Nonlinear Parametric and Nonparametric Population Pharmacokinetic Modeling on a Supercomputer

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Why Make Population Models?

• To describe and understand Drug PK/PD Behavior

• To use as Bayesian Prior for designing Goal-Oriented, Model-Based, individualized dosage regimens for patients
Goal-Oriented, Model-Based Individualized Drug Dosage Regimens: the Structure

• Use Population Model as Bayesian Prior.
• Set *specific* target(s): Serum conc goal(s) at desired time(s), for example.
• Compute the regimen to achieve the goal(s).
• But: just *how precisely* will the regimen achieve the goal(s)? A good question!
• Even with feedback from serum levels, etc.
Parametric Population PK/PD Models

- **Assume** shape (normal, etc.) of param distrib.s.
- Get Population Parameter Means, SD’s, covariances, ranges.
- Separate “inter” from “intra” - individual from assay Variability
- But, only **one** value for each parameter, so
- **Cannot** evaluate expected therapeutic precision
- Can get confidence limits, do signif. tests.
- Not consistent.
Inter-Individual Variability

• A single number (SD, CV%) in parametric population models
• But there may be sub-populations
• eg, fast, slow, and medium acetylators
• How describe all this with one number?
• A good question!
Intra-Individual Variability

- Assay error pattern
- Errors in Recording Sampling Times
- Errors in Dosage Prep and Admin
- Changing parameter values with time
- Structural Model Mis-specification
- However, all this is a mixture of
  - Measurement Noise, and
  - Process Noise (Noise in the DE’s)
Determine the Assay Variability

- As first suggested by Tom Gilman,
- Measure blank, low, medium, high, and very high samples at least in quadruplicate.
- Get mean + SD for each quadruplicate sample
- \( SD = A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3 \)
- Then can weight each measurement by the reciprocal of its variance (Fisher Info)
- No lower detectable limit!
More on Intra - Individual Variability

• \( \text{Var} = \text{Gamma} \times \text{assay SD} \)
• or, \( \text{Var} = (A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3) \)
• Thus, Var can be a single number
  – Just by itself, as often, where get \( A_0 \), (all other A’s set to zero)
  – Or, scaling the assay error polynomial
  – Or, an entire polynomial.
• A possible relative index of quality of care.
Nonparametric Population Models

• Get not only means, SD’s, etc, but also the entire distribution, a Discrete Joint Density.
• Can evaluate expected therapeutic precision.
• Can discover unsuspected subpopulations.
• Behavior is consistent.
• Use Var +/- or assay SD, stated ranges.
• No confidence limits or tests of signif yet.
  – Bootstrap, etc. in future.
A Population Model, as made by Breugel!
An NPML Population Joint Density, as made by Mallet
An NPEM Pop Model by Schumitzky
A Parametric Population joint density

V_{d} \text{ mean} = 0.318, \text{ SD} = 0.1243, \text{ mode} = 0.2415L/kg
CL_{slope} \text{ mean} = 0.0688, \text{ SD} = 0.02599, \text{ mode} = 0.05218
Cov (V_{d}-CL_{slope}) = 0.001429
r (V_{d}-CL_{slope}) = 0.442
How to do Pop Modeling best? Use Both Methods

- Parametric: First, get assay errors, gamma, ranges, for assay and intraindividual variability.
- Nonparametric: Then, get the full discrete joint density
  - Find the best dose to achieve target goals.
  - Use Multiple Model Dosage design
“Multiple Model” Dosage Design

- Start with multiple models in pop model
- e.g., each pop subject’s indiv PK model.
- Give a regimen to each subject’s model,
- Predict each subject’s future levels,
- Compare each with chosen goal, get MSE.
- A better tool: use an NPEM joint density.
- Compute regimen having least weighted squared error in target goal achievement.
User Manual for
The Non-Parametric EM Program for Population Pharmacokinetic Modeling
Version 3.0, August 26, 1995.

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Continuous IV Vanco. Predictions when regimen based on means is given to all subjects
Continuous IV MM Vanco regimen, Day 1.

95% and 99% most likely predictions.
Getting Nonparametric Bayesian Posteriors with Serum Level Feedback

• Start with Population discrete joint density
• Use the patient’s measured serum levels
• Recompute probability of each pop model, given the patient’s measured levels.
Continuous IV Vanco, Day 2. 95% and 99%
Larger + Nonlinear
IT2B and NPEM Models

- Linear or Nonlinear Structural Models
- Serum Levels +/- or Effects
- Available over the Internet
- Prepare Model + data on PC
- SSH to SDSC Cray T3E, FTP data.
- Do the analysis, get results and density.
- FTP back to PC, see them there
Our USC Lab

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