The USC*PACK *BigWinPops* and *MM-USCPACK* Programs, USC Laboratory of Applied Pharmacokinetics (www.lapk.org)

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Abstract

The BigWinPops maximum likelihood nonparametric adaptive grid **(NPAG)** population modeling software runs in XP. The user defines the structural PK/PD model using the BOXES program. This is compiled and linked transparently. The subject data files are entered, and instructions. Routines for checking data files and for viewing results are provided. Likelihoods are exact. Behavior is statistically consistent, so studying more subjects gives estimates progressively closer to the true values. Stochastic convergence is as good as theory predicts. Parameter estimates are precise [1]. The software is available by license from the University for a nominal donation.

The **MM-USCPACK** clinical software [2] uses NPAG population models, currently for a 3 compartment linear system, and computes the dosage regimen to hit desired targets with minimum expected weighted squared error, thus providing maximal precision in dosage regimen design, a feature not seen with other current clinical software. Population models for planning, monitoring, and adjusting therapy with aminoglycosides, vancomycin (including continuous IV vancomycin), digoxin, carbamazepine, and valproate are available. The interactive multiple model **(IMM)** Bayesian fitting option [3] allows parameter values to change if needed during the period of data analysis, and provides more precise tracking of the changing behavior of drugs in clinically unstable patients. In all the software, creatinine clearance is estimated based on one or two either stable or unstable serum creatinines, age, gender, height, and weight [4].

References:

[1] Bustad A, Terziivanov D, Leary R, Port R, Schumitzky A, and Jelliffe R: Parametric and Nonparametric Population Methods: Their Comparative Performance in Analysing a Clinical Data Set and Two Monte Carlo Simulation Studies. Clin. Pharmacokinet., 45: 365-383,2006.

[2] 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.

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

[4]. Jelliffe R: Estimation of Creatinine Clearance in Patients with Unstable Renal Function, without a Urine Specimen. Am. J. Nephrology. 22: 3200-324, 2002.

Nonparametric population models

- Get the entire ML distribution, a Discrete Joint Density: up to one parameter set per subject, + its prob.
- Multiple individual models, up to one model set per subject.
- Distributions are not determined by some equation, only by the data itself.
- Can discover, locate, unsuspected subpopulations.
- Computes environmental noise.
- Behavior is statistically consistent. Study more subjects, guaranteed better results.
- The multiple models permit multiple predictions.
- Can optimize precision of goal achievement by a dosage regimen. Minimum weighted least squares error.

NPAG – Non parametric adaptive grid

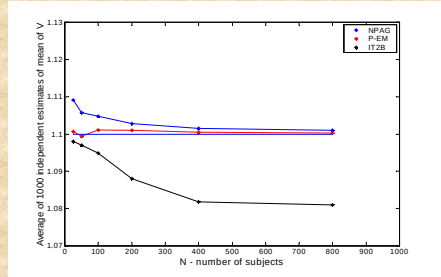
- Initiate by solving the ML problem on a small grid
- Refine grid by adding perturbations about each support point from previous optimal solution
- Solve the ML problem on the refined grid
- Iterate solve-refine-solve cycle until convergence, with decreasing perturbations
- Best of both worlds - improved solution quality with far less computational effort!

Efficiency and Relative Error

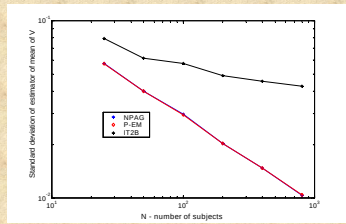
Estimator	Relative Efficiency %	Relative Error
Direct Observation	100	1.00
PEM	75.4	1.33
NPAG	61.4	1.63
NONMEM FOCE	29.0	3.45
IT2B FOCE	25.3	3.95
NONMEM FO	0.9	111.11

Advantages of NPAG

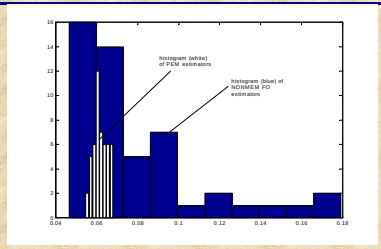
- Many models previously requiring a supercomputer now run on a PC.
- Speedup over NPEM = 1000.
- Some models containing up to 16 parameters (Drusano, 2000) previously beyond the range of any computer have been run with NPAG
- NPAG improves the likelihood with much less computation
- NPAG computes both both intra- and inter-individual variability – environmental noise



NPAG and PEM are consistent (true value of mV = 1.1)



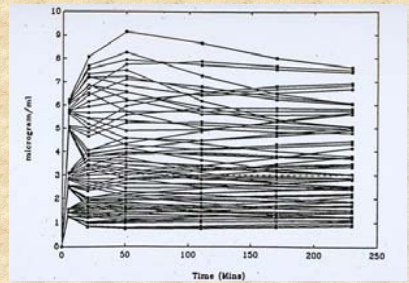
Asymptotic stochastic convergence rate of IT2B is 1/N1/4 vs. 1/N1/2 for NPAG and PEM



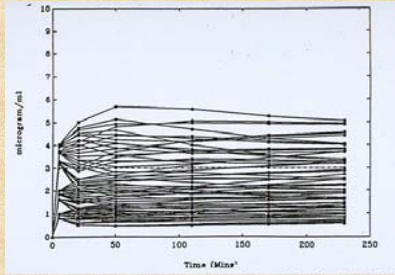
Approximate likelihoods can destroy statistical efficiency

MM-USCPACK dosage design

- Use a prior with discrete multiple models - an NPEM or NPAG model, for example.
- Give a candidate regimen to each model.
- Predict results with each model.
- Compute weighted squared error of failure to hit target goal at target time.
- Find the regimen hitting target with minimal weighted squared error. This is multiple model (MM) dosage design - the clinical reason for using nonparametric models.



Lidocaine Regimen based on Parameter MEANS: Predicted response of full 81 point lidocaine population model



MM maximally precise lido regimen: Predicted response of full 81 point lidocaine population model