

Population PK Model Prior for Sequential Interacting Multiple Model Bayesian Analysis.

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ABSTRACT: An Improved Population Model Prior for Nonparametric Sequential Interacting Multiple Model (IMM) Bayesian Analysis.

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Objectives A current limitation of IMM Bayesian sequential analysis [1] is that the changing parameter distributions which take place during the period of data analysis may lie in a region of the nonparametric population model which has few support points.

Methods To improve this situation, our group has added extra support points from the augmented population model currently used for our hybrid Bayesian analysis of fixed parameter distributions during the data analysis. The hybrid procedure starts with a maximum a posteriori probability Bayesian analysis. Extra support points were added near the MAP Bayesian estimate to form a 4 x 4 grid of support points. This has now been upgraded to 10 x 10 points, with an adjustable percent change between them, ranging from 5 to 20 percent.

Results This augmented population model now provides a much larger set of points for the changing parameter values of the unstable patient to attach to, and provides a richer set of support points from which to compute the next adjustment of the dosage regimen to achieve the desired target goal most precisely, with minimum expected weighted squared error.

Conclusions Past versions of this software have tracked drug behavior in patients better than other Bayesian methods [2]. This new improved population model prior enhances this capability.

References: [1]. Bayard D, and Jelliffe R: A Bayesian Approach to Tracking Patients having Changing Pharmacokinetic Parameters. J. Pharmacokin. Pharmacodyn. 31 (1): 75-107, 2004.

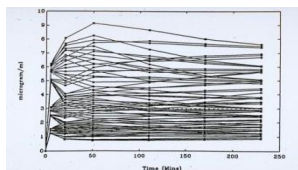
[2]. Macdonald I, Staats C, Jelliffe R, and Thomson A: Evaluation and Comparison of Simple Multiple Model, Richer Data Multiple Model, and Sequential Interacting Multiple Model (IMM) Bayesian Analyses of Gentamicin and Vancomycin Data Collected From Patients Undergoing Cardiothoracic Surgery. Ther. Drug Monit. 30:671-74, 2008.

NONPARAMETRIC POPULATION MODELS

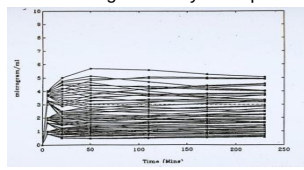
Get the entire ML distribution, a Discrete Joint Density: one parameter set per subject, + its probability. Shape of distribution determined only by the data itself. Multiple individual models, up to one model set per subject, give multiple predictions. Maximize precision of goal achievement by MM dosage regimens. Compute environmental noise.

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 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. Dose itself is an IMPORTANT tool reducing variability in response.



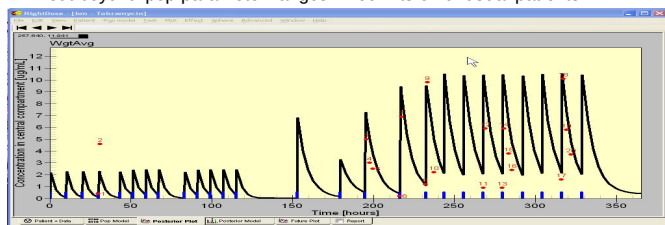
Lidocaine stepwise infusion regimen based on Parameter MEANS: Predicted response of full 81 point lidocaine population model. Target = 3ug/ml



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

MULTIPLE MODEL BAYESIAN ANALYSIS.

Pop support point values don't change. Compute Bayesian posterior probability of each support point, given patient's data. Will not reach out beyond pop parameter ranges. Poor fits on unusual patients.



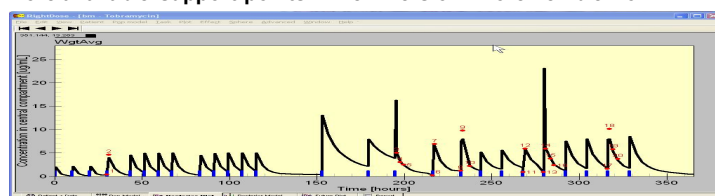
MM Bayesian fit, unstable, changing patient, poor fit.

IMPROVED HYBRID BAYESIAN ANALYSIS

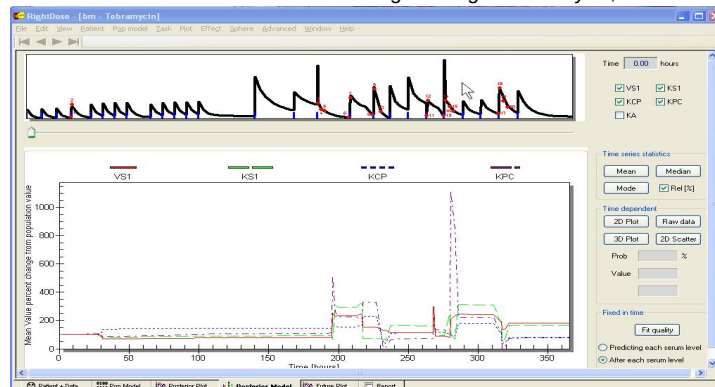
Start with MAP Bayesian estimate. Reaches out pop ranges to unusual patients. Can now add up to 100 extra support points nearby, to augment original pop model. Then MM Bayesian analysis. More flexible, informed, safer.

IMM-CHANGING PARAMETERS DURING DATA ANALYSIS

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.

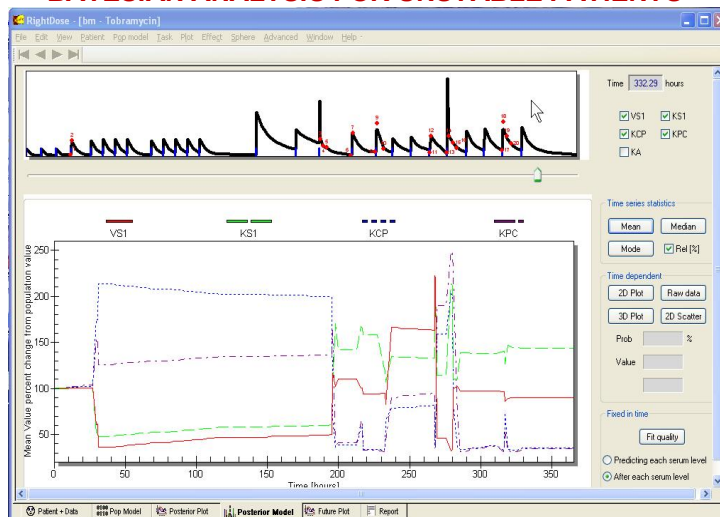


IMM i Good fit now. Parameters change during data analysis, as below



But parameter changes are volatile, with few points in pop model.

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



New HYBRID - IMM Bayesian analysis. More support points, more plausible tracking