Using optimization algorithms to estimate parameters in a simple PK model with bifurcations

Prakash Packrisamy & Rukmini Kumar
Vantage Research, Chennai, India

Introduction
Estimating parameters for Ordinary Differential Equation models can be challenging, especially for systems with complex bifurcation structures [2]. Even simple compartmental PK models can display complex behavior including multiple steady-states and chaos. Prior knowledge of the model’s bifurcation structure and range of parameter values, based on physiological information can be used in Bayesian algorithms. Bayesian algorithms can use sparse and noisy data to estimate a distribution for each parameter value, instead of a unique value. This would also give us an idea about the sensitivity of the model output to the parameter value.

Main Objectives
1. Propose a simple compartmental PK model that captures the expected behaviour of drug
2. Create a Bayesian algorithm, such as a Markov Chain Monte Carlo (MCMC) to estimate the parameters for this dynamical system
3. Generate training data from model to test algorithm. Vary the sparsity and noise to determine robustness of algorithm
4. Estimate the range of PK parameters using Bayesian inference

Methods
A pharmacokinetic model with three compartments was the exemplary system for parameter estimation. This is a model of injectable subcutaneous long-acting insulin pharmaco kinetic studies [3]. The equations of the PK model are given below:

\[
\begin{align*}
\frac{dI_c}{dt} &= k_{alb}I_{sc} - k_dI_c \\
\frac{dI_n}{dt} &= D_0(t) - k_sI_{sc} \\
\frac{dI_{st}}{dt} &= k_aI_c - k_{alb}I_{sc}
\end{align*}
\]

where, \(I_{sc}, I_{st}, \) and \(I_n\) are the insulin concentration in subcutaneous, interstitial fluid and plasma compartments respectively. \(D_0\) is the dose and \(k_a, k_{alb}, \) and \(k_d\) are the rate parameters of the model, which are estimated.

We generated data for once daily injections for 1 week and used the last day’s \(I_n\) for evaluating the algorithm. We used readily available functional minimization [1], global search [1] and Bayesian optimization algorithms to estimate the model parameters. In Bayesian method, MCMC algorithm is used to sample the posterior distribution. Initial hypotheses of parameter ranges were determined based on knowledge of the biological range of parameters and from avoiding unphysical regimes from bifurcation analysis.

Results
Functional minimization (fminsearch) algorithms got trapped in multimodal minima and global search algorithms (Genetic algorithms with default mutation rates) were successful only with very specific initial guesses.

For Bayesian estimation, the initial guesses based on bifurcation analyses and physically feasible range for parameters were the adequate prior information. The parameter estimation using this prior information is shown in Fig.1. To test our algorithm, sparsity is introduced in to the system by decreasing the number of data points available to the algorithm. The parameters are estimated and the relative error is shown in Fig. 2.

It shows that the algorithm is relatively robust to number of data points from \(\approx 10^2\) to \(\approx 10^5\). We also introduced different levels of noise in to the system and the algorithm was found to be robust in estimating the parameters (data not shown). With the Bayesian, an estimated range of each of the parameters is available, and the predicted outcomes account for the uncertainty in the parameters (see Fig. 3).

Conclusions
From functional minimization to global search algorithms, every algorithm has limitations. A simple Bayesian algorithm was found to estimate the parameters much better than other algorithms in this case. Even after introducing highly sparse data to the system, Bayesian estimation is robust in estimating the parameters.

Bayesian approach to model development may be appropriate for Quantitative Systems Pharmacology as it provides a framework for explicit introduction of modeler hypotheses and clinical data. Developing formal methods to estimate the deviation of the parameter based on the available data, also allows for estimating parameter distribution in the population.

References

Acknowledgements
We thank the Vantage team, especially Ananthakrishnan Ganesh for productive discussions and support.