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PERSPECTIVE

A Bayesian Perspective on Estimation of Variability and Uncertainty in Mechanism-Based Models

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Mechanism-based pharmacokinetic/pharmacodynamic models have a fundamental basis in biology and pharmacology and, thus, are useful for hypothesis generation and extrapolation beyond the conditions of the original analysis data. The complexity of these models necessitates the incorporation of prior knowledge to inform many of the model parameters. Markov chain Monte Carlo Bayesian estimation offers a robust and statistically rigorous approach for incorporation of prior information into mechanism-based models. This article provides a perspective on the utility of this approach.
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Dr Lewis Sheiner and his colleagues established nonlinear mixed effects (NLME) modeling three decades ago as an integral part of the analysis of pharmacokinetic (PK) and pharmacodynamic (PD) data.[1] Since then improvements in computation, estimation algorithms, and our understanding of biology and pharmacology have led to an increase in the development and application of mechanism-based models of PK and PD using NLME. A PubMed literature search with the terms "mechanistic model" plus either "pharmacology" or "biology" returned 516 publications, with 87% of the articles published since the year 2000. Mechanism-based or physiologically based models have advantages over empirical ones, which apply arbitrary mathematical functions to establish a parsimonious fit to the data. One of the most challenging and important objectives in biomedical research is the need to translate between one experimental condition and/or model to another one (i.e., from animal to human). Mechanism-based models can facilitate this process of translation/extrapolation beyond the experimental conditions from which the data have been collected. This is because the parameters of mechanism-based models have a fundamental basis in our understanding of the biological/pharmacological system, and thus, reasonable hypotheses can be developed to predict how these parameters will change under new experimental conditions or in different experimental models. The use of mechanistic models to characterize biomarker data is not new; in the 1930s, Torsten Teorell used physiologically based models to characterize the PK of xenobiotics.[2] However, mechanism-based PK/PD models that account for different sources of variability using NLME are a relatively recent development. Incorporation of random effects using NLME in mechanism-based PK/PD models is important because it permits prediction of not only the expected outcome but also the variability and uncertainty regarding that outcome. The development and application of these types of models have increased as more pharmacologists and clinical pharmacologists learned to adopt NLME estimation in the last three decades.

CHALLENGES FOR MECHANISM-BASED NLME MODELING

There are major challenges for development of mechanism-based models using NLME approaches. Mechanism-based PK/PD models typically describe first-order physiological processes that require systems of ordinary differential equations. Repeatedly solving these complex systems of ordinary differential equations during the iterative estimation of random and fixed effects can be very computationally intensive.

Another challenge is that mechanism-based models have many parameters to be estimated, permitting more degrees of freedom for which to describe the data. The limited size and breadth of typical experimental data sets do not permit estimation of all of the physiological parameters of complex mechanistic models; often because many of the PD markers needed to describe the system are lacking and/or the number of samples collected over time too few. Traditional "frequentist" statistics suggests that a model should not have more degrees of freedom than are supported by the current analysis data set. However, physiological parameters are useful for extrapolation and may be informed by prior knowledge if the current analysis data set does not support their estimation. Markov chain Monte Carlo (MCMC) Bayesian estimation approaches allow this to be done in a more statistically rigorous manner.

APPLICATION OF BAYESIAN APPROACH TO NLME

Traditional NLME estimation approaches, such as weighted least squares and maximum likelihood, have limited options for incorporation of prior information; parameters can be fixed to a specific value, or they can be estimated based on the analysis data set. MCMC Bayesian approaches allow the incorporation of a probability distribution to the prior knowledge, with means and variance for the model's prior parameters. The variance of the prior means for the model parameters determines how much weight should be given to the prior relative to current analysis data set (**Figure 1**). The resulting posterior model is thus based on the combination

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of prior knowledge and the current experimental data. With Bayesian estimation approaches, there is no need to either completely ignore prior knowledge (an unrealistic prospect for mechanism-based models) or assume it is correct with absolute certainty.

The theory of Bayesian statistics goes back to the 18th century, when Thomas Bayes introduced the theorem for how one may update the probability estimate for a hypothesis as additional evidence is acquired. His theory provided the mathematical equation for indicating that future outcome has a probability that is based on current data and prior knowledge:

$$\text{Bayes theorem} \quad P(H \mid E) = \frac{P(E \mid H)P(H)}{P(E)}$$

where the probability of a hypothesis H conditional on a given body of data E is the ratio of the unconditional probability of the conjunction of the hypothesis with the data to the unconditional probability of the data alone ($P(E)$). In Bayesian model optimization, $P(E|H)$ is the marginal posterior density for model, given the priors and the analysis data set.[3]

Bayesian theory fits quite well with the need for mechanistic PK/PD models to incorporate prior knowledge to adequately inform the parameters of the system of ordinary differential equations. This theory has been difficult to implement for statistical modeling until the advent of more powerful computing resources and MCMC sampling approaches.[4] For nearly all statistical models, there is no closed form solution for the Bayesian posterior density estimator needed for model optimization; therefore, computational methods with numerical integration are a necessity. The MCMC sampling technique provides an effective approach for sampling from a distribution of parameters to solve this problem using iterative numerical integration. The MCMC approach samples a distribution of parameters at each iteration that is dependent on the conditional distribution, which is in turn dependent on the values sampled from the previous iterations. The posterior distribution is arrived at through this stochastic, iterative process that is informed by a combination of the current model, the model priors, and the analysis data set. The optimal set of fixed and random effects of the model is derived once the iterative MCMC process has reached a state of equilibrium, often called the "stationary" distribution. In this equilibrium state, the parameters vary stochastically about their means with a defined variance that is based on the optimal relationship between the model/priors and the analysis data. During the initial series of MCMC iterations, efficiently obtaining the stationary can be challenging. There are different approaches to arrive at the stationary distribution, but the most common is to use a "burn-in" period of MCMC iterations during which a large number of iterations are discarded. Following a sufficiently long "burn-in" period, the posterior parameters will converge to the stationary distribution. This is analogous to convergence to the maximum likelihood using more traditional estimation algorithms, with the exception that there is not convergence to a single maximum likelihood, but rather a probability distribution from which various useful statistics can be derived (e.g., mean, median, and SD). Determining the appropriate number of burn-in iterations to achieve convergence to the stationary distribution is the greatest challenge for model optimization using MCMC Bayesian estimation algorithms, particularly with complex PK/PD models.

Two problems that cause difficulty for convergence to the stationary distribution are as follows: correlation of the parameters with their initial estimates and autocorrelation, which is a systematic sequential within chain correlation. Diagnostic tests have been developed to determine whether convergence to the stationary distribution has occurred and include single chain vs. multiple MCMC approaches.[5] Many of these convergence diagnostics are available in the Bayesian Output Analysis package available for R or S-Plus

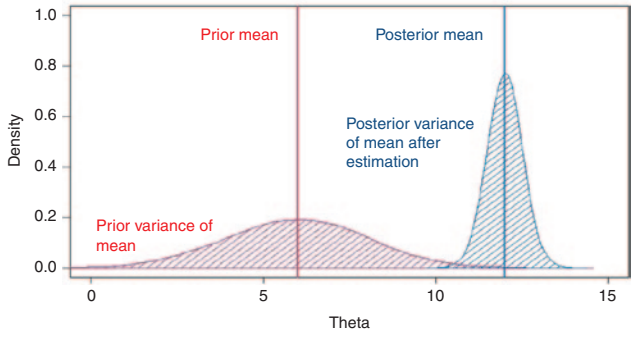

Figure 1 Illustration of the update to the prior mean and variance of hypothetical parameter, theta. The prior mean has a wide variance, but after MCMC Bayesian estimation, the mean has shifted to the right and the posterior variance has narrowed due to the information content of the analysis data set.

Table 1 MCMC Bayesian convergence diagnostics

Single chain diagnostics	
Geweke	MCMC is divided into two "windows," containing the first 10% and last 50% of the iterations. The convergence diagnostic Z is the difference between the two means divided by the asymptotic standard error of their difference
	$P < 0.05$ indicates lack of convergence
Heiderlberg and Welch	Compare sequential intervals of the MCMC to determine whether stationarity and a sufficient number of samples have been collected to estimate posterior mean
Raftery and Lewis	Estimates the number of iterations required to achieve convergence and the number iterations for the stationary distribution required to estimate the parameter at the desired confidence level
Multiple chain diagnostics	
Gelman and Rubin	Essentially the ratio of between-chain variance to within-chain variance. Statistic should approximate 1 once stationary distribution has been achieved. Can also be performed as a multivariate test on all of the parameters
	Rule of thumb is that the 0.975 quantile should be ≤1.2

MCMC, Markov chain Monte Carlo.

(**Table 1**).[6] The Geweke and Gelman and Rubin diagnostics can be plotted as a function of iteration to determine the progress of convergence as a function of the number of iterations. To determine whether the posterior parameters are uncorrelated with their initial estimates, it is typical to perform at least three MCMC with parameters that have different starting values. If the three chains converge to similar posterior distributions as determined by a multiple chain convergence diagnostic (e.g., Gelman and Rubin), then it is assumed that they are no longer correlated with their initial estimates. Autocorrelation is typically a more difficult problem for Bayesian NLME PK/PD modeling because it is often caused by correlation between parameters in the model (often related to the structure of the model) and may require tens of thousands of MCMC iterations before the autocorrelation is corrected. The degree of autocorrelation is typically assessed using a lag-autocorrelation plot, which determines the degree of autocorrelation within chains based on the distance (i.e., number of iterations or lag) between the sampled parameters. NONMEM and BUGS (WinBUGS or OpenBUGS) are two common platforms for implementation of MCMC Bayesian estimation for PK/PD modeling.[7,8] However, neither platform incorporates these convergence diagnostics; thus, assessment of convergence must be conducted using an external tool.

CONCLUDING REMARKS

Few published examples exist of the application of MCMC Bayesian estimation to complex, mechanism-based PK/PD models. The approach has been more commonly adopted in the field of toxicology for physiologically based PK modeling of xenobiotic compounds in humans and animals.[9] This is, in part, due to the fact that environmental toxicologists often need to estimate the risk posed by different xenobiotic agents, which fits in well with the ability of Bayesian approaches to provide a posterior probability distribution for the model. In addition, there has been widespread adoption in toxicology of ordinary differential equation modeling software tools such as acslX, which have incorporated MCMC Bayesian algorithms.

The use of MCMC Bayesian NLME approaches for application to clinical PK/PD problems is much less common. In 2007, Jonsson *et al*[10] published a "reanalysis" of a mechanism-based PK/PD model of neutropenia, which was the first example of the fully transparent application of MCMC Bayesian methods to a complex, hierarchical mechanistic PK/PD problem. They highlighted the difficulties with determining convergence and the time-consuming model optimization process using MCMC Bayesian estimation. Jonsson and co-authors conclude that the MCMC Bayesian approach enables efficient use of all available information from data, scientific evidence, and more reliable predictions based on that information. In the current issue of *Pharmacometrics & Systems Pharmacology*, Leil *et al* report the application of an MCMC Bayesian approach to a mechanism-based PK/PD model for prediction of CYP3A4-mediated drug interactions. These examples demonstrate that the Bayesian approach to PK/PD modeling will require a shift in the approach to PK/PD modeling, with more effort being invested in identifying a biologically plausible model and in finding informative priors than in achieving parsimony. The MCMC Bayesian approach currently represents the most robust and statistically rigorous manner in which to make use of prior knowledge to develop NLME PK/PD models that can be used to improve decision making in biomedical research and development.

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Conflict of Interest. The author is an employee of Bristol-Myers Squibb.

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