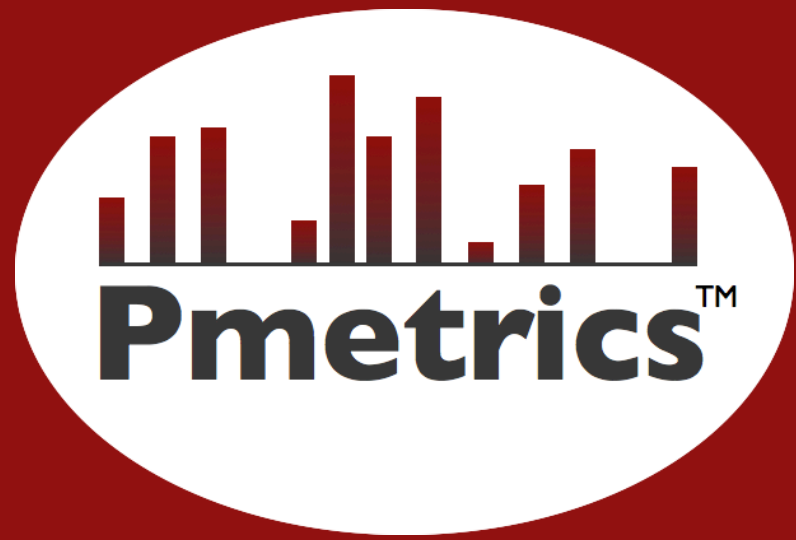




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Non-Parametric Bayesian Fitting: A Novel Approach to Population Pharmacokinetic Modeling



Michael Neely, Tatania Tatarinova, Jay Bartroff, Michael van Guilder, Walter Yamada, David Bayard, Roger Jelliffe, Alan Schumitzky

University of Southern California Laboratory of Applied Pharmacokinetics, 134-B Alcazar Ave, Los Angeles, CA 90033 USA

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Objectives

Compared with most parametric population modeling methods, our Non-Parametric Expectation Maximization (NPBM) and Adaptive Grid (NPAG) interior point maximum likelihood algorithms [1,2] calculate exact, rather than approximate likelihoods, and they easily discover unexpected sub-groups and outliers.

However, NPAG cannot calculate credibility intervals around parameter estimates.

Therefore, we tested our novel NP Bayesian (NPB) algorithm, derived from [3], that uses stick-breaking to construct a Dirichlet process prior and combines the best of parametric and NP methods.

Methods

We took dosing, sample times and weights, from 35 infants enrolled in an IV zidovudine PK study as a template to simulate new observations after a short IV infusion into one compartment with simulated PK parameter values.

For the PK parameter values, we set elimination (KEL) as a bimodal distribution, with means of 0.5 and 1.0 1/h and weights of 0.3 and 0.7. Volume of distribution (VOL) was unimodal, with a mean of 2.0 L/kg.

The SD for each distribution was a CV% of 25%.

Noise, as a normal distribution with mean 0 and SD 0.01 was added to each simulated observation.

Using the Pmetrics and rjags packages for R, plus the JAGS software [4], we compared simulated vs. predicted KEL, VOL, and observations from our NPB and NPAG algorithms. For NPB fitting, we used one Markov Chain for the Monte Carlo simulation, drawing every 10th posterior sample from iteration 10000 to 10500.

Results

Simulated observations with realistic, unbalanced sampling times and sample numbers ranged from <0.01 to 1.64 mg/L, calculated up to 8 hours after dosing, with 5–6 samples per subject at times that varied throughout the population, and corresponded to the times that the real infants in the source population had been sampled (Figure 1).

We chose the number of stick breaks (support points) for the NPB Dirichlet process prior to be 17. This was based on the number of clusters fitted by the NPB algorithm and inspection of the probabilities of each support point, which diminished to negligible levels when more than 17 points were allowed. Each point is a sample from the joint posterior distribution for the population, and is itself a bivariate distribution with an associated probability based on the 50 samples from the MCMC chain.

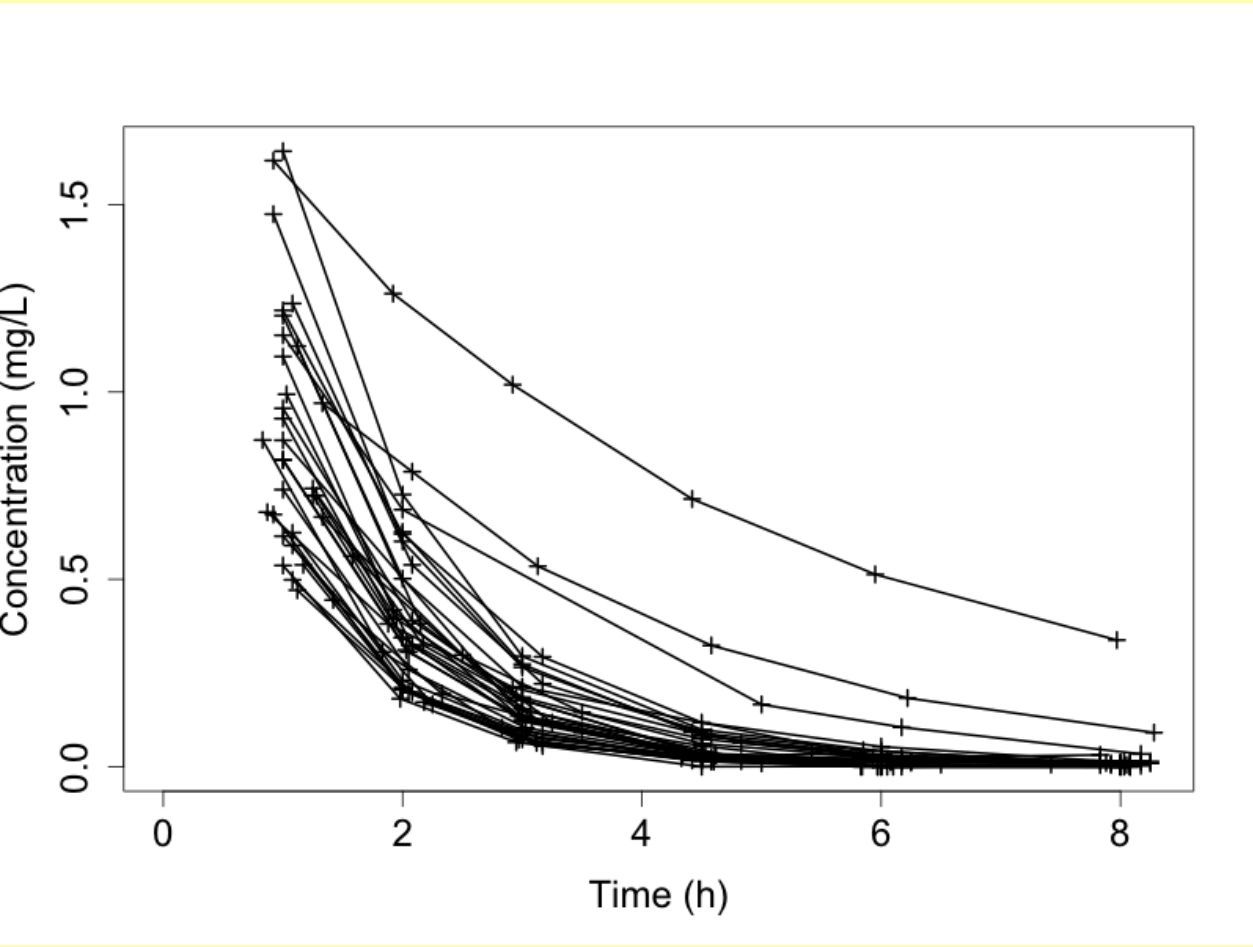


Figure 1 Time concentration profiles for each of the 35 simulated subjects

	Simulated (True)	NPAG fitted	NPB fitted
Number of Points	35	23	17
KEL (1/h)			
mean (95% CI)	0.77 (NA)	0.77 (NA)	0.76 (0.73–0.79)
SD (95% CI)	0.27 (NA)	0.27 (NA)	0.24 (0.20–0.32)
VOL (L/kg)			
mean (95% CI)	2.03 (NA)	2.03 (NA)	1.98 (1.92–2.03)
SD (95% CI)	0.28 (NA)	0.27 (NA)	0.30 (0.25–0.40)

Table 1 Summaries of the simulated (true) values for elimination (KEL), volume of distribution (VOL), and the weighted support points fitted by the Non-Parametric Bayesian (NPB) and Non-Parametric Adaptive Grid (NPAG) algorithms.

Parameter Value Estimation

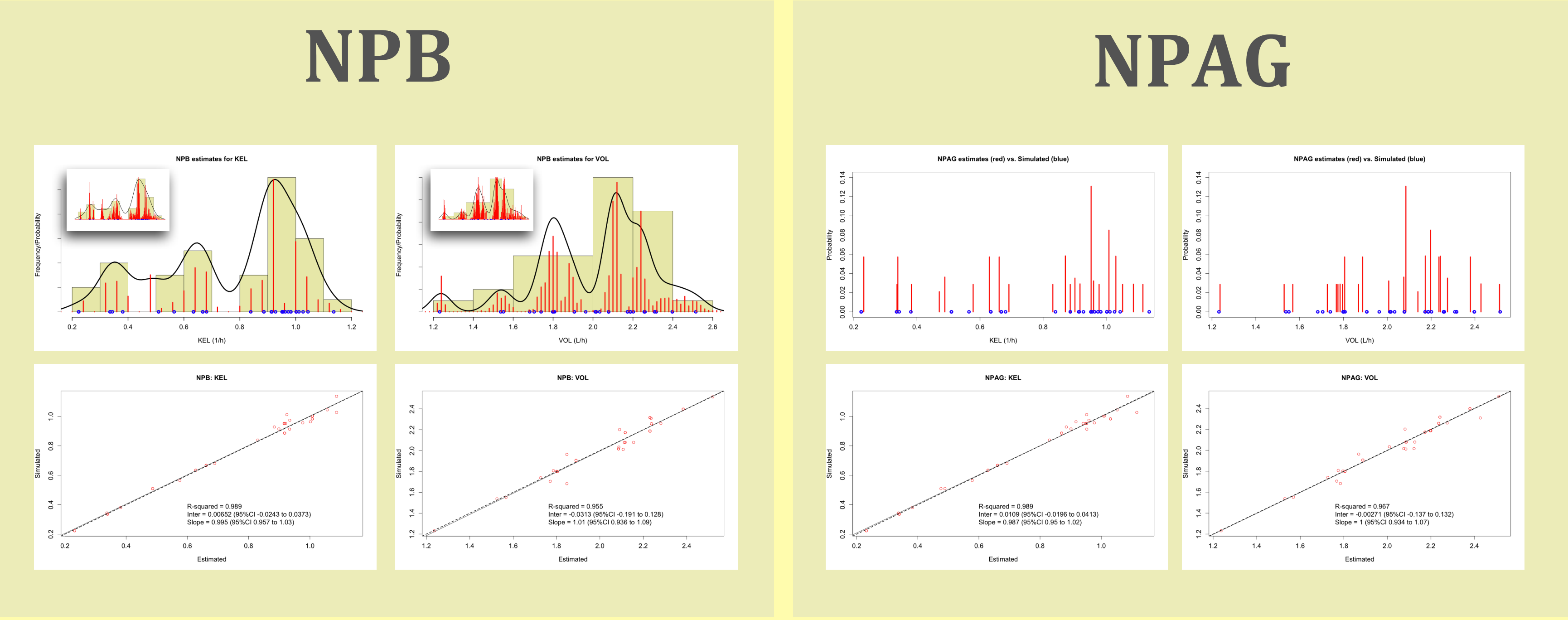


Figure 2 (TOP ROW) Marginal distributions for simulated (true) population parameter values (blue circles, filled histograms) for elimination (KEL) and volume of distribution (VOL) as estimated by our Non-Parametric Bayesian (NPB) and Non-Parametric Adaptive Grid (NPAG) algorithms. In the NPB plots, the distributions are represented in several ways: 1) red bars with no binning (inset) or with arbitrary binning (nbin=50); 2) a smoothed sum of normal distributions about the means of the distribution for each of the 17 support points. **(BOTTOM ROW)** Linear regressions of simulated (true) parameter values vs. those estimated by NPB and NPAG. For NPB, the estimates are the means of the distribution for each of the 17 support points. For NPAG, they are the maximum likelihood point estimates.

Observed vs. Predicted Concentrations

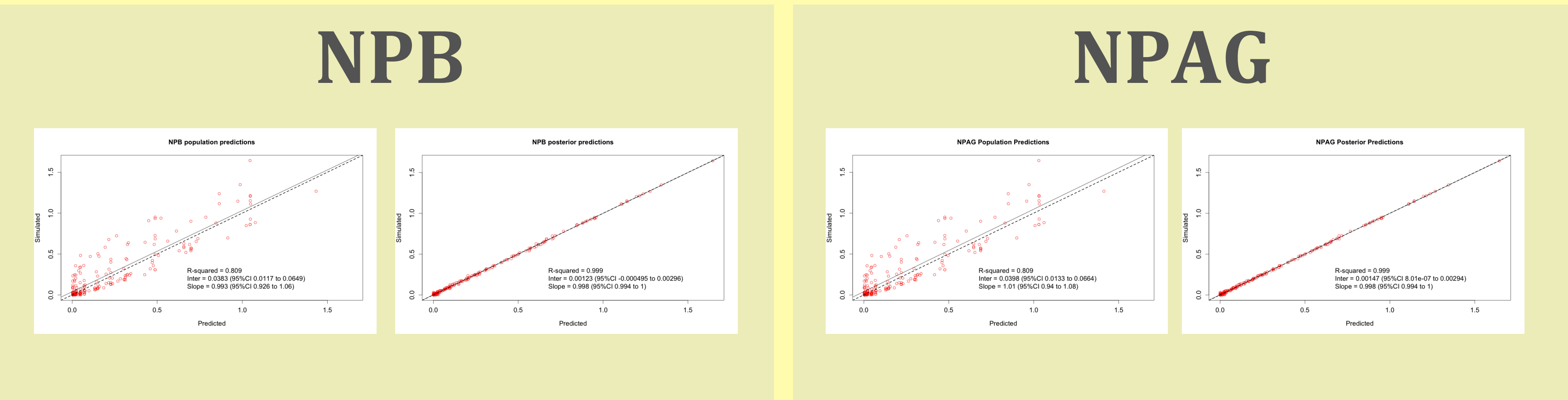


Figure 3 Linear regressions of simulated concentrations vs. concentrations predicted by the mean of the population or individual posterior distributions as estimated by the Non-Parametric Bayesian (NPB) or Non-Parametric Adaptive Grid (NPAG) algorithms.

Conclusions

- Our Non-Parametric Bayesian (NPB) and Non-Parametric Adaptive Grid (NPAG) population algorithms both accurately estimate PK parameter values from a realistic simulated dataset with unbalanced sample times and sample numbers and with inclusion of a covariate (weight).
- Both methods find accurate parameter values without assuming any underlying parameter value distribution.
- Although fully non-parametric, NPB fitting additionally provides robust credibility intervals for all parameter estimates.
- Work still to be done includes exploring convergence criteria, further optimization of the number of stick breaks, and generalization to even more complex PK models.

References

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2. Baek, Y. An Interior Point Approach to Constrained Nonparametric Mixture Models, PhD Dissertation, University of Washington, Department of Mathematics (2006)
3. Sethuraman J. A constructive definition of Dirichlet priors. Statistica Sinica 1994; 4:639–650.
4. The Pmetrics R package is available from <http://www.lapk.org>. The rjags R package can be downloaded from <http://cran.r-project.org>. JAGS can be accessed from <http://mcmc-jags.sourceforge.net/>.

Acknowledgements/Declarations

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