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Statistical Signal processing for an implantable ethanol biosensor

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Abstract— **The understanding of drinking patterns leading to alcoholism has been hindered by an inability to unobtrusively measure ethanol consumption over periods of weeks to months in the community environment. Signal processing for an implantable ethanol MEMS bio sensor under simultaneous development is described where the sensor-signal processing system will provide a novel approach to this need. For safety and user acceptability issues, the sensor will be implanted subcutaneously and therefore measure peripheral-tissue ethanol concentration. A statistical signal processing system based on detailed models of the physiology and using extended Kalman filtering and dynamic programming tools is described which determines ethanol consumption and kinetics in other compartments from the time course of peripheral-tissue ethanol concentration.**

I. Introduction

NEARLY eight percent of people who use ethanol will become addicted during the course of their life [1], [2] and a large research effort of diverse content focuses on the effects of ethanol at levels ranging from the biochemical to the cognitive and behavioral. Measuring drinking behavior in natural settings over long intervals is, so far, an unsolvable problem. Even if such a record of voluntary ad-lib ingestion existed, the problem of deducing the true course of the individual's brain exposure to alcohol is compounded by a full range of absorption, distribution, and elimination kinetics across people ingesting the same drink.

This paper describes part of a system that is intended to open a new window on ethanol use by enabling unobtrusive measurement of the time course of ethanol concentration over periods of weeks to months in the community environment. Signal processing is an important part of this system. The sensor, a MEMS transducer with a DAC, memory, and wireless telemetry link, is located subcutaneously to address safety and user acceptability issues. Therefore only one ethanol concentration, that of peripheral tissue, is actually measured.

We employ a model-based approach to estimating ethanol concentrations and oral ethanol consumption from the noisy measurements of peripheral-tissue ethanol concentration. Based on the Sensor output and the generative model (Ethanol Consumption (abbreviated by EC) model, the Gastrointestinal absorption (abbreviated by Gut) model, the physiologically-based pharmacokinetic (PBPK) model of ethanol distribution and elimination, and the subcutaneous Bio-sensor (abbreviated by Sensor) model) the signal processing occurs in three major steps. The first step is to estimate the time course of all the state variables in the generative model by approximately computing the time-varying conditional means of all state variables using an extended Kalman filter [3] (abbreviated by EKF). The EKF is based on an approximation to the EC model and itself only approximately computes the conditional mean. Therefore, the EKF is followed by a second stage of processing which is maximum likelihood trajectory estimation for the state variables of the EC model treating the estimates from the EKF of the oral-consumption time series as the measured input. The third stage takes the estimated state-transition times and estimates consumption rates that are piecewise constant by least squares. The results of these three stages of processing are accurate and robust estimates of the time series of ethanol concentration in blood, liver, and peripheral tissue and the time series of ethanol consumption.

Three key difficulties have to be overcome. First, the PBPK model is nonlinear and the state variables in the PBPK model are masses of ethanol in different compartments, so the state variables are constrained to be positive. Second, the Gut model, though linear, has a time constant on the order of 30 minutes to 1 hour so the oral consumption input is severely low-pass filtered before it even excites the PBPK model. Third, statistical modeling of the source, i.e., the oral consumption, is very challenging because of the range of drinking style across people.

II. Models

A. The Gut and PBPK models

The Gut model describes the absorption process so what matters in the PBPK model is the mass flux of ethanol into the portal vein. As is described in detail in Refs. [4], [5], the experimental data is consistent with a linear time-invariant system with a critically-damped second-order impulse response. Let $M_{\mathrm{oral}}(t)$ (units of [Mass]/[Time]) denote the oral input mass flow and $M_{\mathrm{Gut}}(t)$, denote the mass flow from the gut into the portal vein. Let the impulse response be denoted by $h_{\mathrm{Gut}}(t)$. Then $h_{\mathrm{Gut}}(t) = \beta^2 t \exp(-\beta t) u(t)$. A state-space realization of $h_{\mathrm{Gut}}(\cdot)$ requires a 2-D state vector, denoted by $\mathbf{x}_{\mathrm{G}}$, and is not unique. The realization we have used is

$$\begin{aligned} \mathrm{d}\mathbf{x}_{\mathrm{G}}/\mathrm{d}t(t) &= F_{\mathrm{G}}\mathbf{x}_{\mathrm{G}}(t) + g_{\mathrm{G}} M_{\mathrm{Oral}}(t) \\ M_{\mathrm{Gut}}(t) &= h_{\mathrm{G}}'\mathbf{x}_{\mathrm{G}}(t), \end{aligned} \tag{1}$$

where F_{G} has components $F_{\mathrm{G}}^{1,1} = F_{\mathrm{G}}^{2,2} = -\beta$, $F_{\mathrm{G}}^{1,2} = 0$, and $F_{\mathrm{G}}^{2,1} = \beta$, $g_{\mathrm{G}} \doteq [\ \beta \quad 0\ ]'$, and $h_{\mathrm{G}} = [\ 0 \quad 1\ ]'$.

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The PBPK model is presented in detail in Ref. [4]. What matters here are the input, state, and output variables which need to be connected to the other components of the complete model. The input to the PBPK model is the mass flow of ethanol from the gut into the portal vein ($M_{\rm Gut}(t)$). The state variables in the PBPK model are the masses of ethanol in each compartment, denoted by $\mu_{\mathcal{X}}(t)$ (units of [Mass]) where $\mathcal{X}$ takes values $\mathcal{V}$ for the Vascular, $\mathcal{T}$ for the peripheral Tissue, and $\mathcal{L}$ for the Liver parenchyma. In addition, there are volumes for each compartment, denoted by $V_{\mathcal{X}}$, and concentrations for each compartment, denoted by $C_{\mathcal{X}}(t) \doteq \mu_{\mathcal{X}}(t)/V_{\mathcal{X}}(t)$. The output of the PBPK model is the peripheral tissue ethanol concentration which is $C_{\mathcal{T}}(t) \doteq \mu_{\mathcal{T}}(t)/V_{\mathcal{T}}(t)$. Define the state vector, denoted by $\mathbf{x}_{\rm P}(t)$, by $\mathbf{x}_{\rm P}(t) \doteq (\mu_{\mathcal{V}}(t), \mu_{\mathcal{L}}(t), \mu_{\mathcal{T}}(t))'$, the vector-valued function for computing the derivative of the state vector, denoted by $f_{\rm P}(\cdot)$, by $f_{\rm P}(\cdot) \doteq (f_{\mathcal{V}}(\cdot), f_{\mathcal{L}}(\cdot), f_{\mathcal{T}}(\cdot))'$ where the functions $f_{\mathcal{X}}(\cdot)$ are defined in Ref. [4], $g_{\rm P} = (1, 0, 0)'$, and $h_{\rm P} = (0, 0, 1/V_{\mathcal{T}})'$. Then the PBPK model is

$$\begin{aligned} {\rm d}\mathbf{x}_{\rm P}/{\rm d}t(t) &= f_{\rm P}(\mathbf{x}_{\rm P}(t), M_{\rm Gut}(t)) && (2)\\ C_{\mathcal{T}}(t) &= h'_{\rm P}\mathbf{x}_{\rm P}(t) && (3)\end{aligned}$$

with initial conditions on $\mathbf{x}_{\rm P}(t_0)$ such that every component is positive.

B. The Sensor model

The MEMS sensor is under simultaneous development so its precise performance is uncertain. However, the bandwidth of the Gut and PBPK systems is quite narrow and the Sensor is broad-band in comparison. Preliminary tests indicate that the Sensor will have a noise standard deviation that is less than 5% of the peak value. The need to save a series of sensed values for later telemetry is implemented digitally, thus we treat the sensor as a discrete-time device. Therefore, the Sensor model is $y[n] = h'_{\rm P}\mathbf{x}_{\rm P}(nT) + v[n]$ where T denotes the discrete time sampling interval, and $v[\cdot]$ is i.i.d. white Gaussian noise with mean 0 and known variance σ^2.

C. The Ethanol Consumption (EC) model

The key aspect of ethanol consumption in our analysis is the presence of periods of drinking and periods of no drinking. Therefore, a two-state continuous-time Markov chain [6], [7] is defined where State 1 correspondings to "no drinking" and State 2 corresponds to "drinking".

At each state transition a random variable called a mark is drawn independently depending on the state that is being entered and the rate of drinking (mass of ethanol per unit time) while the Markov chain is in that state is the value of the mark. The distribution when entering State 1 is deterministic with all marks having value 0. The distribution when entering State 2 is a nontrivial distribution and is denoted by $p_m(\cdot)$.

To get mixtures of long periods with no drinking intermixed with daily (or more frequent) drinking, each rate is modeled as a mean plus a first-order autoregressive process driven by a white Gaussian stochastic process with zero mean and constant power spectral density $\sigma^2_{1,2}$ or $\sigma^2_{2,1}$ for $\lambda_{1,2}$ or $\lambda_{2,1}$, respectively. For the transition from State 1 to State 2, the rate model is

$$\begin{aligned} \lambda_{1,2}(t) &= \lambda^0_{1,2} + \epsilon_{1,2}(t) && (4)\\ {\rm d}\epsilon_{1,2}/{\rm d}t(t) &= \alpha_{1,2}\epsilon_{1,2}(t) + w_{1,2}(t) && (5)\end{aligned}$$

where $w_{1,2}(\cdot)$ is a white Gaussian stochastic process with mean zero and power spectral density $\sigma^2_{1,2}$. The model for the transition from State 2 to State 1 is the same but with "1,2" replaced by "2,1". Notice that these models do not guarantee that the rates will be nonnegative and that constraint will be added when the rates are used.

III. The time-varying conditional mean of the state variables

Using the model described in Section II, as sketched in Section I, we focus on conditional mean estimators and approximate computation of such estimators using EKF [3], [8], [9], [10], [11] techniques. EKF techniques are designed for discrete-time models in the form

$$\begin{aligned} x_{k+1} &= f_k(x_k) + g_k(x_k)w_k && (6)\\ z_k &= h_k(x_k) + v_k && (7)\end{aligned}$$

where w_k and v_k are i.i.d. Gaussian sequences with zero mean and known covariance. Therefore, the model of Section II requires alteration in two aspects: it must be transformed to discrete time and the EC part, which acts as the source, must be approximated by a Gaussian model. In addition, in order to improve performance, a fixed-lag smoothing approach based on EKF ideas is used rather than a filtering approach directly using EKF ideas.

A. A Gaussian equivalent EC model

The EC model described in Section II-C plays the role of the process noise w_k in (6). Because $M_{\rm Oral}(t)$, the output of the EC model, is not a Gaussian sequence, the EC model is approximated by a Gaussian model, which we refer to as the equivalent Gaussian model, with the same first- and second-order statistics. However, the equivalent Gaussian model we use here is for the case where the rates $\lambda_{1,2}(t)$ and $\lambda_{2,1}(t)$ are constant with respect to time. Since the variations in the rates are arranged to be at a much slower time scale than the transitions in the Markov chain, this is a quasi-static approximation. The Gut and PBPK models are designed for the case where $M_{\rm Oral}(t) \geq 0$ for all t. Therefore, a unit ramp function is introducted to guarantee positivity of the Gaussian equivalent model and the rate model.

The Gaussian equivalent EC model (with output $\tilde{M}_{\rm Oral}(t)$) is (4) and (5) and

$$\begin{aligned} \frac{{\rm d}\mathbf{x}_{\rm EC}}{{\rm d}t}(t) &= F_{\rm EC}\left(r\left(\lambda_{1,2}(t)\right), r\left(\lambda_{2,1}(t)\right)\right)\mathbf{x}_{\rm EC}(t) \\ &\quad + g_{\rm EC}\left(r\left(\lambda_{1,2}(t)\right), r\left(\lambda_{2,1}(t)\right)\right)w_{\rm EC}(t) && (8)\\ \tilde{M}_{\rm Oral}(t) &= r\left(h'_{\rm EC}\mathbf{x}_{\rm EC}(t)\right) + \frac{m_p\lambda_{1,2}(t)}{(\lambda_{1,2}(t) + \lambda_{2,1}(t))} && (9)\end{aligned}$$

where $w_{\rm EC}(\cdot)$ is a zero-mean white Gaussian process with power spectral density 1,

$F_{\rm EC}(\lambda_{1,2},\lambda_{2,1}) = {\rm diag}(-\lambda_{2,1},-(\lambda_{1,2}+\lambda_{2,1}))$, $h_{\rm EC} = [\ 1\ \ 1\ ]'$, $g_{\rm EC}(\lambda_{1,2},\lambda_{2,1}) = [\ A\ \ B\ ]'$, $A = \sqrt{2\lambda_{2,1}/(\lambda_{1,2}(\lambda_{1,2}+\lambda_{2,1}))}[\sqrt{m_m^2\lambda_{2,1}^2+\sigma_m^2(\lambda_{1,2}+\lambda_{2,1})^2}-\sqrt{(m_m^2+\sigma_m^2)\lambda_{2,1}^2}]$, $B = \sqrt{\frac{2\lambda_{1,2}\lambda_{2,1}(m_m^2+\sigma_m^2)}{(\lambda_{1,2}+\lambda_{2,1})}} - A$, and m_m and σ_m^2 are the mean and variance of the mark distribution $p_m(\cdot)$. Notice that the Gaussian equivalent EC model depends only on the mean and variance of the mark distribution so more details of the mark distribution, which would be difficult to determine, are not required.

B. Transformation to discrete time

The forward Euler approximation [12] is used to discretize the differential equations. The sampling intervals are T_h (PBPK, (2), Gut, (1) and Gaussian equivalent EC model, (8)) and T_λ (autoregressive models for the rates of the Markov chain transitions, (5)). Consistent with the quasistatic approximation in Section III-A we assure T_λ/T_h and in fact that $l = T_\lambda/T_h$ is an integer.

C. Fixed lag smoothing at multiple sampling rates

In order to enforce slow variation in the parameters of the oral input model, the sampling rate for those parameters is reduced by a factor of 60 relative to the sampling rate for the PBPK model. Since the Sensor data will be provided in batch rather than real time, it is possible to compute the conditional mean of the state at time n given either all the measurements (a so-called interval smoother) or the measurements up to and including time $n+L$ (a so-called L-order fixed lag smoother). Because the measurements from days in the future contain little information about the current ethanol concentrations, this paper focuses on fixed lag smoothers. In discrete time, a fix-lag smoother and a filter are closely related by state augmentation [3]. Direct application of augmentation leads to a high computational burden. However since the state variables are slowly varying we employ multirate ideas which drastically reduce computation by a factor of $l = T_\lambda/T_h$ [13]. Simulations indicated that an adequate value for the total lag l is 60min.

IV. Identification of the parameters

The parameters of the Gut model, the PBPK model and the Sensor model are determined as described in Refs. [4], [14], [15]. The resulting values are[1] $1/\beta = 30$min, $R_A = 50.3547$dL/min, $V_{\mathcal{T}} = 23.5734$L, $V_{\mathcal{V}} = 12.4899$L, $V_{\mathcal{L}} = 1.7198$L, $M_{\max} = V_{\mathcal{L}}V_{\max} = 134.47$mg/min, and $k_{x,y} = 0.3243$ (for all values of x, y), $F_{\rm L} = .26$, $F_{\rm PV} = .75$, and $K_m = 10$mg/dL. The noise standard deviation σ for Sensor has the value 5% of the maximum value of the peripheral tissue ethanol concentration.

Continuous monitoring of interstitial fluid ethanol consumption has yet to be achieved in people. For that reason, there are no *in vivo* ethanol consumption trajectories from which to estimate the parameters in the EC or Gaussian equivalent EC model. However, based on his clinical expertise, Dr. S. J. O'Connor has provided one trajectory of duration 4 weeks for each of nine different classes of ethanol user. The key property of these trajectories is how they mimic human ethanol use, e.g., different behavior on the weekends, patterns with long correlation times, etc. These trajectories will be referred to as prototypical clinical oral ethanol input trajectories. The six parameters describing the dynamics (three for the State 1 to 2 transition and three for the State 2 to 1 transition) were set based on qualitative ideas The resulting values are $\lambda_{1,2}^0 = 0.0022$, $\lambda_{2,1}^0 = 0.0167$, $\alpha_{1,2} = \alpha_{2,1} = 0.005$, and $\sigma_{1,2} = \sigma_{2,1} = 0.000017$. The sampling intervals are $T_h = 1$min and $T_\lambda = 60$min.

The final parameter is the pmf for the marks conditioned on being in the drinking state (State 2). Exploiting the batch nature of the processing, the pmf is adapted to each time series which allows the use of a pmf with only one level so the pmf is described by the mean rate of drinking (m_m, gram per minute). Let m_T denote the mean of the true duration of a drinking period and m_s the mean of the peak Sensor response. As before, $V_{\mathcal{T}}$ is the volume of the peripheral tissue compartment. The value of m_m is determined by the approximate equation $m_m \approx m_s V_{\mathcal{T}}/m_T$ where $V_{\mathcal{T}}$ and m_s have known values and $1/m_T$ is determined by linear regression determined by least squares on measured drinking event durations in the nine prototypical clinical oral ethanol input trajectories.

V. The maximum likelihood trajectory estimate of the ethanol consumption and least squares estimation of mark levels

The model of the corrupted measurements is that they are the true mark value plus an independent zero-mean Gaussian random variable with known variance. The corrupted measurements of the marks are actually the oral input estimates from the EKF and the the known variance is the variance of the oral input estimate as calculated by the EKF. The EKF-computed variance is only an approximation to the true variance. Furthermore, the errors in the EKF estimate are correlated while the trajectory estimate problem assumes that the errors are independent and therefore ignores the correlations. With only one possible mark value for each state, the maximum likelihood trajectory estimation problem is a standard problem in hidden Markov models [16], which can be solved by forward dynamic programming. When using DP the mark level is set at 2/3 of the level used to compute the Gaussian equivalent EC model because the EKF tends to underestimate the oral ethanol input.

The final stage of the processing is least squares estimation of mark levels using the Markov chain transition times that were determined by DP and the continuous-valued oral input estimate determined by EKF. The time between an estimated State 1 (no drinking) to State 2 (drinking) transition and the following estimated State 2 to State 1 transition is divided into 60min segments starting at the time of the estimated State 1 to State 2 trajectory and ending with a sort segment

[1]In keeping with the bulk of ethanol pharmacokinetic research, we use units of minutes (min) for time, liters (L) or deciliters (dL) for volume, centimeters (cm) for distance, and milligrams (mg) or kilograms (kg) for mass.

TABLE I

PERFORMANCE FOR SELECTED SUBJECTS AMONG THE NINE PROTOTYPICAL CLINICAL ORAL ETHANOL INPUT TRAJECTORIES. MSE: SQUARE ROOT OF NORMALIZED MEAN SQUARED ERROR. AREA: INTEGRAL OF DIFFERENCE BETWEEN TRUE AND ESTIMATED TRAJECTORIES.

		Social	PU grad.	Binge	Sales
MSE for Blood		0.0009	0.0013	0.0012	0.0009
MSE for oral	EKF	0.0006	0.0005	0.0006	0.0006
	SLDP	0.0008	0.0009	0.0011	0.0011
	LSDP	0.0006	0.0003	0.0004	0.0007
Area for oral	EKF	0.3959	0.6251	0.3804	0.0889
	SLDP	0.0216	0.1524	0.1090	0.0456
	LSDP	0.0008	0.0039	0.0030	0.0039

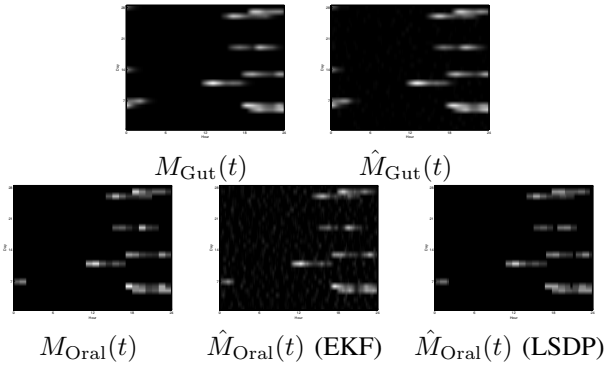

Fig. 1. Results for the binge drinker with time series show as image intensity.

just before the estimated State 2 to State 1 transition. Within each segment the estimated mark level is determined by solving a linear least squares problem where the regressor is a constant within the segment.

VI. NUMERICAL RESULTS ON PROTOTYPICAL CLINICAL ORAL ETHANOL INPUT TRAJECTORIES

Figure 1 displays the true and estimated time series for one of the prototypical clinical oral ethanol input trajectories. Performance on estimating the PBPK variables, $\mu_{\mathcal{T}}(t)/V_{\mathcal{T}}$, $\mu_{\mathcal{L}}(t)/V_{\mathcal{L}}$, and $\mu_{\mathcal{V}}(t)/V_{\mathcal{V}}$, and on the Gut output, $M_{\mathrm{Gut}}(t)$, is excellent, e.g., $M_{\mathrm{Gut}}(t)$ and $\hat{M}_{\mathrm{Gut}}(t)$ are very similar. Performance on estimating the oral input, $M_{\mathrm{Oral}}(t)$, by the EKF alone is not as good ($M_{\mathrm{Oral}}(t)$ and $\hat{M}_{\mathrm{Oral}}(t)$ (EKF) differ) because the oral input is separated from the other variables by the Gut and the Gut is a low pass filter with a low cutoff frequency. However, $\hat{M}_{\mathrm{Oral}}(t)$ (LSDP), which is the output of the third stage, does accurately track the oral input, hereby justifying the further processing.

Table I describes performance in terms of three quantitative criteria. The first criterion ("Area" in Table I) is whether the estimated oral input has the same total amount of ethanol as the true oral input. While the estimate from Stage 1 (EKF) has rather large errors, the estimate of Stage 3 (LSDP) has errors that are on the order of 1%. The second criterion is "MSE" in Table I. Performance, e.g., MSE on the order of 2-3%, is satisfactory for the clinical application.

VII. DISCUSSION

In this paper, a three-stage algorithm is described for estimating liver, blood, and peripheral tissue ethanol concentrations, and ethanol ingestion, from Sensor time series measurements of interstitial fluid ethanol concentration. The computational complexity is low, in part because it is possible to exploit multiple sampling rates in the EKF. A key challenge is the extensive nonlinear low pass filtering the occurs between the oral input and the Sensor data. With this system, we are able to provide clinically-relevant levels of performance both in Monte Carlo simulation and with the nine prototypical clinical oral ethanol input trajectories based on clinical practice. Sensor experimental data is not yet available because the Sensor is under co-development. Development of the Sensor is costly, but the "planning" analysis carried out in this paper justifies the expectation that the Sensor and signal processing system will be able to achieve the sponsor's objectives.

REFERENCES

[1] M. A. Schuckit, T. L. Smith, G. P. Danko, J. Kramer, J. Godinez, K. K. Bucholz, J. I. Nurnberger Jr., and V. Hesselbrock, "Prospective evaluation of the four DSM-IV criteria for alcohol abuse in a large population," *American Journal of Psychiatry*, vol. 162, no. 2, pp. 350–360, Feb. 2005.

[2] H. D. Paykin, "A. alcohol dependence and abuse diagnoses: Concurrent validity in a nationally respresentative sample," *Alcoholism: Clinical and Experimental Research*, vol. 23, no. 1, pp. 144–150, Jan. 1999.

[3] B. D. O. Anderson and J. B. Moore, *Optimal Filtering*. Englewood Cliffs, New Jersey: Prentice-Hall, Inc., 1979.

[4] M. H. Plawecki, J.-J. Han, P. C. Doerschuk, V. Ramchandani, and S. O'Connor, "Physiologically-based pharmacokinetic (PBPK) models for ethanol," *IEEE Trans. Biomed. Eng.*, 2005, submitted.

[5] V. A. Ramchandani, T. K. Li, M. H. Plawecki, and S. O'Connor, "Mimicking the breath alcohol exposure following oral alcohol administration using IV ethanol infusions in healthy volunteers: Characterization of pharmacokinetic variability," 2004, submitted.

[6] S. Karlin and H. M. Taylor, *A First Course in Stochastic Processes*, 2nd ed. San Diego: Academic Press, Inc., 1975.

[7] S. M. Ross, *Stochastic Processes*, 2nd ed. New York: John Wiley & Sons, Inc., 1996.

[8] Y. Bar-Shalom and X. R. Li, *Estimation and Tracking: Principles, Techniques and Software*. Artech House, 1993.

[9] S. Haykin, *Kalman Filtering and Neural Networks*. New York: John Wiley & Sons, Inc., 2001.

[10] E. Mazor, J. Dayan, A. Averbuch, and Y. Bar-Shalom, "Interacting multiple model methods in target tracking: A survey," *IEEE Trans. Aero. Elect. Syst.*, vol. 34, no. 1, pp. 103–123, 1998.

[11] R. Togneri and L. Deng, "Joint state and parameter estimation for a target-directed nonlinear dynamic system model," *IEEE Trans. Sig. Proc.*, vol. 51, pp. 1361–1370, 2003.

[12] A. D. Poularikas and S. Seely, *Signals And Systems*, 2nd ed. Boston, MA: PWS-KENT Publishing Company, 1990.

[13] J.-J. Han, "Stochastic models and nonlinear filtering algorithms for an ethanol biosensor," Ph.D. dissertation, School of Electrical and Computer Engineering, Purdue University, West Lafayette, Indiana, USA, 2006, tentative title and date.

[14] 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 ten minutes," *Alcohol Clin. Exp. Res.*, vol. 24, pp. 426–427, 2000.

[15] M. H. Plawecki, R. A. DeCarlo, V. A. Ramchandani, and S. O'Connor, "Estimation of ethanol infusion profile to produce specified BrAC time course using physiologically based pharmacokinetic (PBPK) models based upon morphometrics," 2004, submitted.

[16] L. R. Rabiner, "A tutorial on hidden Markov models and selected applications in speech recognition," *Proc. IEEE*, vol. 77, no. 2, pp. 257–286, 1989.