A Fuzzy Physiologically Based Pharmacokinetic Modeling Framework to Predict Drug Disposition in Humans

Kok-Yong Seng*, Paolo Vicini and Ivan A. Nestorov[1]

Department of Bioengineering, University of Washington, Seattle, WA 98105
[1]ZymoGenetics, Inc, Seattle, WA 98102

Abstract—**To date, the application of physiologically based pharmacokinetic (PBPK) models in support of drug discovery remains limited, in part due to information deficit and uncertainty regarding model parameters. Fuzzy set theory provides a suitable way to objectively account for parameter uncertainty in models. Here, we present a fuzzy set-based PBPK modeling framework and demonstrate its utility in predicting diazepam pharmacokinetics in human plasma, following intravenous dosing, from available animal *in vivo* and literature data. For computationally expensive PBPK models, the sparse grid method is proposed as an efficient alternative to commonly used fuzzy arithmetic algorithms for function simulation.**

I. Introduction

THE physiologically based pharmacokinetic (PBPK) model is a powerful tool for predicting quantitatively drug disposition in different animal species, including humans [1]. Despite its inherent advantages for cross-species extrapolation, the application of PBPK modeling in support of drug development in the pharmaceutical industry has, thus far, remained rather limited. One of the main reasons for this limited applicability is the deficiency or imprecision of experimental data from which to estimate and extrapolate parameters for human PBPK models. Particularly, during early-stage drug development, information stemming from 'exploratory' animal *in vivo* and *in vitro* studies for each novel drug compound is likely to be limited, incomplete, vague or quasi-quantitative [2]. A suitable way to represent, aggregate and propagate the effects of data paucity and uncertainty in mathematical models is with a possibilistic approach, e.g. fuzzy arithmetic [3]–[4].

The primary aim of our study is to build upon a previous PBPK modeling strategy for incorporating measures of variability and uncertainty [5] into the prediction of human pharmacokinetics during preclinical and early drug design. Forming the core of our approach is a fuzzy set-based simulation technique that identifies worst-case scenarios without assigning a level of probability to the set of possible pharmacokinetic outcomes. To this end, we propose the use of sparse grid interpolation [6]–[7], over commonly used algorithms [8], as an efficient tool to perform fuzzy simulation, especially for computationally expensive multivariate functions, e.g. PBPK model of drug disposition. The early application of PBPK modeling in humans can potentially serve as a powerful and cost-effective tool during the clinical candidate selection process.

* Correspondence: kyseng@u.washington.edu

II. Materials and Methods

A. Fuzzy sets and numbers

Under the fuzzy set theory [9], a membership level $\mu_{\tilde{S}}(x) \in [0,1]$ is assigned to all elements x of a set $\tilde{S}$, i.e., the elements belong to $\tilde{S}$ to a certain degree. The core of the set is defined as the subset for which $\mu_{\tilde{S}} = 1$. The support of $\tilde{S}$ contains elements for which $\mu_{\tilde{S}} > 0$. The α-cut or α-sublevel, representing intervals of confidence, is a generalized support: the subset for which $\mu_{\tilde{S}} \geq \alpha$. A fuzzy number is a fuzzy set with some specific attributes: the set is convex and normal, the membership function is piecewise continuous, and the core consists of at least a single element. The membership function of a fuzzy number can be of arbitrary shape, either derived from experimental data or "expert" knowledge of the data values. Using available tools, this information can then be coded into a possibility distribution, which may be represented by a fuzzy number [10]–[11].

B. Fuzzy arithmetic with sparse grids

The principle behind simulating a continuous fuzzy function using sparse grids is to construct a sparse grid interpolant $A_{q,d}(f)$ of the original function f with sufficient accuracy at the lowest α-sublevel. This means that a full set of deterministic computations, combining the pertinent interval extrema and values in-between, is only performed at the lowest membership level of the fuzzy parameters. The hierarchical structure of the sparse grid interpolation scheme enables adjustments of the interpolation depth so that a desired relative or absolute accuracy can be achieved. The interpolant then replaces the original function f in estimating values of the fuzzy output variables at the higher membership levels. Briefly, the sparse grid algorithm is composed of four main parts:

1) Discretize the range of membership of each fuzzy parameter $\tilde{p}_i$, $i = 1,\ldots,d$, into m equally spaced

intervals. This leads to the decomposed representations:

$$P_i = \left\{ I_i^0, I_i^1, ..., I_i^m \right\}$$

with the intervals of confidence at the α-sublevel

$$\alpha = \frac{j}{m} \in [0,1]$$

$$I_i^j = [a_i^j, b_i^j], a_i^j \le b_i^j, \quad i = 1,2,\ldots,d, j = 0,1,\ldots,m.$$

2) Referring I_i^0 as the support of the ith fuzzy parameter $\tilde{p}_i$, define the Cartesian product of the supports of all fuzzy parameters as the support box Ω:

$$\Omega = I_1^0 \times I_2^0 \times \cdots \times I_d^0 .$$

3) Compute the sparse grid interpolant $A_{q,d}(f)$ with sufficient accuracy for the support box of the fuzzy parameters. Details on the construction of $A_{q,d}(f)$ can be found in [6]–[7].

4) The fuzzy-valued output variable $\tilde{q}_r$, $r = 1,\ldots,w$, at membership level j is obtained in its decomposed form:

$$q_r^j = [a_r^j, b_r^j], \quad a_r^j \le b_r^j, r = 1,2,\ldots,w, j = 0,1,\ldots,m$$

by solving:

$$a^j = \min_{\mathbf{x} \in I_1^j \times \cdots \times I_d^j} A_{q,d}(f)(\mathbf{x}),$$

$$b^j = \max_{\mathbf{x} \in I_1^j \times \cdots \times I_d^j} A_{q,d}(f)(\mathbf{x}),$$

where $I_1^j \times \cdots \times I_d^j$ are d-dimensional boxes formed by the Cartesian product of the intervals I_i^j of all fuzzy parameters $\tilde{p}_i$, $i = 1,2,\ldots,d, j = 1,\ldots,m$.

The accuracy of the fuzzy result depends primarily on the accuracy of the interpolant, which can be monitored during its hierarchical construction. It has been shown that the asymptotic quadratic error decay of full grid interpolation with increasing grid resolution is preserved up to a logarithmic factor [6]–[7].

C. Fuzzy arithmetic with the vertex method

In this study, we compared the performance of the sparse grid method at simulating the fuzzy output of the PBPK model of diazepam disposition in humans with a commonly used fuzzy arithmetic algorithm, the vertex method [8]. The vertex method performs a full-factorial Design of Experiments on the interval extrema of the fuzzy problem. More concretely, each of the d parameters $\tilde{p}_i$, $i = 1,\ldots,d$, is either assigned its minimum or it maximum value, and all possible combinations of individual parameter maxima or minima are listed per α-cut. Each of the 2^d parameter combinations is then successively analyzed in a regular deterministic analysis run, and the membership function of the fuzzy output is reconstructed based on the deterministic results from all α-sublevels.

D. PBPK modeling

The PBPK model for diazepam disposition in humans was based upon that published by Gueorguieva and colleagues [5], as shown in Fig. 1. The model was composed of 12 physical tissue compartments: liver (LI), kidney (KI), brain (BR), intestine (SPL), stomach (ST), muscle from the hind limb (MU), adipose (AD), skin after removal of hair (SK), testes (TE), heart (HT), lungs (LU) and rest of the body (RE)) and two blood compartments (mixed venous (VEN) and arterial (ART)).

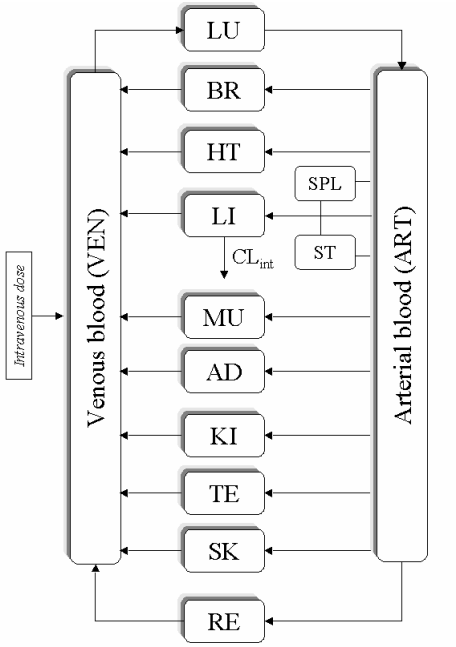

Fig. 1. PBPK framework used for prediction of the disposition profile of diazepam in humans. CL_{int} denotes the hepatic intrinsic clearance. 5 mg of diazepam was administered intravenously over 1 min (adapted from [5]).

Well-stirred and blood flow-limited conditions were assumed in all compartments. Additionally, it was assumed that diazepam distributes instantaneously and homogeneously within each compartment, and the liver was considered as the main site of elimination. The compartmental mass balance equations for each compartment are described in [5].

The physiological parameters, blood flow rates and tissue volumes used in the model were obtained from [12]. For intravenous administration, values on the tissue-plasma partition ratios K_p for drug distribution and on the hepatic intrinsic clearance CL_{int} for drug elimination are also required. The procedure of generating fuzzy-valued K_p's is detailed in [5]. In brief, the probability density functions of K_p's were first estimated in a closed loop system by fitting the set of differential equations describing the PBPK model in Fig. 1 to experimental data obtained from a study of intravenous dosing of diazepam in 24 male Sprague-Dawley

rats [5]. The K_p's were next transformed into fuzzy numbers using the optimal membership function criterion [10]. To scale the rat $\widetilde{K}_p$'s to humans, we divided the former by the fraction of unbound diazepam f_u in rat plasma, based on the assumption that the tissue-plasma unbound concentration ratio and distribution volume for unbound diazepam are the same in rats and humans [13]–[14]. Furthermore, to capture the imprecision inherent in the scaling of rat *in vivo* $\widetilde{K}_p$'s to the human situation, rat f_u was modeled as a triangular fuzzy number with spread $0.1\times f_u$, i.e., $\widetilde{f}_u = \langle f_u, f_u - 0.1\times f_u, f_u + 0.1\times f_u \rangle$ according to the triplet notation of Hanss [4]. Deterministic or crisp-valued CL_{int}, blood-plasma concentration ratio R and fraction unbound in plasma f_u of diazepam for man were obtained from the report by Klotz et al [15]. The interval extrema at $\alpha = 0$, 0.5 and 1 of $\widetilde{K}_p$'s implemented in the human PBPK model for this study are listed in Table I.

To objectively evaluate the performance of the fuzzy PBPK modeling approach, an independent set of human *in vivo* test data was obtained from the literature [16]. This

TABLE I
FUZZY-VALUED HUMAN PBPK MODEL PARAMETERS

Parameter	Interval at $\alpha = 0$	Interval at $\alpha = 0.5$	Interval at $\alpha = 1$
LU K_p[a]	[16.7, 57.9]	[26.9, 44.4]	[30.4, 40]
LI K_p	[28.1, 89.9]	[44.8, 68.2]	[51.8, 60.1]
ST K_p	[19.7, 59.3]	[29.3, 46.5]	[32.8, 42.2]
SPL K_p	[14, 41.7]	[20.2, 33.3]	[22.4, 30.4]
KI K_p	[19, 58.5]	[28.6, 45.8]	[32.1, 41.5]
MU K_p	[6.8, 21.5]	[9.8, 17.4]	[10.8, 16.1]
AD K_p	[48.1, 278.3]	[93.1, 216.3]	[105.4, 197.9]
SK K_p	[10.8, 39.6]	[17.4, 30.8]	[19.6, 28]
HT K_p	[21.3, 62.4]	[31.4, 49.1]	[35, 44.6]
BR K_p	[6.1, 19.4]	[8.8, 15.7]	[9.6, 14.5]
TE K_p	[18.9, 60.1]	[29, 46.7]	[32.6, 42.2]
RE K_p	[20.7, 262.8]	[90.1, 173.3]	[120.1, 139.2]

[a] K_p = tissue-plasma partition ratio.

consisted of 7 instances of plasma concentration-time data (where an instance corresponds to a single plasma concentration-time profile sampled at 5, 8, 11, 15, 20, 30, 45 and 60 min) for diazepam dosed intravenously in human subjects (weight, 84±17 kg). The diazepam dose was 5 mg, intravenously administered over 1 min. The simultaneous differential equations were solved by the Runge-Kutta method in MATLAB 7.0 (MATLAB manual, 2004; The MathWorks Inc., Natick, MA).

III. RESULTS AND DISCUSSION

The fuzzy-valued diazepam concentration C in the various human tissues at any given time t (t = 0–60, in intervals of 1 min) was composed from the α-sublevel sets $C^j, j = 1,\ldots,m$. In particular, the output envelopes for a specific interval of confidence α were obtained by profiling the minimum and maximum concentration values over t = 0–60 min. Fig. 2 depicts the PBPK simulations of the concentrations of diazepam in the mixed venous, liver, heart, brain, adipose tissue and lungs of a 70 kg human. Although the sparse grid and vertex methods yielded identical solutions, the CPU run time for the sparse grid method was significantly lower (1.7 hr versus 10.2 hr). Thus, for computationally expensive multivariate functions, we inferred that the sparse grid method was the superior approach in terms of solution accuracy per CPU run time. Further, the vertex method is known to provide inaccurate solutions when the model is non-monotonic in the parameters [17]. Since the sparse grid method can simulate functions using combinations of parameter values in-between interval extrema, the effect of model non-monotonicity on the sparse grid and the vertex

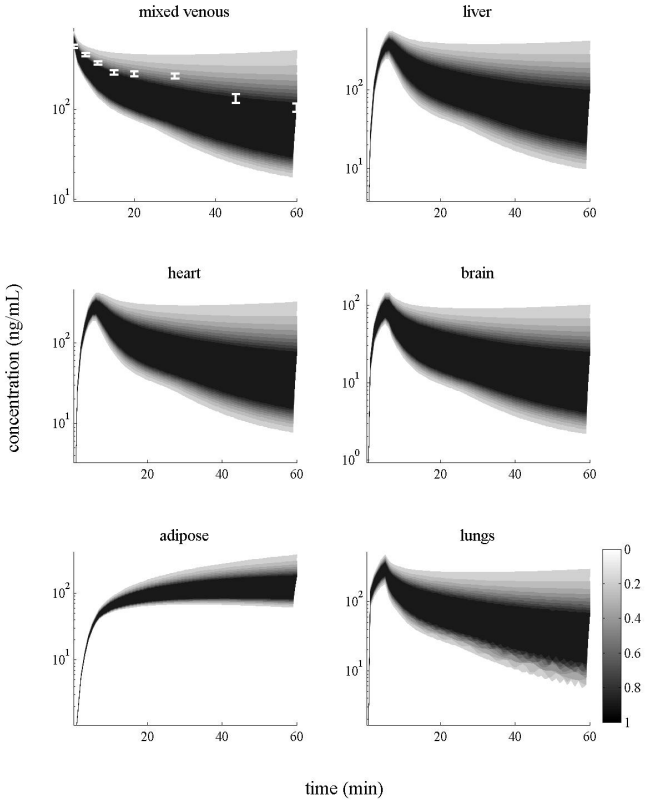

Fig. 2. Fuzzy-valued diazepam concentration (ng/ml) versus time (min) in the mixed venous blood pool, liver, heart, brain, adipose tissue and lungs, as predicted by the sparse grid and vertex methods. As denoted by the legend at the bottom right, a darker color represents a higher level of membership (or more certain prediction) of the fuzzy concentration. The mean (±s.d.) experimental concentration-time values (from [16]) for the mixed venous compartment are also shown for comparison.

methods' solutions will be investigated in the future.

The closeness of fit between the simulated plasma concentration-time envelopes and the corresponding mean *in vivo* data [16] indicates that the plasma pharmacokinetics in humans was relatively well simulated for the intravenous administration. We noted that the mean experimental values largely fell within the diazepam concentration envelopes corresponding to the fuzzy predictions of mid-to-high

certainty (α = 0.5–1). As illustrated in Fig. 2, our simulation efforts were also extrapolated to other tissues for which experimental concentration-time data were not available, e.g. heart. The results showed that the diazepam concentrations in most compartments attained their respective peak values within 10 min after administration, before decreasing steadily thereafter (the marginal numerical instability for the predicted concentrations at larger time instances and lower α-sublevels in the lungs was due to the large uncertainties in $\widetilde{K}_p$'s). Although the aforementioned concentration-time profiles were not validated, previous accurate estimations of rat tissues' *in vivo* diazepam concentration-time data via the same fuzzy set-based PBPK model [5], coupled with the common utilization of the rat as a surrogate species for the pharmacokinetic characterization of drug candidates in humans [18] suggest that our present predictions of diazepam disposition in various compartments over time ought to be adequately reliable.

A significant advantage of the fuzzy PBPK model is that it can be implemented to mechanistically inform drug selection during early drug discovery, when information stemming from limited 'preliminary' experiments on novel drug candidates is predominantly insufficient or vague. In this regard, the representation, aggregation and propagation of parameter uncertainty through the use of fuzzy sets in PBPK models can (1) replace empirical analysis approaches, e.g. best-guess estimates, when little or no quantitative data is available, and (2) facilitate objective chemical risk assessment in humans when there is insufficient and/or imprecise data available to justify the use of probability distributions for traditional stochastic techniques, e.g. Monte-Carlo simulations.

IV. Conclusions

Building upon a previous simulation methodology [5], the PBPK model described in this paper represents the first attempt to predict, within a fuzzy set-based framework, intravenous pharmacokinetic profile in humans before *in vivo* experiments are conducted. The suggested approach evaluates the incomplete or imprecise data available during drug discovery and early development in a more integrated manner by formally capturing and propagating parameter uncertainty in human PBPK models. Further development of the modeling strategy, for example, through estimation of $\widetilde{K}_p$'s via nonlinear fuzzy regression and extension to predict oral pharmacokinetics, will serve to further enhance its predictive capability.

Acknowledgment

This work was partially supported by grant NIH P41 EB001975, "Resource Facility for Population Kinetics".

References

[1] G. M. Grass and P. J. Sinko, "Physiologically based pharmacokinetic simulation modeling," *Adv. Drug Deliv. Rev.*, vol. 54, no. 3, pp. 433–451, 2002.

[2] I. Nestorov, "Modeling and simulation of variability and uncertainty in toxicokinetics and pharmacokinetics," *Toxicol. Lett.*, vol. 120, no. 1–3, pp. 411–420, 2001.

[3] T. J. Ross, *Fuzzy Logic with Engineering Applications*. West Sussex, England: John Wiley & Sons, 2004, pp. 445–469.

[4] M. Hanss, *Applied Fuzzy Arithmetic*. Berlin, Germany: Springer-Verlag, 2005, pp. 45–73.

[5] I. I. Gueorguieva, I. A. Nestorov and M. Rowland, "Fuzzy simulation of pharmacokinetic models: case study of whole body physiologically based model of diazepam," *J. Pharmacokinet. Phar.*, vol. 31, no. 3, pp. 185–213, 2004.

[6] A. Klimke and B. Wohlmuth, "Algorithm 847: Spinterp: Piecewise multilinear hierarchical sparse grid interpolation in MATLAB," *ACM Trans. Math. Software*, vol. 31, no. 4, pp. 561–579, 2005.

[7] A. Klimke, "Sparse grid interpolation toolbox: User's guide," University of Stuttgart, Germany, IANS Tech. Rep. 2006/001, 2006.

[8] W. M. Dong and H. C. Shah, "Vertex method for computing functions of fuzzy variables," *Fuzzy Set. Syst.*, vol. 24, no. 1, pp. 65–78, 1987.

[9] L. A. Zadeh, "Fuzzy sets," *Inform. Comput.*, vol. 8, pp. 338–353, 1965.

[10] M. R. Civanlar and H. J. Trussel, "Constructing membership functions using statistical data," *Fuzzy Set. Syst.*, vol. 18, no. 1, pp. 1–13, 1986.

[11] I. B. Turksen, "Measurement of membership functions and their acquisition," *Fuzzy Set. Syst.*, vol. 40, no. 1, pp. 5–38 (1991).

[12] F. A. Brightman, D. E. Leahy, G. E. Searle and S. Thomas, "Application of a generic physiologically based pharmacokinetic model to the estimation of xenobiotic levels in human plasma," *Drug Metab. Dispos.*, vol. 34, no. 1, pp. 94–101, 2006.

[13] Y. Igari, Y. Sugiyama, Y. Sawada, T. Iga and M. Hanano, "Prediction of diazepam disposition in the rat and man by a physiologically based pharmacokinetic model," *J. Pharmacokinet. Biopharm.*, vol. 11, no. 6, pp. 577–593, 1983.

[14] Y. Sawada, M. Hanano, Y. Sugiyama, H. Harashima and Y. Iga, "Prediction of the volume of distribution of basic drugs in human based on data from animals," *J. Pharmacokinet. Biopharm.*, vol. 12, no. 6, pp. 587–596, 1984.

[15] U. Klotz, K. H. Antonin and P. R. Bieck, "Pharmacokinetics and plasma protein binding of diazepam in man, dog rabbit, guinea pig and rat," *J. Pharmacol. Exp. Ther.*, vol. 199, pp. 67–73, 1976.

[16] K. Lindhardt, S. Gizurarson, S. B. Stefansson, D. R. Olafsson and E. Bechgaard, "Electroencephalographic effects and serum concentrations after intranasal and intravenous administration of diazepam to healthy volunteers," *Br. J. Clini. Pharmacol.*, vol. 52, no. 5, pp. 521–527, 2001.

[17] H. Q. Yang, H. Yao and J. D. Jones, "Calculating functions of fuzzy numbers," *Fuzzy Set. Syst.*, vol. 55, no. 3, pp. 273–283, 1993.

[18] F.-P. Theil, T. W. Guentert, S. Haddad and P. Poulin, "Utility of physiologically based pharmacokinetic models to drug development and rational drug discovery candidate selection," *Toxicol. Lett.*, vol. 138, no. 1–2, pp. 29–49, 2003.