Available online at www.sciencedirect.com
ScienceDirect
Biomedical Signal Processing and Control 2 (2007) 97–110
Biomedical Signal Processing and Control
www.elsevier.com/locate/bspc

Improved transformation of morphometric measurements for *a priori* parameter estimation in a physiologically-based pharmacokinetic model of ethanol

Martin H. Plawecki [a,b], Raymond A. DeCarlo [c,*], Vijay A. Ramchandani [d,1], Sean O'Connor [e,f,a]

[a] *Purdue University Weldon School of Biomedical Engineering, West Lafayette, IN 47906, United States*
[b] *Indiana University School of Medicine, Indianapolis, IN 46202, United States*
[c] *Purdue University School of Electrical and Computer Engineering, West Lafayette, IN, United States*
[d] *Department of Medicine, Indiana University School of Medicine, Indianapolis, IN, United States*
[e] *Department of Psychiatry, Indiana University School of Medicine, Indianapolis, IN, United States*
[f] *R. L. Roudebush VA Medical Center, Indianapolis, IN, United States*

Received 5 November 2006; received in revised form 28 March 2007; accepted 11 April 2007
Available online 18 May 2007

Abstract

Prescription of the brain's time course of exposure to experimentally administered ethanol can be achieved with intravenous infusion profiles computed from a physiologically-based pharmacokinetic (PBPK) model of alcohol distribution and elimination. Previous parameter estimation employed transformations of an individual's age, height, weight and gender inferred from the literature, with modeling errors overcome with real-time, intermittent feedback. Current research applications, such as ethanol exposures administered during fMRI scanning, require open-loop infusions, thus improved transformation of morphometric measurements.

Records of human breath alcohol concentration (BrAC) clamp experiments were analyzed. Optimal, unique PBPK parameters of a model of the distribution and elimination of ethanol were determined for each record and found to be in concordance with parameter values published by other investigators. A linear transformation between the readily measurable physical characteristics or morphometrics, including gender, age, height, weight, and TBW estimates, and the model parameters were then determined in a least squares sense according to the formula $\theta = F(x) = F_m x$ where $x = (\text{age height weight TBW})^T \in R^4$ and $\theta = (R_C\ V_P\ V_B\ m_{max}\ k_{AT})^T \in R^5$.

The transformation was then evaluated with several parameter prediction performance measures. A substantial improvement in all error statistics, in relation to an earlier affine transformation that used only body weight as the relevant morphometric was obtained. Deviation from the measured response was reduced from 27 to 20%. Error in parameter estimation was reduced from 109 to 38%. Percent alcohol provided in error was reduced from 46 to 28%. Error in infusion profile estimation was reduced from 55 to 33%.

The algorithm described, which optimizes individual pharmacokinetic parameter values and then subsequent extension to *a priori* prediction, while not unique, can be readily be adapted to other molecules and pharmacokinetic models. This includes those used for distinct purposes, such as automated control of anesthetic agents.
© 2007 Elsevier Ltd. All rights reserved.

Keywords: Alcohol; Breath alcohol concentration time course; Least squares approximation; Morphometrics; Parameter identification; Optimization; Pharmacokinetics; Physiologically-based pharmacokinetic model

1. Introduction

Alcohol dependence is a major cause of morbidity and mortality in America. Nearly one in ten people who imbibe will develop a serious addiction to alcohol in their lifetime and one-third of those will die from complications of the illness [1,2]. In people with a familial history of alcoholism, more than 40% of the lifetime risk for alcohol dependence is attributable to

* Corresponding author at: 465 Northwestern Ave, West Lafayette, IN 47907-2035, United States. Tel.: +1 765 494 3523; fax: +1 765 494 3371.
E-mail address: mplaweck@iupui.edu (R.A. DeCarlo).
[1] Present affiliation: National Institute on Alcohol Abuse and Alcoholism, Bethesda, MD, United States.

1746-8094/$ – see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bspc.2007.04.001

genetic influences [3]. The influence of genes on the brain's response to ethanol is thought to be an important contributor to the risk for dependence. An enormous amount of research continues on the premise that there is a genetic influence on the central nervous system reinforcing properties of ethanol exposure that can be ascertained. The experimental measurement of the brain's response to alcohol exposure is a phenotype of interest in this search for susceptibility genes and gene-environmental interactions. Hopefully, this information can be then used to identify those individuals who are at high risk in time for effective prevention.

Research that attempts to quantify the brain's response to alcohol depends on the conditions and constraints of an alcohol challenge: the methods used to prescribe the brain's exposure to alcohol following alcohol administration. One of the most common alcohol challenge research paradigms employs directed oral consumption (please see [4–7] as examples). The advantages of the oral route of administration include the reality that most social use of alcohol is the result of voluntary ingestion, and this route embraces the cultural, gustatory and olfactory cues that influence, via expectation learned from experience, the drinker's subjective responses to consumption. However, with the current availability of more than 500 commercial preparations of alcohol beverages, any attempt to control subjective expectation makes the selection of some standard beverage(s) for a particular experiment virtually impossible.

A more serious problem facing oral alcohol-challenge research is overcoming the variability in alcohol pharmacokinetics [8–10]. Pharmacokinetics is formally defined as ''the study of the time course of a drug and its metabolites in the body after administration by any route'' [11]. Sound pharmacologic research requires delivery of the proper drug at the appropriate concentration at the desired site of action over the desired time course. Unfortunately, substantial, potentially heritable [8], pharmacokinetic variability exists within and among individuals who ingest ethanol [9,10,12]. These pharmacokinetic parameter values have been evaluated as risk factors for developing dependence [13].

Despite the inability to control the subsequent brain exposure to alcohol, oral ethanol challenge paradigms are common in the literature, dosing subjects according to their body weight or total body water. Typically, results are reported with respect to the time course of mean and standard error of the mean breath alcohol concentrations (BrAC) over time. However, back calculation based upon the number of participating subjects reveals standard deviations of 20–50 mg% of the desired target peak BrAC [14–16] requiring consideration of this variation as a group covariate [17]. Recently, this effect has been formally studied and the variability confirmed, e.g. a 2.5-fold range in peak concentrations, an 8-fold range in the time to peak alcohol concentration, and a 3-fold range in the estimated area underneath the blood alcohol concentration curve [9] (graphical results can also be seen within [10]).

The major source of variability in alcohol pharmacokinetics arises due to factors influencing the uncontrollable absorption kinetics of alcohol. This experimental uncertainty has led to the use of an intravenously (IV) administered alcohol, which avoids both the process and variability associated with absorption kinetics. An additional advantage of IV administration is the ability to manipulate or minimize a subject's expectation of potential effects attributed to the consumption of alcohol. However, the major advantage is the potential for controlling the time course of alcohol exposure in the brain. IV infusion is the method of alcohol delivery used in the investigation described below, and the basis for numerous other investigations [8–10,12,18–31].

Early paradigms employed constant IV infusion rates of ethanol [16], but inter-individual variability of distribution and elimination kinetics remained; making large group comparisons still inefficient at best. An alternative, developed in Neural Systems Laboratory of the Alcohol Research Center at the Indiana University School of Medicine, was to administer intravenous infusions of solutions of a low concentration of ethanol in saline or Ringer's lactate, with manual adjustments of the ethanol infusion rate [26,28]. These adjustments were based upon manual feedback of serial BrAC measurements so that a linear rise to a target concentration in a specified interval was achieved and then maintained over 2–3 h of testing of brain function, after which elimination took place without any control. This experimental paradigm, known as the ''Indiana Alcohol Clamp'' and shown in Fig. 1, is particularly useful for assessing the brain's *adaptation* to alcohol as a function of time ([29,30], please also see [23] for the use of this application in animal subjects), with BrAC used as a reasonable surrogate for arterial concentration in the cooperative human subject [32]. During the ''clamp'' at the target concentration, a standardized battery of tests was administered so that the brain's response to alcohol can be assessed at precisely prescheduled intervals. Components of this battery include, but are not limited to, electroencephalography, evoked response potential tasks, eye-movement tasks, neuropsychological and subjective perception tasks (please see [18,19,22,29,30] for examples).

Although adequate, the ability to achieve the desired tracking of the clamp with manual feedback was limited; the frequent BrAC measurements required for near perfect tracking

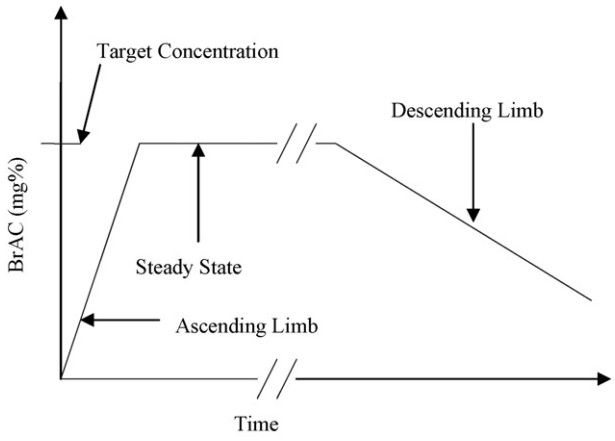

Fig. 1. Graphical depiction of an ideal alcohol clamp, denoted by $C_{Ref}(t)$. For the experimental records described here, the clamp consisted of a linear rise in concentration to 60 mg% in 15 min, 180 min at 60 mg%, and then an uncontrolled, but monitored descent. Major experimental regions are identified.

interfered with the collection of dependent measurements of the brain's response to alcohol. In addition, time courses of brain exposure that manual clamping methods could not achieve were of interest. For example, infusions achieving a sawtooth waveform of BrAC might address the question of whether and when the brain responds to the rate of change of ethanol exposure versus the absolute level. Finally, a pre-experimental computation of an individual's alcohol infusion profile that would reliably achieve a prescribed time course of brain exposure could be used as a first step towards open-loop/technician-free experimental control, allowing for the use of ethanol challenge paradigms in previously untenable environments. Examples include fMRI and PET scanning environments, where subject movement required for BrAC determination would ruin image acquisition and analysis.

The pre-computation was based upon a physiologically-based pharmacokinetic (PBPK) model for the distribution and elimination of ethanol. PBPK models are compartmental models that extract the underlying mathematical nature with respect to specific physiological behavior. This physiological approach is in contrast to phemenologically based PK compartmental models, which utilize generic compartments that may not have any relationship to physiological function [33]. A major appeal of the PBPK modeling approach is that all the coefficients in the equations can have a physiologic interpretation. Moreover, the values can be estimated from regression analysis of a mathematical transformation of morphometric measurements of a subject's age, weight, height and gender.

When an accurate PBPK model of an individual's BrAC produced by intravenous infusion of ethanol is available, then that model's output can be made to follow nearly any desired time course by proper tuning of a mathematically rendered infusion profile. The computation is achieved by greatly amplifying the error, the difference between the model and desired outputs, and using it to drive a control that generates the desired mathematical infusion profile and results in the desired simulated BrAC output. Computer-controlled pumps can then be used to deliver the pre-computed profile in the experimental, human subject, setting. Our results have demonstrated that, compared to oral administration, this approach yielded good experimental fidelity to the task of achieving nearly the same time course of brain exposure to alcohol in all subjects [25,26,28]. This model-based pre-computed infusion approach has previously demonstrated its utility for overcoming variable inter-individual kinetics [8–10,12,18–31]) in studies evaluating the pharmacokinetics and brain responses to alcohol in humans and animals.

Nonetheless, the utility of PBPK modeling was constrained by inaccuracies in a naïve morphometric transformation, and the investigators reasoned that better estimates of an individual's PBPK model parameters of alcohol distribution and elimination should yield closer fidelity to the desired experimental time course of brain exposure to alcohol. Our resource was a wealth of input/output measurements obtained on many subjects from the Indiana clamp experiments. The purpose of this investigation was to improve the ability to prescribe the time course of brain exposure to alcohol in human subjects employed in laboratory research on the genetics of the response to alcohol. This paper presents the methods used to improve *a priori* PBPK modeling of individual subjects and the results obtained from retrospective application of those methods in our laboratory.

2. Modeling the pharmacokinetics of ethanol

A previously published three-compartment PBPK model of the distribution and elimination of alcohol was used to estimate the required infusion profile based on an individual's readily measurable physical characteristics [26,28] and is a component of the methodology described herein. As such, the basics of alcohol metabolic modeling will be discussed, with focus upon the parameters of interest to this application. (For more information, including examples of model validity or mathematical derivation, please see [26–28].) The compartments within this model represent the liver, the periphery (the slowly-perfused volume of distribution for alcohol), and the vasculature (the rapidly-perfused volume of distribution for alcohol) likely including arterial, venous, capillary, and some interstitial fluid.

The ''liver'' is the alcohol eliminator, with behavior defined by Michaelis–Menten [34] enzyme kinetics adapted to ethanol mass flow with a constant liver volume,

$$\frac{\partial M_{\text{Liver}}}{\partial t} = M_{\text{Liver}} - \frac{m_{\max} C_{\text{Liver}}}{k_{\text{m}} + C_{\text{Liver}}} \tag{2.1}$$

where M_{Liver} denotes the mass flux of ethanol in the liver, $m_{\max}$ is the maximal metabolism rate of alcohol, k_{m} is the Michaelis–Menten constant or concentration of the alcohol at which metabolism is one-half the maximal rate, and t is time. Finally, the concentration entering the liver, C_{L}, can be computed as:

$$C_{\text{Liver}} = \frac{M_{\text{Arterial}} + M_{\text{Vena\_Cava}}}{R_{\text{C}} F_{\text{L}}} \tag{2.2}$$

where volume flow is physiologically apportioned at resting cardiac output rates (R_{C}), e.g. the volume flow to the liver would be the product of the fractional blood flow to the liver (the remainder attributed to the periphery), F_{L}, and the resting cardiac output rate, R_{C}, and $M_{\text{Vena\_Cava}} = (1 - F_{\text{L}}) \times M_{\text{Arterial}} - M_{\text{Periphery}}$ is the mass flow leaving the peripheral compartment.

Mass flow in the ''vasculature,'' the rapidly-perfused compartment, follows a first order differential equation for equilibration;

$$\frac{\partial M_{\text{Arterial}}}{\partial t} = \frac{R_{\text{C}}}{V_{\text{B}}} (M_{\text{Venous}} + M_{\text{Infused}} - M_{\text{Arterial}}) \tag{2.3}$$

Here V_{B} is the volume of the ''blood'' or vascular compartment, and $M_{\text{Infused}}(t)$ is the input alcohol concentration time profile that is to be tuned to the individuals morphometrics and therefore their pharmacokinetic model parameters. M_{Venous} can be calculated as

$$M_{\text{Venous}} = M_{\text{Hepatic\_Vein}} + M_{\text{Vena\_Cava}} \tag{2.4}$$

where $M_{\text{Hepatic\_Vein}} = F_{\text{L}}(M_{\text{Arterial}} + M_{\text{Venacava}}) - m_{\max} C_{\text{Liver}} / (k_{\text{m}} + C_{\text{Liver}})$ is the mass flow leaving the liver. The terms ''artery'' and ''vein'' or ''venous'' reflect mass flow to and

from the mentioned compartments, with nomenclature taken from physiology when possible. These terms can be derived with proper cardiac apportionment as mentioned herein, the mass flow and concentration equations for each compartment, and the fact the model, and therefore each compartment, obeys conservation of mass of ethanol. This states that the total ethanol mass stored within the model at a given time T is the total ethanol provided and metabolized until that time and can be expressed mathematically as below, with.

$$\left[C_{\text{Periphery}}(T) \times V_{\text{P}} + \frac{V_{\text{B}}}{R_{\text{C}}}\left(M_{\text{Arterial}}(T) + M_{\text{Venous}}(T)\right)\right] = \int_0^T \left(M_{\text{Infused}}(t) - \frac{m_{\max} C_{\text{Liver}}(t)}{k_{\text{m}} + C_{\text{Liver}}(t)}\right)\partial t \tag{2.5}$$

These calculations and further derivations are both beyond the scope and interest of this manuscript. Those interested are encouraged to see [26–28] for numerical and analytical examples.

The ''periphery,'' the slowly-perfused compartment, acts as a storage reservoir obeying a linear diffusion process.

$$\frac{\partial C_{\text{Periphery}}}{\partial t} = \frac{M_{\text{Periphery}}}{V_{\text{P}}} \tag{2.6}$$

with

$$M_{\text{Periphery}} = k_{\text{AT}} R_{\text{Periphery}} \times r(C_{\text{Model}} - C_{\text{Periphery}}) - k_{\text{TV}} R_{\text{Periphery}} \times r(C_{\text{Periphery}} - C_{\text{Model}}) \tag{2.7}$$

where k_{AT} is the partition coefficient from the arterial supply to the tissue, k_{TV} is the partition coefficient from the tissue to the venous system, $R_{\text{Periphery}} = R_{\text{C}} \times (1 - F_{\text{L}})$ is the volume flow to the peripheral component of the model, V_{P} is the volume of the peripheral compartment, $C_{\text{Model}}(t, \Omega)$ is the model estimated breath and thus arterial alcohol concentration, Ω is the complete set of model parameters to be defined explicitly later, and $r(x)$ is defined to be the unit ramp function (i.e. $r(x) = xu(x)$ where $u(x)$ is the unit step function). Eqs. (2.1)–(2.7) constitute the basics of the PBPK model of the metabolic process of interest with respect to the application presented within this manuscript. Emphasizing parsimony of parameters, numerous experiments employing this model adequately predict the heterogeneity of human pharmacokinetic responses to intravenous administration of alcohol [8–10,12,18–31]. This model is scalable across species, with demonstrated application to animal studies with appropriate parameter selection [21,23].

3. The morphometric transformation and input profile construction

3.1. Mathematical definition of morphometric transformation

Parameters of the PBPK model may not be directly observable, and estimates based upon the pharmacokinetic literature and morphometrics, or readily measurable physical characteristics, are used [28]. Specifically, let x = (age height weight TBW)$^{\text{T}} \in R^4$ denote a vector of morphometric measurements given in units of years, cm, kg, and L respectively, where TBW denotes estimated total body water [35,36]. Inherent in this selection is the assumption that TBW is the principal volume of distribution for the tiny, polar molecule, ethanol [36–38], and that age, height, weight, and gender (by group separation) [35,40] account for body fat into which ethanol also perfuses, albeit weakly [40].

We define a morphometric transformation as a mapping from the relationship between the morphometric variables to the model parameters $\theta = (R_{\text{C}}\ V_{\text{P}}\ V_{\text{B}}\ m_{\max}\ k_{\text{AT}})^{\text{T}} \in R^5$, i.e., $\theta = F(x)$ for some mapping $F(\cdot)$ with units expressed in dL/min, L, L, g/h, mg/dL, and unitless fraction. ($m_{\max}$ is determined in the clinically relevant, previously published, unit of g/h. For use within Eqs. (2.1)–(2.7) multiplication by a scaling factor of 16.67 converts it to mg/min.) This approach is consistent with the literature as peripheral and vascular volumes have been related to weight, height, age, and lean body mass [35,39,41]; body surface area [42,43] is estimated as a function of height and weight; and TBW can be estimated as a function of age, gender, height, and weight [36]. To the best of the authors knowledge, there is no known analytical form for the (nonlinear) mapping $F(\cdot)$.

Prior to the developments reported herein, parameter values for the PBPK ethanol model were calculated with the following empirically determined morphometric transformation as an affine map, denoted by $\theta = F(x) = F_{\text{m1}}(x)$:

$$\theta = \begin{bmatrix} R_{\text{C}} \\ V_{\text{P}} \\ V_{\text{B}} \\ m_{\max} \\ k_{\text{AT}} \end{bmatrix} = \begin{bmatrix} 0 & 0 & 56/70 & 0 \\ 0 & 0 & 56/(70 \times 2.4) & 0 \\ 0 & 0 & 0.2 & 0 \\ 0 & 0 & 0 & 0.17 \\ 0 & 0 & 0 & 0 \end{bmatrix} \begin{bmatrix} \text{age} \\ \text{height} \\ \text{weight} \\ \text{TBW} \end{bmatrix} + \begin{bmatrix} 0 \\ 0 \\ 0 \\ 1.53 \\ 0.7 \end{bmatrix}$$

with $k_{\text{AT}} = k_{\text{TV}} = 0.7$, $F_{\text{L}} = 0.8$, and $k_{\text{M}} = 5$ mg/dL [12,26].

Of note, these baseline parameter calculations can vary with respect to previously published pharmacokinetic studies of a similar fashion. In a prior study, Takeda and Reeve examined the metabolism of autologous radiolabeled albumin with several previously published models. Their results, and a review of other investigations, showed plasma volume estimates, determined as the quotient of delivered radioactivity to measured per milliliter, to be 0.0383–.0435 L/kg [44]. However, as previously mentioned, the ''blood volume,'' as adopted from prior investigations, might better be termed ''rapidly perfusing'' as it comprises a much larger distribution space. DeFronzo et al. used intravenous glucose solutions to ''clamp'' subjects to a hyperglycemic or euglycemic state with a ''glucose space'' or volume of distribution calculation of 0.19 × weight [45]. Saad et al. then used this methodology as a benchmark for the development of minimal model of insulin sensitivity, including a determination of distribution volume [46]. However, as glucose is metabolized, synthesized, actively

transported and concentrated under hormonal influence, direct comparison is difficult.

For ethanol, however, the physiological distribution is approximately equal to the total body water space [36–38] including extra- and intra-cellular volumes; a relationship maintained in this manuscript, as well as prior studies with this model. Thus, it would be expected that the compartmentalized volumes of distribution of ethanol would be substantially different based solely upon molecular weight (~67 kDa, ~180 Da, and ~46 Da for albumin, glucose, and ethanol, respectively) and co-transport requirements (e.g. glucose) [47].

As it was primarily dependent upon body weight, it is clear that F_{m1} failed to account for the full use of the readily available information provided by additional, easily attained measurements that are commonly used for pharmacokinetic parameter estimation [39–43]. Further, this formulation did not explicitly allow for gender variation in parameter determination, as other investigators have observed [12,20,48]. Finally, success of the clinical experiment was highly dependent upon technician feedback adjustments to the estimated infusion profile. Hence, a rigorous derivation of a new transformation, denoted F_{m2}, was needed to achieve better initial profile estimates and an improved level of automation.

The structure of a simple yet meaningful map was taken as a linear one which is valid in a neighborhood of the statistical averages of the morphometics of each gender, i.e., $\theta = F(x) = F_m x$ where the matrix $F_m \in R^{5x4}$ and for which $\bar{\theta} = F(\bar{x}) = F_m \bar{x}$ is an exact relationship at the average values denoted by $\bar{x}$ and $\bar{\theta}$ for each gender.

Further, let $\Psi = (k_m\ k_{TV}\ F_L)^T = (10\ k_{TV} = k_{AT}\ 0.26)^T \in R^3$ with units expressed in mg/dL, unitless fraction, and unitless fraction, respectively, be the set of fixed PBPK parameters consistent with the literature as per other investigators [48–54]. Finally, let $\Omega = [\theta, \Psi]$ be the complete set of PBPK model parameters.

3.2. Input profile construction

Based upon the estimated parameter values of the PBPK model, an individual's approximate infusion rate profile, $M_{Infused}(t)$, initialized at a value of zero, of a 6% ethanol solution is pre-computed as per the algorithm depicted in Fig. 2 to achieve the "clamped" BrAC time course, $C_{Model}(t, \Omega) \cong C_{Ref}(t)$, which is the ideal alcohol clamp depicted within Fig. 1. In the algorithm of Fig. 2, $M_{Infused}(t) = M_0$ for $0 \le t \le T_1$ for some small constant rate M_0 and a small time increment set by T_1. A model simulation is then implemented over $[0, T_1]$ to produce $C_{Model}(t, \Omega)$ over $[0, T_1]$. The error, $e(T_1) = C_{Ref}(T_1) - C_{Model}(t, \Omega)$ is then computed. The computer adjust box in Fig. 2, simply a high gain amplifier with saturation limits representing the infusion pump capability, modifies the infusion profile over the next interval of time $[T_1, T_2]$ according to the formula, $M_{Infused}(t) = k(e(t))$ where

$$k(e(t)) = \begin{cases} k_{sat}^{+} = 2000\,\text{mL/hr} & e(t) > 0.2 \\ k_0 e(t) = 10{,}000\,\text{mL} \cdot e(t)/(\text{mg\%hr}) & 0 < e(t) \le 0.2 \\ k_{sat}^{-} = 0 & e(t) \le 0 \end{cases}$$

This is simply a proportional controller, which strongly, within the limits of the physical infusion pump, drives the "instantaneous value" of the infusion profile up or down to achieve the clamp. Of course, a more sophisticated controller (e.g. a proportional-integral-derivative type controller) and/or infusion pumps that have a broader and faster infusion rate change capability (when and if they become available) should achieve better results. The resulting time course of $M_{Infused}(t)$, smoothed using interpolation techniques in MATLAB for example, represents the estimated infusion profile tuned to an individual's morphometrics.

Compared to attempts at maintaining a target BrAC using oral administration of quantlets of ethanol, the intravenous infusion methodology displayed a high degree of reliability [10,26]. In addition, it provided the pharmacologic background upon which numerous investigations have been based [19,20,24–26,29–31].

The input profile computed via $\theta = F_{m1}(x)$, however useful, was not sufficient to produce an accurate nominal BrAC time course. For the experimental procedure recounted in the Appendix A to achieve the desired time course of blood alcohol concentration, proper BrAC monitoring and infusion adjustments by a trained technician were still necessary to achieve the desired time course of blood alcohol concentration, $C_{BrAC}(t) \cong C_{Ref}(t)$ where $t = t_k, k = 0, 1, \ldots, K$ the determination of which is described within the Appendix A. Since the input profile depends critically on the conversion of the morphometrics into the model parameters, the investigators reasoned that an improved morphometric transformation linearized about statistical gender dependent averages would significantly improve results.

4. Development of a new morphometric transformation F_{m2}

To develop F_{m2}, experimental manual BrAC clamping records of 126 women and 91 men were collected for use as a data source. The collection was divided into experimental and control sets: 50 men and 50 women were randomly assigned to the experimental set with the remaining 76 females and 41 males assigned to the control sets. Table 1 demonstrates a proper match of both demographics and physical characteristics.

For each subject, the actual infusion profile, denoted $M_{EtOH}(t)$, that produced a clamp of the type of Fig. 1, i.e., $C_{BrAC}(t) \cong C_{Ref}(t)$, was used in a separate algorithm that computed an optimal set of PBPK model parameters, Ω^*, such that when the PBPK model input $M_{Infused}(t) = M_{EtOH}(t)$ the model's output response matched the measured $C_{BrAC}(t)$, i.e., $C_{Model}(t, \Omega) \cong C_{BrAC}(t)$. This process is known as model parameter identification based on input–output measurements [55,56]. The parameter identification scheme (Fig. 4) employs repeated simulations of the PBPK model inside a parameter optimization algorithm as will be described.

4.1. Determination of optimal parameter values

In order to set up the parameter identification, the actual infusion profile was reconstructed as a piecewise constant

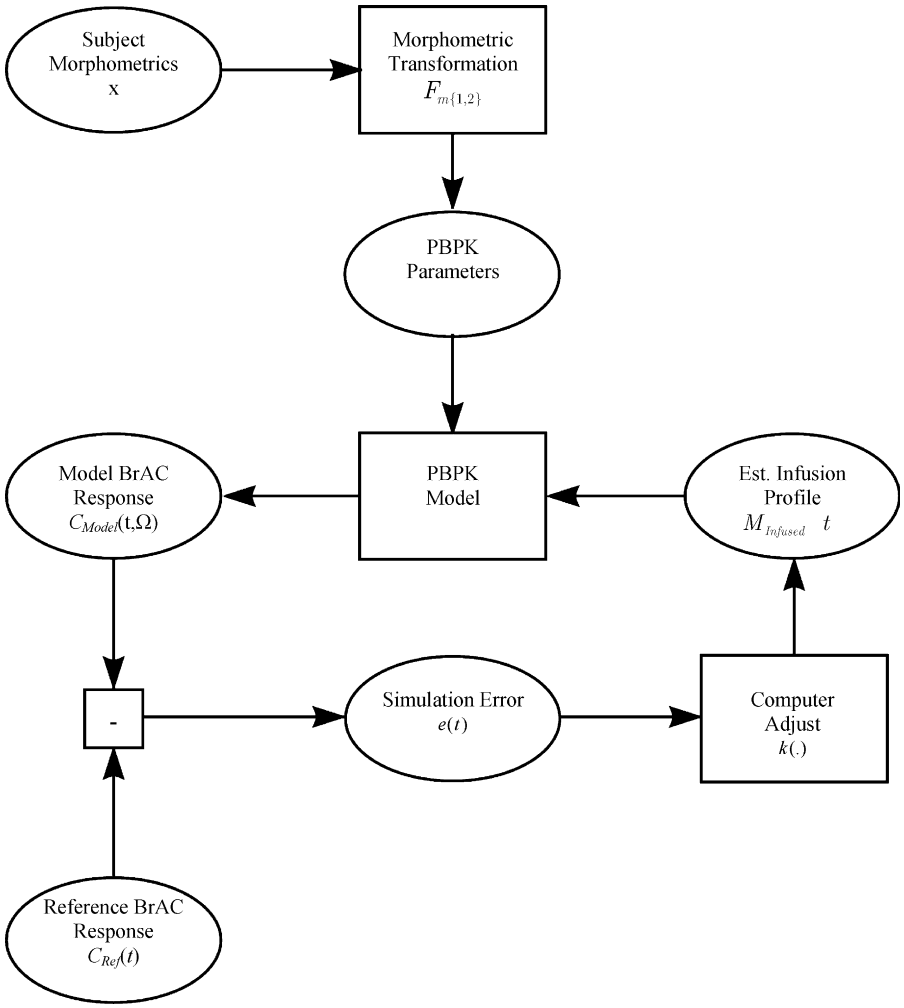

Fig. 2. Estimation procedure for the alcohol infusion profile. To begin, a desired Reference BrAC response, $C_{\mathrm{Ref}}(t)$, is identified; an alcohol clamp for the context of this paper. Next, the model response to an initially zero infusion profile, $M_{\mathrm{Infused}}(t)$, is calculated, yielding Model BrAC response $C_{\mathrm{Model}}(t, \Omega)$. This is compared to the reference response, creating an error signal, $e(t)$, which drives the computer adjust $k(\cdot)$. This process adjusts the next value of the estimated infusion profile. This process is repeated for each step of the simulation interval, pre-computing the infusion profile.

(staircase) function $M_{\mathrm{Infused}}(t) = M_{\mathrm{EtOH}}(t_k)$, $t_k \leq t < t_{k+1}$, where $M_{\mathrm{EtOH}}(t_k)$ are the values of the actual input rate profile as implemented by the infusion pump at time t_{k}, which is consistent with the experimental procedure used in clamping.

Next, a continuous BrAC response, denoted $C_{\mathrm{BrAC}}(t)$, was interpolated from the recorded samples, with results illustrated in Fig. 3. Because the measured input and output were to be used in a continuous time simulation of the PBPK model as part of the parameter identification, interpolation of the discrete measurements was necessary, especially since the measured samples were taken over infrequent and non-uniform time intervals due to practical constraints during the clinical trials. The interpolation process entailed time intervals associated with the ascending, steady state, and descending segments (the "knees") of the experimental time course of BrAC. Then, for each segment, a least squares fit polynomial, whose maximum order was six, fifteen, or three respectively, subject to continuity constraints at the knees, was determined by the MATLAB® (Math Works Inc., Natick, MA) function *polyfit*. The maximal polynomial orders were selected based upon the nature of the data of the segment (e.g. six was chosen to accommodate the potential oscillations at the "knee" of the predominantly linear ascending limb), if non-feasible physiological or experimental behaviors were detected the maximal order for that segment was reduced and the polynomial re-determined. Examples of impossible behaviors within the ascending limb would include inflection points or,

Table 1
Subject characteristics

	Experimental set		Control set	
	Men	Women	Men	Women
Number	50	50	41	76
Age [years]	25.7 (3.5)	26.0 (4.0)	26.4 (3.7)	25.9 (3.6)
Height [cm]	178.7 (7.9)	165.7 (6.8)	178.7 (7.8)	165.7 (6.1)
Weight [kg]	89.3 (22.6)	75.6 (19.2)	89.5 (20.6)	72.4 (17.1)
Range	61.2–183.8	51.4–122.6	59.9–163.2	48.9–120.7
TBW [L]	49.2 (7.9)	34.3 (5.0)	49.2 (7.2)	33.5 (4.5)
Range	39.2–81.5	27.6–47.0	38.0–73.1	26.7–45.9

Mean (standard deviation) and range, if indicated, are provided.

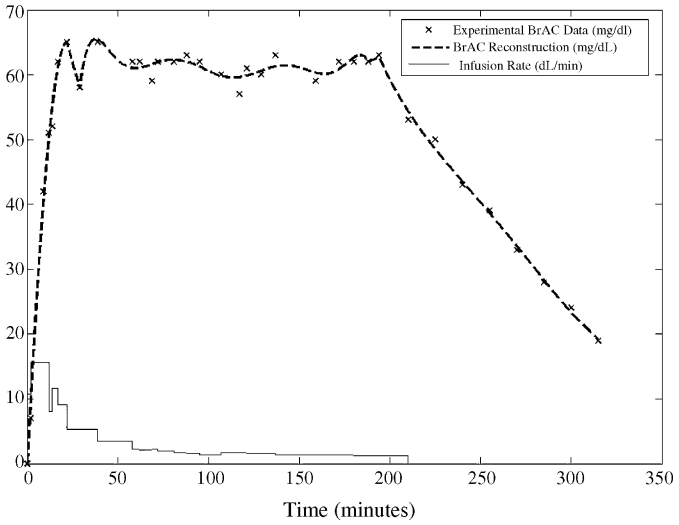

Fig. 3. Infusion profile and BrAC reconstruction. A typical clamp infusion profile and its resultant BrAC and reconsultant are depicted. As noted within Appendix A, the infusion rate is provided in terms of dL of infusate per hour where the infusate is a 6% by volume mixture of alcohol in Ringer's lactate.

alternatively, too large an estimate (caused by remnant "blinding" mouth alcohol as explained in the Appendix A); either of which would have been weighted significantly less in other approaches. When an interpolation adequately fit the data, without violation of physiological and experimental constraints, the process was stopped for that segment.

Two advantages of the algorithm were that the combination of least-squares curve-fitting and experimental constraints upon the results served as an automatic weighting system regarding the accuracy of the measured data (independent of user intervention and therefore bias) and that it provided a method of arbitrary sample-rate determination for compatibility with the Simulink® implementation of the PBPK model as mentioned earlier.

To complete the set up of the parameter identification, the set of independent parameters, Ψ, was determined using information from the literature [48–54], and an initial guess for the model parameters was computed based on the individuals morphometrics according to the formula $\theta^1 = F_{m1}x$. It is well known that parameter identification algorithms are initial condition sensitive [55,56].

Using the actual input, $M_{EtOH}(t)$, and interpolated response profile, $C_{BrAC}(t)$, an identification strategy (see Fig. 4), consisting of two steps within a loop, was implemented. In the first cycle of the algorithm, the model BrAC response, $C_{Model}(t, \Omega^1)$, to the actual infusion, $M_{EtOH}(t)$ was calculated. Second, a set of physiological constraints on the ranges and relationship between of the entries in θ, x were fed to *fmincon*. These included $0 < k_{AT} < 1$, $0 \leq V_P + V_B \leq 1.2 \cdot TBW$, $0.25\ \text{min} \leq V_B/R_C \leq 0.5\ \text{min}$, $V_P > V_B$, and $20 \leq R_C \leq 100$. The outside loop of the parameter identification algorithm uses the MATLAB function *fmincon,* then computes an improved values θ^j with entries satisfying the physiologically constrained

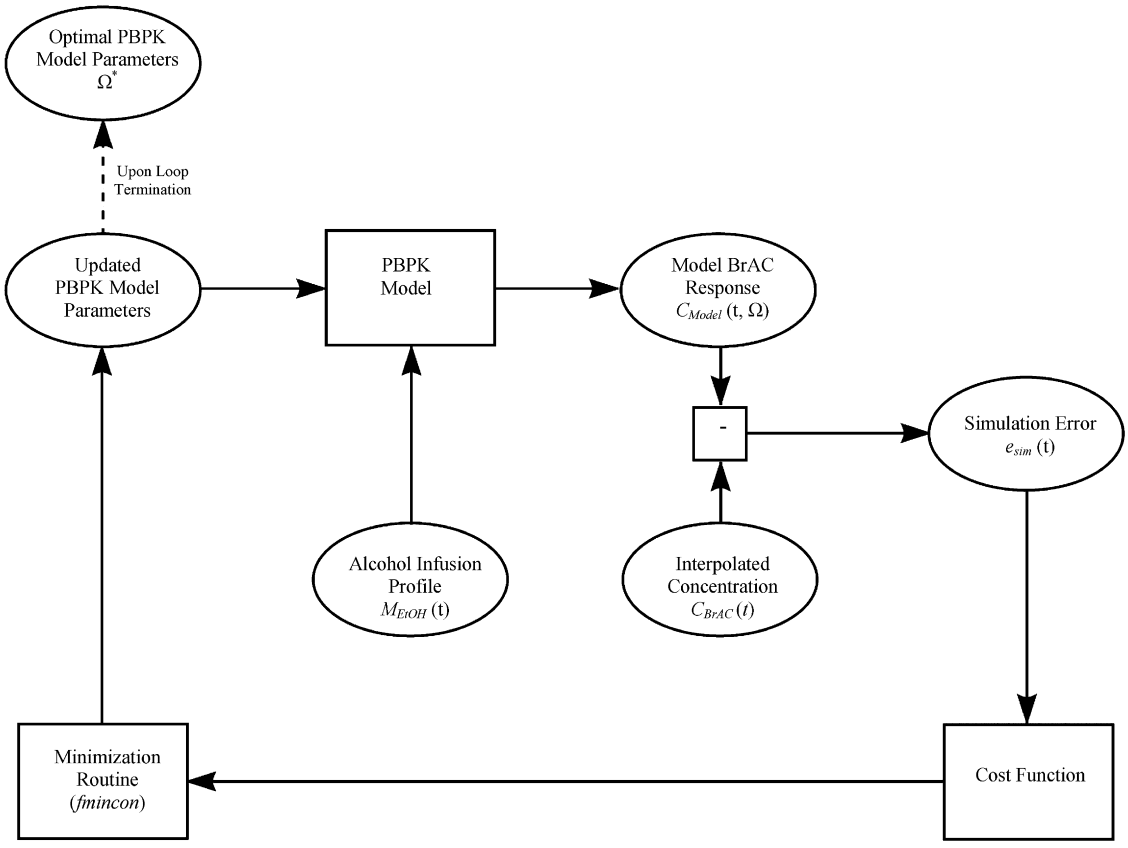

Fig. 4. Optimization block diagram. The computations required for the optimization loop are illustrated.

parameter ranges so that:

$$\min_{\theta} \frac{1}{N}\sum_{k=1}^{N}[e(t,\theta)]^2 = \min_{\theta} \frac{1}{N}\sum_{k=1}^{N}[C_{\mathrm{BrAC}}(k\Delta t) - C_{\mathrm{Model}}(k\Delta t,\theta)]^2 \quad (4.1)$$

is achieved to some tolerance by numerically implementing a steepest descent algorithm. The process of simulation using the latest estimate θ^j or more generally Ω^j is then repeated and the simulation result $C_{\mathrm{Model}}(t, \Omega^j)$ is returned to *fmincon* to compute θ^{j+1}.

It is important to indicate how the physiological constraints that were imposed in *fmincon* were determined. First, a numerical algorithm such as *fmincon* simply chooses the "best" parameter set to meet the given data. Hence, it was important and physiologically meaningful to make the PBPK model parameter values consistent with ranges documented in the pharmacokinetic literature and with other experimental observations. For example, the blood compartment time constant was observed experimentally to fall within the range of 2–4 min, specifying that the ratio V_B/R_C fall between 0.25 min and 0.5 min. As suggested, an unconstrained optimization does not mandate that V_P (the "peripheral" volume) be larger than V_B (the "blood" volume) or even positive, an obvious physiological constraint. Further, as the estimated volume of distribution for alcohol is approximately equal to the entire total body water [36–38,57], the sum of V_P and V_B was constrained to be less than 120% of TBW, allowing for error in that estimation and the influence of weak perfusion of alcohol into body fat [40,57]. Additionally, the diffusion constant k_{AT} was held to be within the bounds of [0 1], mandating that this process must occur (non-zero), and is neither instantaneous and not facilitated (less than unity). Finally, R_C was constrained to be positive and within a range greatly encompassing values reported elsewhere [50].

As mentioned, these physiologic constraints are necessary because parameter optimization schemes produce values that best match the input-output data. Attaching a physiological or clinical metric to values determined only by least squares matching is, at best, misleading. Both mathematically and clinically, it is critically important to find a select set of parameter values within a physiologically meaningful set of possible parameter values. Only under such constrained solution values would it be possible to attach a clinical metric to the obtained parameter values. This process was repeated for each individual in the test set producing the set of parameter vectors θ_k^* and consequently Ω_k^*, for $k = 1, 2, \ldots, 100$.

4.2. Morphometric transformation determination

From these parameters and the corresponding morphometrics, a least squares fit for F_{m2} was obtained using SVD techniques [58]. Specifically, a linear morphometric transform F_{m2} was then computed for each gender, as pharmacokinetic differences by sex are now being routinely observed [13,48], according to the formula:

$$\hat{F}_{m2\{m,f\}} = [\theta_1^*, \ldots, \theta_{50}^*] \times [x_1, \ldots, x_{50}]^+ \quad (4.2)$$

where "+" indicates pseudoinverse which produces a least squares solution [60].

$$F_{m2m} = \begin{bmatrix} 1.1619 & -1.3864 & -3.7935 & 12.4370 \\ -0.5368 & 0.6768 & 2.0088 & -5.0372 \\ -0.2708 & 0.0791 & 0.1673 & -0.1484 \\ 0.0491 & -0.0583 & -0.1533 & 0.6755 \\ 0.0065 & 0.0035 & 0.0045 & -0.0167 \end{bmatrix},$$

$$F_{m2f} = \begin{bmatrix} -0.2368 & -3.4172 & -9.1239 & 38.1773 \\ 0.1290 & 0.1923 & 0.6101 & -1.5920 \\ -0.1435 & -0.7215 & -1.9897 & 8.3123 \\ 0.0348 & -0.3374 & -0.8957 & 3.8095 \\ 0.0060 & 0.0274 & 0.0696 & -0.2801 \end{bmatrix}$$

The resulting PBK model parameters are denoted $\theta^2 = F_{m2}$, $x \in R^4$ for each gender respectively, where x = (age height weight TBW)$^T \in R^4$ expressed in (years, cm, Kg and liters), respectively, and $\theta = (R_C\ V_P\ V_B\ m_{max}\ k_{AT})^T \in R^5$ expressed in (dL/min, L, L, g-ethanol/h, unitless fraction).

For example, a 26.4-year-old, 178.7 cm, 89.5 kg, and 49.2 L male, e.g. x = (26.4 year 178.7 cm 89.5 kg 49.2 L)^T, corresponding to the average control male subject morphometrics as seen in Table 1, would have parameter values of $\theta = F_{m2m} \times x$ = (55.3dL/min 38.7 L 14.7 L 10.4 gm/hr 0.38)^T, Ψ = (10 mg/dL 0.38 0.26)^T as previously defined, and $\Omega = [\theta, \Psi]$. Similarly, for the average control female subject depicted in Table 1 x = (25.9 year 165.7 cm 72.4 kg 33.5 L)^T and $\theta = F_{m2f} \times x$ = (46.0 dL/min 26.0 L 11.1 L 7.8 gm/hr 0.35)^T.

5. Results and analysis

5.1. Results

As previously mentioned, all morphometric transforms were evaluated on a set of experimental data from each of 76 females and 41 males included in the control sets. Table 2 displays the results of the PBPK parameter identification. When reported, these results are compatible with other parameter estimates. More specifically, as reported in the table, it is observed that the approximate volume of distribution (V_D), the sum of V_B and V_P, was found to be 45.6 L, and 109.2% of the estimated TBW. This trend is as expected, and consistent with other published estimations of V_D, since it is believed that alcohol distributes to a volume approximately equal to the entire TBW space [37,38], but potentially slightly high. This overestimation may be explained as the average body mass index (BMI) of the experimental group was 28.0 and 27.5 kg/m^2 for men and women respectively, near the obesity definition of greater than or equal to 30 kg/m^2 [59], and the presence of body fat may distort body fluid volume estimates [39]. However, the ratio of V_D to body weight as reported by this study is 0.59 L/kg and

Table 2
PBPK parameter identification results for the experimental subject set

	F_{m2} identification		
	Men	Women	All
R_C [mL/min]	55.4 (19.4)	45.8 (16.6)	50.6 (18.6)
V_P [L]	38.6 (9.3)	26.8 (5.8)	32.7 (9.7)
V_P [%TBW]	78.1 (11.7)	78.1 (11.6)	78.1 (11.6)
V_B [L]	14.8 (5.5)	11.1 (3.3)	12.9 (4.9)
V_B [%TBW]	30.0 (9.9)	32.3 (8.7)	31.1 (9.3)
V_D [L]	53.4 (12.1)	37.9 (7.8)	45.6 (12.8)
V_D [%TBW]	108.1 (13.5)	110.4 (15.5)	109.2 (14.5)
M_{max} [gm/h]	10.4 (2.3)	7.8 (1.5)	9.1 (2.3)
k_{AT}	0.376 (0.164)	0.364 (0.184)	0.370 (0.174)

Mean (standard deviation) provided.

0.501 L/Kg, for men and women, respectively, and falls well within the estimates of other investigators. Baraona et al. reported ratios of 0.68 and 0.63 L/Kg for men and women [48]. Mumenthaler et al. reported 0.457 L/kg in women [60]. Further, based upon other reports of Norberg et al. [61], a mean value of 0.501 L/kg could be calculated. Also as reported in Table 2, the mean value of R_C was 50.6 dL/min, with a standard deviation of 18.6. Compared to the ''representative value'' of 52 dL/min and a range of 46–65 dL/min reported by Brown et al. [50] and determined in a very different context, the obtained value appears to be in direct agreement. Other PBPK model parameters also displayed gender variation, as would be expected [48]. Specifically, R_C, a variable representing cardiac outflow, was found to be larger in men than in women. Finally, m_{max}, a variable representing the maximal mass elimination rate was also larger in men than women, directly corresponding to larger alcohol elimination rates in men versus women observed in some studies [12], although this relationship is not uniformly observed [20,48]. These observations, and support by the work of other investigators [12,20,48], provided further evidence and justification to distinguish between men and women for F_{m2}.

5.2. Performance evaluation

As the principal use of improved morphometric transformation is to estimate PBPK parameters *a priori* in an attempt to control BrAC response in newly-recruited subjects, quantification of the input error in the test and control sets was undertaken. The most obvious measure, given the experimentally recorded subject data, was a dual of the Output Error. An infusion profile, denoted $M_{EtOH}(t)$, was calculated as per the original experimental procedure (see Fig. 2), with one exception: the reference BrAC response, $C_{Ref}(t)$, was replaced by the experimental data, $C_{BrAC}(t)$. Two relevant statistics emerged; a normalized input comparison, denoted $e_{InputError}$, and percent grams of alcohol in error, labeled $e_{alcoholError}$. The statistics were calculated as follows:

$$e_{InputError} = \sqrt{\frac{\sum_{i=1}^{N}\left(M_{BrAC}(t_i) - M_{est}(t_i,\theta^j)\right)^2}{\sum_{i=1}^{N}\left(M_{BrAC}(t_i)^2\right)}} \times 100$$

and

$$e_{AlcoholError} = \frac{\sum_{i=1}^{N} 0.8\Delta t \times \left|M_{BrAC}(t_i) - M_{est}(t_i,\theta^j)\right|}{\sum_{i=1}^{N}\left(M_{BrAC}(t_i) \times \Delta t\right)} \times 100$$

As the mean of the squared output error signal was the minimization criterion, a normalization of this statistic was an additional validation metric, denoted as Output Error, and is calculated as follows:

$$e_{OutputError} = \sqrt{\frac{\sum_{i=1}^{N}\left(C_{BrAC}(t_i) - C_{Model}(t_i,\Omega^j)\right)^2}{\sum_{i=1}^{N}\left(C_{BrAC}(t_i)^2\right)}} \times 100,$$

where the model was driven by the actual infusion profile, $M_{BrAC}(t)$, and with $\Omega^j, j \in \{1,2\}$ designating the version of the morphometric transform which was utilized (e.g. F_{m1} or F_{m2}).

Finally, the mean parameter distance from the ideal, or Parameter Error, was examined and determined with the relationship.

$$e_{ParameterError} = \sqrt{\frac{1}{6}\sum_{k=1}^{6}\left(\frac{(\theta_k^* - \theta_k^j)}{\theta_k^*}\right)^2} \times 100$$

where k designates the current element of the parameter vector θ. Obvious improvements were observed, and are discussed in Section 5.3. Table 3 provides error statistics comparing F_{m1} and F_{m2}.

5.3. Analysis

If successful, one result of this work would be to reduce the amount of technician feedback required to produce an acceptable ''clamp''. Reduced feedback would require a more accurate pre-clinical trial estimate of the input infusion profile. From F_{m1} to F_{m2}, the results depicted within Table 3 demonstrate that this statistic, $e_{InputError}$, went from 55% error to 34% error. Further, across the entire sample population, the

Table 3
Error statistics for the control group

	F_{m1} transformation			F_{m2} transformation		
	Men	Women	All	Men	Women	All
$e_{InputError}$	55.1 (17.7)	55.5 (17.9)	55.4 (17.8)	35.4 (15.4)	32.3 (9.7)	33.4 (11.8)
$e_{OutputError}$	25.3 (11.8)	28.2 (16.4)	27.2 (14.9)	17.4 (13.0)	20.8 (15.4)	19.6 (14.6)
$e_{AlcoholError}$	47.9 (15.3)	45.6 (10.0)	46.4 (12.1)	30.9 (17.1)	27.1 (6.2)	28.4 (11.4)
$e_{ParameterError}$	109.6 (59.2)	109.0 (65.5)	109.2 (63.1)	39.1 (23.5)	37.0 (26.4)	37.7 (25.3)

standard deviation of this error was reduced from 18 to 12%. Dramatic improvements were found in all investigated error statistics for F_{m2} compared to F_{m1} (See Table 3).

An estimate of the percent of alcohol delivered in error, $e_{AlcoholError}$, also demonstrated a substantial reduction in mean error, dropping from 46.4 to 28.4%. However, a substantial reduction in the standard deviation of this metric was not observed.

Investigators must consider what type of controls were in place if somewhere between 30 and 50% of delivered alcohol was given in error? In practice, good experimental control still may have been achieved. Since all deviances from the predicted input profile contribute equally in the calculation of $e_{InputError}$ and $e_{AlcoholError}$, mean values are artificially high from an experimental and clinical perspective. For example, a technician may over adjust (positive deviance) during one time interval and then later compensate by reducing the rate below the predicted value (negative deviance). Therefore, the manual control method may still provide the same net alcohol with respect to the prediction, yielding in an inflation of the input error statistics. Consequently, the absolute values are likely exaggerated by the technician feedback, but the net mean reduction is still indicative of a significantly improved morphometric transformation.

Table 3 also contains the output error, $e_{OutputError}$, in which the model response to θ^1 and θ^2 are compared to the measured response $C_{BrAC}(t)$. In other words, this metric is an indicator of how well the model response, with morphometrically determined parameters, duplicated the actual responses, given the actual experimental input. Once again, overall improvement was apparent: an error of 27% associated with F_{m1} dropped to 20% with F_{m2}, with similar standard deviation values.

Finally, the most dramatic performance improvement was in the proximity of the parameter estimates from F_{m2} to optimal versus the parameter estimates from F_{m1} to optimal. To make this calculation, an optimal parameter set, $\theta_k^*, \quad k = 1, \ldots, 117$, was determined in an identical manner as the test set, which is explained in Section 4.1. Comparing F_{m2} to F_{m1}, an overall mean reduction of 109–38% and a standard deviation reduction of 63–25% was observed.

6. Conclusions

The foregoing analysis leads to two immediate conclusions: (1) the procedure for constructing the new morphometric transform, F_{m2} was well-posed and valid, and (2) model responses based on morphometrically determined parameters from F_{m2} are reasonable.

This paper reports an algorithm for a priori PBPK parameter estimation for computation of an input signal designed to produce a specific response. For this particular application, the input signal of interest was an alcohol infusion rate profile to produce a desired BrAC response in newly recruited individual subjects for the purpose of performing clinical trials to determine the effect of the time course of brain alcohol exposure on brain function. The estimation algorithm is based on a statistically determined morphometric transformation that maps the individual's age, height, weight, and TBW into parameters of a differential equation model that simulates the individual's distribution and elimination of alcohol.

Our approach in achieving a pre-determined brain exposure to alcohol based on a BrAC for arterial measurement surrogate through modeling is directly analogous to the use of target-controlled infusions in anesthesia. In this approach, closed-loop systems are used to process information coming from the patient and the anesthesia delivery system, and compare it to pre-determined set point. The difference is then used to adjust the output so that the desired set point is reached and maintained [62]. The algorithms used in these systems are based on integration of pharmacokinetic and pharmacodynamic models of the anesthetic agent to continuously predict and customize target organ concentration and expected effects (level of anesthesia, mean arterial pressure, etc.). Similar approaches have been used for other anesthetics (see [63–66] for examples), as well as for vasoactive and chronotropic drugs such as nitroglycerin and nitroprusside [67,68]. The method outlined herein may thus be readily applied to systems such as those described above to improve pharmacokinetic parameter prediction. This would lead to better prediction of effects and more effective control of outcomes. These improvements have significant potential for cross-disciplinary impact as inpatient surgery was performed 45 million times in 2004 in the United States alone [69].

Limitations of this study are found in several domains: model-architecture, morphometric dimensionality and assumed linearity, and input-signal selection. As noted previously, a subset of PBPK parameters was defined with respect to previous published values or relationships. This does not allow for the expected inter-subject variability, but does minimize the dimensionality of the model, increasing the likelihood of convergence to a unique minimum. Methodology that would allow for their direct measurement or calculation should be investigated. Further, as currently defined, five morphometrics (including gender separation) are mapped to five PBPK parameters. It would be worthwhile to determine the effects of additional independent morphometric measures (e.g. body impedance analysis data) on this, and similar, transformations. Continuing, it might be beneficial to investigate the distribution of these parameters in more depth, potentially providing evidence for a non-linear transformation matrix. To the knowledge of the authors, no analytical relationship exists between the PBPK model parameters of interest and the morphometric measurements. In fact, one would expect that any analytical relationship would be nonlinear. Nevertheless, it would also be expected that the average values of morphometrics of a group of individuals would map to a set of average PBPK model parameters. These values can be thought of as a set of operating points in the space of morphometrics and an equivalent set of operating points in the PBPK model parameter space. A linear mapping would then be approximate in a neighborhood around these operating points. Thus, when an individual's morphometrics are close to the average values, the PBPK model parameters would likely be good approximations. Conversely, if the individual's morphometrics are far from the average values, the PBPK estimates would likely be correspondingly skewed.

Finally, the effect of higher-bandwidth input and output experiments should be determined. The input signal and resultant ''clamp'' are far from the ideal impulse- or step-response used in classic system identification procedures. The use of more dynamic input–output signals may excite more modes of the system, allowing for better parameter identification. The design of such signals, however, is beyond the scope of this manuscript and is an avenue for potential research.

For this particular model, a significantly improved morphometric transformation, F_{m2}, over a previously empirically determined F_{m1}, was demonstrated. These advancements reduced the amount of technician adjustment in the clinical experiment to achieve the required alcohol clamp.

The application of a morphometric transformation is found in the experimental setting where a newly recruited subject is to be exposed to a compound, alcohol in this context, without an expensive extra experimental session from which an individually-optimized set of PBPK parameters could be derived. These results suggest that for a reasonable model of a physiological process, an algorithm that produces a F_{m2} transformation is this manner provided more accurate *a priori* PBPK model parameter estimates for individual subjects. This enabled calculation of infusion profiles with improved performance with respect to prior methods of intravenous ethanol, the experimental method in the laboratory.

Acknowledgement

Supported by N01AA23102, P60 AA07611-17-19 and NIAA R01 AA12555-05.

Appendix A. The clinical experiment

A.1. Set up

Subjects are admitted to the General Clinical Research Center at Indiana University Hospital between 7:00 and 7:30 AM having been previously instructed to abstain from alcohol for at least 24 h and food for at least 8 h. Abstinence from alcohol is verified through examination of a recent drinking history log or diary and BrAC determination. Each individual's morphometrics, or age (years), height (cm), and weight (kg) is directly measured and total body water estimated (L) [36]. Furthermore, a negative urine β-HCG pregnancy test is required of female participants. An indwelling catheter is inserted into the antecubital fossa of each arm, one for the infusion and the other for the acquisition of blood samples for later off-line analysis. At approximately 8:00 am, subjects are provided standardized 350 calorie breakfasts consisting of cereal, milk, toast, and juice. Once breakfast is consumed, the subject is prepared for testing through explanation for the proper use of the breath alcohol meter, an Alcosensor IV BrAC meter (Intoximeters, Inc., St. Louis, MO) for the original subject group and a Drager Alcotest 7410 Plus (Drager Safety Inc., Durango, CO) for subsequent groups, and an explanation of the method used to obtain blood samples. Finally, the subjects are given a sample battery of dependent measures to acquaint them to both the equipment and tasks.

Then, using the morphometrics determined at check-in, the morphometric transformation is used to convert these measures into PBPK model parameters, $\theta = F_{m(1,2)x}$. The parameters, Ω, in conjunction with the desired experimental or reference BrAC response, denoted $C_{Ref}(t)$, are then utilized to pre-compute the infusion profile, $M_{Infused}(t)$ by a controlled computer simulation (See Section 3.1). To accomplish this, the point-wise difference (or error), $e(t_n)$, between the reference response and the simulation value drives a proportional feedback controller with saturation to increase or decrease the simulated alcohol infusion pump rate. This closed loop feedback simulation produces an input profile which forces the PBPK model to track the reference BrAC response. It should be noted that the infusate consists of a 6% by volume mixture of alcohol in Ringer's lactate. The process is illustrated in Fig. 2 [28].

A.2. The physiological experiment

Subjects were required to participate in both a placebo and test session for use with the subjective measures and physiologic tests. Before each session, the subjects are provided a drink with ~0.2 mL of 95% ethanol floated on top of the beverage to blind them to the session type. For the test session, the reference input profile is used to govern the actual alcohol infusion provided to the patient under the auspices of trained technicians who monitor the resultant BrAC response. The technicians were trained to adjust the amount of alcohol, delivered as necessary to minimize the error of the response as compared to the reference. The process is illustrated in Fig. 5. Thus, throughout the experiment, a record of the BrAC measurements, denoted by $C_{BrAC}(t_k)$, $k = 1, \ldots, K$, and the actual delivered infusion profile, denoted by $M_{EtOH}(t_k)$, is maintained for future analysis. As all infusion rate changes were accomplished manually and coupled to a BrAC determination, the minimum interval between samples was limited to approximately one minute and was accomplished during the ascending limb of the clamp. A faster rate of change was not feasible during any other phase of that type of experiment to minimize the potential for hyperventilation, as each BrAC measurement requires a deep breath and full exhalation. Furthermore, even the ascending limb infusion rate of change was not achievable during the steady state as these measurements would have interrupted or prevented the completion of the serial administered batteries of dependent measures and physiologic tests.

Manual adjustments to the pre-computed infusion profile remain necessary because the morphometric transformation is not tuned to the individual but rather to the averages across an ensemble of people. In the laboratory setting, manual compensation is also required for unexpected events such as the subject's need to stop the infusion for a brief bathroom break, infusion catheters that clog or infiltrate, etc. It is possible that the parameter identification methods employed here could be used to improve the clamping performance on *individual* subjects who, in some experimental paradigms, returns to the laboratory for a second or third infusion. The methodology presented here also seems like a reasonable first step towards

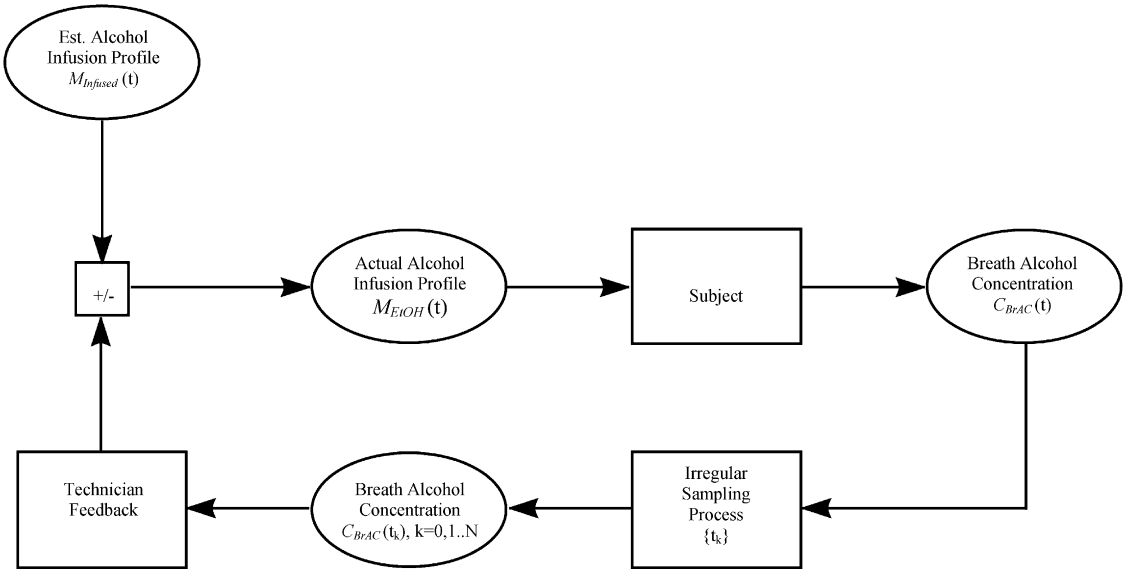

Fig. 5. Original experiment. The subject BrAC response control algorithm, as implemented within the laboratory, is illustrated.

the development of identification procedures and optimal waveform design such that reasonable open-loop (technician free) control is obtained. The main purpose of this paper, though, was to describe a method for analyzing experimental records to identify individual sets of PBPK model parameters that are then aggregated to recalibrate the morphometric transformation, thus reducing the required technician feedback on the very first infusion. Even with the feedback requirement, these techniques are useful in developing drug infusion profiles to establish blood concentration levels for other drugs whose effect on human behaviors is of importance and also in the development of pharmaceuticals to counteract the effects of drugs at these levels.

References

[1] D. Hasin, A. Paykin, Alcohol dependence and abuse diagnoses: concurrent validity in a nationally representative sample, Alcohol. Clin. Exp. Res. 23 (1) (1999) 144–150.

[2] M.A. Schuckit, T.L. Smith, G.P. Danko, J. Kramer, J. Godinez, K.K. Bucholz, J.I. Nurnberger Jr., V. Hesselbrock, Prospective evaluation of the four DSM-IV criteria for alcohol abuse in a large population, Am. J. Psychiatry 162 (2) (2005) 350–360.

[3] C.R. Cloninger, S. Sigvardsson, T. Reich, M. Bohman, Inheritance of risk to develop alcoholism, NIDA Res. Monogr. 66 (1986) 86–96.

[4] J. Erblich, M. Earleywine, Children of alcoholics exhibit attenuated cognitive impairment during an ethanol challenge, Alcohol. Clin. Exp. Res. 23 (3) (1999) 476–482.

[5] S. Kahkonen, M. Kesaniemi, V.V. Nikouline, J. Karhu, M. Ollikainen, M. Holi, R.J. Ilmoniemi, Ethanol modulates cortical activity: direct evidence with combined TMS and EEG, Neuroimage 14 (2) (2001) 322–328.

[6] M.P. Paulus, S.F. Tapert, C. Pulido, M.A. Schuckit, Alcohol attenuates load-related activation during a working memory task: relation to level of response to alcohol, Alcohol. Clin. Exp. Res. 30 (8) (2006) 1363–1371.

[7] M. Schuckit, T. Smith, J. Pierson, G. Danko, I.A. Beltran, Relationships among the level of response to alcohol and the number of alcoholic relatives in predicting alcohol-related outcomes, Alcohol. Clin. Exp. Res. 30 (8) (2006) 1308–1314.

[8] V.A. Ramchandani, L. Flury, M.H. Plawecki, T. Foroud, S. O'Connor, Heritability of Alcohol Elimination Kinetics in Sibling Pairs, in: 28th Annual Meeting of the Research Society on Alcoholism, June 25–30, 2005 – Santa Barbara, California. 29(5), Alcohol. Clin. Exp. Res. (Supplement) (2005) 84a, P567.

[9] V.A. Ramchandani, T.K. Li, M. Plawecki, S. O'Connor, Mimicking the breath alcohol exposure following oral alcohol administration using IV ethanol infusions in healthy volunteers, submitted for publication.

[10] V.A. Ramchandani, S. O'Connor, Y. Neumark, U.S. Zimmermann, S.L. Morzorati, H. de Wit, The alcohol clamp: applications, challenges, and new directions—an RSA 2004 symposium summary, Alcohol. Clin. Exp. Res. 30 (1) (2006) 155–164.

[11] M.H. Beers, R. Berkow, The Merck Manual of Diagnosis and Therapy, seventeenth ed., Merck Research Laboratories, Whitehouse Station, NJ, 1999, pp. 2566–2574.

[12] V.A. Ramchandani, P.Y. Kwo, T.K. Li, Influence of food and food composition on alcohol elimination rates in healthy men and women, J. Clin. Pharmacol. 41 (2001) 1345–1350.

[13] J.B. Whitfield, G. Zhu, D.L. Duffy, A.J. Birley, P.A.F. Madden, A.C. Heath, N.G. Martin, Variation in alcohol pharmacokinetics as a risk factor for alcohol dependence, Alcohol. Clin. Exp. Res. 25 (9) (2001) 1257–1263.

[14] C.L. Ehlers, C. Garcia-Andrade, T.L. Wall, D. Cloutier, E. Phillips, Electroencephalographic responses to alcohol challenges in native American mission Indians, Biol. Psychiatry 45 (1999) 776–787.

[15] J.C. Froelich, R.W. Zink, T.-K. Li, J.C. Christian, Analysis of heritability of hormonal responses to alcohol in twins: beta-endorphin as a potential biomarker of genetic risk for alcoholism, Alcohol. Clin. Exp. Res. 24 (3) (2000) 265–277.

[16] P.K. Wilkinson, A.J. Sedman, E. Sakmar, R.H. Earhart, D.J. Weidler, J.G. Wagner, Blood ethanol concentrations during and following constant-rate intravenous infusions of alcohol, Clin. Pharmacol. Therap. 19 (1976) 213–223.

[17] D.J. Drobes, R.F. Anton, S.E. Thomas, K. Voronin, Effects of naltrexone and nalmefene on subjective response to alcohol among non-treatment-seeking alcoholics and social drinkers, Alcohol. Clin. Exp. Res. 28 (9) (2004) 1362–1370.

[18] T. Blekher, J.D. Beard, S. O'Connor, W.E. Orr, V.A. Ramchandani, K. Miller, R.D. Yee, T.K. Li, Response of saccadic eye movements to alcohol in African American and non-Hispanic white college students, Alcohol. Clin. Exp. Res. 26 (2) (2002) 232–238.

[19] T. Blekher, V.A. Ramchandani, L. Flury, T. Foroud, D. Kareken, R.D. Yee, T.K. Li, S. O'Connor, Saccadic eye movements are associated with a family history of alcoholism at baseline and after exposure to alcohol, Alcohol. Clin. Exp. Res. 26 (10) (2002) 1568–1573.

[20] P.Y. Kwo, V.A. Ramchandani, et al., Gender differences in alcohol metabolism: relationship to liver volume and effect of adjusting for body mass, Gastroenterology 115 (6) (1998) 1552–1557.
[21] S.L. Morzorati, V.A. Ramchandani, T.K. Li, S. O'Connor, A method to achieve and maintain steady state blood alcohol levels in rats using a physiologically-based pharmacokinetic model, Alcohol 28 (2002) 189–195.
[22] S.L. Morzorati, V.A. Ramchandani, L. Flury, T.K. Li, S. O'Connor, Self-reported subjective perception of intoxication reflects family history of alcoholism when breath alcohol levels are constant, Alcohol. Clin. Exp. Res. 26 (8) (2002) 1299–1306.
[23] S.L. Morzorati, R.B. Stewart, Development of acute tolerance during steady-state arterial alcohol concentrations: a study of auditory event-related potentials in rats, Alcohol. Clin. Exp. Res. 29 (3) (2005) 347–352.
[24] Y.D. Neumark, Y. Friedlander, R. Durst, E. Leitersdorf, D. Jaffe, V.A. Ramchandani, S. O'Connor, L.G. Carr, T.K. Li, Alcohol dehydrogenase polymorphisms influence alcohol-elimination rates in a male Jewish population, Alcohol. Clin. Exp. Res. 28 (2004) 10–14.
[25] S. O'Connor, S. Morzorati, J. Christian, T.K. Li, Clamping breath alcohol concentration reduces experimental variance: application to the study of acute tolerance to alcohol and alcohol elimination rate, Alcohol. Clin. Exp. Res. 22 (1998) 202–210.
[26] S. O'Connor, V.A. Ramchandani, and T-K Li, PBPK modeling as a basis for achieving a steady BrAC of 60 ± 5 mg% within 10 min, Alcohol Clin. Exp. Res. 24 (2000) 426–427.
[27] M.H. Plawecki, P.C. Doerschuk, V.A. Ramchandani, S. O'Connor, Physiologically-based pharmacokinetic (PBPK) models for ethanol, submitted for publication.
[28] V.A. Ramchandani, J. Bolane, T.K. Li, S. O'Connor, A physiologically-based pharmacokinetic (PBPK) model for alcohol facilitates rapid BrAC clamping, Alcohol. Clin. Exp. Res. 23 (1999) 617–623.
[29] V.A. Ramchandani, L. Flury, S.L. Morzorati, D. Kareken, T. Blekher, T. Foroud, T.K. Li, S. O'Connor, Recent drinking history: association with family history of alcoholism and the acute response to alcohol during a 60 mg% clamp, J. Stud. Alcohol 63 (6) (2002) 734–744.
[30] V.A. Ramchandani, S. O'Connor, T. Blekher, D. Kareken, S. Morzorati, J. Nurnberger Jr., A preliminary study of acute responses to clamped alcohol concentration and family history of alcoholism, Alcohol. Clin. Exp. Res. 23 (8) (1999) 1320–1330.
[31] M.G. Subramanian, S.H. Heil, M.L. Kruger, K.L. Collins, P.O. Buck, T. Zawacki, A. Abbey, R.J. Sokol, M.P. Diamond, A three-stage alcohol clamp procedure in human subjects, Alcohol. Clin. Exp. Res. 26 (2002) 1479–1483.
[32] K.A. Gibb, A.S. Yee, C.C. Johnston, S.D. Martin, R.M. Nowak, Accuracy and usefulness of a breath alcohol analyzer, Ann. Emerg. Med. 13 (7) (1984) 516–520.
[33] H.W. Leung, Development and utilization of physiologically based pharmacokinetic models for toxicological applications, L. Toxicol. Environ. Health. 32 (1991) 247–267.
[34] L. Stryer, Biochemistry, Fourth Ed., W.H. Freeman and Co, New York, 1999, pp. 192–194.
[35] R. Hume, E. Weyers, Relationship between total body water and surface area in normal and obese subjects, J. Clin. Pathol. 24 (3) (1971) 234–238.
[36] P.E. Watson, in: K.E. Crow, R.D. Batt (Eds.), Total Body Water and Blood Alcohol Levels: Updating the Fundamentals. Human Metabolism of Alcohol, vol.1, CRC Press, Boca Raton, 1989, pp. 53–54.
[37] H.G. Endres, O. Gruner, Comparison of D_2O and ethanol dilutions in total body water measurements in humans, Clin. Investig. 72 (11) (1994) 830–837.
[38] J.A. Loeppky, L.G. Myhre, M.D. Venters, U.C. Luft, Total body water and lean body mass estimated by ethanol dilution, J. Appl. Physiol. 42 (6) (1977) 803–808.
[39] P. Boer, Estimated lean body mass as an index for normalization of body fluid volumes in humans, Am. J. Physiol. 247 (4 Pt 2) (1984) F632–F636.
[40] J.M. Khanna, A.D. Le, H. Kalant, A. Chau, G. Shah, Effect of lipid solubility on the development of chronic cross-tolerance between ethanol and different alcohols and barbiturates, Pharmacol. Biochem. Behav. 57 (1–2) (1997) 101–110.
[41] A. Raes, S. Van Aken, M. Craen, R. Donckerwolcke, J. Vande Walle, A reference frame for blood volume in children and adolescents, BMC Pediatr. 6 (2006) 3.
[42] D. DuBois, E.F. DuBois, A formula to estimate the approximate surface area if height and weight be known, Arch. Intern. Med. 17 (1916) 863–871.
[43] Y. Wang, J. Moss, R. Thisted, Predictors of body surface area, J. Clin. Anesth. 4 (1) (1992) 4–10.
[44] Y. Takeda, E.B. Reeve, Studies of the metabolism and distribution of albumin with autologous I131-albumin in healthy men, J. Lab. Clin. Med. 61 (1963) 183–202.
[45] R.A. DeFronzo, J.D. Tobin, R. Andres, Glucose clamp technique: a method for quantifying insulin secretion and resistance, Am. J. Physiol. 237 (3) (1979) E214–E223.
[46] M.F. Saad, R.L. Anderson, A. Laws, R.M. Watanabe, W.W. Kades, Y.D. Chen, R.E. Sands, D. Pei, P.J. Savage, R.N. Bergman, A comparison between the minimal model and the glucose clamp in the assessment of insulin sensitivity across the spectrum of glucose tolerance: insulin resistance atherosclerosis Study, Diabetes 43 (9) (1994) 1114–1121.
[47] H. Lodish, A. Berk, S.L. Zipursky, P. Matsudaira, D. Baltimore, J. Darnell, Molecular Cell Biology, fourth ed., W.H. Freeman and Co, New York, 2000, pp. 579–615.
[48] E. Baraona, C.S. Abittan, K. Dohmen, M. Moretti, G. Pozzato, Z.W. Chayes, C. Schaefer, C.S. Lieber, Gender differences in pharmacokinetics of alcohol, Alcohol. Clin. Exp. Res. 25 (4) (2001) 502–507.
[49] M.E. Andersen, H.J. Clewell III, M.L. Gargas, F.A. Smith, R.H. Reitz, Physiologically based pharmacokinetics and the risk assessment process for methylene chloride, Toxicol. Appl. Pharmacol. 87 (2) (1987) 185–205.
[50] R.P. Brown, M.D. Delp, S.L. Lindstedt, L.R. Rhomberg, R.P. Beliles, Physiological parameter values for physiologically based pharmacokinetic models, Toxicol. Ind. Health 13 (1997) 407–484.
[51] R.R. Kennedy, R.A. French, C. Spencer, Predictive accuracy of a model of volatile anesthetic uptake, Anesth. Analg. 95 (6) (2002) 1616–1621.
[52] J.L. Rheingold, R.E. Lindstrom, P.K. Wilkinson, A new blood-flow pharmacokinetic model for ethanol, J. Pharmacokinet. Biopharm. 9 (3) (1981) 261–278.
[53] S.E. Shoaf, Pharmacokinetics of intravenous alcohol: two compartment, dual Michaelis–Menten elimination, Alcohol. Clin. Exp. Res. 24 (4) (2000) 424–425.
[54] J.G. Wagner, P.K. Wilkinson, D.A. Ganes, Parameters Vm' and Km for elimination of alcohol in young male subjects following low doses of alcohol, Alcohol Alcohol. 24 (6) (1989) 555–564.
[55] M. Gevers, G. Li, Parametrizations in Control, in: Estimation and Filtering Problems: Accuracy Aspects, Springer Verlag, Communication and Control Engineering Series, New York, 1993.
[56] L. Ljung, System Identification – Theory for the User, second ed., PTR Prentice Hall, Upper Saddle River, N.J, 1999.
[57] A. Norberg, B. Sandhagen, L.E. Bratteby, J. Gabrielsson, A.W. Jones, H. Fan, R.G. Hahn, Do ethanol and deuterium oxide distribute into the same water space in healthy volunteers? Alcohol. Clin. Exp. Res. 25 (10) (2001) 1423–1430.
[58] V.C. Klemma, A.J. Laub, The singular value decomposition: it's computation and some applications, IEEE Trans. Autom. Contr. AC-15 (2) (1980) 164–176.
[59] BMI – Body Mass Index: Adult BMI Calculator: English, Department of Health and Human Services Centers for Disease Control and Prevention, http://www.cdc.gov/nccdphp/dnpa/bmi/adult_BMI/english_bmi_calculator/bmi_calculator.htm, 2006.
[60] M.S. Mumenthaler, J.L. Taylor, J.A. Yesavage, Ethanol pharmacokinetics in white women: nonlinear model fitting versus zero-order elimination analyses, Alcohol. Clin. Exp. Res. 24 (9) (2000) 1353–1362.
[61] A. Norberg, J. Gabrielsson, A.W. Jones, R.G. Hahn, Within- and between-subject variations in pharmacokinetic parameters of ethanol by analysis of breath, venous blood and urine, Br. J. Clin. Pharmacol. 49 (5) (2000) 399–408.
[62] S. Locher, K.S. Stadler, T. Boehlen, T. Bouillon, D. Leibundgut, P.M. Schumacher, R. Wymann, A.M. Zbinden, A new closed-loop control system for isoflurane using bispectral index outperforms manual control, Anesthesiology 101 (2004) 591–602.

[63] A.R. Absalom, G.N. Kenny, Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery, Br. J. Anaesth. 90 (6) (2003) 737–741.

[64] D.S. Breslin, R.K. Mirakhur, J.E. Reid, A. Kyle, Manual versus target-controlled infusions of propofol, Anaesthesia 59 (11) (2004) 1059–1063.

[65] A.N. Edginton, W. Schmitt, S. Willmann, Application of physiology-based pharmacokinetic and pharmacodynamic modeling to individualized target-controlled propofol infusions, Adv. Ther. 23 (1) (2006) 143–158.

[66] M. Luginbuhl, C. Bieniok, D. Leibundgut, R. Wymann, A. Gentilini, T.W. Schnider, Closed-loop control of mean arterial blood pressure during surgery with alfentanil: clinical evaluation of a novel model-based predictive controller, Anesthesiology 105 (2006) 462–470.

[67] S.A. Hoeksel, J.A. Blom, J.R. Jansen, J.G. Maessen, J.J. Schreuder, Automated infusion of vasoactive and inotropic drugs to control arterial and pulmonary pressures during cardiac surgery, Crit. Care Med. 27 (1999) 2792–2798.

[68] S.A. Hoeksel, J.A. Blom, J.R. Jansen, J.G. Maessen, J.J. Schreuder, Computer control versus manual control of systemic hypertension during cardiac surgery, Acta Anaesthesiol. Scand. 45 (2001) 553–557.

[69] Fast Facts A to Z: Inpatient Procedures, Centers for Disease Control – National Center for Health Statistics, http://www.cdc.gov/nchs/fastats/insurg.htm, 2004.