Proceedings of the 2009 Winter Simulation Conference
M. D. Rossetti, R. R. Hill, B. Johansson, A. Dunkin and R. G. Ingalls, eds.

A BAYESIAN PHARMACOMETRIC APPROACH FOR PERSONALIZED MEDICINE - A PROOF OF CONCEPT STUDY WITH SIMULATED DATA

Gary Blau

School of Industrial Engineering
Purdue University
West Lafayette, IN 47907, USA

Seza Orcun

e-Enterprise Center, Discovery Park
Purdue University
West Lafayette, IN 47907, USA

ABSTRACT

The objective of this research program is to optimize drug dose regimen for an individual, using minimally invasive clinical testing, in order to reduce both the total cost of treatment and the risk for over or under-medication using a Bayesian modeling approach. The challenge is to extract the PharmacoKinetic/PharmacoDynamic(PK/PD) parameters for an individual from population level plasma concentration information gathered in clinical trials along with one or two plasma samples from an individual and use these personalized parameters in determining most appropriate dose regimen for a specific patient. In this study we illustrate the plausibility of our methodology through a proof-of-concept study with simulated data.

1 INTRODUCTION

During development of new drugs large amounts of data are collected and used to establish PK/PD parameters for physiologically based pharmacometric (PBPK) models during animal and human trials (Phase I – III). These parameters are used by the drug developers to characterize the patient population and make commercial decisions and gain regulatory approval from the FDA during new drug development process but quickly orphaned when the necessary regulatory approvals are granted. PBPK models and their parameters are rarely translated into clinical practice to determine a personalized optimum dose regimen for an individual patients. A major roadblock in translating this knowledge into clinical utility is the lack of a methodology for estimating patient's individual PK/PD parameters since the individual may behave dramatically different than the population. Unfortunately, invasive clinical testing on a patient to estimate their unique or "personalized" pharmacometric profile for a drug is both expensive and uncomfortable for the patient.

How is the dosage regimen determined in practice? A common approach to determine the optimum dose is to "titrate" the patient. Based on the weight, age, sex and other idiosyncrasies of a patient, drug suppliers provide the practicing physician with suggestions for an initial dose and dosage interval. After a period of time, the patient returns for a follow-up visit to the physician and the dose is adjusted up or down depending on the effectiveness of the drug as measured by subjective inputs from the patient (e.g. symptoms reduced, increased in intensity, or disappeared entirely) or side effects (e.g. headaches, diarrhea, insomnia, etc). The patient is then dispatched with a new dosage regimen and another follow up appointment is scheduled. This process of repeated visits for dose adjustment continues until the drug behaves acceptably or a new candidate is chosen (if one exists) and the process is repeated. Not only is this process expensive and cumbersome, but it is also easy to overmedicate an individual especially if the side effects are less pronounced. This can be especially challenging when drugs are prescribed for the elderly. A recent article by Steed (2008) suggests that in Canada "85- and 90-year old overmedicated seniors are clogging emergency departments, blocking hospital beds and are sicker than they have any reason to be". For the dose regimen to be truly optimized for an individual (i.e. personalized dosage regimen) it is necessary to understand how the drug level changes with time and whether or not this is within the therapeutic window

The objective of this research program is to build a mathematical model-based methodology for optimizing drug dose regimen for an individual, using minimally invasive clinical testing, in order to reduce both

- the total cost of treatment, and
- the risk for over or under-medication.

Such a methodology will increase the quality of healthcare for an individual by maximizing the efficacy and minimizing the toxicity of orally administered drugs while simultaneously reducing their cost and potential for over- or under-medication using minimal clinical testing (one or two tests).

2 THE STATE OF THE ART

The emerging science of pharmacometrics is the overarching term for the use of quantitative methods such as pharmacokinetics and pharmacodynamics to influence decision making in drug development, therapeutic dose regimens and regulatory decisions (Powell and Gobburu 2007). These methods provide an important vehicle for relating the therapeutic efficacy and potential toxicity of drugs to drug concentrations in the blood plasma or serum rather than to the overall dose itself (Figure 1).

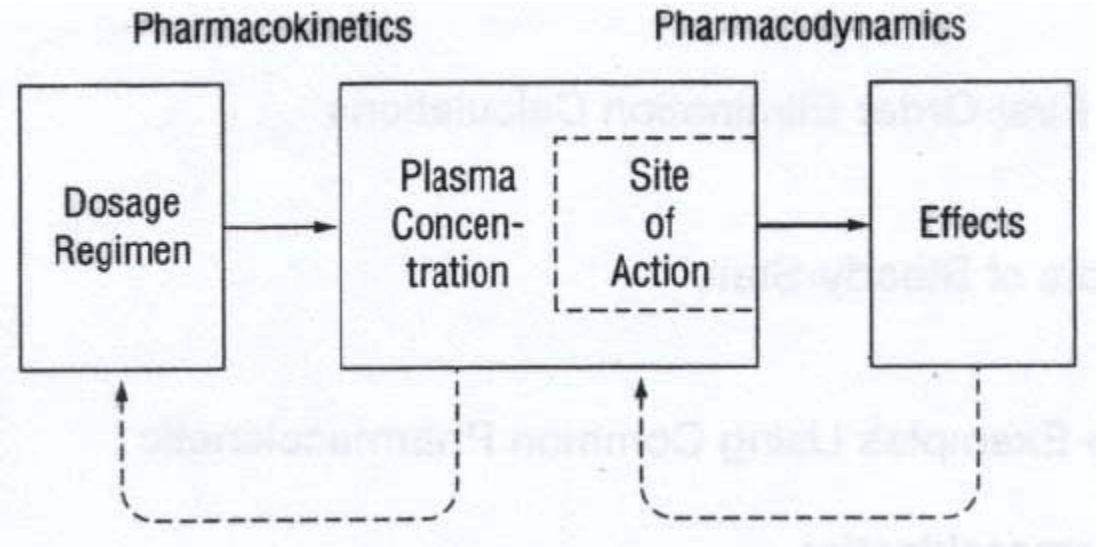


Figure 1: Relationship between Pharmacokinetics and Pharmacodynamics (Wishkro 2004)

Extensive testing is conducted on each new drug candidate by the pharmaceutical industry to assess the pharmacokinetics as embodied in a kinetic model and its associated kinetic parameters to support the registration process e.g. FDA approval. In most cases the key pharmacokinetic parameters are the absorption coefficient, ka, elimination coefficient, ke, volume of distribution, V, and distribution coefficients to the tissues or deep compartment k12, k21. A typical two-compartment model for a drug following oral absorption is shown in Figure 2.

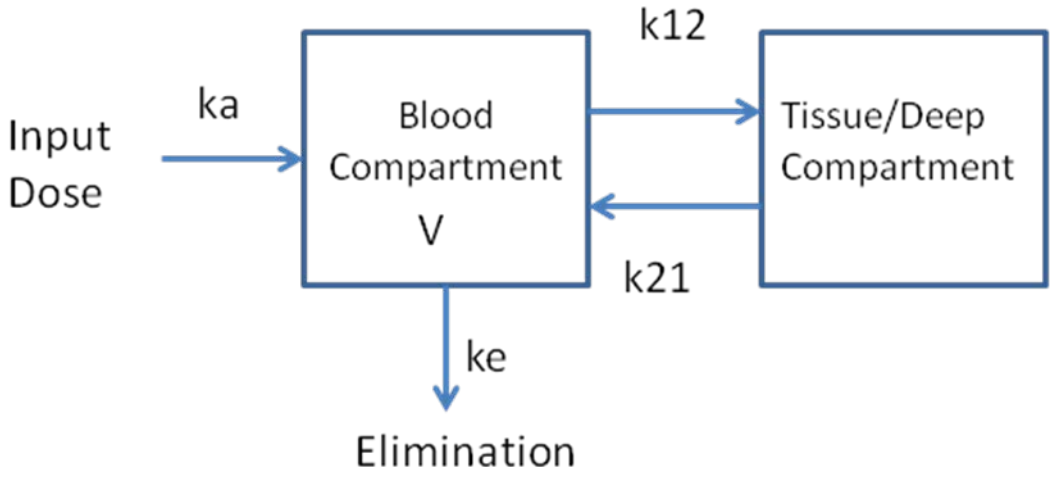


Figure 2: Two Compartment Pharmacokinetic Model

Because of the specific expertise required to perform pharmacometric studies, an entire industry has sprung up providing decision support services to the health care industry. Larger pharmaceutical companies have built in-house expertise to develop this important data and associated model in a cost effective manner. For example, Pharsight Corporation, based in Mountain View CA, provides a range of tools for pharmacokinetic (PK) and pharmacodynamic (PD) modeling, biostatistics and data management. Although PK/PD data is available and has been used by the FDA for regulatory decisions, it has not

been used at the point of care by the health care providers, clinicians or practicing physicians to determine the optimal dosage regimen for a specific individual. Health care professionals select doses based on easily measured characteristics of a patient such as age, weight, etc. and information supplied by pharmaceutical firms. Unfortunately, there are real complexities behind proper use: efficacy and possible interactions are often reduced to a simple set of tabular or graphical aids. Jeliffe et al. (2008), representing the laboratory of applied pharmacokinetics of the USC Medical Center, decries the fact that "the optimal care for specific individuals is usually not considered either by the pharmaceutical industry or by medical and pharmacy school curricula or by most clinical pharmacologists. Specific techniques for individualizing the initial dosage regimen and monitoring each patient clinically by measuring serum concentrations and other responses are generally not considered." While this is a generalized statement, it is not meant to imply a belief that practitioners are not acting in the best interest of the patient. We also know this statement to have some exceptions. For example, medicines that have a very narrow therapeutic window may require collecting a series of blood samples to determine correct dosage for each patient before or during their administration. Our definition of an optimal dosage regimen for an individual is a combination of dose amount and dose interval (time between doses) which maximizes the time that the drug level remains in the desired therapeutic window defined as the drug plasma concentration, which is less than an acceptable risk of a toxic side effect and greater than an acceptable level of efficacy. Figure 3 uses simulated data to show the concentration vs. time course compared to the therapeutic window for different drug intervals of the same total daily dosage. The large amplitude wave represents plasma concentration with a dose administered once per day (i.e. 10 mg once a day). The smaller amplitude sinusoidal wave represents plasma concentration with half the dose administered twice per day (i.e. 5 mg administered in the morning and at night).

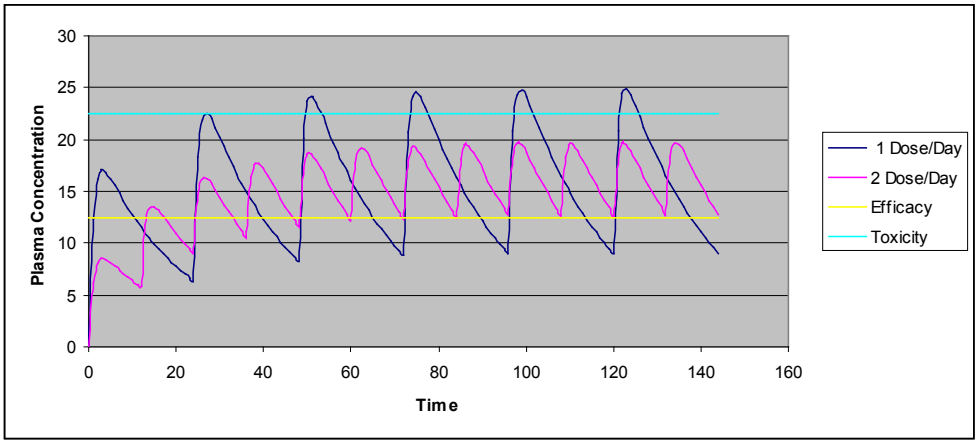


Figure 3: Therapeutic Window for Different Drug Regimen

In the case of a single daily dose, the plasma concentration soon enters the effective region and then exceeds the toxic side effect level. By cutting the dose in half and administering it twice a day, an effective concentration is achieved and maintained throughout the day without incurring the risk of toxicity. This is the goal of any dosing program: to ensure that we maximize the time in the therapeutic window. The drawback of the commonly applied practice of titrating an individual has been alluded to above. For the dose regimen to be truly optimized for an individual (i.e. personalized dosage regimen) it is clear from Figure 3 that it is necessary to understand the precise drug concentration vs. time course and whether this is within the therapeutic window or not.

3 THE BAYESIAN APPROACH TO PHARMACOMETRIC MODELING

One approach to determine the correct dosage is to conduct clinical tests on the individual following a single oral dose or after multiple doses and record the exact time between doses and samples. A typical study to generate well-defined pharmacokinetic pharmacodynamics parameters requires a minimum of seven or more tests over time. Figure 4 for example, using simulated data, shows the blood plasma concentrations for eight different individuals following a single oral dose where the subjects differ only in their pharmacokinetic parameters. Note the difference in uptake and elimination between individuals. Collecting such data for each patient is expensive, time-consuming and unpleasant for an individual. However, with this data it would be possible to estimate the PK/PD parameters for the individual and predict the drug concentration levels as a function of time for a variety of dosage regimens. If the therapeutic window is known then an optimization procedure is needed to search among the possible drug doses available and candidate dose intervals convenient to the individual to find a regimen that maximizes the time in the therapeutic window.

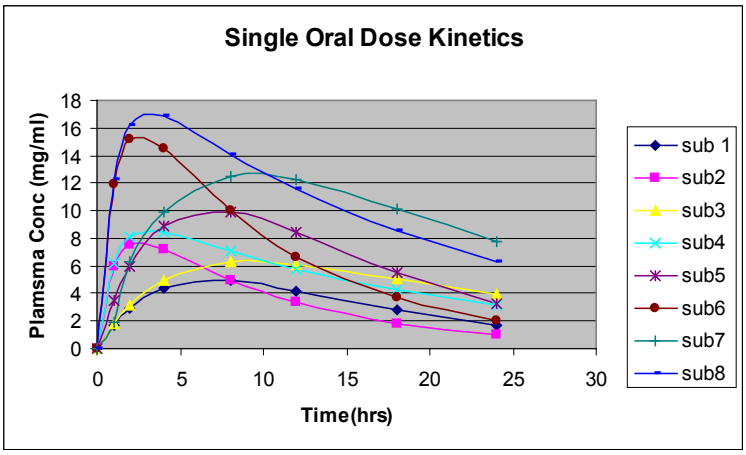


Figure 4: Single Oral Dose Kinetic Data with Seven Data Points for Eight Simulated Subjects

Blau et al. (2008) have developed a novel methodology for building mathematical models from experimental data using Bayesian methods. The basic ideas are classical. Mathematical models are postulated to describe the behavior of physical, chemical or biological systems. Probabilities, called priors, are assigned to the plausibility of each model, as well as the model parameters. This approach uses literature data combined with the experience of the modeler/scientists. New experimental data are then designed, collected and analyzed using Bayes' theorem to determine the plausibility of each model "after" the data has been collected. This plausibility is captured as another probability distribution called the posterior, and used to select the most appropriate model, and, if it is adequate, the distributions of the model parameters are determined. If an adequate model is not found, the new data generally suggest additional models which are then introduced to the process and additional data are generated. This sequential postulation, data generation, postulation, data analysis process continues until an adequate model is identified (see Figure 5).

This Bayesian model building approach is attractive to the scientists because it mimics the thinking that is engrained in the scientific method. It is challenging, however, because of the computational burden required to calculate the posterior distributions and subsequently use these to reflect uncertainties in predictions made with the model. Previous computational challenges have been ameliorated by the speed and power of readily available computational resources and advances in algorithm engineering. In our case, these computational gymnastics have been captured in a custom designed, PC based software package trademarked ModQuest™ which can be used for dose optimization applications as well as a myriad of other health care engineering and scientifically based applications (Blau et al. 2008).

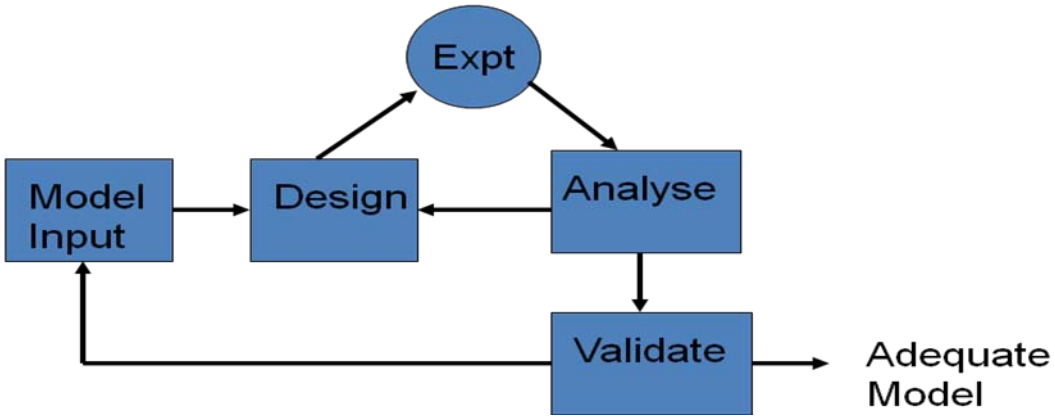


Figure 5: Bayesian Model Building

How can this powerful software package be used to determine the optimal dosage regimen for an individual? Consider the existing population PK/PD data collected during drug development as the "prior". By Bayesian analysis it is possible to generate joint probability distributions for the population pharmacokinetic parameters. The decision of whether the model is a one or two compartment model or even a nonlinear model will have been made as part of the regulatory process so it is suffi-

cient to concentrate only on generating meaningful probability distributions for the kinetic parameters. By using techniques such as the Markov Chain Monte Carlo (MCMC) sampling schemes (Gilks, Richardson and Spiegelhalter 1998) captured in ModQuest, it is possible to generate prior probability distributions for an individual accounting for various populations' demographics such as age, sex, and weight etc, alluded to earlier.

The challenge is to extract the posterior pharmacokinetic pharmacodynamics parameters for an individual from this prior information and use it to predict the drug levels after a single or multiple doses. In other words, the goal is to personalize the dosage regimen from the population data. The prior information from the population data is entered into ModQuest™ as a joint prior distribution. Then, a single dose or dosage regimen is selected based on the traditional patient titration approach. A single clinical test must then be performed on the patient following the first dose "at a time convenient to the patient". Interestingly this time can occur after several doses provided the time following the doses are recorded. Once the complete concentration vs. time course has been determined, probably in a laboratory, the result is fed into ModQuest and the posterior probability distributions for the kinetics and dynamics parameters are determined using Bayesian methods. These posterior distributions are subsequently used to determine the fractions of the dose time interval that the drug levels are within the therapeutic window. For indeterminate results, another clinical test may be ordered and the Bayesian analysis repeated.

4 THE PROOF-OF-CONCEPT STUDY WITH SIMULATED DATA

In this section we present use of simulation in developing and proofing the new methodology. Such a use of simulation is especially beneficial when acquiring actual data is prohibitively costly and/or the methodology development is deemed to be a high risk activity. Though our approach has been successfully applied in other domains, namely reaction kinetics and enzyme kinetics (Blau et al. 2009; Blau, Orcun, and Stamatis 2009), our goal in this work, i.e. to personalize the dosage regimen from the population PK/PD data, is high risk due to potential large difference between individuals and the data need to characterize an individual is very expensive to obtain. Therefore, before pursuing this costly next stage we performed a preliminary study by simulating pharmacokinetics data for a small population. We assumed that the concentration of the drug in the blood can be described by

$$C_b = \frac{Dk_a}{V_d\left(k_a - k_e\right)}\left(e^{-k_e t} - e^{-k_a t}\right)$$

where k_a is absorption coefficient, k_e is elimination coefficient and V_d is volume of distribution. A population of 8 subjects has been generated by using a full two level factorial design over reasonable ranges of the parameters (see Table 1) and experimental error: a normally distributed random error proportional to the blood concentration level as given by the following equation

$$\varepsilon\big|_t \sim N\left(0, \omega\left(C_b\big|_t\right)^{\gamma} + \alpha\right)$$

where α=0.05, γ=1 and ω=0.1 and ε_t is biological and measurement error at sample/measurement time t (1 hour, 2 hours, 4 hours, 8 hours, 12 hours, 18 hours and 24 hours after the drug has been orally administered). This PK model for estimating plasma concentrations and the error model are used to simulate actual individual plasma concentration data for eight subjects (presented in Figure 4). In this way, 56 blood concentration levels have been generated to represent the population data usually collected in phase I clinical trials.

Table 1: Parameters used to generate the simulated population data of Figure 4.

	D	Ln(V_d)	Ln(k_a)	Ln(k_e)
Subject 1	100	2.30	-0.69	-1.61
Subject 2	100	2.30	0.00	-1.61
Subject 3	100	2.30	-0.69	-3.00
Subject 4	100	2.30	0.00	-3.00
Subject 5	100	1.61	-0.69	-1.61
Subject 6	100	1.61	0.00	-1.61
Subject 7	100	1.61	-0.69	-3.00
Subject 8	100	1.61	0.00	-3.00

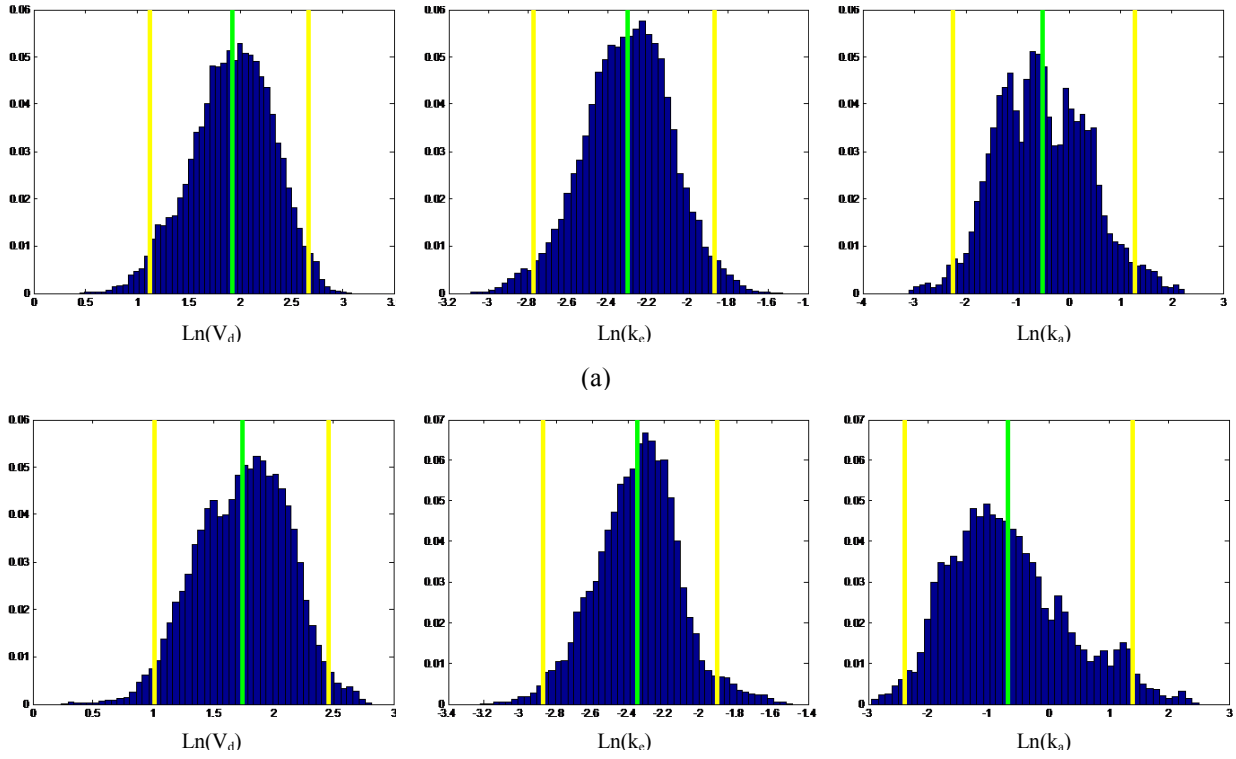
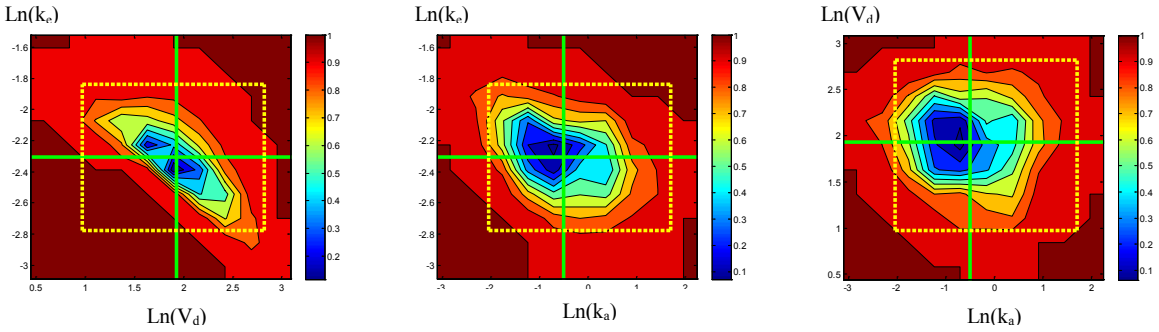


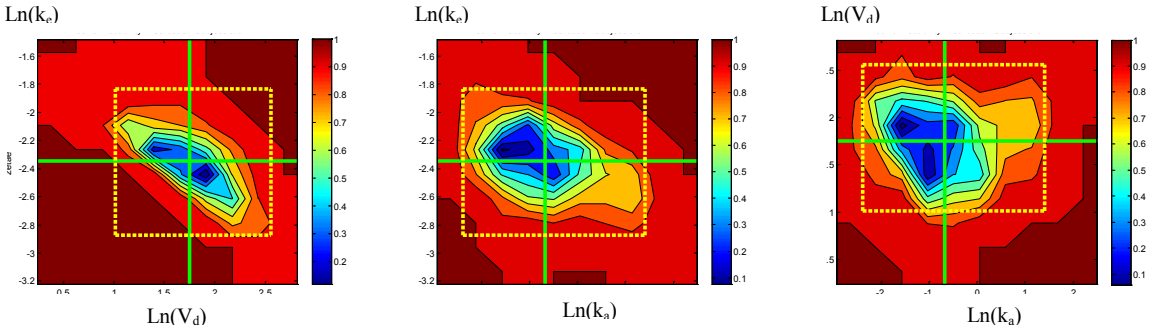
Figure 6: Personalized Pharmacometric Parameters Marginal Distributions from Simulated Population Data. (a) Pharmacometric parameter distributions for Subject 1 by a single clinical test after 24 hours of first dose. The parameters used to generate subject one data in simulation study were $Ln(V_d)$ =2.30, $Ln(k_e)$=-2.30 and $Ln(k_a)$=-1.61; (b) Pharmacometric parameters marginal distributions determined for Subject 6 by a single clinical test after 24 hours of first dose. The parameters used to generate subject one data in simulation study were $Ln(V_d)$=1.61, $Ln(k_e)$=-2.30 and $Ln(k_a)$=0.00.

ModQuest is used to determine the posterior probability distribution for the aggregate population data parameter estimates with a very broad (i.e. uninformative prior) distribution for the population parameters of both the PK model and the error model. For comparison purpose this posterior parameter distribution is compared with the posterior probability distribution obtained where the means of the individual posterior parameter distribution for the eight subjects are averaged and the standard deviation obtained. In either case, these posterior population parameter distributions become the prior when we are looking for the posterior probability distribution for an individual. Then a simulated plasma concentration from a subject at one point in time is selected. Using the posterior for the population as the prior, ModQuest is utilized to determine the posterior probability distribution for the three parameters for an individual using the single data point as the additional information needed from that individual. The personalized marginal and joint probability distributions of personalized pharmacokinetic parameters determined for subjects 1 and 6 are summarized in Figure 6 and Figure 7, respectively. The personalized pharmacokinetic parameters are in good agreement with the values used to generate them. Based on the work done in our laboratory, rarely more than one test was necessary.

Once the personalized PK/PD parameters are available, the personal optimal dosage regimen can be determined. This approach substitutes the cost of repeated titration visits to the physician by the cost of one or two blood samples. It ensures a higher probability of the drug performing in the therapeutic window for the individual. It protects the patients from pressures of health care stakeholders' agenda to drive the drug costs down at the expense of safety and treatment effectiveness (Calabrese and Baldinger 2002).



(a)



(b)

Figure 7: Personalized Joint Probability Distributions of Pharmacometric Parameters from Simulated Population Data. (a) Joint probability distribution of pharmacometric parameters determined for Subject 1 by a single clinical test after 24 hours of first dose. The parameters used to generate subject one data in simulation study were $Ln(V_d)$ =2.30, $Ln(k_e)$=-2.30 and $Ln(k_a)$=-1.61; (b) Joint probability distribution of pharmacometric parameters determined for Subject 6 by a single clinical test after 24 hours of first dose. The parameters used to generate subject one data in simulation study were $Ln(V_d)$=1.61, $Ln(k_e)$=-2.30 and $Ln(k_a)$=0.00.

5 FUTURE WORK

The success outlined in the preceding paragraph has been based on simulated data. In order to gain credibility with the health care community, it is necessary to repeat the success on (a) real clinical data available from the literature and (b) data generated in a clinical setting. We are currently working to complete part (a).

REFERENCES

Bhattaram, V. A., B. P. Booth, R. P. Ramchandani, B. N. Beasley, Y. Wang, V. Tandon, J. Z. Duan, R. K. Baweja, P. J. Marroum, R. S. Uppoor, N. A. Rahman, C. G. Sahajwalla, J. R. Powell, M. U. Mehta, and J. V. Gobburu. 2005. Impact of pharmacometrics on drug approval and labeling decisions: a survey of 42 new drug applications. *AAPS Journal* 7(3):E503-E512.

Blau, G, M.Lasinski, S.Orcun, S.Hsu, J.Caruthers, N. Delgass, and V. Venkatasubramanian. 2008. High fidelity mathematical model building with experimental data: A Bayesian Approach. *Computers and Chemical Engineering* 32:971-989.

Blau, G., M. Lasinski, S. Orcun, S. H. Hsu, D. Stamatis, J. Caruthers, N. Delgass, and V. Venkatasubramanian. 2009. A Bayesian Framework for Building Kinetic Models of Catalytic Systems. *Industrial & Engineering Chemistry Research* 48:4768-4790.

Blau, G., S. Orcun, and D. Stamatis. 2009. A Bayesian Approach To Building Mathematical Models For Enzyme Catalysis Using Modquest. In *Proceedings of World Conference of Chemical Engineering.*

Calabrese, D.C., and S.L. Baldinger .2002. Dose-Optimization Intervention Yields Significant Drug Cost Savings. *Journal of Managed Care Pharmacy* 8(2):146-151.

Gilks, W.R., S. Richardson, and D.J. Spiegelhalter. 1998. *Markov Chain Monte Carlo in Practice*. Chapman & Hall/CRC .

Jeliffe, R., A. Schumitzky, D. Bayard, R. Leary, A. Thompson, A. Boten, M. Van Guilder, A. Bustad, and M. Neely. 2008. *Pharmacokinetic Tools to Optimize Control of Drug PK/PD Models for Best Patient Care*. Laboratory of Applied Pharmacokinetics, USC School of Medicine, <www.lapk.org/pubsinfo/pdf/More_Tools.pdf>

Powell, J. R., and J. V. S. Gobburu. 2007. Pharmacokinetics at FDA:Evolution and Impact on Decisions. *Clinical Pharmacology & Therapeutics* 82(1): 97-102.

Steed, J. 2008. *Drugged-out seniors a prescription for disaster* Toronto Star, Nov 25.

Wrishkro, R. E. 2008. *Clinical Pharmacokinetics Therapeutic Drug Monitoring*. Department of Clinical Pharmacology, Eli Lilly & Company, bc.inter.edu.

AUTHOR BIOGRAPHIES

GARY BLAU is a visiting Professor in the School of Industrial Engineering at Purdue University. In 1998, after 30 years with Dow Chemical as a Research Engineer, Engineering Research Manager, Associate Scientist, Senior Advisor and finally as a Fellow, Professor Blau both launched his own business, The Modeling Connection, LLC, and began the new century as a visiting industrial professor in the School of Chemical Engineering at Purdue University. In 2006, e-Enterprise Center welcomed Prof. Blau as Research Professor before his current appointment. His interests are in development of novel statistical nonlinear model building methodology for design and analysis of high throughput kinetic experiments, risk management of new products in highly regulated industries, simulation optimization of supply chain and pipeline management, and process modeling in new product development. In 1997, he received the prestigious "Computing Practice Award" by the Computing and Systems Technology Division of the American Institute of Chemical Engineering. His email is <blau@purdue.edu>.

SEZA ORCUN is an associate research scientist at the e-Enterprise Center at Discovery Park of Purdue University. He has completed BS (1994), MS (1995) and Ph.D. (1999) programs in Chemical Engineering at Bogazici University, Istanbul-Turkey. He joined to Purdue University as a post-doctoral research associate in early 1999 and promoted to a fulltime research associate appointment in early 2002 in the School of Chemical Engineering before accepting his current appointment in mid 2004. His research in scheduling and planning of process industries focuses on developing novel and practically usable scheduling and planning tools/environments, which can be used in daily decision making as well as in training programs for industrial practices. His affiliation with Laboratory for Extended Enterprises at Purdue (LEEAP) expands his research area and vision to supply chain modeling, design and management. His e-mail address is <sorcun@purdue.edu>.