MODELING OF POPULATION PK-PD DATA

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Raleigh, NC, July 13, 2010

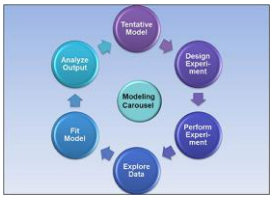
Disclosures, Affiliations, and Acknowledgements

Contributors to the ideas presented today include:

- All the authors of the work that is cited in the presentation
- **Disclosures**
- PV is an employee of MedImmune, a wholly owned subsidiary of AstraZeneca
- PV is on the Editorial Advisory Board of the *Journal of Pharmacokinetics and Pharmacodynamics* and is an Associate Editor of *Clinical Pharmacology & Therapeutics: Pharmacometrics & Systems Pharmacology*
- PV past employment includes Pfizer and the University of Washington
- PV receives royalties from the University of Washington Center for Commercialization

Suggested additional reading

- Additional reading has been hyperlinked in the slides
- Accessing the hyperlink will take the reader to the NCBI/PubMed link or to the original source



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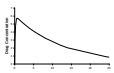
Pharmacokinetics (PK) and Pharmacodynamics (PD)

Dose
↓
Pharmacokinetics
↓
Concentration
↓
Pharmacodynamics
↓
Effect

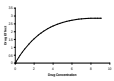
Pharmacokinetics

- "What the body does to the drug"
- Fairly established
- Key: **concentration**

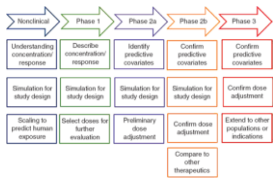


Pharmacodynamics

- "What the drug does to the body"
- Less certain
- Key: **effect**



Modeling and Simulation During Drug Development



CPT: Pharmacometrics & Systems Pharmacology
Volume: 1, Issue: 2, pages 1-14, 26 SEP 2012 DOI: 10.1038/psp.2012.4
http://onlinelibrary.wiley.com/doi/10.1038/psp.2012.4/full#psp4201x24-fig-5001

What Is Pharmacometrics?

- "*Pharmacometrics can be defined as that branch of science concerned with mathematical models of biology, pharmacology, disease, and physiology used to describe and quantify interactions between xenobiotics and patients, including beneficial effects and side effects resultant from such interfaces.*"
- Pharmacometrics is the science that quantifies drug, disease and trial information to aid efficient drug development and/or regulatory decisions.
  - Drug models describe the relationship between exposure (or pharmacokinetics), response (or pharmacodynamics) for both desired and undesired effects, and individual patient characteristics. Disease models describe the relationship between biomarkers and clinical outcomes, time course of disease and placebo effects.
  - The trial models describe the inclusion/exclusion criteria, patient dis-continuation and adherence.

Pharmacometrics: a multidisciplinary field to facilitate critical thinking in drug development and translational research settings. Barrett JS, Fossler MJ, Cadieu KD, Gastonguay MR. J Clin Pharmacol. 2008 May;48(5):632-49. doi: 10.1177/0091270008315318.
Pharmacometrics at FDA: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm167032.htm

PK-PD Models (Mechanistic or Descriptive)

- There is a large variety of nonlinear models (usually based on ordinary differential equations) to describe PK and PD data
- The unknown parameters of these models are thought to reflect the biological processes at the basis of drug disposition and efficacy
- Challenge: how to estimate these parameters from measurements gathered in the practice of drug development

Pharmacodynamics: Direct Effect

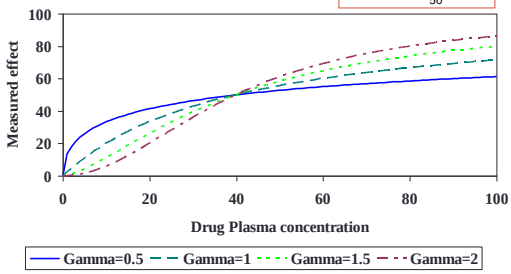
- Pharmacodynamic effect E is directly linked to the plasma concentration C
- Model: *Emax model* or *Hill function*

$$E(C) = \frac{E_{max} \cdot C}{EC_{50} + C}$$

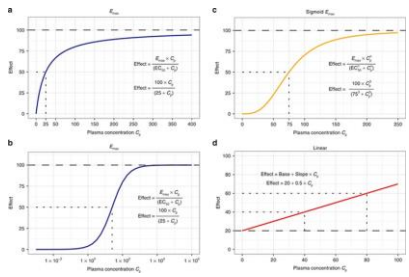
$$E(C) = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\ \gamma} + C^{\gamma}}$$

A Graphical Representation of Direct Effects

$$E(C) = \frac{E_{max} \cdot C^{\gamma}}{EC_{50}^{\ \gamma} + C^{\gamma}}$$



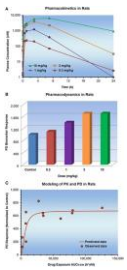
Pharmacodynamic Relationships



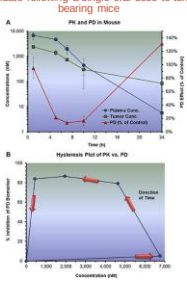
CPT: Pharmacometrics & Systems Pharmacology
Volume 3, Issue 1, pages 1-16, 2 JAN 2014 DOI: 10.1038/psp.2013.71
http://onlinelibrary.wiley.com/doi/10.1038/psp.2013.71/full#psp4201371-fig-0003

Direct vs. Indirect Pharmacodynamics

Dose dependent PK and PD observed in a rat model of diabetes



Effect vs. plasma concentration of a drug candidate following a single oral dose to tumor bearing mice



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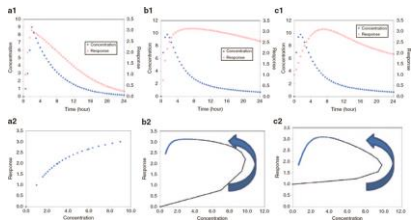
Interpreting Pharmacodynamic Plots



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http://onlinelibrary.wiley.com/doi/10.1038/psp.2013.71/full#psp4201371-fig-0002

Delay (Link) Models

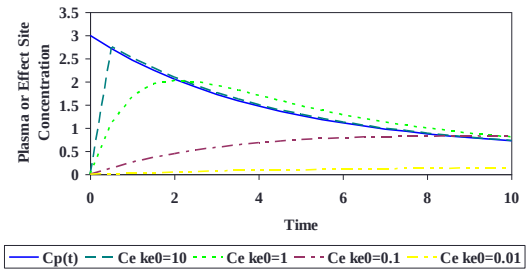
- When the effect is delayed with respect to observed plasma concentration

$$Cp(t) = \frac{D}{V} e^{-\frac{CL}{V}t}$$ Plasma Concentration

$$\frac{dCe(t)}{dt} = k_{e0}[Cp(t) - Ce(t)]$$ Effect Site Concentration

$$E(Ce) = \frac{E_{max} \cdot Ce^{\gamma}}{EC_{50}^{\gamma} + Ce^{\gamma}}$$ Pharmacodynamic Effect

Delay (Link) Model in Practice

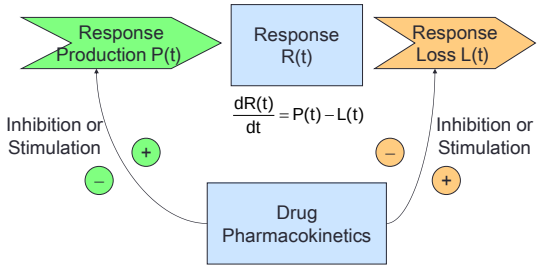


Cp(t) = Plasma concentration; Ce(t) = Effect site concentration

Holford NH, Sheiner LB. "Kinetics of pharmacologic response" Pharmacol Ther. 1982;16(2):143-66. Review. http://www.ncbi.nlm.nih.gov/pubmed/6752972

Indirect Response (Turnover) Models

- Based on the drug eliciting (changes in) the homeostasis of endogenous substances (we will revisit this later)



Types of Indirect Response Models

(Intuition: Balance between Production and Loss)

- Inhibition of production

$$\frac{dR(t)}{dt} = k_{in}\left[1 - \frac{I_{max} \cdot Cp(t)}{IC_{50} + Cp(t)}\right] - k_{out}R(t)$$

- Stimulation of production

$$\frac{dR(t)}{dt} = k_{in}\left[1 + \frac{S_{max} \cdot Cp(t)}{SC_{50} + Cp(t)}\right] - k_{out}R(t)$$

- Inhibition of loss

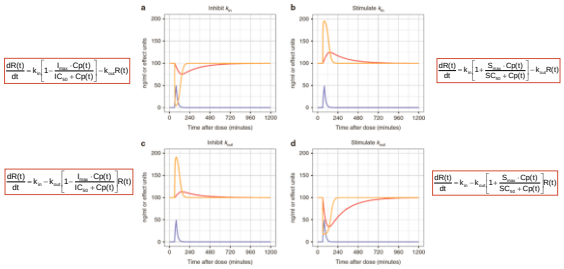
$$\frac{dR(t)}{dt} = k_{in} - k_{out}\left[1 - \frac{I_{max} \cdot Cp(t)}{IC_{50} + Cp(t)}\right]R(t)$$

- Stimulation of loss

$$\frac{dR(t)}{dt} = k_{in} - k_{out}\left[1 + \frac{S_{max} \cdot Cp(t)}{SC_{50} + Cp(t)}\right]R(t)$$

Sharma A, Jusko WJ, "Characteristics of indirect pharmacodynamic models and applications to clinical drug responses" Br J Clin Pharmacol. 1998 Mar;45(3):229-39. Review. http://www.ncbi.nlm.nih.gov/pubmed/9517366

Drug Effects in Turnover Models



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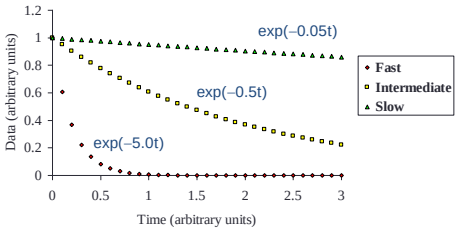
The Role of Variability

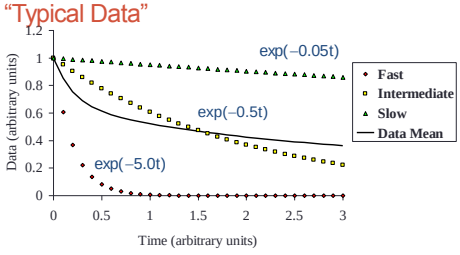
- Biological *variability*, superimposed to *typical values*, is always present when dealing with PK and PD measurements
- It must be distinguished from *uncertainty*
- First and foremost is quantification of variability from available data
- Once quantified, variability can then be used to simulate (extrapolate or predict) unobserved experiments

Estimating Variability with Nonlinear Models



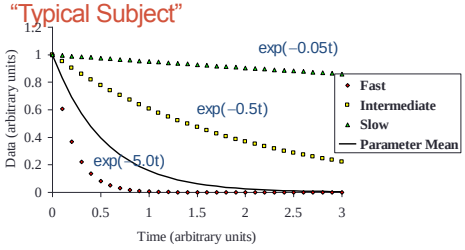
What would be the "right typical value"?

Averaging Measurements "Typical Data"



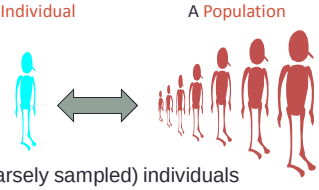
$$\text{Mean of the Data} = \frac{\exp(-0.05t) + \exp(-0.5t) + \exp(-5.0t)}{3}$$

Averaging Model Parameters "Typical Subject"



$$\text{Mean of the Parameters} = \exp\left(\frac{-0.05 + 0.5 + 5.0}{3} t\right)$$

How To Estimate Parameters from Sparse Data? Statistical Modeling Is Needed



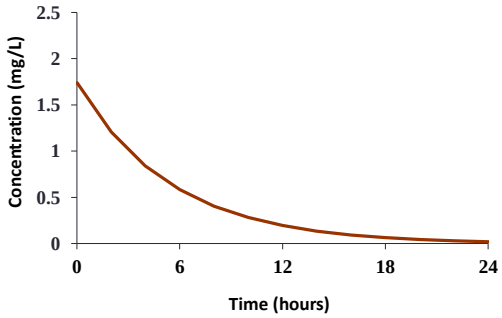
- Many (sparsely sampled) individuals

⇒*population* rather than *individual* response

- Statistical issues become paramount
- Goal: characterize (by modeling) variability sources

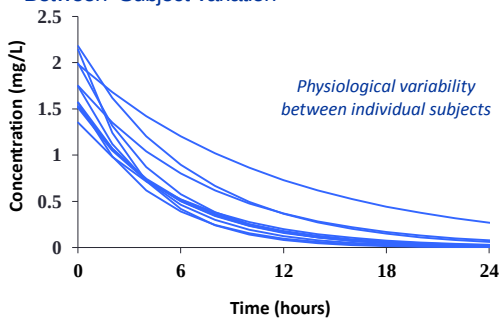
Sources of Hierarchical Variability

No Variation



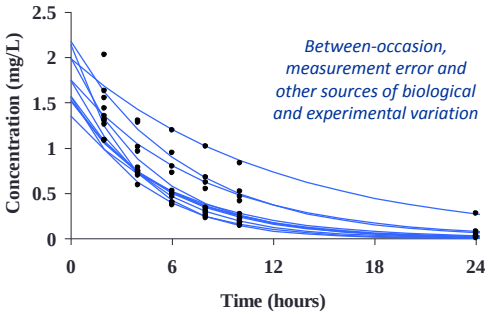
Sources of Hierarchical Variability

Between–Subject Variation



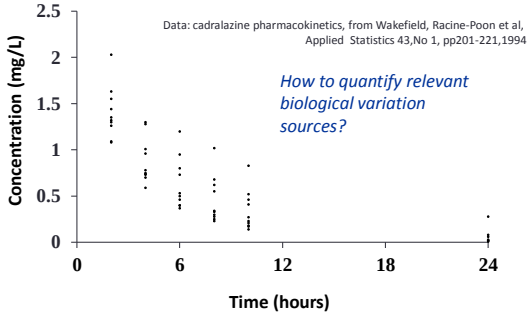
Sources of Hierarchical Variability

Residual Unknown Variation



Sources of Hierarchical Variability

Actual Measurements



Individual vs. Population

- Population data are necessary to extract biological variability information
- Individual parameter estimation is the cornerstone of population analysis
- It turns out that it is often preferable to extract population parameters directly (from the ensemble of population data) as opposed to deriving them from individual estimates
- From a didactic standpoint, we will start with individual analysis and now we will move on to parametric population analysis

Parameter Estimation

- The idea is to "match" model prediction to measurements in some unambiguous, meaningful way and in doing so quantify parameters that relate to biology and drug action
- Most often, parameters are estimated via some kind of maximum likelihood approach; the approach is usually termed "extended least squares"
- Optimization (most often minimization) of an objective function matching model to data is used to choose the "best" parameters

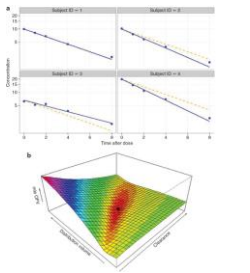
Individual Extended Least Squares

- Extended least squares (ELS) was introduced by Stuart Beal (UCSF) in the context of development of the software NONMEM
- It arises from Gaussian maximum likelihood and the hypothesis of prediction-dependent measurement errors

$$\hat{\theta},\hat{\sigma} = \underset{\theta,\sigma}{\operatorname{argmin}} -\log L(\theta,\sigma)$$

$$-\log L(\theta,\sigma) = \frac{1}{2}\sum_{j=1}^{n}\left[\frac{y_j - s_j(\theta)}{V_j(\theta,\sigma)}\right]^2 + \frac{1}{2}\ln\left[V_j(\theta,\sigma)\right]$$

A simple population pharmacokinetics model



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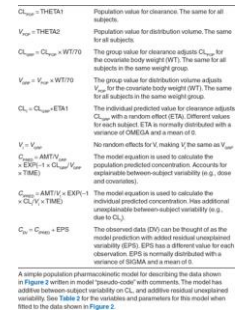
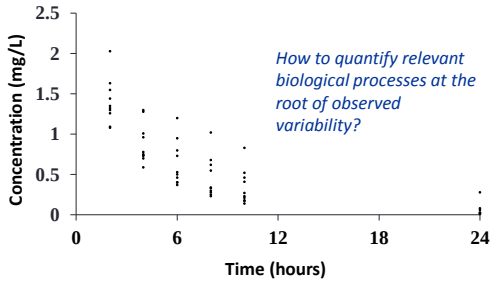


$Cl_{pop} = THETA1$	Population value for clearance. The same for all subjects.
$V_{pop} = THETA2$	Population value for distribution volume. The same for all subjects.
$Cl_{pop} = Cl_{pop} \times WT/70$	The group value for clearance adjusts Cl_{pop} for the covariate body weight (WT). The same for all subjects in the same weight group.
$V_{par} = V_{pop} \times WT/70$	The group value for distribution volume adjusts V_{pop} for the covariate body weight (WT). The same for all subjects in the same weight group.
$Cl_i = Cl_{pop} + ETA1$	The individual predicted value for clearance adjusts Cl_{pop} with a random effect (ETA). Different values for each subject. ETA is normally distributed with a variance of OMEGA and a mean of 0.
$V_i = V_{par}$	No random effects for V_i making V_i the same as V_{par}
$C_{pred} = AMT/V_{par} \times EXP(-1 \times Cl_{pop}/V_{par} \times TIME)$	The model equation is used to calculate the population predicted concentration. Accounts for explainable between-subject variability (e.g., dose and covariates).
$C_{pred} = AMT/V_i \times EXP(-1 \times Cl_i/V_i \times TIME)$	The model equation is used to calculate the individual predicted concentration. Has additional unexplainable between-subject variability (e.g., due to Cl_i).
$C_{ob} = C_{pred} + EPS$	The observed data (DV) can be thought of as the model prediction with added residual unexplained variability (EPS). EPS has a different value for each observation. EPS is normally distributed with a variance of SIGMA and a mean of 0.

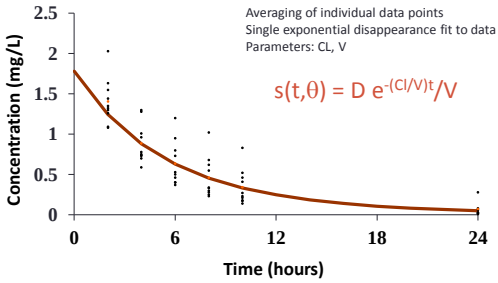
A simple population pharmacokinetic model for describing the data shown in Figure 2 written in model "pseudo-code" with comments. The model has additive between-subject variability on CL, and additive residual unexplained variability. See Table 2 for the variables and parameters for this model when fitted to the data shown in Figure 2.

From Individual to Population Analysis

This Is Where We Start From



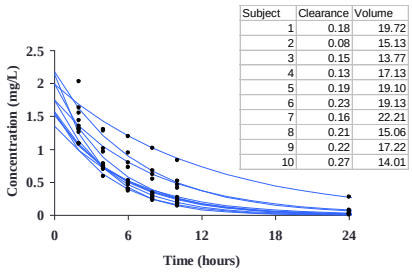
Averaging or Naïve Pooling



Averaging or Naïve Pooling

- It treats all the subjects as if they were a single subject, either by
  - (biased for the reasons we discussed) Averaging the measurements over time, or
  - (slightly preferable) fitting the ensemble of all individual measurements as if they came from a single subject
- Not recommended since it neglects and cannot quantify between-subject variation

Average of Individual Estimates



Subject	Clearance	Volume
1	0.18	19.72
2	0.08	15.13
3	0.15	13.77
4	0.13	17.13
5	0.19	19.10
6	0.23	19.13
7	0.16	22.21
8	0.21	15.06
9	0.22	17.22
10	0.27	14.01

"Standard Two–Stage"

- Population parameters are calculated by sample averaging:

Typical value (sample mean)

$$\hat{\theta} = \frac{1}{N}\sum_{i=1}^{N}\hat{\theta}_i$$

Variability (sample variance)

$$\hat{\omega} = \frac{1}{N}\sum_{i=1}^{N}(\hat{\theta}_i - \hat{\theta})(\hat{\theta}_i - \hat{\theta})^T$$

- Potential issues:
  - All individual estimates must be available
  - They all have the same weight in mean and variance
  - Uncertain estimates may inflate measured variability

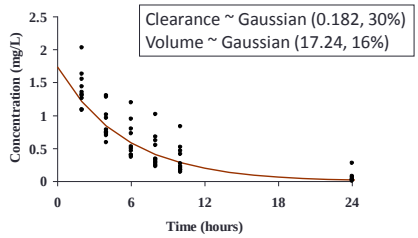
Mixed Effects Models

- Two-Stage methods require the availability of individual parameter estimates for every subject; at the same time, they may postulate a statistical (additive) model for the BSV (more later)
- Further analytical needs are:
  - The individual estimates may not be available (for some or all individuals)
  - The statistical BSV model may need to be more flexible

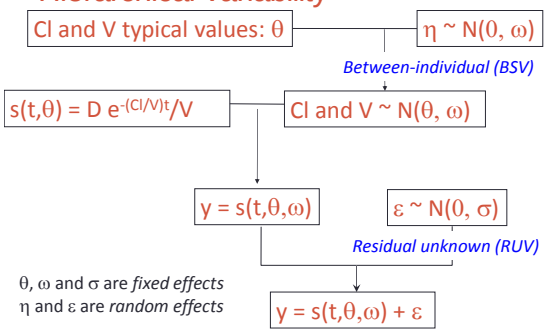
Mixed Effects Models

- Parameters in the model are represented as the combination of other parameters that:
  - do not vary in the population (*fixed effects*)
  - vary in the population (*random effects*)
- An example of fixed effect is the mean clearance in the population, or its variance
- An example of random effect is the clearance of a particular individual, or rather the deviation of that clearance from the population mean

The Population Approach



Hierarchical Variability

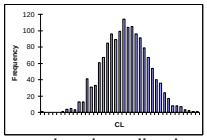


θ, ω and σ are *fixed effects*
η and ε are *random effects*

Back To The Standard Two-Stage

Typical value (sample mean) Variability (sample variance)

$$\hat{\theta} = \frac{1}{N}\sum_{i=1}^{N}\hat{\theta}_i \qquad \hat{\omega} = \frac{1}{N}\sum_{i=1}^{N}(\hat{\theta}_i - \hat{\theta})(\hat{\theta}_i - \hat{\theta})^T$$



- STS results can be described as arising from a Gaussian BSV distribution for the parameters:
  e.g., for CL: CL= θ_{CL} + η, η ~ N(0, ω_{CL})
  then CL ~ N(θ_{CL}, ω_{CL})

BSV for Mixed Effects Models

- Between–subject variability in the model parameters can be *explicitly modeled*
- BSV random effects are assumed Normal, zero mean and variance ω, thus if:

  CL = θ + η, η ~ N(0, ω)

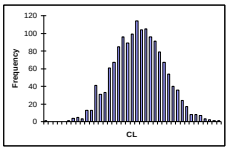
  then CL ~ N(θ, ω) *(Gaussian BSV)*
- If on the other hand:

  CL = θ exp(η), η ~ N(0, ω)

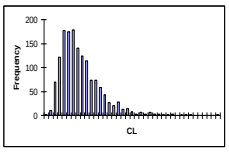
  then CL ~ LN(θ, ω) *(log-normal BSV)*

Population Distributions

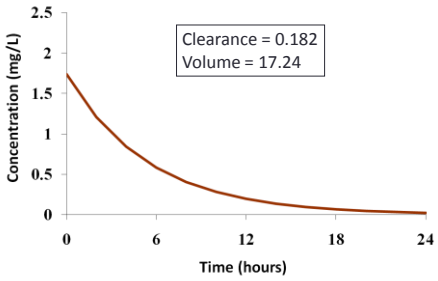
- <u>Normal Distribution</u>:
  CL = θ + η, η ~ N(0, ω)
  then CL ~ N(θ, ω)



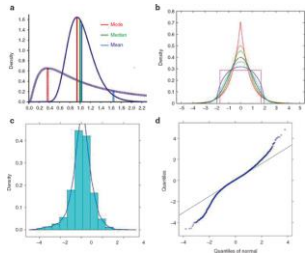
- <u>Log–Normal Distribution</u>:
  CL = θ exp(η), η ~ N(0, ω)
  then CL ~ LN(θ, ω)



Summary: Typical Temporal Profile



A Primer on Statistical Distributions



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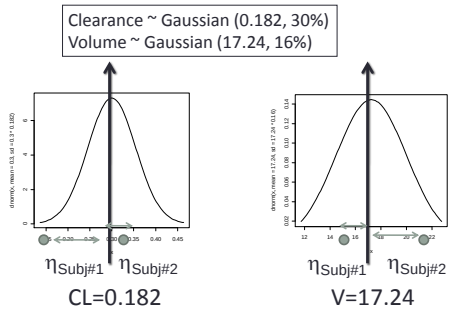
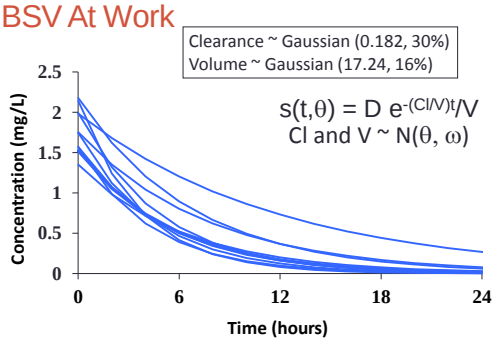
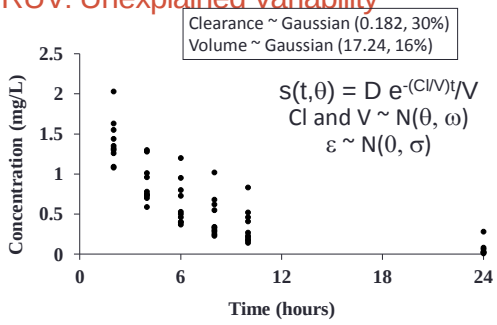
BSV On Parameters



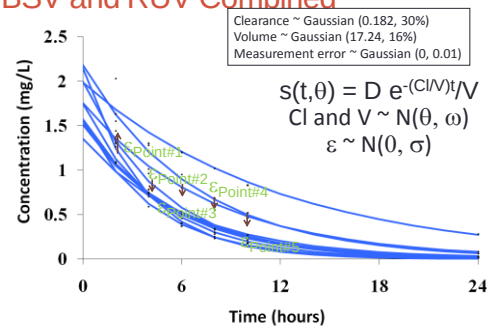
BSV At Work



RUV: Unexplained Variability



BSV and RUV Combined



Residual Unknown Variation Structures

- RUV can also be flexibly modeled, just like BSV
- RUV random effects are also assumed Normal, zero mean and variance σ, thus we can have e.g.:
- $y(t, \theta, \omega, \varepsilon) = D\, e^{-(Cl/V)t}/V + \varepsilon$, $\eta \sim N(0, \omega)$, $\varepsilon \sim N(0, \sigma)$
  (Additive RUV)
- $y(t, \theta, \omega, \varepsilon) = D\, e^{-(Cl/V)t}/V\, (1 + \varepsilon)$, $\eta \sim N(0, \omega)$, $\varepsilon \sim N(0, \sigma)$
  (Proportional RUV)
- $y(t, \theta, \omega, \varepsilon) = D\, e^{-(Cl/V)t}/V \exp(\varepsilon)$, $\eta \sim N(0, \omega)$, $\varepsilon \sim N(0, \sigma)$
  (Log-normal or exponential)

Residual Unknown Variation Structures

- A very general RUV model is:
  $y(t, \theta, \omega, \varepsilon) = D\, e^{-(Cl/V)t}/V\, (1 + \varepsilon_1) + \varepsilon_2$
  $\eta \sim N(0, \omega)$
  $\varepsilon_1 \sim N(0, \sigma_1)$
  $\varepsilon_2 \sim N(0, \sigma_2)$
  (Additive and Proportional RUV)
- Note that we are using s() for the model of the data, and y for the data themselves

Common Terms

- These are the terms we will consistently use:
  - Typical Values (θ)
  - Between-Subject Variation (ω) (BSV)
  - Residual Unknown Variation (σ) (RUV)
- Other commonly used terms include:
  - Inter- and intra-subject variability
  - Fixed and random effects
  - Typical values and population means
  - Inter-occasion or between-occasion variability

How Is Parameter Estimation Done?

- In brief: maximum likelihood estimation based on the marginal probability density of the population data
- Since the population likelihood cannot be explicitly calculated for our models, which are nonlinear in the parameters, various approximations are often employed
- All the data are analyzed together, i.e. the estimate for every individual builds on the population parameters

Summary: Model Assumptions

- We assume that the system response for the i-th subject (N subjects total) is given by:
  $y_i = s_i(\beta_i) + \varepsilon_i, \quad i=1, \ldots, N$
  where:
- y is the *random* vector of measurements
- s() is a known (nonlinear) model function
- β_i is the vector of model parameters (e.g. CL and V), which are functions of fixed (θ) and random (η_i) effects
  $\beta_i = \beta_i(\theta, \eta_i)$
- ε_i is the measurement error *random* vector

Reference: M Davidian, DM Giltinan. *Nonlinear Models for Repeated Measurement Data*. Chapman & Hall/CRC (1995).

A Major Obstacle

- The individual model prediction
  $$y_i = s_i(\beta_i) + \varepsilon_i = s_i(\theta, \eta_i) + \varepsilon_i$$
  implies the joint population likelihood:
  $$L(\theta, \eta_i) = \prod_{i=1}^{N} L_i(\theta, \eta_i, \varepsilon_i)$$
- However, L depends on the function s()!
- The integral needed to express the likelihood as a function of fixed effects only cannot be analytically solved:
  $$L(\theta, \omega, \sigma) = \int_{-\infty}^{+\infty} \prod_{i=1}^{N} L_i(\theta, \eta_i, \varepsilon_i) d\eta_i$$

First–Order Approximation

- Given the model of the i–th individual:

$$y_i = s_i(\beta_i) + \varepsilon_i, \qquad i=1, \ldots, N$$

- Given a relationship between the random and the fixed effects and the distribution of the random effects: $\beta_i = \beta_i(\theta, \eta_i)$, with $\eta_i \sim N(0, \omega)$
- The First-Order (FO) method is based on the linearization of the model function around the mean random effects of the population (i.e. 0)

$$y_i \approx s_i[\beta_i(\theta,0)] + \left\{ \left. \frac{\partial s_i[\beta_i(\theta,\eta)]}{\partial \eta} \right|_{\eta=0} \right\} \eta_i + \varepsilon_i$$

First–Order Method

- Given the linearization:

$$y_i \approx s_i[\beta_i(\theta,0)] + \left\{ \left. \frac{\partial s_i[\beta_i(\theta,\eta)]}{\partial \eta} \right|_{\eta=0} \right\} \eta_i + \varepsilon_i$$

we can also write:

$$y_i \approx s_i[\beta_i(\theta,0)] + Z_i(\theta,0)\eta_i + \varepsilon_i$$

where $Z_i(\theta,0)$ is a sensitivity matrix which depends on the model parameters – the integration can now be done. Expectation and covariance of Y are:

$$E[y_i] \approx s_i[\beta_i(\theta,0)]$$

$$Cov[y_i] \approx Z_i(\theta,0)\,\omega\,Z_i(\theta,0)^T + Cov[\varepsilon_i] = V_i(\theta,0,\omega,\sigma)$$

Maximum Likelihood (FO)

- If we make the assumption that Y is Gaussian, from the expectation and covariance of Y we can write an extended least squares estimator:

$$E[Y_i] \approx s_i[\beta_i(\theta,0)]$$

$$Cov[Y_i] \approx Z_i(\theta,0)\,\omega\,Z_i(\theta,0)^T + Cov[\varepsilon_i] = V_i(\theta,0,\omega,\sigma)$$

which is (over all the subjects):

$$-\log L(\theta,\omega,\sigma) = \sum_{i=1}^{N} \left\{ \begin{array}{l} \frac{1}{2}\log[2\pi \det V_i(\theta,0,\omega,\sigma)] \\ + \frac{1}{2}[Y_i - s_i(\theta,0)]^T V_i^{-1}(\theta,0,\omega,\sigma)[Y_i - s_i(\theta,0)]^T \end{array} \right\}$$

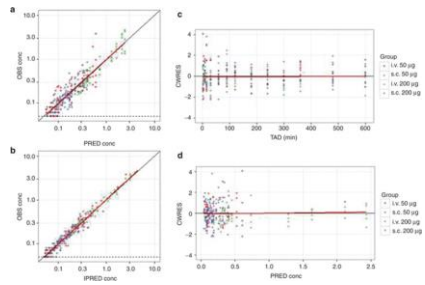
Other Approximations

- Increase in accuracy especially for large BSV
- Linearization around individual random effects
  - Lindstrom and Bates (1988)
  - Beal and Sheiner, First-Order Conditional Estimation (in NONMEM)
- Second-order approximations
  - Laplacian
  - Gaussian quadrature

Change in Emphasis from Individual Analysis

- With population analysis, the focus shifts to the *population* parameters, as opposed to the individual
- The unknowns in population analysis are:
  - Expected values (means, typical values) of the parameters (**θ**)
  - BSV (variances and covariances) of the parameters (**ω**)
  - RUV (variances and covariances) of the model (**σ**)
- **Challenge**: find good starting values for θ, ω, σ
- *Note*: Individual parameters can be calculated as a byproduct, once population parameters are known

Key Diagnostic Plots



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Balance Between Information at the Individual and Population Level

# of subjects (N) / # of data per subject (n)	Many	Few
Many	Reliable individual and population information	Reliable individual information only
Few	Reliable population information only	Unreliable individual and population information

Balance Between Information at the Individual and Population Level

Phase	Objective	Mode	Design	Questions
Cycle 1—Early development				
1	Pharmacokinetics/pharmacodynamics Tolerance/safety	Learning	Small numbers of subjects, several doses, dense sampling	Basic PK/PD relationship? Achieve PD at tolerated doses? PK changes in special populations?
2A	Proof-of-concept/indication of efficacy	Confirming	Larger numbers of subjects/patients, fewer doses, sparse sampling	Evidence of response?
Cycle 2—Late development				
2B/3	Optimal use/dose adjustments	Learning	Larger numbers of subjects, few doses, very sparse sampling	Will proposed dose adjustments work? PK/PD in patients?
3/4	Safety and efficacy in clinical use – primary regulatory responsibility	Confirming (Learning)	Large number of subjects, labeled dose, very few samples	Demonstration of safety and efficacy

PD, pharmacodynamics; PK, pharmacokinetics.

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Models for Covariate Functions

- Linear function

$$CL = (\theta_1 + (\text{Weight}) \cdot \theta_2) \cdot \exp(\eta_1)$$

- Centering (to a reference value)

$$CL = \theta_1 \cdot (\text{Weight} - 70)^{\theta_2} \cdot \exp(\eta_1) \quad \text{Centered}$$

$$CL = \theta_1 \cdot \left(\frac{\text{Weight}}{70}\right)^{\theta_2} \cdot \exp(\eta_1) \quad \text{Normalized}$$

- Centering (using allometry)

$$CL = \theta_1 \cdot \left(\frac{\text{Weight}}{70}\right)^{0.75} \cdot \exp(\eta_1)$$

$$V = \theta_2 \cdot \left(\frac{\text{Weight}}{70}\right) \cdot \exp(\eta_2)$$

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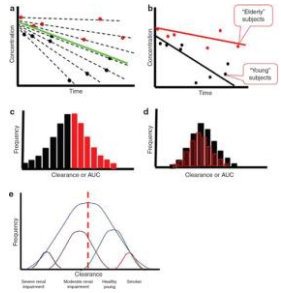
Effect of Covariates on Variability



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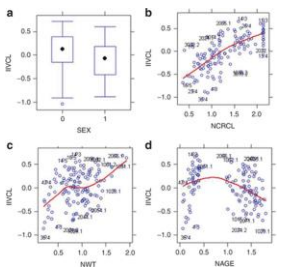
Graphical Evaluation of Covariates



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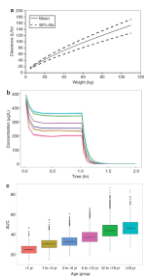
Simulated Drug Exposures for Different Age Groups



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List (Timeline) of Approaches

Year	Event	Description
1972	Concept of "population pharmacokinetics"	The concept was published
1977	The first population pharmacokinetic analysis conducted	Application to digoxin data
1980	Announcement of NONMEM	An IBM-specific software for population pharmacokinetics
1984	NONMEM 77	A "portable" version of NONMEM
1989	NONMEM III	An improved user-interface with the MMTRAN front-end. NONMEM Users Guide published
1989	BUGS software group forms	Different method: Markov chain Monte Carlo method
1991	USC*PACK	Different method: nonparametric population pharmacokinetic modeling (NPEM)
1992	NONMEM IV	New methods: FOCE
1992	Publication with NPEM	First publication using NPEM method
1998	NONMEM V	New methods: mixture models
2001	Winbugs publication	First publication using Winbugs
2002	Publication with PKBUGs	Winbugs application designed for pharmacokinetic models
2003	Monolix Group Forms	Different method: stochastic approximation expectation maximization (SAEM)
2003	WinNonMix publication	Population modeling software with graphical user interface
2006	NONMEM VI	New methods: centering, HYBRID, nonparametric
2006	Monolix publications	First publications using Monolix
2009	Phoenix NLME	User-friendly GUI
2010	NONMEM 7	New methods: Bayes, SAEM, and others, parallel processing enabled
2012	Monolix 4.1	Full-script version (MLXTRAN, XML) and/or user-friendly GUI

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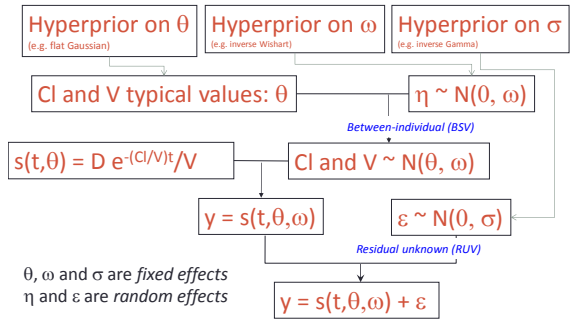
Additional Hierarchical Structure



Bayesian Methods

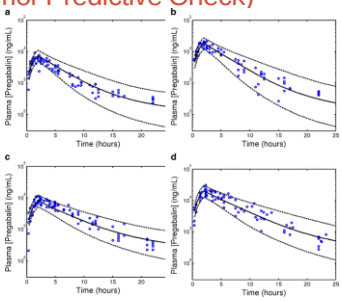
Introduction to Simulation

- The purpose of estimating parameters describing typical values and variability in the "subject" and "measurements" dimensions is to use the model and parameters to simulate unobserved conditions
  - These may include: dosing schemes, sampling strategies, trials of different sizes, etc.
- Once parameters for the model are available, all the elements that are needed to use the model to simulate are in place

"Deterministic" vs. "Stochastic" Simulations

- One can envision two kinds of simulation:
  - Deterministic ("engineering")
    - One realization of the simulation
    - No variability included
  - Stochastic ("statistical")
    - Multiple realizations of the simulation
    - Variability is used to drive the multiple realizations
- Variability can be either present or not
- Both kinds can be useful depending on the specifics of the question to be addressed

Example Simulation (Posterior Predictive Check)



Population pharmacokinetic model of the pregabalin-sildenafil interaction in rats: application of simulation to preclinical PK-PD study design.
Bender G, Gosset J, Florian J, Tan K, Field M, Marshall S, DeJongh J, Bies R, Danhof M. Pharm Res. 2009 Oct;26(10):2259-69. doi: 10.1007/s11095-009-9942-y. Epub 2009 Aug 11.