Discrete-Time Blind Deconvolution for Distributed Parameter Systems with Dirichlet Boundary Input and Unbounded Output with Application to a Transdermal Alcohol Biosensor

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Abstract
A scheme for the blind deconvolution of blood or breath alcohol concentration from biosensor measured transdermal alcohol concentration based on a parabolic PDE with Dirichlet boundary input and point-wise boundary output is developed. The estimation of the convolution filter corresponding to a particular patient and device is formulated as a nonlinear least squares fit to data. The deconvolution is then formulated as a regularized linear-quadratic programming problem. Numerical results involving patient data are presented.

1 Introduction
We develop a mathematical model-based approach to extracting quantitative estimates of blood alcohol (BAC) or breath alcohol (BrAC) concentration (which one depends on the genesis of the data used to calibrate the models) from biosensor measurement of transdermal alcohol concentration (TAC). Approximately 1% of alcohol consumed by humans is excreted through the skin [8]. It can be measured and correlated to BAC or BrAC and used for monitoring BACs over longer periods of time. However, to date TAC sensors have primarily been used as abstinence monitors since 1) significant variance is observed from device to device and from subject to subject and 2) BAC (or BrAC) peaks have been observed to be attenuated and displaced in TAC readings.

We develop a first principles forward model for the transport of ethanol from the blood through the skin to the TAC sensor and its oxidation by the TAC sensor hardware. The model must be calibrated to the device being worn and the subject being tested using simultaneous BAC or BrAC and TAC measurements obtained during a laboratory alcohol administration session (or alcohol challenge). Then we use the fit model to produce estimates for BAC or BrAC during the period that the sensor was worn in the field. Our model is a parabolic partial differential equation with input (BAC or BrAC) and output (TAC) on the boundary. The inverse problem of determining the BAC or BrAC input from the TAC output is formulated as a blind deconvolution problem with non-negativity constraints. Estimating the convolution filter, or the calibration problem, is formulated as a nonlinear least squares fit to data. We deal with the inherent ill-posedness in these inverse problems by augmenting the performance indices with regularization terms. We have developed a scheme that optimally sets the values of the associated regularization parameters.

2 Discrete Time Distributed Parameter Systems with Unbounded Input and Output
We consider a class of abstract distributed parameter initial-boundary value problem that have been studied earlier in the context of linear quadratic control (see, for example, [2, 4, 7]). Let $W, V,$ and $H$ be Hilbert spaces such $W, V \leftrightarrow H$ with the embeddings dense and continuous. Pivoting on the space $H$, it then follows that $V \leftrightarrow H \leftrightarrow V^*$ and $W \leftrightarrow H \leftrightarrow W^*$, with the dual embeddings also dense and continuous. Let $Q$, a parameter set, be a compact subset of $R^p$ and for each $q \in Q$ let $\Delta(q) \in \mathcal{L}(W,H)$, $\Gamma(q) \in \mathcal{L}(W,R^p)$, and $C(q) \in \mathcal{L}(V,R^p)$. We are interested in abstract input/output systems of the form

\begin{align}
\hat{\phi}(t) = \Delta(q)\phi(t), & \quad t > 0, \quad \phi(0) = \phi_0, \\
\Gamma(q)\phi(t) = u(t), & \quad y(t) = C(q)\phi(t), \quad t > 0.
\end{align}

where $\phi_0 \in H$, and $u \in L^2_T(0,T)$. We make no assumptions concerning the continuity of the linear operators $\Gamma(q)$ and $C(q)$ with respect to the $H$ norm, $H$ being the natural state space in which to formulate...
this problem. Consequently, we say this system has, in
general, unbounded input and output.

We require a number of additional assumptions on the operators $\Delta(q)$ and $\Gamma(q)$: We assume that $\Gamma(q)$ is surjective and that its null space, $\mathcal{N}(\Gamma(q)) = \{ \psi \in W : \Gamma(q)\psi = 0 \}$ is dense in $H$, and that the operator $A(q) : \text{Dom}(A(q)) \subseteq H \to H$ defined by $\text{Dom}(A(q)) = \mathcal{N}(\Gamma(q))$, $A(q)\psi = \Delta(q)\psi$, for $\psi \in \mathcal{N}(\Gamma(q))$, is closed, densely defined and has nonempty resolvent set. We assume also that for each $T > 0$, all $\phi_0 \in W$, and all $u \in C^1(0,T; R^\mu)$ with $\Gamma(q)\phi_0 = u(0)$, there exists a unique function $\phi \in C(0,T;W) \cap C^1(0,T;H)$ that depends continuously on $\phi_0$ and $u$ and that satisfies (2.1), (2.2) on $[0,T]$.

Under these assumptions, it can be shown that $A(q) : \text{Dom}(A(q)) \subseteq H \to H$ is the infinitesimal generator of a $C_0$ semigroup, $e^{A(q)t} : \text{Dom}(A(q)) \subseteq H \to H$, of bounded linear operators on $H$. Now since the operators $\Gamma(q)$ and $C$ are unbounded with respect to $H$, the existence of the semigroup $e^{A(q)t} : t \geq 0$ on $H$ by itself is not sufficient to define even a mild solution to (2.1), (2.2) and 2) to make sense of the output given in (2.2). This requires the extension of $e^{A(q)t} : t \geq 0$ to a semigroup defined on a space larger than $H$. Curtain and Salamon [2] have shown how to do this.

Briefly, since $A(q) : \text{Dom}(A(q)) \subseteq H \to H$ is densely defined, closed, and the infinitesimal generator of a $C_0$ semigroup on $H$, its adjoint, $(A(q))^* : \text{Dom}(A(q))^* \subseteq H \to H$, is also densely defined and closed. Let $Z^*$ denote the Hilbert space $\text{Dom}(A(q))^*$ endowed with the graph Hilbert space norm associated with the operator $A(q)^*$. It follows [2] that $Z^* \to H \to Z$, i.e. the space $Z^*$ is embedded in $H$ with the embedding dense and continuous and $H$ in turn is densely and continuously embedded in the space $Z$ defined to be the dual of the space $Z^*$. The semigroup, $e^{A(q)t} : t \geq 0$, can now be uniquely extended to a $C_0$-semigroup $\{ e^{A(q)t} : t \geq 0 \}$ of bounded linear operators on $Z$. The infinitesimal generator of the semigroup $\{ e^{A(q)t} : t \geq 0 \}$ is the extension of the operator $A(q)$ to an operator $\hat{A}(q) : H \subseteq Z \to Z$ in $\mathcal{L}(H,Z)$ defined by the expression $\langle \hat{A}(q)\psi, \zeta \rangle_Z = \langle \psi, (A(q))^* \zeta \rangle_H$, for $\psi \in \text{Dom}(\hat{A}(q)) = H$, and $\zeta \in \text{Dom}(A(q)^*) = Z^*$. In this expression, $\langle \cdot, \cdot \rangle_Z$, $\text{Dom}(A(q)^*)$ denotes the duality pairing between the space $Z^* = \text{Dom}(A(q)^*)$ and its dual $Z$.

Next, for each $q \in Q$, let $\Gamma^+(q) \in \mathcal{L}(R^\mu, W)$ be any right inverse of the surjection $\Gamma(q) \in \mathcal{L}(W,R^\mu)$ and define $\hat{B}(q) \in \mathcal{L}(R^\mu, Z)$ by $\hat{B}(q) = (\Delta(q) - \hat{A}(q))^+$. The operator $\hat{B}(q)$ is well defined since if $\Gamma^+_1(q)$ and $\Gamma^+_2(q)$ are two right inverses of $\Gamma(q)$, then $\Gamma^+_1(q) - \Gamma^+_2(q) \subseteq \mathcal{N}(\Gamma(q))$ and hence $\hat{B}(q) = \hat{B}_2(q)$ since $\hat{A}(q) = \Delta(q)$ on $\mathcal{N}(\Gamma(q))$. Following [2] the mild solution to the initial boundary value problem (2.1), (2.2) is defined as the unique mild solution to the abstract initial value problem in $Z$ given by

$$
\phi(t) = \hat{A}(q)\phi(t) + \hat{B}(q)u(t), \quad t > 0, \quad \phi(0) = \phi_0,
$$

that is, as $\phi \in C([0,T],H) \cap H^1((0,T),Z)$ given by $\phi(t) = e^{\hat{A}(q)t}\phi_0 + \int_0^t e^{A(q)(t-s)}\hat{B}(q)u(s)ds$.

For the output equation in (2.2) to make sense, further assumptions are required. Indeed, we must assume that the operators $e^{A(q)t}$, for $t > 0$ have range in $V$, and that $\int_0^t e^{A(q)(t-s)}\hat{B}(q)u(s)ds \in V$ for $t > 0$. These assumptions typically require additional assumptions on the operators $\Delta(q)$ and $\Gamma(q)$, the initial data $\phi_0$ and/or the input $u$. When these additional assumptions hold, for $t \geq 0$ we have $y(t) = C(q)e^{A(q)t}\phi_0 + C(q) \int_0^t e^{A(q)(t-s)}\hat{B}(q)u(s)ds$.

The integrals in the previous paragraph are in $Z$. In general, the operator $C(q)$ may not be closed with respect to the $Z$ norm and hence cannot be passed around the integral. In the case of the deconvolution problems of interest to us here, we have $\phi_0 = 0$. In this case, if we take the input $u$ to be a Dirac delta distribution in the $i$-th input, $u(t) = \delta(t)e_i, t \geq 0$, where $e_i$ denotes the standard unit vector in the $i$-th coordinate direction, $i = 1, 2, \ldots, \mu$, then the $i, j$-th entry in the $\nu \times \mu$ matrix function

$$(2.3) \quad K(t; q) = C(q)e^{\hat{A}(q)t}\hat{B}(q), \quad t > 0,$$

gives the response at time $t > 0$ of the systems $i$-th output channel to a unit impulse in the systems $j$-th input channel.

Let the sampling time $\tau > 0$ be given and consider zero order hold inputs of the form $u(t) = u_i, t \in [i\tau, (i+1)\tau), i = 0, 1, 2, \ldots$, (typically $u_i = u(i\tau), i = 0, 1, 2, \ldots$, where $u$ is a given continuous time input). Set $\phi_i = \phi(i\tau), i = 0, 1, 2, \ldots$ and let $\phi_i(t) = \phi(t) - \Gamma^+(q)u_i, \quad t \in [i\tau, (i+1)\tau), i = 0, 1, 2, \ldots$. Then since $\psi_i(t) = \phi(t) - \hat{A}(q)\phi_i(t) + \hat{B}(q)u_i = \hat{A}(q)\psi_i(t) + \hat{B}(q)(\hat{A}(q)\Gamma^+(q)u_i, \quad \psi_i$ satisfies the initial value problem (IVP) $\psi_i(t) = \hat{A}(q)\psi_i(t) + \Delta(q)\Gamma^+(q)u_i, \quad t \in [i\tau, (i+1)\tau), \psi_i(i\tau) = \phi_i - \Gamma^+(q)u_i$. The solution to this IVP can be obtained from the variation of constants formula and since $u$ is constant on each subinterval $[i\tau, (i+1)\tau)$ and the initial data and forcing term are all elements in $H$, it follows that it is in fact a classical solution [6]. Thus we obtain

$$(2.4) \quad \phi_i(t) = \hat{A}(q)\phi_i + \hat{B}(q)u_i, \quad i = 0, 1, 2, \ldots, \quad \phi_0 \in H$$

where $\hat{A}(q) = e^{\hat{A}(q)t} \in \mathcal{L}(H, H)$, and $\hat{B}(q) = (I - e^{\hat{A}(q)t})\Gamma^+(q) + \int_0^t e^{A(q)(t-s)}\Delta(q)\Gamma^+(q)ds \in \mathcal{L}(R^\mu, H)$. 

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It can be shown [4] that as in the continuous time case, the operator $\hat{B}(q)$ in (2.4) is well defined and does not depend on the particular choice of $\Gamma^+(q)$. It can also be shown that $B(q) = \int_0^\gamma e^{\hat{A}(q)\tau} \hat{B}(q) \, d\tau$ is in agreement with the standard formula for the input operator when a (finite dimensional or bounded input) continuous time system is converted to a discrete or sampled time system. We note also that if $\Gamma^+(q)$ can be chosen so that $\text{Range}(\Gamma^+(q)) \subseteq \mathcal{N}(\Delta(q))$, then the expression for $\hat{B}(q)$ given above simplifies to $\hat{B}(q) = (I - e^{\hat{A}(q)\tau})\Gamma^+(q)$.

Making sense of the output equation (2.2) in the discrete time case requires additional assumptions. In general, we require that $\hat{A}(q) = e^{\hat{A}(q)\tau} \in \mathcal{L}(V,V)$, $\hat{B}(q) \in \mathcal{L}(R^n,V)$ and $\phi_0 \in V$. When $\text{Range}(\Gamma^+(q)) \subseteq \mathcal{N}(\Delta(q))$, it is enough to require that $\hat{A}(q) = e^{\hat{A}(q)\tau} \in \mathcal{L}(V,V)$, $\text{Range}(\Gamma^+(q)) \subseteq V$, and $\phi_0 \in V$. In this case, with $\phi_0$ fixed, the output sequence $y_i, i = 0, 1, 2, \ldots$, is given by $y_i = \int_{(i-1)c}^{ic} \phi(\gamma) \Gamma^+(q) u_j \, d\gamma = \sum_{j=0}^{i-1} C(q)\hat{A}(q)^{i-j-1} \hat{B}(q) u_j$, $i = 0, 1, 2, \ldots$, with the discrete or sampled time response at time $t = i\tau$ of the systems $i$-th output channel to a unit impulse in the systems $j$-th input channel given by the $i, j$-th entry in the $v \times \mu$ matrix function

$$K(t;q) = C(q)\hat{A}(q)^{[t/\tau]-1}(I - \hat{A}(q))\Gamma^+(q),$$

$t \geq \tau$, where for $t \geq 0$, $[t]$ denotes the greatest integer less than or equal to $t$.

3 A Diffusion Based Model for the Transdermal Transport of Ethanol and Its Abstract Formulation

Let $\phi(t,x)$ denote the concentration in moles/cm$^2$ of ethanol in the interstitial fluid in the epidermal layer of the skin at depth $x$ cm and time $t$ in seconds. Let $L$ denote the skin thickness in cm. We model the transport of ethanol through the skin as a diffusion process

$$\frac{\partial \phi}{\partial t}(t,x) = D \frac{\partial^2 \phi}{\partial x^2}(t,x), \quad 0 < x < L, \quad t > 0,$$

where $D$ denotes the diffusivity in units of cm$^2$/sec. We model the boundary condition at the interface of the skin and the sensor (i.e. on the surface of the skin) by setting the flux at the boundary to be proportional to the difference in concentrations on either side of the interface

$$-D \frac{\partial \phi}{\partial x}(t,0) = \alpha(0 - \phi(t,0)), \quad t > 0,$$

where $\alpha$ denotes the constant of proportionality in units of cm/sec. We have assumed that the sensor immediately processes the ethanol upon its arrival in vapor form in the sensor collection chamber. The sensor functions like a fuel cell and produces 4 electrons for each molecule of ethanol, $CH_3CHOH$, according to the oxidation reduction reactions $CH_3CHOH + H_2O \rightarrow CH_3COOH + 4e^- + 4H^+$, $O_2(air) + 4e^- + 4H^+ \rightarrow 2H_2O$.

At the interface of the epidermal layer of the skin, which is avascular, with the dermal layer which is nourished by the blood, we impose a concentration matching Dirichlet boundary condition of the form $\phi(t,L) = \beta u(t)$, $t > 0$, where the parameter $\beta$ is effectively the partition coefficient for ethanol between the blood and the interstitial fluid in units of moles/cm$^2 \times$ Bac (or BrAC) units, and $u$ denotes the concentration of ethanol in the blood as given in Bac (or BrAC) units. We assume that there is no alcohol in the skin at time $t = 0$ which yields the initial conditions $\phi(0,x) = 0, 0 < x < L$. We model the processing by the TAC sensor of the ethanol evaporating from the surface of the skin via a linear relation $y(t) = \gamma \phi(t,0)$, $t > 0$, where $\gamma$ denotes the constant of proportionality in units of TAC units $\times$ cm$^2$/mole.

As it stands, the model as given by (3.6), (3.7) and the expressions for the boundary input and output in the previous paragraph, is determined by five parameters: $D, L, \alpha, \beta$ and $\gamma$. However, not all five of the parameters are independent nor are they uniquely identifiable from input/output data. By converting to what are essentially dimensionless parameters, without loss of generality, the number of unknown parameters to be fit can be reduced to two, which we denote by the vector $q = [q_1, q_2]^T$. The model can be simplified as

$$\frac{\partial \phi}{\partial t}(t,x) = q_1 \frac{\partial^2 \phi}{\partial x^2}(t,x), \quad 0 < x < 1, \quad t > 0,$$

$$q_1 \frac{\partial \phi}{\partial x}(t,0) - \phi(t,0) = 0, \quad t > 0,$$

$$q_2 u(t), \quad y(t) = \phi(t,0), \quad t > 0,$$

$$\phi(0,x) = 0, \quad 0 < x < 1.$$
Then we have the usual dense and continuous embeddings $V \hookrightarrow H \hookrightarrow V^*$, where $V^*$ denotes the space of distributions dual to $V$, and similarly for the spaces $V_1$ and $W$ (see, for example, [9]).

Let $\Delta(q) \in \mathcal{L}(W, H)$ and $\Gamma(q) \in \mathcal{L}(W, R)$ be given by $\Delta(q)\psi = q_1 d^2 \psi / dx^2$ and $\Gamma(q)\psi = q_2 \psi(1)$, respectively, for $\psi \in W$, and let $C(q) = C \in \mathcal{L}(V, R)$ be given by $C\psi = \psi(0)$, for $\psi \in V$. In this case we have that $\Gamma(q)$ is clearly surjective and that $\mathcal{N}(\Gamma(q)) = W \cap V_1 = \{ \psi \in H_2(0, 1) : q_1 \psi'(0) - \psi(0) = 0, \psi(1) = 0 \}$ is dense in $H = L_2(0, 1)$. It follows, as in Section 2, that the operator $A(q) : \text{Dom}(A(q)) \subseteq H \to H$ defined by \[ \text{Dom}(A(q)) = W \cap V_1, A(q)\psi = q_1 d^2 \psi / dx^2, \psi \in W \cap V_1, \] is closed, densely defined and has nonempty resolvent set. It can also be shown [3] that for each $T > 0$, all $\phi_0 \in W$, and $u \in C^1(0, T; R)$ with $\Gamma(q)\phi_0 = u(0)$, there exists a unique function $\phi \in C(0, T; W) \cap C^1(0, T; H)$ that depends continuously on $\phi_0$ and $u$ and that satisfies (3.8)-(3.11) on $[0, T]$ with $\phi(0, x) = \phi_0, 0 < x < 1$. It follows that the operator $A(q)$ is the infinitesimal generator of a $C_0$-semigroup, $\{e^{A(q)t} : t \geq 0\}$ of bounded linear operators on $H$. Note that in our case here, the Lumer Phillips Theorem can be used directly and in a straightforward manner to show that $A(q)$ is the infinitesimal generator of a $C_0$-semigroup (see, for example, [6]). Indeed, it is not difficult to show that the operator $A(q)$ is self adjoint and dissipative and therefore maximal dissipative on its domain.

As it turns out for the system of interest to us here, since we in fact have $V_1 \hookrightarrow H$ with the embedding dense and continuous, we can make use of the theory of abstract parabolic systems (see, for example, [9]) to reformulate the system (3.8)-(3.11) as an equivalent abstract system with bounded input in the space $V_1^*$, a somewhat smaller space than the space $Z$ defined in Section 2.

For $q \in Q$, a compact subset of $R^+ \times R^+$, we define the bilinear form $a(q; \cdot, \cdot) : V_1 \times V_1 \to R$ by

$$ a(q; \psi_1, \psi_2) = \psi_1(0)\psi_2(0) + \int_0^1 \psi_1'(x)\psi_2'(x) \, dx, $$

$\psi_1, \psi_2 \in V$. For $q \in Q$ the $q$-dependent bilinear form on $V_1 \times V_1, a(q; \cdot, \cdot) : V_1 \times V_1 \to R$, defines a bounded linear operator $A(q) \in \mathcal{L}(V_1, V_1^*)$ by $A(q)\psi_1, \psi_2) = -a(q; \psi_1, \psi_2)$, for $\psi_1, \psi_2 \in V_1$. Then, if we let $H$ denote any of the Hilbert spaces $V_1, H$ or $V_1^*$ and we consider the linear operator $A(q) : D_q \subseteq H \to H$, given by $A(q)\psi = \tilde{A}(q)\psi$ for $\psi \in D_q = \{ \psi \in V_1 : \tilde{A}(q)\psi \in H \}$, then, it can be shown [1] that $A(q)$ is a closed, densely defined unbounded linear operator and the infinitesimal generator of an analytic semigroup of bounded linear operators, $\{e^{A(q)t} : t \geq 0\}$ on $H$. When the space $H = H$, the space $D_q = \mathcal{N}(\Gamma(q)) = W \cap V_1$ and the operator $A(q) : D_q \subseteq H \to H$ agrees with the operator defined above also denoted by $A(q)$. Let $\tilde{A}(q)$ denote the operator $A(q)$ in the case that $H = V_1^*$ and $D_q = V_1$.

For $q \in Q$ define the linear operator $\Gamma(q) \in \mathcal{L}(R, W)$ by $(\Gamma(q)\psi)(x) = \frac{q_2}{q_1} x^2 + \frac{q_2}{q_1+1} \psi, x \in [0, 1]$. Then $A(q)\Gamma(q)\psi = \psi, \psi \in R$, and Range($\Gamma(q)$) $\subset \mathcal{N}(\Delta(q))$. Noting that $W \subset V_1 = D_q = \text{Dom}(A(q)), \tilde{B}(q)$ given by $\tilde{B}(q) = (\Delta(q) - A(q))\Gamma(q)$ satisfies $\tilde{B}(q) \in \mathcal{L}(R, V_1^*)$. We can now rewrite the initial-boundary value problem (3.8)-(3.11) as an abstract evolution equation in $V_1^*$ with bounded input as

$$ \dot{\phi}(t) = \tilde{A}(q)(\phi)(t) + \tilde{B}(q)u(t), t > 0, \phi(0) = 0, $$

with output equation $y(t) = C\phi(t), t > 0$. Then using the fact that $\{e^{A(q)t} : t \geq 0\}$ is an analytic semigroup on $V_1^*$ and therefore that $e^{A(q)t}\psi \in D_q = V_1 \subset V$, for $\psi \in V_1^*$, we obtain from the abstract variation of constants formula that $y(t) = C \int_0^t e^{A(q)(t-s)} \tilde{B}(q)u(s) \, ds$. We note that the output operator, $C$, can not be pushed around the integral since it is not a closed operator with respect to $V_1^*$. Nevertheless, formally taking $u$ to be a Dirac delta distribution with impulse at time $t = 0$, it follows that for $q \in Q, K(t; q)$ from (2.3) for our model (3.8)-(3.11) is given by $K(t; q) = Ce^{A(q)t}\tilde{B}(q), t > 0$, with the understanding that the input/output relation between $u$ and $y$ must be interpreted in its integral form. For every $q \in Q, \{e^{A(q)t} : t \geq 0\}$ an analytic semigroup on $V_1$, ensures that $e^{A(q)t}\tilde{B}(q) \in D_q = V_1 \subset V$ for every $t > 0$, and that although it cannot be directly computed without finite dimensional approximation, it is a well-defined real valued function of $t$ defined for all values of $t > 0$.

For the discrete-time model, letting the sampling time $\tau > 0$ be given, setting $\phi_i = \phi(i\tau), y_i = y(i\tau)$ and $u_i = u(i\tau), i = 0, 1, 2, \ldots$, and taking zero-order hold input of the form $u(t) = u_i, t \in [i\tau, (i+1)\tau), i = 0, 1, 2, \ldots$, we obtain

$$ \phi_{i+1} = \hat{A}(q)\phi_i + \hat{B}(q)u_i, \quad i = 0, 1, 2, \ldots \tag{3.12} $$

$$ \phi_0 = 0, \quad y_i = C\phi_i, \quad i = 0, 1, 2, \ldots \tag{3.13} $$

where $\hat{A}(q) = e^{\hat{A}(q)\tau} \in \mathcal{L}(V, V)$ with $\|\hat{A}(q)\| \leq Mr^k, 0 < r < 1$, and the input operator $\hat{B}(q)$ in the discrete-time IVP (3.12),(3.13) satisfies

$$ \hat{B}(q) = \int_0^T e^{\hat{A}(q)s}\hat{B}(q) ds = (I - e^{\hat{A}(q)\tau})\Gamma(q) = (I - \hat{A}(q))\Gamma(q) \in \mathcal{L}(R, V), $$

where in (3.14) we have used the fact that Range($\Gamma(q)$) $\subset \mathcal{N}(\Delta(q))$. The bound on the norm of
the operator $\hat{A}(q)$ follows from the following calculation which uses well known estimates for analytic semigroups and the fact that $Q$ is a compact subset of $R^2$:
\[
\|\hat{A}(q)\psi\|^2 \leq -c(A(q))e^{A(q)k\tau}\psi, e^{\hat{A}(q)k\tau}\psi
\]
\[
\leq c|A(q)e^{A(q)k\tau}\psi||e^{\hat{A}(q)k\tau}\psi|
\]
\[
\leq \frac{c}{(k\tau)^{3/2}}e^{-2nk\tau}\|\psi\|^2,
\]
for $\psi \in V$ and some positive constants $c, \hat{c} > 0$. It then follows that $y_i = \Sigma_{j=0}^{i-1}CA(q)^{i-j-1}B(q)u_j$, $i = 0, 1, 2, \ldots$, and therefore that $\hat{K}(t; q)$ in (2.5) is given by $\hat{K}(t; q) = CA(q)^{(t/\tau)-1}B(q) = CA(q)^{(t/\tau)-1}(I - \hat{A}(q))\Gamma^{+}(q), t > 0$.

4 Finite Dimensional Approximation

A computational scheme for estimating BrAC from TAC by first estimating the unknown parameters, $q$, in the convolution kernel, (2.5), and then deconvolving the BrAC signal, $u$, from the TAC signal, $y$, requires finite dimensional approximation of the infinite dimensional operators $A(q) \in \mathcal{L}(V, V)$ and $T^{+}(q) \in \mathcal{L}(V, W)$ which appear in (2.5). We achieve this via linear B-splines and Galerkin approximation. For $n = 1, 2, \ldots$, let $\{\psi^n_j\}_{j=0}^n$ denote the set of standard linear B-splines on the interval $[0, 1]$ defined with respect to the usual uniform mesh, $(j/n)_{j=0}^n$, and set $V^n = \text{span}\{\psi^n_j\}_{j=0}^n \subset V$ and $V^n_1 = \text{span}\{\psi^n_j\}_{j=0}^{n-1} \subset V_1$ (note the $\psi^n_n$ are the usual “pup tent” or “chapeau” functions of height one and support of width $2/n$, $(j - 1/n, j + 1/n) \cap [0, 1]$). Let $P^n : H \rightarrow V^n$ denote the orthogonal projection of $H$ onto $V^n$ with respect to the $H$ inner product and let $P^n_1 : H \rightarrow V^n_1$ denote the orthogonal projection of $H$ onto $V^n_1$ with respect to the $H$ inner product. It is not difficult to argue [1] that $\lim_{n \rightarrow \infty} P^n_1 \psi = \psi$ in $H$ for $\psi \in H$ and in $V$ for $\psi \in V$ and that $\lim_{n \rightarrow \infty} P^n_1 \psi = \hat{\psi}$ in $H$ for $\psi \in H$ and in $V_1$ for $\psi \in V_1$. For $n = 1, 2, \ldots$, and $q \in Q$, define $A^n(q) \in \mathcal{L}(V^n_1, V^n)$ to be the finite dimensional linear operator whose matrix representation is given by $[A^n_i(q)]_{i,j} = -[\psi^n_i, \psi^n_j]^{-1}[a(q; \psi^n_i, \psi^n_j)]$, for $i, j = 0, 1, 2, \ldots, n - 1$. It is not difficult to show that $A^n_i(q) = (P^n_1a(q)^{-1})_i$, where $P^n_1a$ is the orthogonal projection of $V_1$ onto $V^n_1$ with respect to the inner product $(\cdot, \cdot)_a = a(q; \cdot, \cdot)$ on $V_1$. Then set $A^n(q) = e^{A^n(q)\tau}$ and $A^n_1(q) = P^n_1e^{A^n(q)\tau} P^n_1 \in \mathcal{L}(V^n_1, V^n)$. A straightforward calculation reveals that the matrix representation for $A^n(q)$ is given by
\[
A^n(q) = \begin{bmatrix}
A^n_1(q) & A^n(q)W^n_1 \\
0 & 0
\end{bmatrix}
\]
where in (4.15) $W^n_1 = (1/6n)[[\psi^n_i, \psi^n_j]]^{-1}$ with $[[\psi^n_i, \psi^n_j]]^{-1}$ denoting the $n$th column of the $n \times n$ matrix $[[\psi^n_i, \psi^n_j]]^{-1}$. Noting that for $v \in R, \Gamma^{+}(q)v = [\Gamma^{+}(q)(0), \Gamma^{+}(q)(1/n), \Gamma^{+}(q)(2/n), \ldots \Gamma^{+}(q)(1)]^Tv$, and define the finite dimensional approximation to the discrete-time convolution kernel $\hat{K}(t; q)$ given in (2.5) by $\hat{K}^{n}(t; q) = C\hat{A}^{n}(q)^{[t/\tau]-1}(I - A^{n}(q))\Gamma^{n}(q)$.

In the next section it will be helpful to notice that the expression for the approximating convolution kernel given above is derived from the approximating finite dimensional discrete-time dynamical system in $V^n$.

\[
\phi_{i+1}^n = \hat{A}(q)\phi_i^n + (I - \hat{A}(q))\Gamma^{n}(q)u_i,
\]
\[
\phi_o = 0 \in V^n, y_i^n = C\phi_i^n, i = 1, 2, \ldots.
\]
\[
\hat{K}^{n}(t; q) = C \left(\hat{A}^{n}(q)^{[t/\tau]-1}(I - \hat{A}(q))\Gamma^{n}(q)\right).
\]

With regard to convergence, using what are now familiar arguments [1] it can be argued that if $q^n_{1n} = 1$ is any sequence with $\lim_{n \rightarrow \infty} q^n = q^*$, we have $\lim_{n \rightarrow \infty} \hat{K}^{n}(t; q^n) = \hat{K}(t;q^*)$, uniformly on compact $t$ intervals. This result follows primarily from a rather strong convergence result for abstract parabolic semigroups that can be found in [1]. That result is that if $t > 0$, then $\lim_{n \rightarrow \infty} P^n e^{A^n(q)\tau} P^n_1 \psi = e^{\hat{A}(q)^{\tau}}(\psi)$ in $V$ for $\psi \in H$, uniformly in $t$ for $t > 0$ in compact subintervals of $R$.

5 Blind Deconvolution: Calibration and Inversion

The blind deconvolution of BrAC from TAC data is accomplished in two steps. First contemporaneous BrAC and TAC data from an alcohol challenge session, $\{a_j, b_j\}, j = 0, 1, 2, \ldots, N$, is used to fit the unknown parameters, $q_1$ and $q_2$, in the approximating convolution kernel given in (4.18). We refer to this as the calibration step or problem. Then TAC data collected in the field by the transdermal biosensor is used together with the now fit convolution kernel to deconvolve an estimate for the field BrAC. We refer to this as the inversion step or problem.

We formulate the calibration problem as a constrained least squares fit to data. To wit, we seek $q^{n*} = [q_1^{n*}, q_2^{n*}]$ in $Q$ which minimizes:
\[
J_C(q) = \sum_{i=0}^{N}||y^n_i(q) - \hat{y}_i||^2.
\]
We denote the calibrated convolution kernel by \( \hat{K}_i^n = \hat{K}_i^n(q^{nn}) = C \left( \hat{A}_i^n(q^{nn}) \right)^{i-1} \left( I - \hat{A}_i^n(q^{nn}) \right) \Gamma^{++n}(q^{nn}), \)
i = 1, 2, \ldots. The optimization problem for the performance index given in (5.19) is solved using an iterative constrained gradient based search. This will require the ability to compute the value of \( J_C(q) \) and its gradient \( \nabla J_C(q) \) for a given value of \( q \in Q \). We compute the gradient using the adjoint method. For \( i = 0, 1, 2, \ldots, N \), set \( v^N_i = [2(C \delta^N_i - \hat{y}_i), 0, \ldots, 0]^T \in R^{n+1} \), and define the adjoint system corresponding to (4.16), (4.17) by

\[
\eta_i^n = \left[ \hat{A}_i^n(q) \right]^T \eta_i^n + v^N_{i-1}, \quad i = N, N - 1, \ldots, 1, \\
\eta_0^n = v_0^n.
\]

The gradient of \( J_C(q) \), given in (5.19), can then be computed as \( \nabla J_C(q) = \sum_{i=1}^N \eta_i^n \frac{\partial \hat{A}_i^n(q)}{\partial q} \eta_i^n + \frac{\partial \hat{A}_i^n(q)}{\partial q} \Gamma^{++n}(q) \eta_i^n - (I - \hat{A}_i^n(q)) \frac{\partial \Gamma^{+n}(q)}{\partial q} \hat{y}_i. \) The partial derivatives in \( \frac{\partial \Gamma^{+n}(q)}{\partial q} \) can be computed directly, while most of the work involved in computing the tensor \( \frac{\partial \hat{A}_i^n(q)}{\partial q} \) is already carried out at the same time that \( \hat{A}_i^n(q) \) is computed by using the sensitivity equations. Indeed, for \( t \geq 0 \) and \( q \in Q \), set \( \hat{A}_i^n(q; t) = e^{A_i^n(t)} \hat{y}_i. \) Then \( \Phi^m(q; \cdot) \) is the unique principal fundamental matrix solution to the initial value problem

\[(5.20) \quad \Phi^m(q; \cdot) = A_i^n(q) \Phi^m(q_1; \cdot), \quad \Phi^m(q; 0) = I. \]

Then setting \( \Psi^m(q; t) = \partial \Phi^m(q; t)/\partial q \), differentiating (5.20) with respect to \( q^n \), changing the order of differentiation, and using the product rule, we find that

\[
\Psi^m(q; t) = A_i^n(q) \Psi^m(q; t) + \left( \partial A_i^n(q)/\partial q \right) \Phi^m(q; t), \quad \Phi^m(q; 0) = 0.
\]

Combining this initial value problem with the one given in (5.20), we obtain

\[
\begin{bmatrix}
\frac{\partial A_i^n(q)}{\partial q} \\
A_i^n(q)
\end{bmatrix}
\begin{bmatrix}
\Phi^m(q; t) \\
\Phi^m(q; t)
\end{bmatrix}
= e^{A_i^n(t)}
\begin{bmatrix}
A_i^n(q) & \left( \partial A_i^n(q)/\partial q \right) \\
0 & \Phi^m(q; t)
\end{bmatrix}
\begin{bmatrix}
0 \\
I
\end{bmatrix}.
\]

Then, once this expression has been used to compute \( \frac{\partial A_i^n(q)}{\partial q} \) and \( \hat{A}_i^n(q) \), \( A_i^n(q) \) and \( \frac{\partial A_i^n(q)}{\partial q} \) are readily computed from (4.15). Having now calibrated the model with the estimation of the parameters \( q^* = [q_1^*, q_2^*] \), we formulate the inversion problem as a linear least squares fit to data with an added positivity constraint resulting in a reasonably standard linear-quadratic programming problem that has to be solved.

Let \( \hat{y}(t), t \in [0, T] \), denote the field TAC data for the drinking episode we want to de-convolve. Let \( T = \nu T \), let \( \{ \hat{y}_j \}_{j=0}^\nu \) denote a uniform sampling of \( \hat{y}(t) \), and let \( \{ \hat{u}_j \}_{j=0}^\nu \) denote the corresponding uniform sampling of the BAC or BrAC, \( \hat{u}(t), t \in [0, T] \), we hope to estimate. Let \( \{ \zeta_i \}_{i=0}^M \) denote a family of functions on \( [0, T] \) with the property that \( \sum_{i=0}^M \zeta_i(t) \geq 0, t \in [0, T] \) and only if \( a_i \geq 0, i = 1, 2, \ldots, M \). Once again, a class of functions that satisfy this condition is the unit height linear B-splines defined with respect to the uniform partition of the interval \( [0, T] \) given by \( \{ \zeta_i \}_{i=0}^M \). We then formulate the de-convolution problem as the constrained minimization problem of determining coefficients \( U_i^* \geq 0, i = 0, 1, 2, \ldots, M \), that minimizes

\[
J_D(\{ U_0, U_1, \ldots, U_M \}) = \sum_{i=0}^M \sum_{j=0}^{i-1} \frac{k_{i-1}}{\zeta_i(t)} \hat{y}_j - \hat{y}_j \big|_2 = \sum_{i=0}^M \sum_{j=0}^{i-1} C \left( A_i^n(q^*) \right)^{i-j-1} \left( I - A_i^n(q^*) \right) \Gamma^{+n}(q^*) \bigg|_2
\]

\[
\sum_{i=0}^M U_i(t) \zeta_i(j) \bigg|_2 \quad \text{where} \quad \hat{u}_j = \sum_{i=0}^M U_i(t) \zeta_i(j), t \in [0, T].
\]

Our optimal estimate for the BAC or BrAC signal \( \hat{u}(t) \) corresponding to TAC signal \( \hat{y}(t) \) is then given by \( \hat{u}(t) = \sum_{j=0}^\nu U_j(t) \zeta_j(t), \quad \text{for } t \in [0, T]. \)

To mitigate the effects of over-fitting (e.g., high amplitude and nonphysical excessive oscillations in \( \hat{u} \)) due to the inherent ill-posedness of the deconvolution problem, we augment the deconvolution performance index, \( J_D \), given above with regularization or penalty terms [1]. These terms are quadratic in the \( U_i^* \)s and are added to the expression for \( J_D \). The performance index for the deconvolution now becomes

\[
J_D,R(\{ U_0, U_1, \ldots, U_M \}) = J_D(\{ U_0, U_1, \ldots, U_M \})
\]

\[
+ r_1 \left( U_0, U_1, \ldots, U_M \right) R_1 \left( U_0, U_1, \ldots, U_M \right)^T
\]

\[
+ r_2 \left( U_0, U_1, \ldots, U_M \right) R_1 \left( U_0, U_1, \ldots, U_M \right)^T,
\]

where \( J_D \) is as given above, \( R_1 \) and \( R_2 \) are \( (M + 1) \times (M + 1) \) regularization matrices that capture, respectively, the magnitude and smoothness of the basis functions \( \{ \zeta_i \}_{i=0}^M \). (e.g. \( R_1 \) and \( R_2 \) are \( (M + 1) \times (M + 1) \) diagonal matrices that capture, respectively, the magnitude and smoothness of the basis functions \( \{ \zeta_i \}_{i=0}^M \).)

To estimate the regularization weights we further modify the calibration procedure and add a second calibration phase that uses the available alcohol challenge calibration data \( \{ \hat{u}, \hat{y} \} \) to optimally choose \( r_1 \) and \( r_2 \). This takes the form of a second calibration phase optimization wherein we choose nonnegative \( r_1^* \) and \( r_2^* \) which minimize
\[ J_{C,R}(r_1, r_2) = \sum_{i=0}^{N} \left\{ C \left( \hat{A}^n(q) \right)^{i-j-1} (\hat{A}^n(q') - I) \Gamma^{+n}(q') \hat{u}^*(j, r_1, r_2) - \hat{y}_i \right\}^2 + |\hat{u}^*(i, r_1, r_2) - \hat{u}_i|^2 \]

where \( \hat{u}^*(t, r_1, r_2) \) denotes the minimizer of \( J_D \) with \( \hat{y} = \hat{y} \) and regularization weights \( r_1 \) and \( r_2 \).

Once again, with regard to convergence, it can be argued that if \( \{ q^{n*} \}_{n=1}^{\infty} \) is any sequence of solutions to the calibration optimization problems, then there exists a convergent subsequence \( \{ q^{n_k*} \}_{k=1}^{\infty} \subseteq \{ q^{n*} \}_{n=1}^{\infty} \) with \( \lim_{k \to \infty} q^{n_k*} = q^* \) and \( q^* \) a solution to the calibration problem with the approximating convolution kernel replaced with the infinite dimensional convolution kernel given in (2.5). Also, in a similar manner, it can be argued that, if \( \{ u^{L_j*} \}_{j=1}^{\infty} \) is a sequence of solutions to the inversion problems with \( L_j = [n_j, M_j] \) satisfying \( n_j < n_{j+1} \) and \( M_j < M_{j+1}, j = 1, 2, \ldots \), then there exists a convergent subsequence \( \{ u^{L_{jk}*} \}_{k=1}^{\infty} \) with \( L_{jk} = [n_{jk}, M_{jk}], \lim_{k \to \infty} u^{L_{jk}*} = u^* \), \( \lim_{k \to \infty} u^{L_{jk}*} = u^* \), \( q^* \) a solution to the infinite dimensional calibration problem and \( u^* \) a solution to the infinite dimensional inversion problem.

### 6 Numerical Results

The second author wore a \textit{WrisTAS}™ sensor over an 18-day period simultaneously collecting breath measurements and maintaining a real-time drinking diary. The \textit{WrisTAS}™, worn like a digital watch, measures the local ethanol vapor concentration over the skin surface at 5-minute intervals. The subject wore the \textit{WrisTAS}™ while consuming her first drink in the laboratory with BrAC being recorded every 15 minutes until it returned to 0.00. The subject then wore the same \textit{WrisTAS}™ device in the field and consumed alcohol ad libitum for the following 17 days. For each drinking episode, the subject would take BrAC readings every 30 minutes until the BrAC returned to 0.00.

Figure 1 shows the entire 18 day TAC record along with the contemporaneous BrAC measurements. The TAC measurements provided by the sensor are in units of milligrams per deciliter (mg/dl), while the BrAC measurements are in units of percent alcohol. The results of the calibration using drinking episode 1 are shown in Figure 2. The upper panel shows the TAC along with the models prediction of the TAC. The lower panel shows the raw BrAC along with the estimated BrAC. In this case we found \( q_1^* = .17, q_2^* = 7.53, r_1^* = .10, \) and \( r_2^* = .11 \). Similar results were obtained using any one of the 11 drinking episodes shown in Figure 1. Across the 11 drinking episodes shown in Figure 1, the value of \( q_1^* \) ranged between 0.08 and 0.24 with mean 0.16 and standard deviation 0.05, \( q_2^* \) ranged between 5.30 and 14.98 with mean 9.17 and standard deviation 2.78, \( r_1^* \) ranged from 0.10 to 0.16 with mean 0.12 and standard deviation 0.02, and \( r_2^* \) ranged from 0.04 and 0.52 with mean 0.18 and standard deviation 0.17.

The calibrated discrete time convolution kernels corresponding to the 11 drinking episodes are plotted in Figure 3. The variance in the models suggests that a more sophisticated model than our two parameter diffusion equation may be in order. However, the fact that we were able to fit each individual drinking episode relatively well suggests that diffusion is the appropriate paradigm for the transdermal transport of ethanol from the blood through the skin to the TAC sensor.

![Figure 1: Complete TAC dataset with 11 distinct drinking episodes.](image1)

![Figure 2: Results of model calibration on drinking episode 1; Upper panel displays TAC while lower panel is estimated and measured BrAC.](image2)
11 drinking episodes shown in Figure 1. In Figure 4 we show the estimated BrAC curve for drinking episode 11. For comparison, we have also plotted the BrAC and TAC measurements and the BrAC curves obtained using other methods including one that estimates BrAC from drink diary data (DD BrAC) [5], and the BrAC curve obtained using episode 11 for calibration (Cal BrAC).

For each of three different statistics (ones which are of particular interest to alcohol researchers) (peak BrAC (P), time of peak BrAC (T), and area under the BrAC curve (A)), we computed the relative absolute difference between the breathalyzer collected BrAC data and estimated BrAC computed by one of three different methods: $M_1$ the deconvolution scheme developed here, $M_2$ deconvolution but using the model calibrated on the drinking episode being deconvolved and $M_3$ the Matthews and Miller [5] formula for estimating BrAC from drinking dairy data. Note that of the three methods, only the first uses only the TAC data and no other information collected in the field. The means across the 11 drinking episodes for the three statistics and the three methods are shown in Table 1.

![Figure 3: Discrete time convolution kernels resulting from calibration using the 11 distinct drinking episodes in the dataset shown in Figure 1.](image1)

![Figure 4: Deconvolution of BrAC for drinking episode 11 using model calibrated using drinking episode 1.](image2)

Table 1: Comparison of three methods for estimation BrAC from field data

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<tr>
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<th>$M_1$</th>
<th>$M_2$</th>
<th>$M_3$</th>
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<td>P</td>
<td>.33</td>
<td>.11</td>
<td>.28</td>
</tr>
<tr>
<td>T</td>
<td>.09</td>
<td>.09</td>
<td>.05</td>
</tr>
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<td>A</td>
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<td>.01</td>
<td>.36</td>
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Our results indicate that our approach is a relatively effective tool for obtaining semi-quantitative and relatively consistent measure of BrACs from TAC devices with low real-time subject burden.

References


