

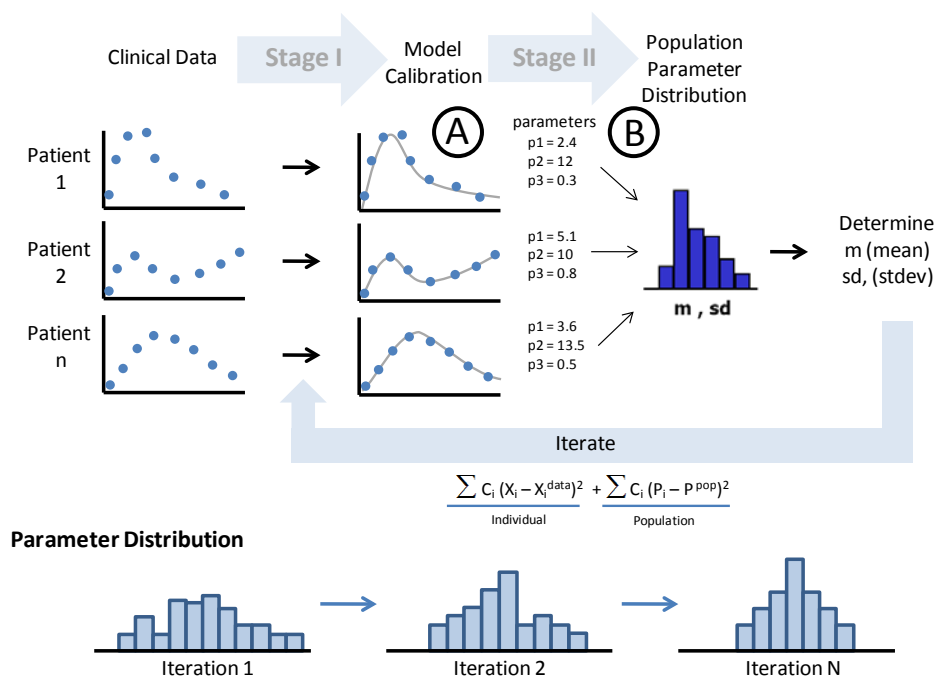
**Introduction**

While empirical & statistical methods remain the cornerstone of population PKPD modeling, there is a growing interest in employing mechanistic-based modeling approaches to uncover additional and better insight from (often underutilized) clinical data, and apply that back to our understanding of drug and disease<sup>1</sup>.

However, mechanistic-based approaches yield larger and more complex models and this presents considerable challenges in calibrating these models to clinical trial data. This computational challenge is often cited to be a major bottleneck in adoption and utilization of mechanistic-based approaches in population PKPD modeling<sup>2</sup>. **This Technical Bulletin describes our recent work in overcoming this bottleneck, and applying it to several clinical trial efforts by major pharmaceutical companies.**

**Methodology and Results**

Figure 1 gives an overview of our methodology. We start with an Iterative Two-Stage (ITS) population PKPD algorithm published by Steimer et al., 1984<sup>3</sup>. The ITS algorithm performs several iterations to converge the prior distributions of population parameters. Since each ITS iteration requires many dynamic simulations, parametric sensitivity analyses and parameter estimations, computation speed and reliability is critical for practical use. We address this need for fast computation speed and reliability by utilizing a set of dynamic simulation and optimization technologies originally developed at MIT and later commercialized by our team at RES Group<sup>4</sup>.



**Figure 1: Summary of ITS algorithm.** A) In the first stage, parameter estimates are computed for all patients using the current set of prior distributions for the population. B) In the second stage, the population parameters are recomputed using the results of the first stage to form a new set of population prior distributions. The large blue arrow marked “Iterate” above illustrates how the current prior distributions are fed back to the first stage in order to balance the fitting between individual patient data and the population average. This two-step procedure is repeated until the prior distributions for the population converge, requiring repeated dynamic simulation, parametric sensitivity analysis and parameter estimation.

Numerous advances including forward and adjoint sensitivity analysis, hybrid discrete/continuous simulation, and robust parameter estimation result in speeding up computations by several orders of magnitude compared to other approaches<sup>5,6,7</sup>. In contrast to the STS approach<sup>8</sup>, ITS can cope with the common occurrence of sparse clinical data (e.g., relatively few measurements per patient). However, ITS sometimes requires more data than algorithms such as FOCE<sup>9</sup> and Bayesian algorithms<sup>10</sup> and this is addressed in the Future Work section below.

The ITS algorithm implemented in the JACOBIAN software enable us to solve large and complex problems that we typically encounter in industrial clinical trial problems. For example, using a 50-core parallel computing cluster, it took 30 minutes to solve a problem with 12 uncertain parameters, 100 differential variables and 250 patient measurement problems. A problem of this size is beyond the scope of what can be solved using any other currently available technologies<sup>2,10</sup>.

Given that numerous iterations – data set construction/revision, model building/revision, model solution through population PKPD algorithm, and interpretation and communication of results – are required during clinical trials. Saving in computation time can translate to months of acceleration in the clinical trials generating significant cost savings and ultimately this could have an important bearing on the success of the clinical trial.

In the past two years, we have been closely working with several of our customers helping them to utilize the JACOBIAN-ITS tool in their clinical trial effort. One of the earlier successes came in the application to a clinical trial on HCV (Hepatitis C Virus) Protease Inhibitor (currently in Clinical Trial Phase III). The mechanistic-based approach successfully predicted percent of PR (Pegylated-Interferon Ribavirin) non-responders that would benefit from the new therapy, determined optimal timing of PR and drug, and identified drug responders vs. non-responders (patients that will reach sustained viral response at the end of trial using data from the first few weeks of therapy). If you would like to hear more about RES Group's work in this area, please contact [pharma@resgroupinc.com](mailto:pharma@resgroupinc.com).

### Future Work

Applying the mechanistic model approach to problems having very sparse data sets is of high interest among our customers. We will next implement Bayesian population PKPD approaches, including interfacing to WinBugs<sup>11</sup>. If you wish to be updated on this development, please contact us at [pharma@resgroupinc.com](mailto:pharma@resgroupinc.com).

<sup>1</sup> J.V.S. Gobburu and L.J. Lesko, "Quantitative Disease, Drug, and Trial Models," *Annu. Rev. Pharmacol. Toxicol.*, 49:291-301, 2009

<sup>2</sup> S. Jönsson and E.N. Jonsson, "Timing and Efficiency in Population Pharmacokinetic/Pharmacodynamic Data Analysis Projects," *Pharmacometrics the Science of Quantitative Pharmacology*, 11:296, 2007.

<sup>3</sup> Jean-Louis Steimer, Alain Mallet, Jean-Louis Golmard and Jean Francois Boisvieux, "Alternative Approaches to Estimation of Population Pharmacokinetic Parameters: Comparison with the Nonlinear Mixed Effect Model," *Drug Metabolism Reviews*, 15 (1&2), pp. 265-292 (1984)

<sup>4</sup> The commercial product is called JACOBIAN Dynamic Simulation and Optimization Software. <http://jacobian.resgroupsoftware.com/>

<sup>5</sup> T.S. Park and P.I. Barton, "State Event Location in Differential-Algebraic Models," *ACM Transactions on Modeling and Computer Simulation*, 6(2):137-165, 1996

<sup>6</sup> W.F. Feehery, J.E. Tolsma and P.I. Barton, "Efficient Sensitivity Analysis of Large-Scale Differential-Algebraic Systems," *Applied Numerical Mathematics*, 25(1):41-54, 1997

<sup>7</sup> J.E. Tolsma and P.I. Barton, "Hidden Discontinuities and Parametric Sensitivity Analysis," *SIAM Journal on Scientific Computing*, 23(6):1861-1874, 2002.

<sup>8</sup> STS: Standard Two-Stage

<sup>9</sup> FOCE: First-Order Conditional Estimation

<sup>10</sup> R.J. Bauer, S. Guzy, and Ng, C., "A Survey of Population Analysis Methods and Software for Complex Pharmacokinetic and Pharmacodynamic Models with Examples", *The AAPS Journal*, 9(1), 2007].

<sup>11</sup> <http://www.mrc-bsu.cam.ac.uk/bugs/>