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Estimation of Ethanol Infusion Profile to Produce Specified BrAC Time Course using Physiologically-Based Pharmacokinetic (PBPK) Models

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Abstract—**A procedure for estimating the alcohol infusion profile required to produce a specific breath alcohol concentration (BrAC) time course using a PBPK model is described. Model parameter values are predicted from linear relationships to readily measurable physical characteristics or morphometrics. An algorithm to optimize this transformation, based upon recorded clinical experimental data, is provided. A substantial improvement in all error statistics, in relation to the original transform was obtained.**

Keywords— **alcohol, breath alcohol concentration time course, least squares approximation, morphometrics, parameter identification, optimization, pharmacokinetics, physiologically-based pharmacokinetic model**

I. Introduction

Pharmacokinetics is "the study of the time course of a drug and its metabolites in the body after administration by any route" [1]. The pharmacokinetic behavior of a particular drug has characteristics that fall into three general categories: absorption, distribution, and elimination. Physiologically-based pharmacokinetic (PBPK) models extract the underlying mathematical nature of such a process with respect to the physiological behavior of interest.

While cellular or tissue specific responses to a particular drug may be well characterized, inter-patient or inter-subject variability in elimination and distribution processes makes large group behavior comparisons much more difficult. By quantitatively compensating for the dramatic pharmacokinetic differences between people, observation and characterization of large group pharmacodynamic ("the study of the (local) biochemical and physiologic effects of drugs and their mechanisms of action"[1]) effects becomes possible. The normalization is achieved by varying the amount of drug delivered to produce a roughly equivalent concentration time course in the body tissue of interest. These input profiles must be pre-computed using a PBPK or similar model with parameters tuned to the individual. The subject of this paper is the determination of these parameters for the examination of human responses to prescribed blood alcohol levels produced by intravenous administration.

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The physiologic effects of ethanol are highly dependent upon the systemic concentration over time, i.e., pharmacodynamic effects are heavily influenced by systemic pharmacokinetics. Unfortunately, even with dosage normalization, the processes of digestion, absorption, and metabolism of alcohol after oral administration are highly variable across individuals [11]. Additionally, digestion itself may alter system physiology and hence pharmacokinetics through a redistribution of blood flow to the gut and liver [4, 11]. Furthermore, drinking history and family history of alcoholism have been shown to modulate systemic effects [2, 5, 12] and potentially affects elimination rates [10]. Even though the use of intravenous ethanol eliminates many of these effects, a high degree of interindividual variability (2.5 to 8 fold range) in distribution and elimination still exists [11].

One technique that achieves and maintains a constant breath alcohol concentration (BrAC) for prolonged intervals is called an "alcohol clamp" [8]. A clamp requires an input profile tuned to an individual's physiology that produces a linear rise to a target BrAC in a specified time period, the maintenance of that concentration for a subsequent time period, and a measured uncontrolled elimination phase as shown in Fig. 1. During the "clamp" at the target BrAC, numerous examinations are performed. When clamps are successfully achieved, the results of this testing battery can be directly compared across individuals, as systemic (and hence brain) alcohol concentrations are equivalent. The goal of the investigation is to reduce the required amount of feedback to produce an acceptable clamp through a more accurate estimation of the input profile.

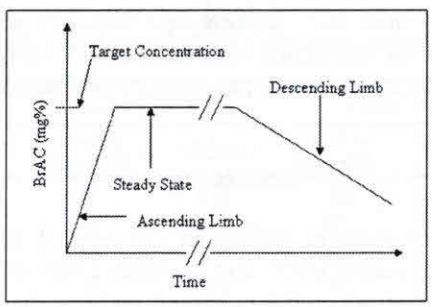

Fig. 1. Graphical depiction of an Ideal Alcohol Clamp. Major experimental regions are identified.

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II. PBPK Modeling

Our clamping procedure uses a three-compartment PBPK model to estimate the required infusion profile tuned to an individual's morphometrics (readily measurable physical characteristics). The compartments within the model represent the liver, the vasculature and the periphery. The "liver" is the alcohol sink, with behavior defined by Michaelis-Menten [13] enzyme kinetics,

$$\frac{\partial C_{Liver}}{\partial t} = \frac{M_{Parenchyma}}{V_{Liver}} - \frac{v_{\max} C_{Liver}}{k_m + C_{Liver}} \quad (1)$$

where V_x denotes the water volume of "x", C_x denotes the concentration of alcohol in x, M_x denotes the mass flux of alcohol in x, $v_{\max}$ is the maximal metabolism rate, and k_m is the Michaelis-Menten constant or concentration of the drug at which metabolism is one-half the maximal rate. The "vasculature," or fast compartment of the model, follows a 1st order differential equation,

$$\frac{\partial M_{Arterial}}{\partial t} = \frac{R_C}{V_{Blood}}\left(M_{Venous} + M_{Infused} - M_{Arterial}\right) \quad (2)$$

where volume flow is apportioned at resting cardiac output rates (R_C). The "periphery," or slow compartment, acts as a storage reservoir obeying a linear diffusion process,

$$\frac{\partial C_{Periphery}}{\partial t} = \frac{M_{Periphery}}{V_{Periphery}} \quad (3)$$

with

$$M_{Periphery} = k_{AT} R_{Periphery} * r(C_{Arterial} - C_{Periphery}) - \ldots \\ k_{TV} R_{Periphery} * r(C_{Periphery} - C_{Arterial}) \quad (4)$$

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, $R_{Periphery}$ is the volume flow to the peripheral component of the model, and r(x) is defined to be the unit ramp . Equations 1 to 4 define the behaviors of the PBPK model. The model is scalable across species with appropriate parameter selection [5].

III. Input Profile Construction and the Morphometric Transformation

A. Input Profile Construction

When parameters of the PBPK model are not directly observable, then estimates based upon the pharmacokinetic literature and morphometrics are used [8]. Based on these parameter values, an individual's approximate drug input profile is generated as per Fig. 2 to achieve the clamp of

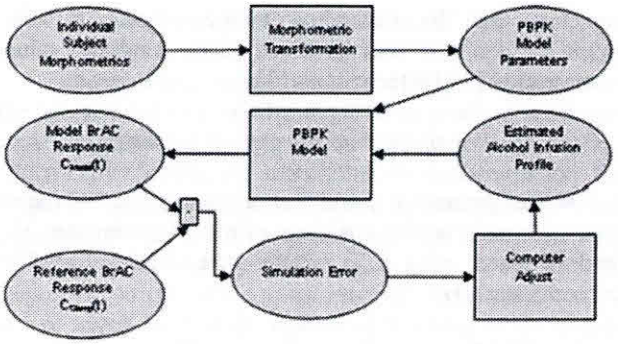

Figure 2: Estimation procedure for the alcohol infusion profile.

Fig. 1. The computer adjust box in Fig. 2 is a high gain amplifier which "instantaneously" drives the infusion profile up or down to achieve the clamp.

Compared to oral clamping attempts, this methodology displayed a high degree of reliability [7] and provided the experimental platform upon which numerous investigations have been based [2, 6, 7, 9].

The pre-computed input profile, however, was not sufficient to produce the rise and steady state segments of Fig. 1 within acceptable tolerances. For the Clinical Experiment to be successful, proper BrAC monitoring and infusion profile adjustment was necessary. Since the input profile depends critically on the transformation of the morphometrics into the model parameters, an improved morphometric transformation was sought.

B. The Morphometric Transformation

Let $x = (age\ \ height\ \ weight\ \ TBW)^T \in R^4$ specify a vector of morphometrics where TBW denotes total body water. Further let the PBPK model parameter vector be $\theta = (R_C\ \ V_{Periphery}\ \ V_{Blood}\ m_{max}\ \ k_{AT}\ \ k_{TV})^T \in R^6$ where $m_{max} = V_{Liver} * v_{max}$. The morphometric transformation, satisfies

$$\theta = F_m x . \quad (5)$$

In this study we were given a specific morphometric transformation, $F_{m1} \in R^{6x4}$, defined with empirically determined rules. Based upon F_{m1}, success of the clinical experiment became too dependent on technician feedback adjustments. A rigorous derivation of a new transformation, denoted $F_{m2} \in R^{5x4}$ (with $k_{TV} = k_{AT}$), was needed.

IV. Development of F_{m2}

To develop F_{m2}, the experimental records of 50 men and 50 women were used. For each record, the sampled infusion profile (that produced a clamp of the type of Fig. 1) was used in an algorithm that generated an optimal set of PBPK model parameters, for which the model response closely approximated the measured response. From these

parameters and the individual morphometrics, a least squares fit for F_{m2} was obtained using singular value decomposition (SVD) techniques [3].

A. Determination of Optimal Parameter Values

Prior to parameter identification, several calculations were performed: (i) the initial set of model parameters, θ^1, was determined using F_{m1}; (ii) the actual infusion profile was reconstructed as

$$U_{EtOH}(t) = U_{EtOH}(t_k), t_k \le t < t_{k+1}, \quad (6)$$

where $U_{BrAC}(t_k)$ are the actual values of the input profile at time t_k; (iii) a complete BrAC response, denoted $C_{BrAC}(t)$, was interpolated from the recorded samples using three appropriately ordered polynomial segments generated using the MATLAB® (Math Works Inc., Natick, MA) function *polyfit* and constrained to physiological behavior.

An identification strategy was then executed as delineated in Fig. 3. Here, the model response, $C_{Model}(t,\theta^1)$, to the actual infusion, $U_{BrAC}(t)$, was calculated using parameters, θ^1, computed with a given morphometric transformation, F_{m1}. The MATLAB function *fmincon* minimized the mean of the squared error signal

$$e(t) = C_{BrAC}(t) - C_{Model}(t,\theta) \quad (7)$$

over the parameter set θ, according to the formula

$$\min_{\theta} \frac{1}{N} \sum_{k=1}^{N} (C_{BrAC}(k\Delta t) - C_{Model}(k\Delta t, \theta))^2 . \quad (8)$$

Unfortunately, the parameter R_C saturated while the other parameters converged to physiologically inconsistent values. Apparently, there was insufficient bandwidth in the signals to accurately determine the short term time constant V_B/R_C. To obtain convergence, R_C was set according to the rule of F_{m1}. The identification was then repeated and convergence occurred with physiologically realizable parameters.

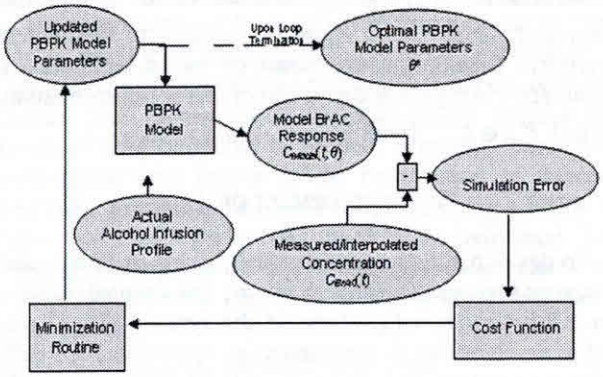

Figure 3: Optimization Block Diagram. The computations required for the optimization loop are illustrated.

This process was repeated for the test set producing θ_k^*, k = 1,...,100.

B. Morphometric Transformation Determination

We associate the individual morphometrics, x_k, with the optimal PBPK-model parameters, $\hat{\theta}_k^* = P\theta_k^*$, where P eliminates R_C from the parameter identification. A linear morphometric transform F_{m2} was then computed according to the formula:

$$\hat{F}_{m2} = \left[\hat{\theta}_1^*, \ldots, \hat{\theta}_{100}^*\right] * \left[x_1, \ldots, x_{100}\right]^+ \quad (9)$$

where "+" indicates pseudoinverse [3]. Augmenting this result with the rule for R_C produces

$$F_{m2} = \begin{bmatrix} 0 & 0 & 0.8 & 0 \\ 0.1182 & -0.0351 & 0.0387 & 0.7769 \\ -0.2713 & 0.0501 & 0.0424 & 0.1827 \\ 0.0077 & 0.0060 & 0.0162 & 0.1587 \\ 0.0053 & 0.0014 & -0.0023 & 0.0019 \end{bmatrix}. \quad (10)$$

V. Results and Analysis

A. Results

F_{m2} was evaluated on a new subject set of 76 females and 41 males. Table I provides error statistics. A normalization of the minimization criterion was an obvious choice, and was calculated as

$$e_{Output} = \sqrt{\frac{\sum_{i=1}^{N} \left(C_{BrAC}(t_i) - C_{Model}(t_i, \theta^j)\right)^2}{\sum_{i=1}^{N} \left(C_{BrAC}(t_i)^2\right)}} \times 100, \quad (11)$$

where the model was driven by the actual infusion profile, $U_{BrAC}(t)$, and with $\theta^j, j \in \{1,2\}$ designating the transform.

Efforts to quantify the input error were then investigated. The most evident, given the experimentally recorded subject data, was a dual of the Output Error. An infusion profile, $U_{est}(t)$, was calculated as per the original experimental procedure (Fig. 2), with one exception: $C_{Clamp}(t)$ was replaced by $C_{BrAC}(t)$. Two relevant statistics were computed: a normalized input comparison, e_{Input}, and percent grams of alcohol in error, $e_{Alcohol}$. e_{Input} was calculated by substitution of $U_{BrAC}(t_i)$ for $C_{BrAC}(t_i)$ and $U_{est}(t_i)$ for $C_{Model}(t_i, \theta^j)$ into (11). $e_{Alcohol}$ was calculated as

$$e_{Alcohol} = \frac{\sum_{i=1}^{N} 0.8\Delta t * \left|U_{BrAC}(t_i) - U_{est}(t_i, \theta^j)\right|}{\sum_{i=1}^{N} \left(U_{BrAC}(t_i) * \Delta t\right)} \times 100 . \quad (12)$$

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

$$e_{Parameter} = \sqrt{\frac{1}{6}\sum_{k=1}^{6}\left(\frac{\left(\theta_k^* - \theta_k^j\right)}{\theta_k^*}\right)^2} \times 100\,, \qquad (14)$$

where k designates the element of the parameter vector.

B. Analysis

As is seen in Table I, dramatic improvements were found in all investigated error statistics. e_{Input}, an input error estimate, went from 55% error to 34% error with a standard deviation across the entire sample population dropping from 18% to 12%. $e_{Alcohol}$, an estimate of the percent of alcohol delivered in error, also displayed the dramatic reduction in mean error (using a normalized absolute error rather than a normalized mean squared error). The next row of Table I contains e_{Output}, which compared the model response to θ^1 and θ^2 to $C_{BrAC}(t)$. In other words, e_{Output} evaluates the morphometrically determined parameters and resultant responses against the actual responses. The overall improvement went from 27% to 20% error with similar values for the standard deviation. The most dramatic improvement, however, was in the closeness of the parameter estimates. An overall mean reduction from 109% to 36% and a standard deviation reduction of 63% to 20% were observed. From these statistics two immediate conclusions can be drawn: 1) the procedure for constructing F_{m2} was well-posed and valid, and 2) model responses based on morphometrically determined parameters from F_{m2} are reasonable.

Table I. Error Statistics for the Control Group

	F_{M1} Transformation			F_{M2} Transformation		
	Men	Women	All	Men	Women	All
$e_{InputError}$	55.1	55.5	55.4	35.3	32.7	33.6
(SD)	(17.7)	(17.9)	(17.8)	(14.0)	(10.6)	(11.9)
$e_{AlcoholError}$	47.9	45.6	46.4	31.0	27.7	28.8
(SD)	(15.3)	(10.0)	(12.1)	(17.3)	(8.0)	(12.1)
$e_{OutputError}$	25.3	28.2	27.2	17.5	20.9	19.7
(SD)	(11.8)	(16.4)	(14.9)	(12.9)	(15.4)	(14.6)
$e_{ParameterError}$	109.6	109.0	109.2	37.5	34.9	35.8
(SD)	(59.2)	(65.5)	(63.1)	(23.3)	(17.4)	(19.6)

VI. Conclusions

This paper has demonstrated an algorithm for estimating the alcohol infusion profile required to produce a clamped BrAC response. The estimation algorithm is based on a statistically determined morphometric transformation that maps the quantities of age, height, weight, and TBW into parameters of a differential equation model that simulates the distribution and elimination of alcohol. A significantly improved morphometric transformation was determined, the use of which reduces the amount of feedback in the clinical experiment to achieve the clamp. Surprisingly, F_{m2} reduced the error between the estimated parameter vector and the optimal parameter vector from 109% error to 34% error.

These results suggest that for a reasonable model of a physiological process, the delineated methodology would provide more accurate input and parameter estimates. Refinements continue to be investigated.

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