The USC Pmetrics and RightDose software
The ONLY software with integrated pop modeling, simulation, and maximally precise dosage

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ABSTRACT,

The **Pmetrics** population modeling software is embedded in R, called by R, and output into R. It runs on PC's and Macs. Minimal experience with R is required, but the user has all the power of R for further analyses and displays, for example. Libraries of many models are available. In addition, differential equations may also be used to describe large models of multiple drugs, with interactions, and with multiple outputs and effects. Analytic solutions may also be used if applicable. The model is compiled with GFortran. Runs are made with simple R commands. Routines for checking data and displaying results are provided. Likelihoods are exact. Behavior is statistically consistent – studying more subjects yields parameter estimates closer to the true ones. Stochastic convergence is as good as theory predicts. Parameter estimates are precise [1].The software is available freely for research uses. In addition, prototype new nonparametric Bayesian (NPB) software has been developed. Standard errors of parameter estimates and rigorous Bayesian credibility intervals are now available. This work, presented at this meeting, is progressing.

The **RightDose** clinical software [2] uses Pmetrics population models, currently for a 3 compartment linear system, and develops multiple model (MM) dosage regimens to hit desired targets with minimum expected weighted squared error, thus providing maximally precise dosage regimens for patient care. If needed, hybrid MAP and NP Bayesian posteriors provide maximum safety with more support points and more precise dosage regimens. In addition, the interacting multiple model (IMM) sequential Bayesian analysis when model parameter distributions are changing during the period of data analysis [[3] has been upgraded by using the hybrid analysis in advance to provide more support points than were present in the original population model, again for more capable Bayesian parameter distributions and more informed dosage regimens than were available before. This work was also presented at this meeting. IMM has tracked drug behavior better than other methods in unstable post surgical cardiac patients [4]. In all the software, creatinine clearance is estimated in either stable or changing clinical situations, based on analyzing pairwise serum creatinine values, age, gender, height, weight, muscle mass, and dialysis status [5].

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NONPARAMETRIC POPULATION MODELS

- **Get the entire ML distribution, a Discrete Joint Density: one parameter set per subject, + its probability.**
- **Shape of distribution determined only by the data itself.**
- **Multiple individual models, up to one model set per subject.**
- **Can discover, locate, unsuspected subpopulations.**
- **Behavior statistically consistent. Study more subjects, better results.**
- **The multiple models permit multiple predictions.**
- **Can optimize precision of goal achievement by a MM dosage regimen.**
- **Use IIV +/or assay SD, stated ranges.**
- **Computes environmental noise.**
- **Bootstrap, for confidence limits, significance tests.**

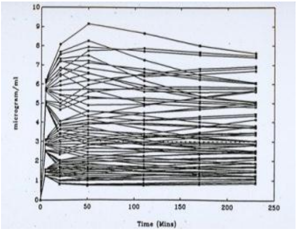
MULTIPLE MODEL (MM) DOSAGE DESIGN

Use a prior with discrete multiple models - an NPEM or NPAG model.

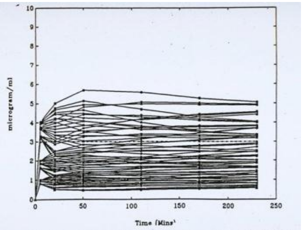
Give a candidate regimen to each model. Predict results with each model. Compute weighted squared error of failure to hit target goal

Find the regimen hitting target with minimal weighted squared error.

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 BAYESIAN ANALYSIS.

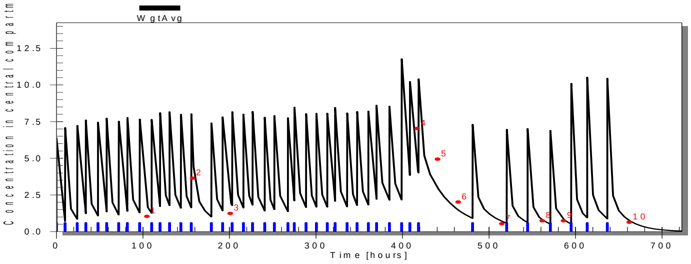
Support point values don't change. Compute Bayesian posterior probability of each support point, given the patient's data. Problem: will not reach out beyond pop parameter ranges. May miss unusual patient.

NEW! IMPROVED HYBRID BAYESIAN ANALYSIS

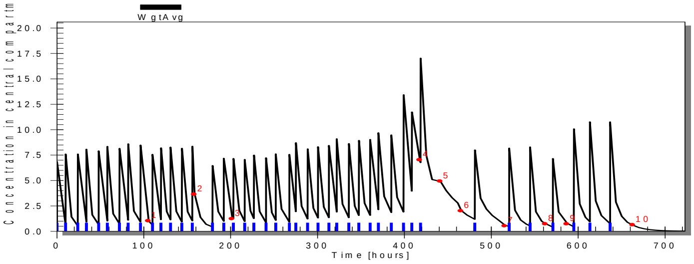
Start with MAP Bayesian estimate. Reaches out pop ranges to unusual patients. Add even more support points nearby, to augment original pop model. Then MM Bayesian analysis. More flexible, informed, safer.

NEW! IMPROVED INTERACTING MULTIPLE MODEL (IMM) BAYESIAN ANALYSIS FOR UNSTABLE PATIENTS

Limitation of all other current Bayesian methods - find only 1 set of fixed parameter values which fit the data.IMM - Relax this assumption. Let "true patient" change during data analysis if more likely to do so. More available support points in new version. More flexible now.



MM Bayesian updating – only fair tracking in unstable patient



IMM: interacting sequential MM Bayesian analysis – best tracking

NEW! Nonparametric Bayesian Population Modeling

We have developed a prototype nonparametric Bayesian pop modeling method based on stick breaking to construct the prior. It has close agreement with Pmetrics (NPAG) but also obtains standard errors of parameters and rigorous Bayesian credibility intervals. A manuscript is in press.