drug over time and AUC.

What Is Needed For MRT?

Estimates for AUC and AUMC.

Equations

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

Equations for AUC and AUMC

Bolus IV Injection

Formulas can be extended to other administration sites

Equations for AUC and AUMC

Estimating AUC And AUMC Using Other Methods

Trapezoidal
Log-trapezoidal
Combinations
Other
Role of extrapolation

Chart showing drug over time.

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.

Equations for AUC and AUMC

Trapezoidal Rule

For every time t_i, i = 1, …, n

Equations

Chart showing drug over time and the use of the trapezoidal rule.

Log-trapezoidal Rule

For every time (equation)

Additional equations to estimate AUC and AUMC.

Trapezoidal Rule Potential Pitfalls

Two charts showing a drug over time.

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:

Equation for t-lambda ½.

Extrapolating From t_n To Infinity

Equations for AUC and AUMC.

From last data point:

From last calculated value:

Extrapolating From t_n To Infinity

Extrapolating function crucial

Chart showing drug over time and how extrapolating function can change terminal slope.

Estimating The Integrals

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

Equations for AUC and AUMC

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

Formula for clearance = elimination rate over concentration in blood.

It can be shown that clearance = drug dose over AUC.

Remember Our Assumptions

If these are not verified the estimates will be incorrect

Illustration showing recirculation/exchange.

The Compartmental Model

Single Accessible Pool

Illustration of system and the source and elimination.

Single Accessible Pool Models

Illustration of a Noncompartmental model

Illustration of a Compartmental model

A Model Of The System

Illustration of a house with multiple systems and a drawing of a human figure trying to determine the accessible and inaccessible components.

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

Differential equations

Time

Differential equations

Demystifying Differential Equations

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

Chart showing concentration over time.

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

Drawing of 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*

Differential equation

Experiment Design
Modeling Input Sites

Drawing of single compartmental model.

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

Differential equation

Experiment Design
Modeling Measurement Sites

Illustration of a single compartmental model.

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

Equation

Notation

Illustration of one-compartment model.

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

Equation for Fji as a function of q,p, and Kji.

(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.

Equation for Kij

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

Differential equation for changes in mass Qj over time.

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

Differential equation for changes in mass Qj over time.

The Compartmental Matrix

Equations for transfer rate constants.

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

Illustration of multiple compartmental model.

SAAM II software system,

System Model with Experiment

Illustration of a multiple compartmental model.

SAAM II software system,

System Model with Experiment

Illustation of a multiple compartmental model.

SAAM II software system,

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?

Illustration of reality (data), conceptualization (model), and data analysis and simulation.

Pharmacokinetic Experiment

Collecting System Knowledge

Chart illustrating concentration (ng/dl) over time (days) and a two compartment model.

Illustration of a hypodermic needle.

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

Data Analysis

Distilling Parameters From Data

Differential equations.

Chart illustrating concentration (ng/dl) over time (days).

- 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

Differential equations. Calculation of clearance as product of K(0,1) times compartment volume.

Compartmental Residence Times

Illustration of a two compartmental model showing

Rate constants
Residence times
Intercompartmental clearances

Parameters Based Upon The Compartmental Matrix

Formulas for transfer rate constants.

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

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

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

Chart

Plasma concentration versus time plot.

Chart

Diagram of 2-compartment model and plasma concentration versus time curve.

Results

Chart showing the trapezoidal analysis, sum of exponentials, and compartment model for volume, clearance, MRT, lambda **z, AUC, and AUMC.**

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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