Population Modeling

Michael Neely, MD
Associate Professor of Pediatrics and Clinical Scholar
Director, Laboratory of Applied Pharmacokinetics and Bioinformatics
University of Southern California
Children’s Hospital Los Angeles
Consider

**Question 1**
What is the initial drug dose most likely to achieve a safe and effective concentration in the maximum number of patients?

**Question 2**
What is the drug dose most likely to achieve a safe and effective concentration in an individual patient?
PK Data
PK Modeling Objective

Describe and summarize drug exposure after a given dose or doses in individuals and populations
Modeling Approaches

PK Data

Compartmental

Traditional

Population

Physiologic

Parametric

Non-parametric

Non-compartmental
Non-Compartmental

• Based on the shape of the time concentration curve

• Driven by estimation of $AUC_{0-\infty}$ and $AUMC_{0-\infty}$

• Typically used in bioequivalence, dose proportionality, and drug interaction studies (e.g. drug-food, drug-drug)
NCA AUC Estimation
Challenges for NCA

- Analysis of sparse or unbalanced data
- Complex dosage regimens
- Non-linear PK
- Simulation of exposure from different regimens than those studied
- Elimination of drug other than from sampling pool
Compartmental Models

Dose

\[ k_{01} \]

\[ k_{10} \]

\[ k_{12} \]

\[ k_{21} \]

2
Traditional Compartmental

\[ C_t = A*e^{-\alpha t} + B*e^{-\beta t} \]
Challenges

• Only uses information from one dosing interval

• Can be biased by sparse or unbalanced data

• Assumes parameters remain constant

• Neglects errors in observations (measurement or timing)

• Need at least one drug level per parameter in the model (e.g. peak and trough to estimate volume and clearance)

• Does not distinguish sources of variability (e.g. interpatient from intrapatient)
Population Modeling

aka “Pharmacometrics”
Why Pop Model?

- To understand and describe...
  - the time course of drug concentrations in the body
  - relationships between drug concentration and effects, both desired and undesired
  - effects of covariates, e.g. renal function, on these relationships
  - sources of PK variability in the population
Why Pop Model?

• To simulate new scenarios which is useful for...
  - hypothesis generation, study design, dose finding
  - extrapolation to dosing in novel populations

• To optimize and personalize therapy for individual patients
Pharmacometric Impact at FDA

- 25% growth in 2010
- Supported 38% of approval and 64% of labeling decisions

FDA Pharmacometrics 2020
Strategic Goals

• Train 20 Pharmacometricians
• Implement 15 Standard Templates
  ○ Develop disease specific data and analysis standards
  ○ Expect industry to follow
• Develop 5 Disease models
• International Harmonization
• Integrated Quantitative Clinical Pharmacology Summary
  ○ All NDAs should have exposure-response analysis
• Design by Simulation: 100% Pediatric Written Requests
My volume, my clearance
The Best Population Model

• The correct structural PK/PD model, e.g. one-, two-compartment, inclusion of relevant covariates,...

• The collection of each subject’s exactly known parameter values for that model, e.g. absorption, volume, clearance
Approximating the best

• observed = f(pred, error)

• For example, obs = pred + error
Approximating the Best

\[ y_{ij} = f(x_j, \beta_j) + \varepsilon_{ij} \]

**Parametric**

\[ \beta_i = h(\theta, \eta) \]

\[ h = \theta + \eta, \theta^*e^\eta, \text{or } \theta^*(1 + \eta) \]

\[ \eta \sim N(0, \omega) \]

**Non-Parametric**

\[ \text{FML}(\beta) = p_1\delta_1(\beta_1) + \ldots + p_K\delta_K(\beta_K), K \leq N \]

\[ \varepsilon \sim N(0, \sigma) \]
Parametric

- Familiar, easy to summarize
  - e.g. Clearance = 0.7 +/- 0.3 L/min
Parametric

Video courtesy of Marc Lavielle, Ph.D.
Non-Parametric

• But what if the real distribution of clearance in the population is this?
Non-Parametric

• Or this?
Non-Parametric

• We don’t need to look at the infinity of all continuous distributions.

• The most likely distribution, given a set of data, can be found in a discrete collection of points, up to one per subject.

• Each (support) point is a vector of estimates for each parameter value, and of the probability of those values.
Non-Parametric

- The shape of this distribution is determined only by the data itself, not by an equation.

- This forms a natural basis for optimal control of dosage regimen with estimates of precision.
Non-Parametric

- Nonparametric – unfamiliar, harder to conceptualize
- Makes no assumptions about underlying parameter distributions
- Assigns a probability to each parameter value in the population based on the frequency of occurrence
- Can detect unexpectedly different subpopulations
Non-Normal Populations

- Simulated population (■)
- Non-parametric estimation of population values (○)
  - Size proportional to probability

The entire population is accurately and precisely described.

Non-Normal Populations

- Simulated population (□)
- Mean (+) and percentile distributions of parametric population parameter estimates

Missed the outlier completely.

Nobody is at the mean!
Non-Parametric Model
## Comparison

<table>
<thead>
<tr>
<th></th>
<th>Parametric</th>
<th>Non-parametric</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Software</strong></td>
<td>NONMEM, Monolix, ADAPT, S-Adapt, ITS</td>
<td>Pmetrics</td>
</tr>
<tr>
<td><strong>Algorithms</strong></td>
<td>FOCE, SAEM, MLEM, ITS</td>
<td>NPAG</td>
</tr>
<tr>
<td><strong>Fixed effects</strong></td>
<td>Population “typical” PK parameter values (TV)</td>
<td>Process and observation noise</td>
</tr>
<tr>
<td><strong>Random effects</strong></td>
<td>Inter-individual variability (IIV) and residual (intra-individual) variability (RV)</td>
<td>Population PK parameter values and residual variability</td>
</tr>
<tr>
<td><strong>Assumptions</strong></td>
<td>Normally distributed IIV and RV</td>
<td>Normally distributed RV</td>
</tr>
</tbody>
</table>
# Software Tools

<table>
<thead>
<tr>
<th></th>
<th>Pmetrics</th>
<th>NONMEM</th>
<th>ADAPT</th>
<th>Phoenix</th>
<th>Monolix</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode</strong></td>
<td>NP, P</td>
<td>P</td>
<td>P</td>
<td>P, NP</td>
<td>P</td>
</tr>
<tr>
<td><strong>Cost</strong></td>
<td>0</td>
<td>$$$</td>
<td>$$$</td>
<td>$$$/0</td>
<td>$$$/0</td>
</tr>
<tr>
<td><strong>Simulate</strong></td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
<td>Y</td>
</tr>
<tr>
<td><strong>GUI</strong></td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Platforms</strong></td>
<td>W, U, L</td>
<td>W</td>
<td>W</td>
<td>W</td>
<td>W, L</td>
</tr>
<tr>
<td><strong>All-in-one</strong></td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*a* Adapt is free, but it only uses the Intel Fortran compiler, which is $$$

*b* Academic license available

*c* With BestDose
Terminology
Model

• The collection of equations that relates the input to the output, AKA the “structural model”

• \( C = \frac{\text{Dose}/V \times e^{-kt}} \)

• Also can refer to the probability distribution of parameter values, which is more properly termed the joint probability density
Parameters

- Variables in the structural model equations
- e.g. $C = \frac{\text{Dose}}{V} \times e^{-ke*t}$
Bayes’ Theorem
Bayes’ Theorem

\[
P(A|B) = \frac{P(B|A) \cdot P(A)}{P(B)}
\]

for binary, \( P(B) = P(B|A) \cdot P(A) + P(B|\neg A) \cdot P(\neg A) \)
Example

- Test with 95% sensitivity and 99% specificity
- 20% of the population have the disease
- Probability of disease with positive test?
## Example

<table>
<thead>
<tr>
<th></th>
<th>+Dis</th>
<th>-Dis</th>
</tr>
</thead>
<tbody>
<tr>
<td>+Test</td>
<td>TP=1900</td>
<td>FP=80</td>
</tr>
<tr>
<td>-Test</td>
<td>FN=100</td>
<td>TN=7920</td>
</tr>
</tbody>
</table>
Bayes’ Theorem

\[ PPV = P(\text{Dis}|+) = \frac{\text{Sen} \times P_{\text{Dis}}}{\text{Sen} \times P_{\text{Dis}} + (1-\text{Spec}) \times P_{\text{NotDis}}} = 0.96 \]

\[ PPV = \frac{TP}{TP + FP} = 0.96 \]
Bayesian Prior

- The probability distribution of parameter values without consideration of current data

- AKA “the model”, “the population prior”
Bayesian Posterior

• The probability distribution of parameter values which has been updated based on new data

• AKA “individual distribution”
Iterative

Prior

Posterior
Convergence

• In the eye of the beholder

• Iterate and search for new parameter value distributions

• Stop when likelihood changes less than a specified threshold
AIC

- Akaike Information Criterion
- AIC = -2*log likelihood + 2K
- Penalizes for the number of parameters in the model
- Useful for comparing any two models, selecting the one with the lowest AIC
BIC

- Bayesian or Schwartz Information Criterion
- Similar to AIC, but greater penalty on parameters
Covariates

- Subject/patient specific factors which are linked to PK/PD behavior

- E.g. volume of distribution linked to body weight or clearance linked to genotype
Covariates

• Typically included in a model if they improve the AIC or some other objective function
Assay Errors

The myth of quantification limits
Assay Precision

- Estimate the SD of every measured observation

- Fisher Information = 1 / Variance = Weight

- Variance = SD^2

CV% vs Fisher

- Assume, for example, 10% assay CV at concentrations >10, and constant SD=2 when concentrations <1.
  - If conc = 10, SD = 1, var = 1, weight = 1
  - If conc = 20, SD = 2, var = 4, weight = ¼
  - If conc = 0.1, SD = 2, var = 4, weight = ¼ but CV% = 2000%

- As concentration approaches zero, CV% approaches infinity
Assay error

- SD vs. CV%
- Concentration (ug/ml)

- SD
- CV%
CV% vs Fisher

- No LOQ with Fisher
- Assay SD, variance, and weight are always finite.
## Fit assay error

<table>
<thead>
<tr>
<th>Conc</th>
<th>SD</th>
<th>CV%</th>
<th>Wt</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.5</td>
<td>∞</td>
<td>4.000000</td>
</tr>
<tr>
<td>25</td>
<td>6.4</td>
<td>26%</td>
<td>0.024414</td>
</tr>
<tr>
<td>50</td>
<td>8.6</td>
<td>17%</td>
<td>0.013521</td>
</tr>
<tr>
<td>100</td>
<td>12</td>
<td>12%</td>
<td>0.006944</td>
</tr>
<tr>
<td>250</td>
<td>8.6</td>
<td>3%</td>
<td>0.013521</td>
</tr>
<tr>
<td>500</td>
<td>37.2</td>
<td>7%</td>
<td>0.000723</td>
</tr>
<tr>
<td>1000</td>
<td>60.1</td>
<td>6%</td>
<td>0.000277</td>
</tr>
<tr>
<td>2000</td>
<td>165.7</td>
<td>8%</td>
<td>0.000036</td>
</tr>
<tr>
<td>5000</td>
<td>483</td>
<td>10%</td>
<td>0.000004</td>
</tr>
</tbody>
</table>

The diagram shows the fit assay error for different concentrations, with each concentration marked by its respective CV%.
Fit assay error

<table>
<thead>
<tr>
<th></th>
<th>C0</th>
<th>C1</th>
<th>C2</th>
<th>C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>-7.9</td>
<td>0.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second</td>
<td>1.0</td>
<td>6.5E-02</td>
<td>6.2E-06</td>
<td></td>
</tr>
<tr>
<td>Third</td>
<td>4.8</td>
<td>3.3E-02</td>
<td>3.1E-05</td>
<td>-3.6E-09</td>
</tr>
</tbody>
</table>

![Graph showing standard deviation over concentration with linear, quadratic, and cubic fits with R² values.]
Process noise

- SD = $C_0[drug]^0 + C_1[drug]^1 + C_2[drug]^2 + C_3[drug]^3$

- Use additive (lambda) or multiplicative (gamma) model for weight:
  - weight = $1/(\lambda + SD)^2$
  - weight = $1/(\gamma \times SD)^2$
Monte Carlo Simulation
Overview

• Repeatedly draw random samples from a joint parameter probability distribution

• Calculate outputs given a set of inputs and the simulated parameter values
Sampling

CL = 5.8
Bimodal

Unimodal
<table>
<thead>
<tr>
<th>Kel</th>
<th>Vd</th>
<th>Probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.382617188</td>
<td>1.795898437</td>
<td>0.028571429</td>
</tr>
<tr>
<td>0.231738281</td>
<td>2.235839842</td>
<td>0.057142857</td>
</tr>
<tr>
<td>1.030468752</td>
<td>2.2421875</td>
<td>0.057142857</td>
</tr>
<tr>
<td>0.952148437</td>
<td>2.084960938</td>
<td>0.130811467</td>
</tr>
<tr>
<td>0.337011719</td>
<td>1.568847656</td>
<td>0.028571429</td>
</tr>
<tr>
<td>0.959960937</td>
<td>2.001</td>
<td>0.028571429</td>
</tr>
</tbody>
</table>

Two Simulation Choices

Unimodal SIMrun(split=F)

Multimodal SIMrun(split=T)

Nonparametric Population Model
Probability of Target Attainment

• Simulation technique

• Calculate the proportion of simulated profiles which meet a predefined success threshold for a given dosage regimen

• E.g. AUC:MIC > 10, or %dosage interval (time) > 0.6
PTA

N=4
Mean: 0.44
SD: 0.39
PTA: 25%
PTA

N = 1000
Mean: 0.91
SD: 0.14
PTA: 95%
PTA

Simulation to test models

- **Visual Predictive Checks**

- **Normalized Prediction Distribution Errors (NPDE)**
Visual Predictive Check

• Simulate using the mean/median population parameter values

• Compare the distribution of simulated observations to the distribution of measured observations in the population
VPC

Visual Predictive Check

© Laboratory of Applied Pharmacokinetics and Bioinformatics
Problems with VPC

- Covariates
- Different dosage regimens used in population
NPDE

- Normalized prediction distribution errors
- Simulate from each subject using the population parameters but their own covariates, doses, etc.
- Decorrelate and center measured and simulated observations
- Calculate the z-score of the measured observation with respect to the simulated observations at the same time
NPDE
Modeling scheme

1. Define purpose
2. Gather/prepare data
3. Define model
4. Fit model
5. Explore covariates
6. Validation
7. Final model