METHODS FOR MAXIMALLY PRECISE DRUG DOSAGE

Roger Jelliffe, MD, Alan Schumitzky, PhD, David Bayard, PhD, Robert Leary, Ph.D, Michael Van Guilder, PhD, Andreas Botnen, M.S., Michael Neely, MD,, Maurice Khayat, B.S., Alison Thomson, Ph.D and Aida Bustad, B. S.,
Laboratory of Applied Pharmacokinetics, USC Keck School of Medicine, Los Angeles CA

ABSTRACT

1. NONPARAMETRIC (NP) POPULATION PK/PD MODELING. NP models estimate the entire most likely joint parameter distribution [1]. The distribution is supported at multiple discrete points, up to one for each subject, each with an estimated probability [1-3].

2. DETERMINING ASSAY ERROR AS SD, NOT CV. CV% provides no method for weighting data assay data. SD [4] does, and avoids censoring low data.

3. ESTIMATING ENVIRONMENTAL NOISE. This can be estimated, as a separate term, quantifying both noise sources.

4. ESTIMATING CHANGING CCR. Most methods for estimating creatinine clearance (CCr) assume stable renal function and use only a single serum creatinine (SCr). We use pairs of SCr's and calculate the CCr that would make SCr change from the first to the second value over a stated time in a acutely ill patient of stated age, gender, height, and weight [5].

5. MULTILE MODEL (MM) DOSAGE DESIGN. The many NP model support points provide multiple predictions of responses to a dosage regimen. Each prediction is weighted by the probability of its support point. One can compute the weighted squared error of the failure of any regimen to hit the target, and find the regimen specifically minimizing this error [6,7].

6. MM BAYESIAN ANALYSIS. This computes the posterior probability of each support point given the population model and an individual patient's data. Usually a few or one point remain. Most become negligible. That distribution is used to develop the next MM dosage regimen.

7. HYBRID BAYESIAN (HB) ANALLYSIS. As an unusual patient may be outside the population parameter range, a MAP Bayesian estimate is first made. Extra support points are added in that area. This "hybrid" population model is then used for MM Bayesian analysis.

8. INTERACTING MM SEQUENTIAL BAYESIAN (IMM) ANALYSIS. An unstable patient's parameter values may change. Current Bayesian methods assume fixed values. We implemented a sequential interacting MM (IMM) Bayesian method which permits a patient's posterior support points to change to others with each new dose or serum concentration if more likely [8]. In over 130 post cardiac surgery patients on gentamicin and over 130 on vancomycin, IMM tracked drugs better than other methods [9].

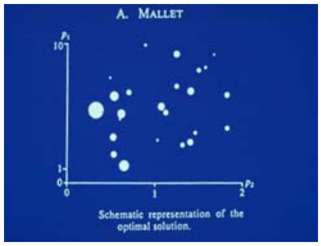
CONCLUSIONS: Maximally precise therapy with toxic drugs requires specific methods. The methods above now provide this [10].

REFERENCES:

[1]. Mallet A: A Maximum Likelihood Estimation Method for Random Coefficient Regression Models. Biometrika. 73: 645-656, 1986.
[2]. Schumitzky A: Nonparametric EM Algorithms for Estimating Prior Distributions. App. Math and Computation. 45: 143-157, 1991.
[3]. Leary R, Jelliffe R, Schumitzky A, and Van Guilder M: Nonparametric Pharmacokinetic/Dynamic Population Modeling with Adaptive Grids. Presented at the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, Orlando, FL, March 6-10, 2001, Proceedings, p. P58.
[4]. DeGroot M: Probability and Statistics, 2nd ed., Addison-Wesley, 1989, p423.
[5]. Jelliffe R: Estimation of Creatinine Clearance in Patients with Unstable Renal Function, without a Urine Specimen. Am. J. Nephrology, 22: 320-324, 2002.
[6]. Jelliffe R, Schumitzky A, Bayard D, Milman M, Van Guilder M, Wang X, Jiang F, Barbaut X, and Maire P: Model-Based, Goal-Oriented, Individualized Drug Therapy: Linkage of Population Modeling, New "Multiple Model" Dosage Design, Bayesian Feedback, and Individualized Target Goals. Clin. Pharmacokinet. 34: 57-77, 1998.
[7]. Bayard D, Jelliffe R, Schumitzky A, Milman M, Van Guilder M, "Precision drug dosage regimens using multiple model adaptive control: Theory and application to simulated Vancomycin therapy," in Selected Topics in Mathematical Physics, Prof. R. Vasudevan Memorial Volume, Ed. by R. Sridhar, K. S. Rao, V. Lakshminarayanan, World Scientific Publishing Co., Madras, 1995.
[8]. Bayard D, and Jelliffe R: A Bayesian Approach to Tracking Patients having Changing Pharmacokinetic Parameters. J. Pharmacokin. Pharmacodyn. 31 (1): 75-107, 2004.
[9]. Macdonald I, Staatz C, Jelliffe R, and Thomson A: Evaluation and Comparison of Simple Multiple Model, Richer Data Multiple Model, and Sequential Interacting Multiple Model (IMM) Bayesian Analyses of Gentamicin and Vancomycin Data Collected From Patients Undergoing Cardiothoracic Surgery. Ther. Drug Monit. 30:67-74, 2008.
[10]. Jelliffe R, Schumitzky A, Bayard D, Leary R, Van Guilder M, Gandhi A, Neely M, and Bustad A: The USC*PACK BigWinPops and MM-USCPACK Software. A software demonstration at the PAGE 15 (2006) abstract 1037, Population Approach Group Europe, Bruges, Belgium, June 14-16, 2006. (Available by license from the first author.)

NONPARAMETRIC POPULATION MODELS

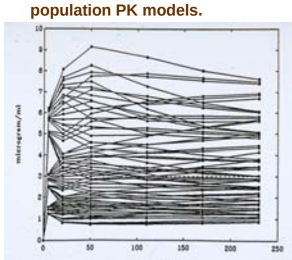
- Theorems of Lindsay, Mallet, and Caratheodory prove the most likely parameter distribution is "to be found" in a discrete joint density supported at up to one such support point per subject, weighted by its probability.
- Shape of distribution not set by any equation, only by the data.
- Can discover, locate, quantify, unsuspected subpopulations.
- Likelihoods are exact. Behavior i statistically consistent. Study mo subjects, guaranteed better result
- Multiple individual models, up to one for each subject.
- The multiple models permit multiple predictions.
- Can optimize precision of goal achievement by a MM dosage regimen.
- Computes environmental noise.
- Bootstrap, for confidence limits, significance tests.



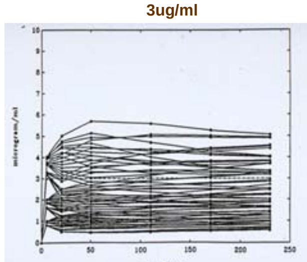
An NP Population Model, made by Mallet

Multiple Model (MM) Dosage Design

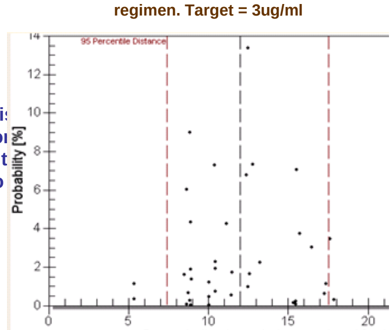
1) Use a prior with discrete multiple models - an NPEM or NPAG model.
2) Give a candidate regimen to each model.
3) Predict results with each model.
4) Compute weighted squared error of failure to hit target goal.
5) Find the regimen hitting target with minimal weighted squared error.
6) This is multiple model (MM) dosage design – the IMPORTANT CLINICAL reason for using nonparametric population PK models.



Lidocaine stepwise infusion regimen based on Parameter MEANS: Predicted response of full 81 point lidocaine population model. Target = 3ug/ml



MM maximally precise stepwise lido infusion regimen: Predicted response of full 81 point lidocaine population model. Most precise regimen. Target = 3ug/ml



MM peak estimates from gent NPAG pop model

MULTIPLE MODEL (MM) BAYESIAN UPDATING

Support point values don't change. Use Bayes' theorem to compute the Bayesian posterior probability of each support point, given the data.

Problem: will not reach out beyond pop parameter ranges.

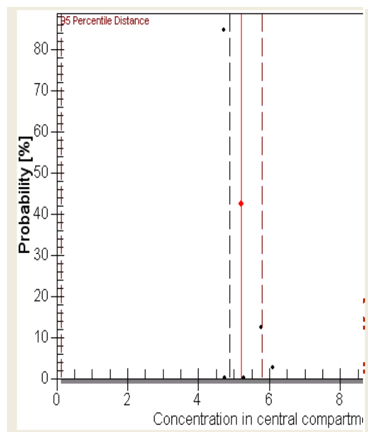
May miss an unusual patient.

HYBRID BAYESIAN UPDATING

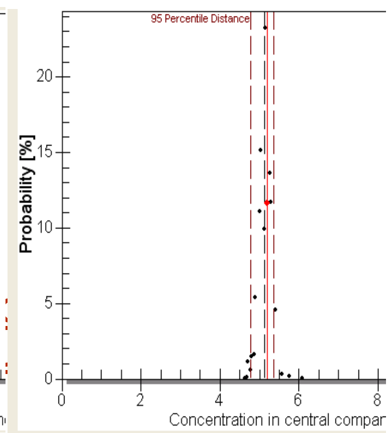
Start with MAP Bayesian. Add more support points nearby, augmenting pop model for the TDM data it will receive.

Then do MM Bayesian on ALL the support points.

We are implementing this now. Out soon.



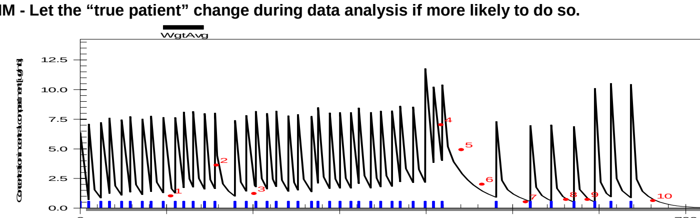
Gent estimates with Regular MM posterior



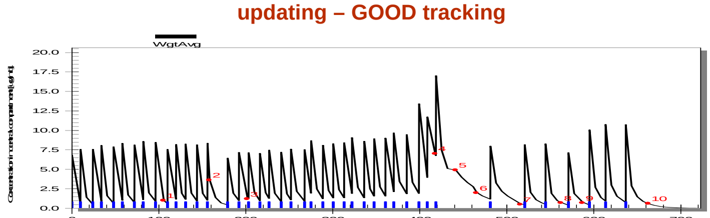
Gent estimates with hybrid MM posterior

INTERACTING MULTIPLE MODEL (IMM) SEQUENTIAL BAYESIAN UPDATING FOR VERY UNSTABLE PATIENTS

Limitation of all other Bayesian methods - find only the fixed parameter values fitting the data.
Sequential MAP or MM Bayesian = same as fitting all at once.
IMM - Let the "true patient" change during data analysis if more likely to do so.



RMM: changing renal function richer data MM Bayesian updating – GOOD tracking



IMM: interacting sequential MM Bayesian updating – BEST tracking

Plots of measured versus estimated gentamicin data from a typical patient with unstable renal function, using (a) SMM, (b) RMM and (c) IMM analysis. IMM tracks drug behavior best.