Noncompartmental vs. Compartmental Approaches to Pharmacokinetic Data Analysis

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October 28, 2010

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 – i.e. measurement error)

Hierarchical Variability
Between-Subject Variation

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

⟶ ADME

- Absorption, Distribution, Metabolism, Excretion

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

➤ <u>Spatial</u>: *Where* in the system
- ● Spatial coordinates
- ● Key variables: (x, y, z)

➤ <u>Temporal</u>: *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:
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Drawing of a man showing internal organs and systems relating to information in graphs of drug concentration versus time.

A Drug In The Body:
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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:
- o Noncompartmental models
  - ▪ Based on algebraic equations
- o 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

(see e.g. Cobelli et al.)

Accessible Pool
Instantaneously Well-Mixed

Two illustrations (A and B) for the accessible pool

➢ A = not mixed
➢ B = well mixed

Ref. see e.g. Cobelli et al.

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 modes

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 t_i, i = 1, …, n

Additional equation 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 λ_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 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

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

➢ In addition, this approach cannot straightforwardly handle nonlinearities in the data (time-varying rates, saturation processes, etc.)

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 a single compartmental 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 a single compartment 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

Drawing of a single compartment 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 <u>mass</u>, the measurement is <u>concentration</u>
  $\square$ s1 = q_1 /V

➢ V = volume of distribution of compartment 1

Equation

Notation

Illustration of one-compartment model

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

Equation for Fij as a function of q, p and Kij

(ref. see Jacquez and Simon)

Nonlinear Kinetics Example

➤ Remember the one-compartment model:

Equations of a single compartment model

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

Nonlinear Kinetics:
Michaelis-Menten

➢ Michaelis-Menten kinetics:

Equation of a single compartment model with Michaelis-Menten elimination

➢ Vm = maximal metabolic rate

➢ Km = Michaelis-Menten constant

Linear vs. Nonlinear Kinetics

➢ If Km >> c(t) then:

Equation showing first-order elimination rate

➢ 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:

Equation showing zero-order elimination rate

➢ 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?

Equation of a single compartment model with nonlinear elimination rate

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

Tracking Nonlinearities

Equation of a single compartment model

Graph of concentration over time on a linear scale

Tracking Nonlinearities

Equation of a single compartment model

Graph of concentration over time on a semilogarithmic scale

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.

Equations for Kij

Compartmental Models And Systems Of Ordinary Differential Equations

➢ Good mixing
- permits writing $q_i(t)$ for the ith compartment.

➢ Kinetic homogeneity
- permits connecting compartments via the k_{ij}.

The ith Compartment

Differential equation for change 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 ith Compartment

Differential equation for change 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

System Model with Experiment

Illustration of a multiple compartmental model

System Model with Experiment

Illustration of a multiple compartmental model

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 (mg/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 (mg/dl) over time (days)

- o Qualitative model -> quantitative differential equations with parameters of physiological interest
- o 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

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

Compartmental Residence Times

Illustration of a two compartment 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

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

Four panels showing AUC, Clearance, VSS and Half-life

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

Diagram of a compartmental model

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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