# Blind Deconvolution for Distributed Parameter Systems with Unbounded Input and Output and Determining Blood Alcohol Concentration from Transdermal Biosensor Data(1) 

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#### Abstract

We develop a blind deconvolution scheme for input-output systems described by distributed parameter systems with boundary input and output. An abstract functional analytic theory based on results for the linear quadratic control of infinite dimensional systems with unbounded input and output operators is presented. The blind deconvolution problem is then reformulated as a series of constrained linear and nonlinear optimization problems involving infinite dimensional dynamical systems. A finite dimensional approximation and convergence theory is developed. The theory is applied to the problem of estimating blood or breath alcohol concentration (respectively, BAC or BrAC ) from biosensor-measured transdermal alcohol concentration (TAC) in the field. A distributed parameter model with boundary input and output is proposed for the transdermal transport of ethanol from the blood through the skin to the sensor. The problem of estimating BAC or BrAC from the TAC data is formulated as a blind deconvolution problem. A scheme to identify distinct drinking episodes in TAC data based on a Hodrick Prescott filter is discussed. Numerical results involving actual patient data are presented.


## Keywords

Blind Deconvolution; Distributed Parameter Systems; Unbounded Input and Output; Blood Alcohol Concentration; Transdermal Alcohol Biosensor

## 1. Introduction

A linear input-output model or system of the form

$$
y(t)=(L u)(t)=\int_{0}^{t} K(t-\tau) u(\tau) d \tau
$$

is known as a convolution or convolution integral. We say the output signal $y(t)$ is the result of convolving the input signal, $u(t)$, with the (typically, but not exclusively nonnegative)

[^0]convolution kernel, filter, or impulse response function $K(t)$. Such a model naturally arises as a result of the variation of constants formula when the underlying dynamics of the system are governed by a time invariant linear system of (ordinary, partial, or functional)
differential equations. In this context, the convolution kernel involves either a scalar or matrix exponential in the case of a finite dimensional system (e.g., the underlying system is either one, or a system of, ordinary differential equation(s)), or in the case of an infinite dimensional or distributed parameter system (e.g., when the underlying system is one, or a system of, functional or partial differential equation(s)), a semigroup of bounded linear operators on the underlying infinite dimensional state space.

It is frequently the case in applications that the output signal, $y(t)$, given by $(1.1)$ is known, measured, or observed, and one wants to determine the input signal, $u(t)$, that produced it. This is known as the deconvolution problem; formally, it is the problem of mathematically inverting the linear transformation $L$ which can be written as $u(t)=\left(L^{-1} y\right)(t)$. In general, this inversion or deconvolution tends to be both mathematically and computationally ill-posed and challenging since the forward process involves filtering with its inherent loss of information. In actual practice, of course, the entire continuous output signal $y(t)$ will not be known for every $t \geq 0$. Rather, we will have a discrete sampling of $y$ in the form $y_{i}=y(i \tau), i$ $=0,1,2, \ldots$, for some sampling time $\tau>0$. In this case, the convolution integral, (1.1), is replaced by its discrete time form as a convolution sum as

$$
\begin{equation*}
y_{i}=\sum_{j=0}^{i-1} \widehat{K}_{i=j} u_{j} . \tag{1.2}
\end{equation*}
$$

The deconvolution problem now takes the form: Given the $y_{i}$ 's, determine an input signal, $u(t)$, such that (1.2) is satisfied where $u_{i}=u(i \tau), i=0,1,2, \ldots$, and $\widehat{K}_{i}$ is a (typically nonnegative) discrete filter or convolution kernel.

In addition, in many applications, the deconvolution problem that has to be solved is blind in that an analytic or numerical representation for the convolution filter or kernel, $K$ or $\widehat{K}$, is unknown or unavailable. Consequently, before the deconvoluion problem can be solved, the kernel $K$ or $\widehat{K}$ must be estimated. The work we present here is motivated by a particular blind deconvolution problem involving a portable wearable biosensor that measures the alcohol (or more precisely, ethanol) content in perspiration.

Approximately $1 \%$ of alcohol consumed by humans is excreted through the skin (Swift, [1]). Alcohol emitted through the skin can be measured and correlated to blood or breath alcohol concentration (BAC or BrAC). Transdermal alcohol sensing, when applied and interpreted properly, may be a useful method for monitoring BACs over relatively long periods of time (Swift and Swette, [2]). Several devices, including the WrisTAS ${ }^{\text {TM }}$ (Giner, Inc., Newton, MA) and SCRAM© (Alcohol Monitoring Systems, Inc., Denver, CO), have been developed to measure transdermal alcohol concentration (TAC) at essentially continuous rates for weeks at a time. Although data from TAC sensors have been shown to correlate with alcohol consumption and BrACs, to date, TAC sensors have primarily been used as abstinence monitors.

There is considerable interest in developing a mathematical model based approach for extracting estimates of BAC or BrAC from TAC signals collected in the field. Now even though TAC sensors are bench calibrated, a high degree of variance in their measurements of transdermal alcohol is observed from device to device and from subject to subject. This may be a result of the fact that, at least at present, the devices are handmade, or that they are highly sensitive to external sources of alcohol, or that the exchange of ethanol between body
water and the environment through the multiple layers of the skin is subject to more variability from individual to individual than is ethanol exchange in the lungs between the blood and exhaled $\mathrm{CO}_{2}$. Indeed, a breath analyzer measures BrAC by relying on a relatively simple model from elementary chemistry (i.e., Henry's Law) for the exchange of gases between circulating pulmonary blood and alveolar air involving a single parameter known as the partition ratio or coefficient (Labianca, [3]) which is reasonably robust and is presumed to not require calibration to each individual. TAC sensors and TAC models, on the other hand, involve a number of parameters that can vary significantly from subject to subject and device to device. Another problem is that, although it is not surprising that the BAC (and therefore, the BrAC ) and TAC signals are highly correlated, the observed TAC signal is in fact the result of passing the BAC signal through a low pass filter, to wit, the skin. Consequently, in comparing contemporaneous BrAC and TAC measurements we typically, but not consistently, observe that peaks have been attenuated and displaced.

As a part of this study, we develop a comprehensive first principles mathematical model based data analysis system that produces estimates of BAC or BrAC from TAC data collected by TAC sensors. The system is based on a forward model for the transport of ethanol from the blood through the skin to the TAC sensor, and its oxidation by the TAC sensor in the form of a Fick's Law based diffusion process for ethanol molecules through the interstitial fluid in the epidermal layer of the skin with input and output on the boundary (see, for example, Okubo, [4], Anderson and Hlastala, [5], and Dumett et al., [6]). To extract BAC or BrAC from TAC data, the model must first be calibrated to the device being worn and to the individual being tested. In this calibration phase, simultaneous BrAC and TAC measurements are obtained during a laboratory alcohol challenge session. These data are then used to fit parameters in the forward model to the individual subject being tested and to the particular TAC unit being worn. At this point the subject is sent out into the field wearing the TAC sensor for a period as long as two weeks. Under normal circumstances, while in the field the subject does not take breath measurements or maintain a drinking diary of the number of standard drinks they consumed or when they consumed them. Then, when the subject has returned from the field and the TAC measurements have been downloaded from the sensor, the fit model and mathematical inversion techniques are used to first identify individual drinking episodes and to then produce estimates for BrAC or BAC from the TAC data collected during the period that subject wore the sensor in the field.

The forward model is a linear time invariant initial-boundary value problem for a parabolic partial differential equation with unknown diffusivity and boundary gains. The input is the BAC or BrAC signal which we want to determine and the output is the TAC signal measured by the sensor. Consequently, the problem of estimating the BAC or BrAC signal from measurements of TAC can be formulated as a deconvolution problem in which, as a result of the unknown parameters in the model, the convolution filter or kernel is unknown. To wit, we have a blind deconvolution problem. Moreover, since the BAC or BrAC input and the TAC output are on the boundary, the input and output operators in the resulting abstract formulation of the model are unbounded with respect to the natural state space for the problem. Indeed, the input operator will have range in a space larger than the natural state space and the output operator will have domain in a space smaller than the natural state space.

Our approach to solving the blind deconvolution problem is to reformulate it as a series of constrained optimization problems. First, we use the data from the alcohol challenge session to fit the unknown parameters in the underlying distributed parameter model (see, for example, Banks and Kunisch, [7] or Banks and Ito, [8]). This takes the form of a nonlinear least squares fit to data which serves to estimate the unknown convolution filter. The subsequent deconvolution of the field BAC or BrAC from the field TAC is then formulated
as a regularized linear least squares fit to data with nonnegativity constraints. This optimization problem takes the form of a quadratic programming problem (see, for example, Bertsekas, [9] and Bradley et al., [10]). A third optimization problem, together with the alcohol challenge data, is used to optimally estimate the regularization parameters. To enhance the accuracy and efficiency of the deconvolution process, we pre-process the field TAC signal to identify individual drinking episodes that can be deconvolved separately. Our scheme is based on the Hodrick Prescott filter (see, for example, Brauer, et al, [11], Hodrick and Prescott, [12], Ley, [13], or Danthine and Girardin, [14]), which itself takes the form of an optimization problem.

An outline of the remainder of the paper is as follows. In Section 2 we rely on results from the theory of linear quadratic control of infinite dimensional systems with unbounded input and output (see, for example, Curtain and Salamon, [15], Pritchard and Salamon, [16], Gibson and Rosen, [17], and Banks and Ito, [18]) to come up with an abstract functional analytic formulation for the class of distributed parameter systems with input and output on the boundary of interest to us here. In Section 3 we formulate the optimization problems that form the basis for our approach to solving the blind deconvolution problem. We also develop an abstract finite dimensional approximation and convergence theory. In Section 4 we derive the first principles mathematical model for the transdermal alcohol biosensor problem of interest to us here and the associated blind deconvolution problem of estimating BAC or BrAC from TAC data. We then show how the abstract theory developed in Sections 2 and 3 can be applied to solve it. In Section 5 we present a sampling of the results from our numerical studies. We present the results of testing our approach as well as comparing it to other methods (Carey and Hustad, [19], Hustad and Carey, [20], Matthews and Miller, [21], National Highway Traffic Safety Administration, [22]) for estimating BAC or BrAC in the field. A final sixth section has some discussion, conclusions, and suggested avenues for further research.

## 2. Discrete Time Distributed Parameter Systems with Unbounded Input and Output

### 2.1. The Abstract Initial-Boundary Value Problem with Unbounded Input and Output

We consider a class of distributed parameter initial-boundary value problems that have been studied earlier in the context of linear quadratic control (see, for example, Curtain and Salamon [15] and Gibson and Rosen [17]). Let $W, V$, and $H$ be Hilbert spaces such that $W, V \hookrightarrow H$ with the embeddings dense and continuous. Taking $H$ as the pivot space, it then follows that $V \hookrightarrow H \hookrightarrow V^{*}$ and $W \hookrightarrow H \hookrightarrow W^{*}$, with the dual embeddings again dense and continuous. Let $Q$ be a compact subset of $R^{\rho}$, for each $q \in Q$ let $\Delta(q) \in \mathscr{L}(W, H)$, $\Gamma(q) \in \mathscr{L}\left(W, R^{\mu}\right)$, and $\mathrm{C}(q) \in \mathscr{L}\left(V, R^{\nu}\right)$, and consider the distributed parameter system with, in general, unbounded input and output given by

$$
\begin{gathered}
\dot{\varphi}(t)=\Delta(q) \varphi(t), \quad t>0, \\
\varphi(0)=\varphi_{0}, \\
\Gamma(q) \varphi(t)=u(t), \quad t>0, \\
y(t)=C(q) \varphi(t), \quad t>0,
\end{gathered}
$$

where $\phi_{0} \in H$, and $u \in L_{2}^{\mu}(0, T)$. We say that this system has unbounded input and output since, in general, the linear operators $\Gamma(q)$ and $\mathrm{C}(q)$ are unbounded or not continuous with respect to the $H$ norm, $H$ being the natural state space in which to formulate the problem.

### 2.2. Re-Formulation as an Abstract Evolution Equation

We require the following additional assumptions on the operators $\Delta(q)$ and $\Gamma(q)$ : We assume that $\Gamma(q)$ is surjective and that its null space, $\mathbb{N}(\Gamma(q))=\{\psi \in W: \Gamma(q) \psi=0\}$ is dense in H , and that the operator $A(q): \operatorname{Dom}(A(q)) \subseteq H \rightarrow H$ defined by $\operatorname{Dom}(A(q))=\mathbb{N}(\Gamma(q))$, $A(q) \psi=\Delta(q) \psi, \psi \in \mathbb{N}(\Gamma(q))$, is closed, densely defined and has nonempty resolvent set. We assume further that for each $T>0$, all $\phi_{0} \in W$, and $u \in C^{1}\left(0, T ; R^{\mu}\right)$ with $\Gamma(q) \phi_{0}=u(0)$, there exists a unique function $\varphi \in C(0, T ; W) \cap C^{1}(0, T ; H)$ that depends continuously on $\phi_{0}$ and $u$ and that satisfies (2.1)-(2.3) on [0,T].

Under these assumptions, it can be shown (see Hille and Phillips, [23]) that the operator $A(q)$ defined above is the infinitesimal generator of a $\mathrm{C}_{0}$ semigroup, $\left\{e^{A(q) t}: t \geq 0\right\}$ of bounded linear operators on $H$. However, as a result of the unboundedness of the operators $\Gamma(q)$ and $\mathrm{C}(q)$ with respect to $H$, the existence of this semigroup on $H$ as it stands is not sufficient to define even a mild solution to (2.1)-(2.3) and to make sense of the output given in (2.4). To do this we must extend this semigroup to a larger space than $H$.

Since the operator $A(q)$ is densely defined, closed, and the infinitesimal generator of a $\mathrm{C}_{0}$ semigroup on $H$, it has an adjoint operator, $A(q)^{*}: \operatorname{Dom}\left(A(q)^{*}\right) \subseteq H \rightarrow H$, that is densely defined and closed (see, for example, Helmberg, [24]). Define the space $Z^{*}$ to be the Hilbert space $\operatorname{Dom}\left(A(q)^{*}\right)$ endowed with the graph Hilbert space norm associated with the operator $A(q)^{*}$. It follows (see Curtain and Salamon, [15]) that $Z^{*} \hookrightarrow H \hookrightarrow Z$. That is, the space $Z^{*}$ is embedded in $H$ with the embedding dense and continuous and therefore $H$ is densely and continuously embedded in the space $Z$ defined to be the dual of the space $Z^{*}$. The
semigroup, $\left\{e^{A(q) t}: t \geq 0\right\}$, can now be uniquely extended to a $C_{0}$ semigroup $\left\{e^{\widetilde{A}(q) t}: t \geq 0\right\}$ of bounded linear operators on Z . The infinitesimal generator is the extension of the operator $A(q)$ to an operator $\widetilde{A}(q): H \subseteq Z \rightarrow Z$ in $\mathscr{L}(H, Z)$ defined by the expression

$$
\langle\tilde{A}(q) \psi, \zeta\rangle_{z, \operatorname{Dom}\left(A(q)^{*}\right)}=\left\langle\psi, A(q)^{*} \zeta\right\rangle_{H}
$$

for $\psi \in \operatorname{Dom}(\widetilde{A}(q))=H$, and $\zeta \in \operatorname{Dom}\left(A(q)^{*}\right)=Z^{*}$. In this expression, $\langle\cdot, \cdot\rangle_{Z, \operatorname{Dom}\left(A(q)^{*}\right)}$ denotes the duality pairing between the space $Z^{*}=\operatorname{Dom}\left(A(q)^{*}\right)$ and its dual $Z$.

For each $q \in Q$, let $\Gamma^{+}(q) \in \mathscr{L}\left(R^{\mu}, W\right)$ denote any right inverse of $\Gamma(q) \in \mathscr{L}\left(W, R^{\mu}\right)$ (recall $\Gamma(q)$ was assumed to be surjective) and define $\widetilde{B}(q) \in \mathscr{L}\left(R^{\mu}, Z\right)$ by

$$
\tilde{B}(q)=(\Delta(q)-\tilde{A}(q)) \Gamma^{+}(q)
$$

Note that $\dot{B(\tilde{q})}$ is well defined since, if $\Gamma_{1}^{+}(q)$ and $\Gamma_{2}^{+}(q)$ are two right inverses of $\Gamma(q)$, then Range $\left(\Gamma_{1}^{+}(q)-\Gamma_{2}^{+}(q)\right) \subseteq \mathbb{N}(\Gamma(q))$ and hence $\tilde{B_{1}} \tilde{(q)}=B_{2} \tilde{(q)}$ since $\tilde{A}(q)=\Delta(q)$ on
$\mathbb{N}(\Gamma(q))$. Following Curtain and Salamon, [15] we define the mild solution to the initial boundary value problem (2.1)-(2.3) to be the mild solution to the abstract initial value problem (IVP) in Z given by

$$
\begin{equation*}
\dot{\varphi}(t)=\tilde{A}(q) \varphi(t)+\tilde{B}(q) u(t), \quad t>0, \quad \varphi(0)=\varphi_{0} \tag{2.5}
\end{equation*}
$$

that is

$$
\begin{equation*}
\varphi(t)=e^{\tilde{A}(q) t} \varphi_{0}+\int_{0}^{t} e^{\tilde{A}(q)(t-s)} \tilde{B}(q) u(s) d s, \quad t \geq 0 \tag{2.6}
\end{equation*}
$$

Curtain and Salamon have shown that $\phi$ given by (2.6) satisfies $\varphi \in C([0, T], H) \cap H^{1}((0, T), Z)$.

In order to make sense of the output equation (2.4), additional assumptions are required. Indeed, we must assume that the operators $e^{\tilde{A}(q) t}$, for $t>0$, have range in $V$, and that

$$
\int_{0}^{t} e^{\tilde{A}(q)(t-s)} \tilde{B}(q) u(s) d s \quad \in V \quad \text { for } \quad t>0
$$

We note that these assumptions will typically require additional assumptions on the operators $\Delta(q)$ and $\Gamma(q)$, the initial data $\phi_{0}$ and/or the input $u$. We will say more about this when we consider abstract parabolic systems in Section 4 below. When these additional assumptions hold, we have

$$
y(t)=C(q) e^{\tilde{A}(q) t} \varphi_{0}+C(q) \int_{0}^{t} e^{\tilde{A}(q)(t-s)} \tilde{B}(q) u(s) d s . \quad t \geq 0
$$

The integral in (2.6) and (2.7) is in $Z$. Consequently, in general, the operator $C(q)$ can not be passed around the integral sign in (2.7) unless it is closed with respect to the $Z$ norm.
Typically, in the case of deconvolution problems, 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, $i=1,2, \cdots, \mu$, then the $\mathrm{i}, \mathrm{j}$-th entry in the $v \times \mu$ matrix function

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

gives the response at time $t>0$ of the system's i-th output channel to a unit impulse in the system's j-th input channel.

### 2.3. The Discrete or Sampled Time Formulation

In this paper, we are primarily concerned with discrete time or sampled systems. Toward this end 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

$$
\psi_{i}(t)=\varphi(t)-\Gamma^{+}(q) u_{i}, \quad \text { for } \quad t \in[i \tau,(i+1) \tau], \quad i=0,1,2, \ldots
$$

Then, since

$$
\dot{\psi}_{i}(t)=\dot{\varphi}(t)=\tilde{A}(q) \varphi(t)+\tilde{B}(q) u_{i}=\tilde{A}(q) \psi_{i}(t)+(\tilde{A}(q)+\tilde{B}(q) \Gamma(q)) \Gamma^{+}(q) u_{i}
$$

$\psi_{i}$ satisfies the initial value problem

$$
\begin{align*}
\psi_{i}(t) & =\tilde{A}(q) \psi_{i}(t)+\Delta(q) \Gamma^{+}(q) u_{i}, \quad t \in(i \tau,(i+1) \tau) \\
\psi_{i}(i \tau) & =\varphi_{i}-\Gamma^{+}(q) u_{i} \tag{2.9}
\end{align*}
$$

The solution to the IVP (2.9) can be obtained from the variation of constants formula (2.6) 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 (see, for example, Pazy, [25]). Thus we obtain

$$
\begin{aligned}
\varphi_{i+1} & =\psi_{i}((i+1) \tau)+\Gamma^{+}(q) u_{i} \\
& =e^{\tilde{A}(q) \tau}\left(\varphi_{i}-\Gamma^{+}(q) u_{i}\right)+\int_{0}^{\tau} e^{\tilde{A}(q) s} \Delta(q) \Gamma^{+}(q) u_{i} d s+\Gamma^{+}(q) u_{i} \\
& =e^{A(q) \tau} \varphi_{i}+\left(I-e^{A(q) \tau}\right) \Gamma^{+}(q) u_{i}+\int_{0}^{\tau} e^{A(q) s} \Delta(q) \Gamma^{+}(q) u_{i} d s,
\end{aligned}
$$

or that

$$
\varphi_{i+1}=\tilde{A}(q) \varphi_{i}+\tilde{B}(q) u_{i}, \quad i=0,1,2, \ldots \varphi_{0} \in H,
$$

where $\widetilde{A}(q)=e^{A(q) \tau} \in \mathscr{L}(H, H)$ and

$$
\begin{equation*}
\widehat{B}(q)=\left(I-e^{A(q) \tau}\right) \Gamma^{+}(q)+\int_{0}^{\tau} e^{A(q) s} \Delta(q) \Gamma^{+}(q) d s \in \mathscr{L}\left(R^{\mu}, H\right) \tag{2.11}
\end{equation*}
$$

It is not difficult to show (see Gibson and Rosen, [17]) that, as in the continuous time case, the operator $\hat{B(q)}$ is well defined and does not depend on the particular choice of $\Gamma^{+}(q)$. It can also be shown that $\widehat{B}(q)=\int_{0}^{\tau} e^{A(q) s} \widetilde{B}(q) d s$ 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 Range $\left(\Gamma^{+}(q)\right) \in \mathbb{N}(\Delta(q))$, then the expression for $B(\hat{q})$ given in (2.11) simplifies to become

$$
\widehat{B}(q)=\left(I-e^{A(q) \tau}\right) \Gamma^{+}(q) .
$$

Once again, as in the continuous time case, making sense of the output equation (2.4) in the discrete time case requires additional assumptions. In general, you would want it to be true that $\hat{A}(q)=e^{A(q) \tau} \in \mathscr{L}(V, V), \widehat{B}(q) \in \mathscr{L}\left(R^{\mu}, V\right)$ and $\phi_{0} \in V$. Note that, in the simplified case in which Range $\left(\Gamma^{+}(q)\right) \in \mathbb{N}(\Delta(q))$, it is enough to require that $\widehat{A}(q)=e^{A(q) \tau} \in \mathscr{L}(V, V)$, Range $\left(\Gamma^{+}(q)\right) \in V$, and $\phi_{0} \in V$. In this case, with $\phi_{0}=0$, we find from (2.10) that the output sequence $y_{i}, \mathrm{t}=0,1,2, \ldots$, is given by

$$
\begin{equation*}
y_{i}=\sum_{j=0}^{i-1} C(q) \widehat{A}(q)^{i-j-1} \widehat{B}(q) u_{j}=\sum_{j=0}^{i-1} C(q) \widehat{A}(q)^{i-j-1}(I-\widehat{A}(q)) \Gamma^{+}(q) u_{j} \tag{2.12}
\end{equation*}
$$

$i=0,1,2, \ldots$, with the discrete or sampled time response at time $t=i \tau$ of the system's i-th output channel to a unit impulse in the system's j -th input channel given by the $\mathrm{i}, \mathrm{j}$-th entry in the $v \times \mu$ matrix function

$$
\begin{equation*}
\widehat{K}(t ; q)=C(q) \widehat{A}(q)^{[t / \tau]-1} \widehat{B}(q)=C(q) \widehat{A}(q)^{[t / \tau]^{-1}}(1-\widehat{A}(q)) \Gamma^{+}(q), \quad t \geq \tau \tag{2.13}
\end{equation*}
$$

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

## 3. The Blind Deconvolution Problem and Abstract Approximation Theory

### 3.1. The Calibration and Deconvolution Problems

We formulate the blind deconvolution problem in two phases: a training or calibration phase, ( $\mathbf{T}$ ), in which the convolution kernel or filter and regularization parameters used in the deconvolution phase are estimated using specifically designated training or calibration data, and a deconvolution phase, (D), in which the estimated kernel and regularization parameters are used to deconvolve the input from the output data that has been provided. In the case of the training phase we assume that training data of the form $\left\{\tilde{y}_{i}, \tilde{u}_{i}\right\}_{i=0}^{n}$ is given where both the $\tilde{y}_{i} \in R^{v}$ and the $\tilde{u}_{i} \in R^{\mu}$ have been uniformly sampled from continuous time signals, $\tilde{y}$ and $\tilde{u}$, respectively, with sampling time $\tau>0$. That is, $\tilde{y}_{i}=\tilde{y}(i \tau)$ and $\tilde{u}_{i}=\tilde{u}(i \tau), i$ $=0,1,2, \ldots, n$. We assume that the system was initially at rest (i.e., that $\phi_{0}=0$ ) and formulate the training or calibration phase as an optimization problem in the form of a nonlinear least squares fit to data.
(T) Find $q^{*} \in Q$ which minimizes the quadratic performance index

$$
J_{T}(q)=\sum_{i=0}^{n}\left\|y_{i}-\tilde{y}_{i}\right\|^{2}
$$

where the $\left\{y_{i}\right\}_{i=0}^{n}$ are given by (2.12) with $u_{i}=\widetilde{u}_{i}, i=0,1,2, \ldots, n$, or equivalently, by

$$
\varphi_{i+1}=\widehat{A}(q) \varphi_{i}+\widehat{B}(q) \tilde{u}_{i}, \quad \varphi_{0}=0, \quad y_{i}=C(q) \varphi_{i}, \quad i=0,1,2, \ldots, n-1
$$

For the deconvolution phase we assume that we have been given output data of the form $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}$ with $\hat{y}_{i} \in R^{v}$ and let $U$ denote a compact subset of $C^{\mu}[0, T]$. Once again, we formulat the deconvolution problem as constrained nonlinear least squares fit to data.
(D) Find $u^{*} \in U$ which minimizes the quadratic performance index

$$
\begin{equation*}
J_{D}(u)=\sum_{i=0}^{m}\left\|y_{i}-\widehat{y}_{i}\right\|^{2} \tag{3.2}
\end{equation*}
$$

where the $\left\{y_{i}\right\}_{i=0}^{n}$ are given by (2.12) with $u_{i}=u(i \tau), i=0,1,2, \ldots, n$ and $q=q^{*}$, or equivalently

$$
\begin{equation*}
\varphi_{i+1}=\widehat{A}\left(q^{*}\right) \varphi_{i}+\widehat{B}\left(q^{*}\right) u(i \tau), \quad \varphi_{0}=0, \quad y_{i}=C\left(q^{*}\right) \varphi_{i}, \quad i=0,1,2, \ldots, m-1 \tag{3.3}
\end{equation*}
$$

### 3.2. Finite Dimensional Approximation and Convergence

The optimization problems (T) and (D) above would have to be solved numerically. And while the constraints given in (3.1) and (3.3) are discrete time, they are still infinite dimensional operator equations and, consequently, require finite dimensional approximation.

For each $N=1,2, \ldots$, let $H^{N}$ denote a finite dimensional subspace of $V$ with basis $\left\{\psi_{j}^{N}\right\}_{j=0}^{M^{N}}$ with the property that for every $\psi \in V$, there exists $\psi^{N} \in H^{N}$ such that $\lim _{N \rightarrow \infty} \psi^{N}=\psi$ in $V$. For each $q \in Q$ and $N=1,2, \ldots$, let $A^{N}(q) \in \mathscr{L}\left(H^{N}, H^{N}\right)_{\text {satisfy }}$
i. There exist constants $M$ and $\omega$, independent of $N$ such that

$$
\left|e^{A^{N}(q) t}\right|_{\mathscr{L}\left(H^{N}, H^{N}\right)} \leq M e^{\omega t}, t \geq 0 .
$$

ii.

For every sequence $\left\{q^{N}\right\}_{N=1}^{\infty} \in Q$ with $\lim _{N \rightarrow \infty} q^{N}=q$, there exists $\lambda \in \rho(A(q)) \cap \rho\left(A^{N}\left(q^{N}\right)\right)$ with $\operatorname{Re} \lambda>\omega$ such that $\lim _{N \rightarrow \infty} R_{\lambda}\left(A^{N}\left(q^{N}\right)\right) P^{N} \psi=R_{\lambda}(A(q)) \psi$ in $V$, for each $\psi \in V$, where $\rho(A)$ denotes the resolvent set of a linear operator $A, R \lambda(A)=(\lambda-A)^{-1}$ denotes the resolvent operator of a linear operator $A$ at $\lambda \in \rho(A)$, and $P^{N}$ denotes the orthogonal projection of $V$ on to $H^{N}$ with respect to either the $V$ or $H$ inner products.
Assumptions (i) and (ii) are a version of the hypotheses of the well-known Trotter Kato semigroup approximation theorem (see, for example, Pazy, [25], Kato [26], or Banks and Ito, [8]). Consequently, we have $\lim _{N \rightarrow \infty} e^{A^{N}\left(q^{N}\right) t} P^{N} \psi=e^{A(q) t} \psi$ in $V$ for each $\psi \in V$ uniformly in $t$ for $t \geq 0$ in compact subintervals of $R$ whenever $\left\{q^{N}\right\}_{N=1}^{\infty} \in Q_{\text {with }}$ $\lim _{N \rightarrow \infty} q^{N}=q$.

For each $q \in Q$ and $N=1,2, \ldots$, we set

$$
\begin{aligned}
& \widehat{A}^{N}(q)=e^{A^{N}(q) \tau} \in \mathscr{L}\left(H^{N}, H^{N}\right) \\
& \widehat{B}^{N}(q)=\left(1-\widehat{A}^{N}(q)\right) P^{N} \Gamma^{+}(q)+\int_{0}^{\tau} e^{A^{N}(q) s} P^{N} \Delta(q) \Gamma^{+}(q) d s \in \mathscr{L}\left(R^{\mu}, H^{N}\right),
\end{aligned}
$$

and consider the finite dimensional linear discrete time systems

$$
\varphi_{i+1}^{N}=\widehat{A}^{N}(q) \varphi_{i}^{N}+\widehat{B}^{N}(q) u_{i}, \quad \varphi_{0}^{N}=0, \quad y_{i}^{N}=C(q) \varphi_{i}^{N} \quad i=0,1,2, \ldots
$$

It follows that $\lim _{N \rightarrow \infty} \widehat{A}^{N}\left(q^{N}\right) P^{N} \psi=\widehat{A}(q) \psi$ in $V$ for each $\psi \in V$,
$\lim _{N \rightarrow \infty} \widehat{B}^{N}\left(q^{N}\right) v=\widehat{B}(q) v$, for each $v \in R^{\mu}, \lim _{N \rightarrow \infty} K^{N}\left(t, q^{N}\right)=K(t ; q)$, and $\lim _{N \rightarrow \infty} \widehat{K}^{N}\left(t, q^{N}\right)=\widehat{K}(t ; q)$ uniformly in $t$ for $t \geq 0$ in compact subintervals of $R$ whenever $\left\{q^{N}\right\}_{N=1}^{\infty} \in Q_{\text {with }} \lim _{N \rightarrow \infty} q^{N}=q$, where $K(t ; q)$ and $\widehat{K}(t ; q)$ are given by (2.8) and (2.13), respectively, and both $K^{N}\left(t, q^{N}\right)$ and $\widehat{K}^{N}\left(t ; q^{N}\right)$ are given by the obvious modifications of those expressions.

We consider the sequence of approximating optimization problems, $\left(\mathbf{T}^{\mathrm{N}}\right)$, defined analogously to problem (T) as follows.
$\left(\mathbf{T}^{\mathrm{N}}\right)$ Find $q^{N^{*}} \in Q$ which minimizes the quadratic performance index

$$
J_{T}^{N}(q)=\sum_{i=0}^{n}\left\|y_{i}^{N}-\tilde{y}_{i}\right\|^{2}
$$

where the $\left\{y_{i}^{N}\right\}_{i=0}^{n}$ are given by (3.4) with $u_{i}=\tilde{u}_{i}, i=0,1,2, \ldots, n$.
In the case of problem (D), there is the additional complexity that the feasible set is also a subset of an infinite dimensional space. Consequently, we introduce a second level of approximation. For each $M=1,2, \ldots$, let $U^{M}$ denote a finite dimensional subspace of $C^{\mu}[0$, $T]$ with basis $\left\{\xi_{j}^{M}\right\}_{j=0}^{M^{M}}$, let $L$ denote the multi-index $L=[N, M]$, and consider the sequence of approximating optimization problems $\left(\mathbf{D}^{\mathbf{L}}\right)$
$\left(\mathbf{D}^{\mathbf{L}}\right)$ Find $u^{L *} \in U \cap U^{M}$ which minimizes the quadratic performance index

$$
\begin{equation*}
J_{D}^{L}\left(u^{M}\right)=\sum_{i=0}^{m}\left\|y_{i}^{L}-\widehat{y}_{i}\right\|^{2} \tag{3.5}
\end{equation*}
$$

where the $\left\{y_{i}^{L}\right\}_{i=0}^{n}$ are given by

$$
\begin{equation*}
\varphi_{i+1}^{L}=\widehat{A}^{N}\left(q^{N *}\right) \varphi_{i}^{L}+\widehat{B}^{N}\left(q^{N *}\right) u^{M}(i \tau), \quad \varphi_{0}^{L}=0, \quad y_{i}^{L}=C\left(q^{N *}\right) \varphi_{i}^{L} \quad i=0,1,2, \ldots \tag{3.6}
\end{equation*}
$$

and where $q^{N^{*}}$ in (3.6) is a solution to problem ( $\mathrm{T}^{\mathrm{N}}$ ) and $u^{M} \in U \cap U^{M}$.
Under the assumptions we have made above, using what are by now familiar arguments (see
Banks and Kunisch, [7]), it can be argued that if $\left\{q^{N *}\right\}_{N=1}^{\infty}$ is any sequence of solutions to the training optimization problems, $\left(\mathbf{T}^{\mathbf{N}}\right)$, then there exists a convergent subsequence $\left\{q^{N_{k} *}\right\}_{k=1}^{\infty} \subseteq\left\{q^{N *}\right\}_{N=1}^{\infty}$ with $\lim _{k \rightarrow \infty} q^{N_{k} *}=q^{*}$ and $q^{*}$ a solution to problem (T). Also, in a similar manner, it can be argued that, if $\left\{u^{L_{j} *}\right\}_{j=1}^{\infty}$ is a sequence of solutions to the deconvolution problems $\left(\mathbf{D}^{\mathbf{L j}}\right)$ with $L_{j}=\left[N_{j}, M_{j}\right]$ satisfying $N_{j}<N_{j+1}$ and $M_{j}<M_{j+1}, j=$ $1,2, \ldots$, then there exists a convergent subsequence $\left\{u^{L_{j_{k}}} *\right\}_{k=1}^{\infty}$ with $L_{j_{k}}=\left[N_{j_{k}}, M_{j_{k}}\right]$, $\lim _{k \rightarrow \infty} q^{N_{j_{k}}}{ }^{*}=q^{*}, \lim _{k \rightarrow \infty} u^{M_{j_{k}}}=u^{*}$, where $q^{*}$ is a solution to problem ( $\mathbf{T}$ ) and $u^{*}$ is a solution to problem (D).

### 3.3. Gradient Computation, the Adjoint, and Differentiating the Matrix Exponential

There are a couple of computational issues related to the solution of the approximating optimization problems $\left(\mathbf{T}^{\mathbf{N}}\right)$ and $\left(\mathbf{D}^{\mathbf{L}}\right)$. Local minima for problem ( $\left.\mathbf{T}^{\mathbf{N}}\right)$ will typically be found using a gradient based scheme. This will require the computation of the gradient (with respect to $q \in Q$ ) of the performance index $J_{T}^{N}(q), \vec{\nabla} J_{T}^{N}(q)$. Since $q \in Q$, the evaluation $J_{T}^{N}(q)$ requires the solution, or integration, of the discrete dynamical system (3.4), which, although linear, its solution depends on the parameters, $q$, in a highly nonlinear fashion.
Consequently, the best way to compute $\vec{\nabla} J_{T}^{N}(q)$ is via the adjoint method (see, for example, Levi and Rosen, [27]).

For $i=0,1,2, \ldots, n, \operatorname{set} v_{i}^{N}=\left[2\left(C(q) \varphi_{i}^{N}-\tilde{y}_{i}\right), 0, \ldots, 0\right]^{T} \in R^{M^{N}+1}$ and define the adjoint system corresponding to (3.4) by

$$
\eta_{i-1}^{N}=\left[\widehat{A}^{N}(q)\right]^{T} \eta_{i}^{N}+v_{i-1}^{N}, \quad i=n, n-1, n-2, \ldots, 1, \quad \eta_{n}^{N}=v_{n}^{N} .
$$

The gradient of $J_{T}^{N}(q), \vec{\nabla} J_{T}^{N}(q)$, can then be computed as

$$
\vec{\nabla} J_{T}^{N}(q)=\sum_{i=1}^{n}\left[\eta_{i}^{N}\right]^{T}\left\{\frac{\partial \widehat{A}^{N}(q)}{\partial q} \varphi_{i-1}^{N}+\frac{\partial \widehat{B}^{N}(q)}{\partial q} \tilde{u}_{i-1}\right\}+\sum_{i=0}^{n}\left(y_{i}^{N}-\tilde{y}_{i}\right)^{T} \frac{\partial C(q)}{\partial q} \varphi_{i}^{N} .
$$

The tensor $\partial C(q) / \partial q$ can be computed directly, but the computation of the tensors $\partial \hat{A}^{N}(q) / \partial q$ and $\partial B^{\hat{N}}(q) / \partial q$ involve the computation of the derivative with respect to $q$ of the matrix exponential $e^{A^{N}(q) t}$. These derivatives can be computed at the same time that $e^{A^{N}(q) t}$ and in particular, $\hat{A}^{N}(q)$ is computed by making use of the sensitivity equations. Indeed, for $t \geq 0$ and $q \in Q$, set $\Phi^{N}(q ; t)=e^{A^{N}(q) t}$. Then $\Phi^{N}(q ; \cdot)$ is the unique principal fundamental matrix solution to the initial value problem

$$
\begin{equation*}
\dot{\Phi}^{N}(q ; \cdot)=A^{N}(q) \Phi^{N}(q ; \cdot), \quad \Phi^{N}(q ; 0)=I . \tag{3.7}
\end{equation*}
$$

Then, setting $\Psi^{N}(q ; t)=\partial \Phi^{N}(q ; t) / \partial q$ (it is easiest to see how this works if one thinks of $q$ as a scalar), differentiating (3.7) with respect to $q$, interchanging the order of differentiation, and using the product rule, we find that

$$
\begin{equation*}
\dot{\Psi}^{N}(q ; \cdot)=A^{N}(q) \Psi^{N}(q ; \cdot)+\left(\partial A^{N}(q) / \partial q\right) \Phi^{N}(q ; \cdot), \quad \Psi^{N}(q ; 0)=0 \tag{3.8}
\end{equation*}
$$

Then, combining the two initial value problems (3.7) and (3.8), we obtain

$$
\left[\begin{array}{c}
\frac{\partial}{\partial q} e^{A^{N}(q) t}  \tag{3.9}\\
e^{A^{N}(q) t}
\end{array}\right]=\left[\begin{array}{c}
\Psi^{N}(q ; t) \\
\Phi^{N}(q ; t)
\end{array}\right]=e^{\left[\begin{array}{cc}
A^{N}(q) & \left(\partial A^{N}(q) / \partial q\right) \\
0 & A^{N}(q)
\end{array}\right] t}\left[\begin{array}{l}
0 \\
I
\end{array}\right] .
$$

We note that a more general derivation of the relationship given in (3.9), based on power series expansions along with even further generalizations from the exponential to any analytic function and efficient computational (numerical) algorithms, can be found in Najfeld and Havel, [28].

### 3.3. Mitigation of the Effects of Over-Fitting and Regularization

To mitigate the effects of over-fitting (e.g., high amplitude and unphysical excessive oscillations in $u^{L *} \in U \cap U^{M}$ ) due to the inherent ill-posedness of the deconvolution problem, we augment the deconvolution performance index given in (3.2) with Tychonov regularization or penalty terms (see, for example, Banks and Kunisch, [7]). Recalling that $U^{M}=\operatorname{span}\left\{\xi_{j}^{M}\right\}_{j=0}^{M^{M}}$ we write $u^{M}=\sum_{j=0}^{M^{M}} u_{j}^{M} \xi_{j}^{M}$, and then augment the performance index, $J_{D}^{L}$, for problem $\left(\mathbf{D}^{\mathbf{L}}\right)$ given by (3.5) with terms that are quadratic in $u^{M}$, or equivalently in the $u_{j}^{M^{\prime}}$ s. Indeed, we let $\langle\cdot, \cdot)_{U^{M}, r}$ denote an appropriately weighted inner product on $U^{M}$
weighted by the entries in a non-negative vector $r$. The performance index for the deconvolution problem ( $\mathbf{D}^{\mathbf{L}}$ ) now becomes

$$
\begin{equation*}
J_{D, R}^{L}\left(u^{M} ; r\right)=\sum_{i=0}^{m}\left\|y_{i}^{L}-\widehat{y}_{i}\right\|^{2}+\left\langle u^{M}, u^{M}\right\rangle_{U^{M}, r} . \tag{3.10}
\end{equation*}
$$

Given nonnegative values for the components of the regularization weight vector, $r$, finding $u^{L *} \in U \cap U^{M}$, or equivalently the $u_{j}^{L *^{\prime}} s$, in an appropriately defined compact subset of $R^{M^{M}}$ that minimize (3.10), is a standard linear-quadratic programming problem (i.e., a problem that has a quadratic pay-off or performance index and linear constraints (in the $u_{j}^{M^{\prime}} s$ ) ) for which accurate and efficient algorithms and software are readily available (e.g., the MATLAB routine LSQNONNEG). One difficulty in actually doing this in practice, however, is making an appropriate choice for the value of the regularization weight vector, $r$, in (3.10). If it is too "small," there will be insufficient regularization and a non-physical (e.g. highly oscillatory) $u^{L^{*}}$ will result. If, on the other hand, it is too "large," excessive regularization occurs and the resulting $u^{L^{*}}$, when convolved with the convolution kernel $\widehat{K}^{N}\left(t, q^{N *}\right)$ to obtain $\left\{y_{i}^{L *}\right\}_{i=0}^{m}$, will not provide a good fit to the data $\{\widehat{y}\}_{i=0}^{m}$.

To remedy this, we make further use of our training data, $\left\{\tilde{y}_{i}, \tilde{u}_{i}\right\}_{i=0}^{n}$, and introduce a modification to our training or calibration procedure that will allow us to estimate an, in some sense, optimal value for the regularization weight vector, $r$. More precisely, we add a second calibration phase in the form of an optimization problem, $\left(D^{L, R}\right)$, wherein we choose a nonnegative $r^{L^{*}}$ which minimizes:

$$
\begin{equation*}
J_{T, R}^{L}(r)=\sum_{i=0}^{n}\left\{\left\|y_{i}^{L}-\tilde{y}_{i}\right\|^{2}+\left|\tilde{u}^{L *}(i \tau, r)-\tilde{u}_{i}\right|^{2}\right\} \tag{3.11}
\end{equation*}
$$

where, for a given value of $r, \tilde{u}^{L^{*}}(\cdot, r)$ is the minimizer of (3.10) with $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}=\left\{\tilde{y}_{i}\right\}_{i=0}^{n}$ and with $\left\{y_{i}^{L}\right\}_{i=0}^{m}$ in (3.10) and $\left\{y_{i}^{L}\right\}_{i=0}^{n}$ in (3.11) being the output resulting from (3.6) corresponding to the inputs $\left\{\tilde{u}^{M}(i \tau)\right\}_{i=0}^{n}$, and $\left\{\tilde{u}^{L *}(i \tau, r)\right\}_{i=0}^{n}$, respectively (note that in this case $m=n$ ). This optimal value of the regularization weighting vector $r, r^{*}$, is then used in the performance index, $J_{D, R}^{L}(. ; r)$, as $J_{D, R}^{L}\left(. ; r^{*}\right)$ when the now regularized deconvoluion problems, ( $\mathbf{D}^{\mathbf{L}, \mathbf{R}}$ ), are solved.

## 4. Estimating Blood or Breath Alcohol Concentration from Biosensor Measurements of Transdermal Ethanol and Abstract Parabolic Systems

### 4.1. A Distributed Parameter Model for the Transdermal Transport and Measurement of Ethanol

We view the blood-skin-TAS system in input-output form, where the underlying process that maps input to output is the transport through, and filtering by, the various layers of the skin and the processing of the perspiration containing the ethanol in the form of a vapor by the TAC sensor. The input signal, $u(t)$, is the BAC or BrAC at time $t$ while the output signal, $y(t)$, is the measured TAC signal at time $t$. Our goal is to produce an estimate of either BAC or $\operatorname{BrAC}, \hat{u}^{*}(t)$, given measured TAC from the field, $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}$, and training data, $\left\{\tilde{y}_{i}, \tilde{u}_{i}\right\}_{i=0}^{n}$, consisting of simultaneous measurements of TAC and BAC or BrAC. To accomplish this, we use the approach presented in the previous two sections by formulating the problem of determining $\hat{u}^{*}(t)$ as a blind deconvolution. We do this by developing a first principles
mathematical model for the forward system based upon physics and physiology in the form of an infinite dimensional distributed parameter system with unbounded (boundary) input and unbounded output.

Towards this end, we let $\phi(t, x)$ denote the concentration in moles $/ \mathrm{cm}^{2}$ of ethanol in the interstitial fluid in the skin at depth $x \mathrm{~cm}$ at time $t$ seconds. Let $L$ denote the skin thickness in cm . We model the transport of ethanol through the skin as a diffusion process

$$
\begin{equation*}
\frac{\partial \varphi}{\partial t}(t, x)=D \frac{\partial^{2} \varphi}{\partial x^{2}}(t, x), \quad 0<x<L, \quad t>0 \tag{4.1}
\end{equation*}
$$

where $D$ denotes the diffusivity in units of $\mathrm{cm}^{2} / \mathrm{sec}$. We model the boundary conditions by setting the flux at the boundaries to be proportional to the difference in concentrations on either side of the boundary. They take the form

$$
\begin{align*}
-D \frac{\partial \varphi}{\partial x}(t, 0) & =\alpha_{0}(\delta \cdot 0-\varphi(t, 0)), \quad t>0  \tag{4.2}\\
-D \frac{\partial \varphi}{\partial x}(t, L) & =\alpha_{L}(\varphi(t, L)-\beta u(t)), \quad t>0 \tag{4.3}
\end{align*}
$$

where $a_{i}, i=0, L$ denote the constants of proportionality in units of $\mathrm{cm} / \mathrm{sec}$, the parameters $\delta$ and $\beta$ respectively denote the partition coefficients for ethanol between air and the interstitial fluid in the epidermal layer of the skin and between the interstitial fluid in the epidermal layer of the skin and blood in appropriate units of concentration, 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

$$
\varphi(0, x)=0, \quad 0<x<L
$$

We model the processing by the TAS sensor of the ethanol evaporating from the surface of the skin via a linear relation. Consequently, we obtain the output equation

$$
y(t)=\gamma \varphi(t, 0), \quad t>0
$$

where $\gamma$ denotes the constant of proportionality in units of TAC units $\times \mathrm{cm}^{2} / \mathrm{mole}$.
We note that there are a number of variations to the model given by (4.1) - (4.5) that could also be considered. For example, we could have included an advection term of the form $-v \frac{\partial \varphi}{\partial x}$ in the partial differential equation (4.1) or we could have reduced the number of distinct parameters in the model by assuming that the constants of proportionality in the flux boundary conditions at the upper and lower boundaries of the skin are the same (i.e., that $\alpha_{0}$ and $a_{L}$ in (4.2) and (4.3) satisfy $a_{0}=a_{L}$ ), to mention just two possible modifications. For the role that the underlying physical model plays in the present study, introducing additional parameters into, or removing parameters from, the model can have significant consequences. Indeed, increasing the number of degrees of freedom when we fit the model to calibration data could potentially enhance the model's ability to capture the underlying dynamics of the process. However, it could also increase the chances of over-fitting and the fitting of the noise in the data rather than the underlying physical or biological process. In our numerical studies, we found that the somewhat simpler model with $a_{0}=a_{L}$ provided highly accurate and more than adequate fits to the calibration data generated by the alcohol challenge protocol we employed here. However, as we will discuss later, one of the models with
additional parameters might be more appropriate when the calibration data is generated via a richer more sophisticated alcohol challenge protocol.

### 4.2. The Calibration problem

As it stands, the model given by the equations (4.1) - (4.5) is determined by the seven parameters $D, L, a_{0}, a_{L} \delta, \beta$ and $\gamma$. These are the parameters that will be used to calibrate the model from a given calibration input and corresponding output data set, $\left\{\tilde{y}_{i}, \tilde{u}_{i}\right\}_{i=0}^{n}$.
However, not all five of the parameters are independent nor are they uniquely identifiable from the input/output data. Indeed, it is an elementary exercise to show that, if $\{u(t), y(t)\}_{t \geq 0}$ and $\phi$ satisfy (4.1) - (4.5), then it follows that $\{u(t), y(t)\}_{t \geq 0}$ and $\widehat{\varphi}$ satisfy

$$
\begin{gathered}
\frac{\partial \widehat{\varphi}}{\partial \widehat{t}}(\hat{t}, \widehat{x})=\widehat{D} \frac{\partial^{2} \hat{\varphi}}{\partial \widehat{x}^{2}}(\widehat{t}, \widehat{x}), \quad 0<\widehat{x}<1, \quad \hat{t}>0, \\
\widehat{D} \frac{\partial \widehat{\varphi}}{\partial \widehat{x}}(\widehat{t}, 0)-\hat{\varphi}(\widehat{t}, 0)=0, \quad \widehat{t}>0, \\
\widehat{D} \frac{\partial \widehat{\varphi}}{\partial \widehat{x}}(\widehat{t}, 1)+\widehat{\alpha} \hat{\varphi}(\widehat{t}, 1)=\widehat{\beta} u(\theta \widehat{t})=\widehat{\beta} u(t), \quad t>0, \\
\hat{\varphi}(0, \widehat{x})=0, \quad 0<\widehat{x}<1 \\
y(t)=y(\theta \hat{t})=\widehat{\varphi}(\widehat{t}, 0), \quad \widehat{t}>0,
\end{gathered}
$$

where $x \hat{=} x / L, t \hat{=} t / \theta, \widehat{D}=D \theta / L^{2}, \widehat{\alpha}=\alpha_{L} \theta / L, \widehat{\beta}=\alpha_{L} \beta \gamma \theta / L, a=L / a_{0}$ and $\hat{\varphi}(\hat{t}, \hat{x})=\gamma \varphi(\theta \widehat{t}, L \widehat{x}), 0 \leq x \leq 1, t \hat{\geq} 0$. Consequently, in calibrating the model, rather than fit the seven parameters $D, L, a_{0}, a_{L} \delta, \beta$ and $\gamma$ in (4.1) - (4.5), it is sufficient to fit the four parameters, $\widehat{D}, \widehat{\beta}, \widehat{\alpha}$ and $\theta$ in (4.6) - (4.10). Moreover, inspection of (4.6) - (4.10) reveals that the parameter $\theta$ simply serves to dilate or compress (relative to the diffusion clock $t$ ) the input, $u$, and output, $y$. Moreover, for a given input signal, $u(t)$, any change in $\theta$ can be compensated for by appropriate changes to $\widehat{D}, \widehat{\beta}$, and $\widehat{\alpha}$ so that the system produces the same output signal $y(t)$. It follows that it would not be possible to uniquely identify all of $\theta, \widehat{\beta}, \widehat{\alpha}$, and $\hat{D}$ based on input/output measurements $\{u(t), y(t)\}_{t \geq 0}$. Without loss of generality, set $\theta=$ 1 , then $t=t$ and the number of unknown parameters to be fit is reduced to three, which we denote by the vector $q=\left[\begin{array}{lll}q_{1} & q_{2} & q_{3}\end{array}\right]^{T}$. The model can now be written in terms of $q, u$, and $y$ as given in (4.11) - (4.15)

$$
\begin{gather*}
\frac{\partial \varphi}{\partial t}(t, x)=q_{1} \frac{\partial^{2} \varphi}{\partial x^{2}}(t, x), 0<x<1, \quad t>0,  \tag{4.11}\\
q_{1} \frac{\partial \varphi}{\partial x}(t, 0)-\varphi(t, 0)=0, \quad t>0, \\
q_{1} \frac{\partial \varphi}{\partial x}(t, 1)+q_{2} \varphi(t, 1)=q_{3} u(t), \quad t>0, \tag{4.13}
\end{gather*}
$$

$$
\begin{align*}
& \varphi(0, x) 0, \quad 0<x<1 \\
& y(t)=\varphi(t, 0), \quad t>0, \tag{4.15}
\end{align*}
$$

where $q_{1}=D / a_{0} L, q_{2}=a_{L} / a_{0}$, and $q_{3}=a_{L} \beta \gamma / a_{0}$ and where, for simplicity, we have now denoted $\hat{\varphi}$, and $x$ simply by $\phi$ and $x$, respectively, with the understanding that they are no longer the same as the $\phi$ and $x$ in equations (4.1) - (4.5).

We next put the system (4.11) - (4.15) into the form of our abstract system (2.1) - (2.4) and formally and precisely identify the relevant spaces and operators that appear in (2.1) - (2.5). It turns out that the resulting system is abstract parabolic, which allows us to make use of the rather extensive linear semigroup theory for this type of system to establish that the necessary assumptions we made to develop the theory in the previous two sections are indeed satisfied.

### 4.3. Abstract Operator Theoretic Formulation

Let $Q \subseteq R^{+} \times R^{+} \times R^{+}$be given and let $q=\left[\begin{array}{ll}q_{1} & q_{2} \\ q_{3}\end{array}\right]^{T} \in Q$. Let $H=L_{2}(0,1)$ together with the standard innerproduct $\left\langle\psi_{1}, \psi_{2}\right\rangle=\int_{0}^{1} \psi_{1}(x) \psi_{2}(x) d x$, and norm denoted by $|\cdot|$, let $W$ be the Sobolev space $W=H_{2, L}(0,1)=\left\{\psi \in H_{2}(0,1): q_{1} \psi^{\prime}(0)-\psi(0)=0\right\}$ endowed with the usual $H_{2}$ innerproduct, and let $V$ be the Sobolev space $V=H_{1}(0,1)$ together with its standard innerproduct $\left\langle\left\langle\psi_{1}, \psi_{2}\right\rangle\right\rangle=\int_{0}^{1} \psi_{1}(x) \psi_{2}(x) d x+\int_{0}^{1} \psi_{1}^{\prime}(x) \psi_{2}^{\prime}(x) d x$ and norm denoted by $\|\cdot\|$. Then we have the usual dense and continuous embeddings $W \hookrightarrow H \hookrightarrow W^{*}$ and $V \hookrightarrow H \hookrightarrow V^{*}$, where $W^{*}$ and $V^{*}$ denote the space of distributions dual to $W$ and $V$, respectively (see, for example, Adams, [29], Wloka, [30], Tanabe, [31], or Showalter, [32]). Let $\Delta(q) \in \mathscr{L}(W, H)$ and $\Gamma(q) \in \mathscr{L}(W, R)$ be given by

$$
\Delta(q) \psi=q_{1} \quad d^{2} \psi / d x^{2}
$$

and

$$
\Gamma(q) \psi=q_{3}^{-1}\left\{q_{1} \psi^{\prime}(1)+q_{2} \psi(1)\right\}
$$

respectively, for $\psi \in W$, and let $\mathrm{C}(q)=C \in \mathscr{L}(V, R)$ be given by $\mathrm{C} \psi=\psi(0)$, for $\psi \in V$. In this case we have that $\Gamma(q)$ is clearly surjective and that

$$
\mathbb{N}(\Gamma(q))=H_{2, L, R}(0,1)=\left\{\psi \in H_{2}(0,1): q_{1} \psi^{\prime}(0)-\psi(0)=0, \quad q_{1} \psi^{\prime}(1)+q_{2} \psi(1)=0\right\}
$$

is dense in $H=L_{2}(0,1)$. It follows, as in Section 2, that the operator $A(q): \operatorname{Dom}(A(q)) \subseteq H \rightarrow H$ defined by

$$
\begin{gathered}
\operatorname{Dom}(A(q))=H_{2, L, R}(0,1) \\
A(q) \psi=q_{1} \quad d^{2} \psi / d x^{2}, \psi \in H_{2, L, R}(0,1),
\end{gathered}
$$

is closed, is densely defined and has nonempty resolvent set. It can also be shown (see, for example, Friedman, [33]) 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 $\varphi \in C(0, T ; W) \cap C^{1}(0, T ; H)$ that depends continuously on $\phi_{0}$ and $u$, and that satisfies (4.11) - (4.13) 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 $\mathrm{C}_{0} \operatorname{semigroup},\left\{e^{A(q) t}: t\right.$ $\geq 0\}$ of bounded linear operators on $H$. Note that in our case here, the Lumer Phillips Theorem can be used directly and in a straight forward manner to show that $A(q)$ is the infinitesimal generator of a $\mathrm{C}_{0}$ semigroup (see, for example, Pazy, [25]). Indeed, it is not difficult to show that the operator $A(q)$ is self adjoint and dissipative and therefore maximal dissipative on its domain.

For the system of interest to us here, since we in fact have $W \hookrightarrow V \hookrightarrow H$ with the embeddings dense and continuous, we can make use of the theory of abstract parabolic systems (see, for example, Tanabe, [31]) and it is sufficient to formulate the abstract system with unbounded input and output in the space $V^{*}$, a somewhat smaller space than the space $Z$ defined in Section 2. We do this by exploiting the weak or variational formulation of (4.11) - (4.15).

For $q \in Q \subseteq R^{+} \times R^{+} \times R^{+}$, we define the bilinear form $a(q ; \cdot, \cdot): V \times V \rightarrow R$ and the functions $b(q ; \cdot): V \rightarrow R$ and $c(\cdot): V \rightarrow R$ by

$$
\begin{aligned}
a\left(q ; \psi_{1}, \psi_{2}\right) & =\psi_{1}(0) \psi_{2}(0)+q_{2} \psi_{1}(1) \psi_{2}(1)+q_{1} \int_{0}^{1} \psi_{1}^{\prime}(x) \psi_{2}^{\prime}(x) d x, \quad \psi_{1}, \psi_{2} \in V \\
b(q ; \psi) & =q_{3} \psi(1)
\end{aligned}
$$

and

$$
c(\psi)=\psi(0),
$$

respectively, then the input-output system (4.11) - (4.15) can be written in weak form as

$$
\begin{gather*}
\langle\dot{\varphi}, \psi\rangle+a(q ; \varphi, \psi)=b(q ; \psi) u, \quad \psi \in V \\
\left.\varphi\right|_{t=0}=0 \in V \\
y=c(\varphi) \tag{4.18}
\end{gather*}
$$

where $\langle\cdot, \cdot)$ now denotes the natural extension of the $H$ innerproduct to the duality pairing between $V$ and $V^{*}$ and where we have suppressed showing explicit dependence on $t$ whereever possible.

For $q \in Q$, a compact subset of $R^{+} \times R^{+} \times R^{+}$, using the Sobolev embedding theorem it is straight forward to show that the bilinear form $a(q ; \cdot, \cdot)$ is bounded and coercive, uniformly in $q \in Q$. That is, there exist positive constants $\lambda, \mu$ and $\rho$, independent of $q \in Q$ such that

$$
\begin{equation*}
\left|a\left(q ; \psi_{1}, \psi_{2}\right)\right| \leq \rho\left\|\psi_{1}\right\|\left\|\psi_{2}\right\|, \quad \psi_{1}, \psi_{2} \in V \tag{4.19}
\end{equation*}
$$

and

$$
\begin{equation*}
a(q ; \psi, \psi)+\lambda|\psi|^{2} \geq \mu\|\psi\|^{2}, \quad \psi \in V \tag{4.20}
\end{equation*}
$$

Moreover, $a\left(\cdot ; \psi_{1}, \psi_{2}\right)$ and $b(q ; \cdot)$ are continuous on $Q$ in the sense that there exist positive constants $\sigma$ and $v$ such that

$$
\left|a\left(q^{1} ; \psi_{1}, \psi_{2}\right)-a\left(q^{2} ; \psi_{1}, \psi_{2}\right)\right| \leq \sigma d\left(q^{1}, q^{2}\right)\left\|\psi_{1}\right\|\left\|\psi_{2}\right\|, \quad \psi_{1}, \psi_{2} \in V
$$

and

$$
\left|a\left(q^{1} ; \psi\right)-b\left(q^{2} ; \psi\right)\right| \leq v d\left(q^{1}, q^{2}\right)\|\psi\|, \quad \psi \in V
$$

where $d(\cdot, \cdot)$ denotes any $p$-metric on $R^{3}$.
If $u \in L_{2}(0, T)$ it can be shown (Lions, [34], Theorem III.1.2) that the system (4.16) - (4.18) admits a uniquey solution
$\varphi \in W(0, T)=\left\{\psi: \psi \in L_{2}(0, T, V), \psi \in L_{2}\left(0, T, V^{*}\right)\right\} \subset C(0, T, H)$ that depends continuously on $u \in L_{2}(0, T)$. It follows that the output $y \in L_{2}(0, T)$.

For $q \in Q$, the form $a(q ; \cdot, \cdot): V \times V \rightarrow R$ defines a bounded linear operator
$\tilde{A}(q) \in \mathscr{L}\left(V, V^{*}\right)$ by $\left\langle\tilde{A}(q) \psi_{1}, \psi_{2}\left\langle=-a\left(q ; \psi_{1}, \psi_{2}\right)\right.\right.$, for $\psi_{1}, \psi_{2} \in V$ (the boundedness follows from (4.19)). Then, if we let $\mathscr{H}$ denote any of the Hilbert spaces $V, H$ or $V^{*}$ and we consider the linear operator $A(q): D_{q} \subset \mathscr{H} \rightarrow \mathscr{H}$ given by

$$
A(q) \psi=\tilde{A}(q) \psi \quad \text { for } \quad \psi \in D_{q}=\{\psi \in V: \tilde{A}(q) \psi \in \mathscr{H}\}
$$

then, using primarily (4.20), it can be shown (Tanabe, [31], Theorem 3.6.1, Banks and Ito, [18]) that $A(q)$ is closed, is densely defined and is the infinitesimal generator of an analytic semigroup of bounded linear operators, $\left\{e^{A(q) t}: t \geq 0\right\}$, on $\mathscr{H}$. It follows that

$$
\left.\left.\left.A(q)\right|_{V} \subseteq A(q)\right|_{H} A(q)\right|_{V^{*}}=\tilde{A}(q)
$$

For $q \in Q$, define the linear operators $B(q): R \rightarrow V^{*}$ and $C: V \rightarrow R$ by

$$
\langle B(q) v, \psi\rangle=b(q ; \psi) v=q_{3} \psi(1) v
$$

and

$$
C \psi=\psi(0),
$$

respectively, for $q \in Q, \psi \in V$, and $v \in R$. Then we may write equations (4.11) - (4.15) in strong form as an abstract evolution equation in $V^{*}$ as

$$
\dot{\varphi}(t)=A(q) \varphi(t)+B(q) u(t), \quad y(t)=C \varphi(t), \quad t>0, \quad \varphi(0)=0
$$

Note that if we take $\Gamma^{+}(q) \in \mathscr{L}(R, W)$ to be given by

$$
\begin{equation*}
\left(\Gamma^{+}(q) v\right)(x)=\left\{\frac{1}{q_{1}+q_{1} q_{2}+q_{2}} x+\frac{q_{1}}{q_{1}+q_{1} q_{2}+q_{2}}\right\} q_{3} v, \quad x \in[0,1] . \quad v \in R \tag{4.21}
\end{equation*}
$$

then $\Gamma(q) \Gamma^{+}(q) v=v, v \in R$, and as in Section 2, we have

$$
\begin{equation*}
B(q) v=(\Delta(q)-\tilde{A}(q)) \Gamma^{+}(q) v, \quad v \in R . \tag{4.22}
\end{equation*}
$$

Using the fact that $\left\{e^{A(q) t}: t \geq 0\right\}$ is an analytic semigroup on $V^{*}$ and therefore that $e^{A(q) t} \psi \in D_{q} \subseteq V$, for $\psi \in V^{*}$, we obtain from the abstract variation of constants formula that

$$
y(t)=C \int_{0}^{t} e^{A(q)(t-s)} B(q) u(s) d s
$$

We note that, as in the more general case presented in Section 2, in the example we are considering here, the output operator $C$ is not closed with respect to $V^{*}$ and therefore cannot be passed around the integral in (4.22). As in Section 2, we take $u$ in (4.22) to be a Dirac delta distribution with impulse at time $t=0$ and obtain that, for $q \in Q$, the impulse respo nse function $k(\cdot)=k(q ; \cdot)$ from (2.1) for (4.11) - (4.15) is given by

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

with the understanding that the actual input/output map must in fact be interpreted in its integral form as given above. Note that, for every $q \in Q,\left\{e^{A(q) t}: t \geq 0\right\}$, an analytic semigroup on $V^{*}$, ensures that $e^{A(q) t} B(q) \in D_{p} \subseteq V$ for every $t>0$ and thus that, although it cannot be directly computed without some form of finite dimensional approximation, the expression given in (4.23) is a well-defined real valued function of $t$ defined for all values of $t>0$.

For the discrete time formulation, let the sampling time $\tau>0$ be given and set $\phi_{i}=\phi(i \tau, \cdot), y_{i}$ $=y(i \tau)$ and $u_{i}=u(i \tau), i=0,1,2, \ldots$ Then, with the zero-order hold input $u(t)=u_{i}, t \in\{i \tau,(i+$ 1) $\tau$ ), $i=0,1,2, \ldots$, the variation of parameters formula yields

$$
\begin{equation*}
\varphi_{i+1}=\tilde{A}(q) \varphi_{i}+\widehat{B}(q) u_{i}, \quad y_{i}=C \varphi_{i}, \quad i=0,1,2, \ldots, \quad \varphi_{0}=0 \in V \tag{4.24}
\end{equation*}
$$

where

$$
\widehat{A}(q)=e^{A(q) \tau} \in \mathscr{L}(V, V)
$$

and

$$
\widehat{B}(q)=\int_{0}^{\tau} e^{A(q) s} B(q) d s \in \mathscr{L}(R, V) .
$$

The fact that $\widehat{A}(q) \in \mathscr{L}(V, V)$ and $\widehat{B}(q) \in \mathscr{L}(R, V)$ follows from $\left\{e^{A(q) t}: t \geq 0\right\}$ being an analytic semigroup on $V, H$ and $V^{*}$. The integral in the definition of $B(\hat{q})$ is an integral in $V^{*}$. Moreover, $a(q ; \cdot, \cdot): V \times V \rightarrow R$ is an inner product on $V$ whose induced norm $\|\cdot\|_{a}$ (via the fundamental theorem of calculus and the Sobolev embedding theorem) is equivalent to the standard norm on $V$. It follows that for $q \in Q$ and $\psi \in V$

$$
\|A(q) \psi\|_{V^{*}}=\sup _{\xi \in V, \xi \neq 0} \frac{|\langle A(q) \psi, \xi\rangle|}{\|\xi\|} \geq \frac{\langle-A(q) \psi, \psi\rangle}{\|\psi\|}=\frac{a(q ; \psi, \psi)}{\|\psi\|}=\frac{\|\psi\|_{a}^{2}}{\|\psi\|} \geq c\|\psi\|
$$

for some constant $c>0$. From (4.20) and the Riesz Theorem, we may conclude that $A(q): V \subset V^{*} \rightarrow V^{*}$ is invertible with a bounded inverse. It then follows that $B(\hat{q})$ in (4.24) is given by

$$
\left.\widehat{B}(q)=\int_{0}^{\tau} e^{A(q) s} B(q) d s=A(q)^{-1} e^{A(q) s} B(q)\right]_{0}^{\tau}=(\widehat{A}(q)-I) A(q)^{-1} B(q) .
$$

Then, noting that $\Gamma^{+}(q) \in \mathscr{L}(R, W)$ given by (4.21) is in $\mathbb{N}(\Delta(q))$, it follows from (4.22) that

$$
\widehat{B}(q)=(\tilde{A}(q)-I) A(q)^{-1} B(q)=(\tilde{A}(q)-I) \tilde{A}(q)^{-1}(\Delta(q)-\tilde{A}(q)) \Gamma^{+}(q)=(I-\widehat{A}(q)) \Gamma^{+}(q)
$$

Consequently, it follows that

$$
y_{i}=\sum_{j=0}^{i-1} C \widehat{A}(q)^{i-j-1} \widehat{B}(q) u_{j}=\sum_{j=0}^{i-1} C \widehat{A}(q)^{i-j-1}(1-\widehat{A}(q)) \Gamma^{+}(q) u_{j}, \quad i=0,1,2, \ldots,
$$

and therefore that

$$
\widehat{K}(t ; q)=C \widehat{A}(q)^{[t / \tau]-1} \widehat{B}(q)=C \widehat{A}(q)^{[t / \tau]-1}(1-\widehat{A}(q)) \Gamma^{+}(q), \quad i=1,2, \ldots
$$

### 4.4. Finite Dimensional Approximation

Finite dimensional approximation is achieved via the discretization of the spatial domain using linear B-splines and Galerkin approximation. For $N=1,2, \ldots$, let $\left\{\psi_{j}^{N}\right\}_{j=0}^{N}$ 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 $H^{N}=\operatorname{span}\left\{\psi_{j}^{N}\right\}_{j=0}^{N} \subset V$ (note the $\psi_{j}^{N}$ are the usual "pup tent" or "chapeau" functions of height one and support of width $2 / N$,
$\lfloor(j-1) / N,(j+1) / N\rfloor\lfloor 0,1\rfloor)$. Let $P^{N}: H \rightarrow H^{N}$ denote the orthogonal projection of $H$ onto $H^{N}$ with respect to the $H$ inner product. Using the approximation properties of linear splines (see, for example, Schultz, [35], Banks and Kunisch, [7], and Banks and Ito, [8]), it is not difficult to argue that $\lim _{N \rightarrow \infty} P^{N} \psi=\psi$ in $H$ for $\psi \in H$ and in $V$ for $\psi \in V$. For $\mathrm{N}=1,2, \ldots$, and $q \in Q$, define $A^{N}(q) \in \mathscr{L}\left(H^{N}, H^{N}\right)$ to be the finite dimensional linear operator whose matrix representation is given by

$$
\begin{equation*}
\left\lfloor A^{N}(q)\right\rfloor=\left[\left\langle\psi_{i}^{N}, \psi_{j}^{N}\right\rangle\right]^{-1}\left[-a\left(q ; \psi_{i}^{N}, \psi_{j}^{N}\right)\right] \tag{4.25}
\end{equation*}
$$

(Note: In what follows, when the meaning is clear from the context, we will not distinguish between finite dimensional operators on $H^{N}$ and elements in $H^{N}$ and their matrix and vector
representations, respectively, with respect to the standard B-spline basis $\left\{\psi_{j}^{N}\right\}_{j-0}^{N}$ ). It is not difficult to show that

$$
A^{N}(q)=\left(P_{a}^{N} A(q)^{-1}\right)^{-1}
$$

where $P_{a}^{N}$ is the orthogonal projection of $V$ onto $H^{N}$ with respect to the inner product

$$
\langle\cdot, \cdot\rangle_{a}=a(q ; \cdot, \cdot) \quad \text { on } \quad V .
$$

We then set

$$
\widehat{A}^{N}(q)=e^{A^{N}(q) \tau}
$$

and, noting that $\Gamma^{+}(q) v \in H^{N}$ for all $v \in \mathrm{R}^{\mathrm{R}}$ and all $N=1,2, \ldots$, we obtain the finite dimensional approximating model equations given by

$$
\varphi_{i+1}^{N}=\widehat{A}^{N}(q) \varphi_{i}^{N}+\left(\widehat{A}^{N}(q)-I\right) \widehat{\Gamma}^{N+}(q) \tilde{u}_{i}, \quad \tilde{y}_{i}^{N}(q)=C^{N} \varphi_{i}^{N}, i=0,1,2, \ldots, \varphi_{0}^{N}=0 \in V
$$

where $\hat{\Gamma}^{N+}(q)$ denotes the vector representation of the linear polynomial given in (4.21) and $C^{N}$ denotes the matrix representation for the operator $C \in \mathscr{L}(R, W)$, both with respect to the basis $\left\{\psi_{j}^{N}\right\}_{j=0}^{N}$ for $H^{N}$. In convolution form we have

$$
\tilde{y}_{i}^{N}(q)=\sum_{j=0}^{i-1} C^{N}\left(\widehat{A}^{N}(q)\right)^{i-j-1}\left(\widehat{A}^{N}(q)-I\right) \widehat{\Gamma}^{N+}(q) \tilde{u}_{j}, \quad i=0,1,2, \ldots
$$

The approximating discrete time convolution kernel or impulse response function is given by

$$
\widehat{K}^{N}(t ; q)=C^{N} \widehat{A}^{N}(q)^{[t / \tau]-1}\left(I-\widehat{A}^{N}(q)\right) \widehat{\Gamma}^{N+}(q), \quad i=1,2, \ldots
$$

The finite dimensional approximation scheme we have used here conforms to the abstract approximation framework for abstract parabolic systems presented in Banks and Kunisch,
[7] and Banks and Ito, [8]. Consequently, it follows that $\lim _{N \rightarrow \infty} \hat{A}^{N}(q) \psi=\psi$ in $V$ for $\psi \in$ $V$, uniformly in $q$, for $q \in Q$ and therefore that $\lim _{N \rightarrow \infty} \tilde{y}_{i}^{N}(q)=\tilde{y}_{i}(q)$ and $\lim _{N \rightarrow \infty} \widehat{K}^{N}(t ; q)=\widehat{K}(t ; q)$ uniformly in $q$, for $q \in Q$ and uniformly in $t$, for $t \in[0, T]$.

To see how, in the case of this example, the requisite gradients for the adjoint scheme described in the previous section are actually computed, we define the following $(N+1) \times$ $(N+1)$ matrices. Let

$$
\begin{aligned}
M=\left[\left\langle\psi_{i}^{N}, \psi_{j}^{N}\right\rangle\right] & =\frac{1}{6 N} \operatorname{Tridiag}\{[1,1, \ldots, 1],[2,4,4, \ldots, 4,2],[1,1, \ldots, 1]\} \\
K=\left[\left\langle\psi_{i}^{N^{\prime}}, \psi_{j}^{N^{\prime}}\right\rangle\right] & =N \operatorname{Tridiag}\{[-1,-1, \ldots,-1],[1,2,2, \ldots, 2,1],[-1,-1, \ldots,-1]\} \\
L & =\left[\psi_{i}^{N}(0) \psi_{j}^{N}(0)\right]=\operatorname{diag}\{[1,0,0, \ldots, 0]\} \\
R & =\left[\psi_{i}^{N}(1) \psi_{j}^{N}(1)\right]=\operatorname{diag}\{[0,0,0, \ldots, 1]\}
\end{aligned}
$$

Then from (4.25), we have $A^{N}(q)=-M^{-1}\left(q_{1} K+L+q_{2} R\right)$, and from (3.9), it follows that $\left[\begin{array}{c}\frac{\partial \widehat{A}^{N}(q)}{\partial q_{1}} \\ \widehat{A}^{N}(q)\end{array}\right]=e^{\left[\begin{array}{cc}A^{N}(q) & -M^{-1} K \\ 0 & A^{N}(q)\end{array}\right] \tau\left[\begin{array}{l}0 \\ I\end{array}\right] \quad \text { and } \quad\left[\begin{array}{c}\frac{\partial \widehat{A}^{N}(q)}{\partial q_{2}} \\ \widehat{A}^{N}(q)\end{array}\right]=e^{\left[\begin{array}{cc}A^{N}(q) & -M^{-1} R \\ 0 & A^{N}(q)\end{array}\right] \tau}\left[\begin{array}{l}0 \\ I\end{array}\right] . . ~ . ~ . ~}$

To compute the other required derivatives note that

$$
\widehat{B}^{N}(q)=\left(\widehat{A}^{N}(q)-I\right) \widehat{\Gamma}^{N+}(q)=\left(\widehat{A}^{N}(q)-I\right) A^{N}(q)^{-1} B^{N}(q)
$$

where

$$
B^{N}(q)=q_{3} M^{-1}[0,0, \ldots, 0,1]^{T}
$$

The other derivatives can now be computed using (4.26), (4.27), and the elementary rules of differentiation. Note further, that since in our case $\langle\cdot, \cdot\rangle_{a}=a(q ; \cdot, \cdot)$ is an innerproduct on $V$, $A^{N}(q)$ is invertible. Consequently,

$$
\frac{\partial A^{N}(q)^{-1}}{\partial q_{1}}=A^{N}(q)^{-1}\left\{M^{-1} K\right\} A^{N}(q)^{-1} \quad \text { and } \quad \frac{\pi A^{N}(q)^{-1}}{\partial q_{2}}=A^{N}(q)^{-1}\left\{M^{-1} R\right\} A^{N}(q)^{-1}
$$

### 4.5. Identifying Drinking Episodes in the Data

A typical data record from the TAC sensor can be two weeks or more in duration and contain multiple distinct drinking episodes. While it is possible to deconvolve the entire two week long signal, it would be preferable, and most likely, more accurate to deconvolve each individual drinking episode separately. This would require either manual or automatic identification of the start and end times of each individual drinking episode. We implement an automated drinking episode identifier as follows. In general, TAC data are noisy. Consequently, recognizing the start of a drinking episode requires more than a simple uptick in TAC value since this may simply be a local short term disturbance. To remedy this, we first pre-process the TAC data signal using a Hodrick-Prescott (HP) filter (see, for example, Brauer, et al, [11] and Hodrick and Prescott, [12]). The HP filter, which is used extensively in econometric analysis, decomposes a time series into a sum of two time series: a cyclic component and a trend component. It does this by solving an optimization problem that minimizes the sum of the squares of the second differences (effectively, variations in the rate of change or the total curvature) in the trend component. More precisely, given field TAC data $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}$ from which we would like to deconvolve a BAC or BrAC signal, $u$, the HP filter decomposes $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}$ as

$$
\widehat{y}_{i}=\widehat{\rho}_{i}+\widehat{\sigma}_{i}, \quad i=0,1,2, \ldots, m
$$

where the cyclical component, $\left\{\widehat{\sigma}_{i}\right\}_{i=0}^{m}$, is given by $\widehat{\sigma}_{i}=\widehat{y}_{i}-\widehat{\rho}_{i}, i=0,1,2, \ldots, m$, and the trend, or smoothed component, $\left\{\widehat{\rho}_{i}\right\}_{i=0}^{m}$, is taken to be the minimizer of

$$
\begin{aligned}
J\left(\left\{\widehat{\rho}_{i}\right\}_{i=0}^{m}\right) & =\sum_{i=0}^{m}\left(\widehat{y}_{i}-\widehat{\rho}_{i}\right)^{2}+\lambda \sum_{i=1}^{m-1}\left\{\Delta^{2} \widehat{\rho}_{i}\right\}^{2} \\
& =\sum_{i=0}^{m}\left(\widehat{y}_{i}-\widehat{\rho}_{i}\right)^{2}+\lambda \sum_{i=1}^{m-1}\left\{\left(\widehat{\rho}_{i+1}-\widehat{\rho}_{i}\right)-\left(\widehat{\rho}_{i}-\widehat{\rho}_{i-1}\right)\right\}^{2}
\end{aligned}
$$

with $\lambda$ a nonnegative weight used to control the degree of smoothing. Not surprisingly, the weight $\lambda$ is chosen to be larger the higher the sampling rate (i.e., the smaller the value of the sampling interval $\tau$ ) of the original field TAC signal $\hat{y}$. It is not difficult to show (see, for example, Ley, [13] or Danthine and Girardin, [14]) that this optimization problem can be solved in closed form as $\hat{\rho}=\left(I+\lambda L^{T} L\right)^{-1} \widehat{y}$, where $L=\left[L_{i j}\right]$ is the $(m-1) \times m$ matrix whose entries are given by

$$
L_{i j}= \begin{cases}1 & \text { if } \quad i=j \quad \text { or } \quad i=j+2 \\ -2 & \text { if } i=j+1 \\ 0 & \text { otherwise }\end{cases}
$$

The resulting trend component, $\left\{\widehat{\rho}_{i}\right\}_{i=0}^{m}$, can be taken to be a smoothed version of the original time series. We then identify the starting and ending times of the individual drinking episodes by locating the times at which the trend series rises above a baseline level (a start time) and then dips below a baseline level (an end time). We found this technique to be quite accurate when applied to TAC data for which we knew, and could therefore compare, the actual starting and ending times of the individual drinking episodes with the ones identified by our scheme.

## 5. Numerical Results

### 5.1. Experimental data and Its Collection

In the results presented here, the second author served as the subject. She wore a WrisTAS ${ }^{\text {TM }} 7$ sensor over an 18-day period of time, during which she collected breath measurements and maintained a real-time drinking diary for all drinking episodes. Although in actual practice BrAC measurements would only be available for a single (most likely the first) drinking episode (for the purpose of calibrating the underlying model), BrAC measurements in these data were collected during each drinking episode so that we could assess how closely the BrAC estimates generated by the software agreed with actual BrAC measurements taken with a breath analyzer.

The WrisTAS ${ }^{\text {TM }} 7$ is worn like a wristwatch with a Velcro strip for securing and removing it. Its sensing system directly measures the local ethanol vapor concentration over the skin surface at 5-minute intervals. The threshold BAC detectable by the WrisTAS device is estimated in the range of $10-20 \mathrm{mg} / \mathrm{dl}$. The TAC device was placed on her wrist 20 minutes prior to consuming alcohol for the alcohol challenge session. The alcoholic beverage for the challenge session was a mixture of $95 \%$ ethanol at room temperature, and a non-caffeinated sugar-free carbonated soft drink in a 1:4 ratio designed to reach a peak BrAC of 0.055 to
$0.060 \mathrm{mg} \%$ as determined by body water weight. The drink was consumed evenly over a 15minute period. Following consumption, the subject rinsed her mouth twice and waited 5 minutes prior to taking the first BrAC reading (to avoid measuring "mouth alcohol"). BrAC was recorded every 15 minutes from the start of the challenge session until BrAC returned to .000 . These are the data that were used for calibration.

The subject continued to wear the TAC device and consume alcohol ad libitum for the following 17 days in the field trial phase. For each drinking episode, the subject would take BrAC readings every 30 minutes until the BrAC returned to .000 . The subject also recorded on her smart phone the quantity of alcohol she had consumed; thus, this drinking diary was a real-time measure of alcohol consumption. She also recorded for each episode the percentage of alcohol in the beer and wine and whether she consumed food before, during, or after drinking. As part of our study we looked at three common BrAC statistics for each drinking episode: maximum BrAC , time of maximum BrAC , and area underneath the BrAC curve.

### 5.2. Identification of the Drinking Episodes

Figure 5.1 shows the entire 18 day TAC signal along with the contemporaneous BrAC measurements. The horizontal axis represents the number of the TAC data point (one every 5 minutes). The TAC measurements provided by the sensor are given in units of milligrams per deciliter ( $\mathrm{mg} / \mathrm{dl}$ ), while the BrAC measurements are in units of percent alcohol. The boldface numerals that appear above the peaks in the plots serve to label the 11 drinking episodes. In Figure 5.2a, (the left hand panel of Figure 5.2) we have plotted the TAC signal along with the smoothed trend component, $\left\{\widehat{\rho}_{i}\right\}_{i=0}^{m}$, as produced by the HP filter described in the previous section. In Figure 5.2b (the right hand panel of Figure 5.2) we have plotted both the trend, $\left\{\widehat{\rho}_{i}\right\}_{i=0}^{m}$, and the cyclical, $\left\{\widehat{\sigma}_{i}\right\}_{i=0}^{m}$, components along with the TAC signal. Note that in these plots the horizontal axis is labeled in hours. Recall, if $\left\{\widehat{y}_{i}\right\}_{i=0}^{m}$ denotes the TAC signal, then $\widehat{y}_{i}=\widehat{\rho}_{i}+\widehat{\sigma}_{i}, i=0,1,2 \ldots, m$. The HP decomposition shown in Figure 5.2 b (the right hand panel of Figure 5.2) was achieved by taking the value of the smoothing parameter $\lambda$ to be $\lambda=75000$.

Note that by identifying local minima below a specified threshold ( $20 \mathrm{mg} / \mathrm{dl}$ ), our scheme was able to automatically identify 13 drinking episodes, including all 11 actual drinking episodes in the TAC data shown in Figure 5.1. The two extraneous drinking episodes identified by our scheme are the ones in Figure 5.2a numbered 2 and 12. Table 5.1 gives the starting and ending times of the 13 identified drinking episodes.

### 5.3. Calibration Results

We implemented our scheme in MATLAB. All optimization was carried out using the MATLAB routine FMINCON for constrained optimization contained in the Optimization Toolbox. All gradients were computed using the adjoint scheme as described above. To check the results we also solved the optimization problems using the MATLAB routine included in the standard installation of MATLAB, FMINSEARCH. This routine is for unconstrained optimization and computes gradients numerically via finite differences. The only real constraint on the parameters is that they remain nonnegative; we guaranteed this by searching on the squares of the parameters rather than the parameters themselves. Both approaches yielded essentially identical results.

In calibrating the model derived in Section 4 using each of the 11 drinking episodes, we observed that, in several episodes, the converged optimal value for $q_{2}$ was $q_{2}^{*}=0$. For the episodes in which $q_{2}^{*} \neq 0$, we observed that $q_{3}^{*} \gg 1$. Consequently, we concluded episodes
which would be equally well described by a modified model in which we fix $q_{2}=0$ and then fit the data by simply adjusting the two remaining parameters, $q_{1}$ and $q_{3}$. The results of calibrating this new two parameter model using each of the 11 drinking episodes in the data as shown in Figure 5.1 are displayed in Table 5.2. A summary of the data presented in Table 5.2 is given in Table 5.3 below.

The results of the model calibration using Drinking Episode 1 are shown in the left panel of Figure 5.3. The results obtained by using the other 10 drinking episodes to calibrate the model are similar. The upper panel in Figure 5.3(a) shows the TAC data from Drinking Episode 1 along with the fit model's prediction of the TAC data. The lower panel of Figure 5.3(a) shows the raw BrAC data along with the estimated BrAC signal deconvolved from the TAC signal using the fit model and the optimal regularization parameters. In the right hand panel of Figure 5.3, Figure 5.3(b), we have plotted the calibrated convolution kernels, or impulse response functions, for the 11 drinking episodes shown in Figure 5.1 obtained using the model derived in Section 4 with the appropriate optimal parameters $q_{1}^{*}$ and $q_{3}^{*}$ (with $q_{2} \equiv 0$ ) as given in Table 5.2. The variance among the curves indicates that a more sophisticated model than our two parameter linear 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 likely the appropriate paradigm to describe the transdermal transport of ethanol from the blood through the skin to the TAC sensor.

### 5.4. Deconvolution Results

We used the model calibrated with Drinking Episode 1 to de-convolve the BrAC signal from the TAC signal for the other 10 remaining drinking episodes shown in Figure 5.1. In Table 5.4 we compare 5 different ways for obtaining BrAC information in the field. In particular, we look at three different statistical measures typically used by alcohol researchers: peak $\operatorname{BrAC}(\mathrm{P})$ in units of percent alcohol over the course of the drinking episode, the time $(\mathrm{T})$ in hours elapsed since the start of the data set at which the peak BrAC occurs, and the area (A) under the BrAC curve.

The five different ways in which we computed these three statistics are: (1) directly from the raw BrAC data provided to us by the subject, (2) from the estimated BrAC curve deconvolved from the field TAC data signal using the approach we have presented here, (3) from the estimated BrAC curve obtained by calibrating the model on each drinking episode, (4) a standard method (see Matthews and Miller, [21], Carey and Hustad, [19], and Hustad and Carey, [20]) for obtaining an estimate of BrAC based on a drinking diary (this method does not use the field TAC data at all), and (5) directly from the raw TAC data collected by the sensor in the field. Note that in comparing these different approaches, they require different amounts of subject supplied data from the field, the collection of which places different levels of burden on the subject. Method 1 requires that the subject use a breath analyzer to provide field measurements of BrAC , Method 2 (the focus of our effort here) requires simultaneous BrAC and TAC measurements for only a single drinking episode (drinking episode 1 in this particular example) and only TAC data for all the remaining drinking episodes in the field, Method 3 requires simultaneous BrAC and TAC measurements from the field for all drinking episodes, Method 4 requires that the subject maintain a drinking diary for all drinking episodes in the field, and Method 5 requires only TAC data for all field drinking episodes.

In the left hand panel of Figure 5.4, Figure 5.4(a), we show a number of BrAC curves for Drinking Episode 7. On the same set of axes we have plotted the raw BrAC data collected with a breath analyzer in the field, an estimated BrAC curve deconvolved from the field TAC signal using the method we have developed here with the model calibrated using Drinking Episode 1, estimated BrAC curves using a field drinking diary and the method
discussed in (Matthews and Miller, [21], Carey and Hustad, [19], and Hustad and Carey, [20]) for both the case of standard drinks and percent alcohol for the drinks consumed, and finally, the raw TAC data for Drinking Episode 7 collected by the sensor in the field. In the right hand panel of Figure 5.4, Figure 5.4(b), we have plotted the convolution kernels or impulse response functions obtained by calibrating the model using the data from Drinking Episodes 3 and 8 . Note that, for these two drinking episodes, the resulting convolution kernels are very close to each other. In the left hand panel of Figure 5.5, Figure 5.5(a) we have plotted the estimated BrAC curves for Drinking Episode 3. In this figure, the estimated BrAC curve deconvolved from the field TAC signal using the method we have developed here was obtained by first calibrating the forward model using the data for Drinking Episode 8. In the right hand panel of Figure 5.5, Figure 5.5(b), we have plotted estimated BrAC curves for Drinking Episode 8. In this case, the estimated BrAC curve deconvolved from the TAC signal was obtained using the technique described here with the forward model calibrated using the data from Drinking Episode 3.

## 6. Discussion and Conclusions

### 6.1 Calibration

It is clear from the plots in Figure 5.3(b) and from the parameter values in Table 5.2 that calibration of the model based on the different drinking episodes in Figure 5.1, lead to different models. It would be valuable to try to identify what exactly it is that differentiates the 11 drinking episodes and to then use this to improve our calibration protocol. Frequency domain analysis could potentially be used to identify drinking patterns that could then be correlated with the optimal values of the model parameters. Indeed, the optimal values of the two model parameters, $q_{1}^{*}$ and $q_{3}^{*}$, may in fact characterize different drinking patterns or profiles. If this were the case, an alcohol challenge protocol yielding richer calibration data and a form of gain scheduling, in which different convolution filters are selected depending on the characteristics of a particular drinking episode, could significantly improve the accuracy of BrAC estimates. Figure 5.5 provides evidence that such an approach might work. In Figure 5.4(b) we plot the impulse response function or convolution filter kernels when the model is calibrated using Drinking Episodes 3 and 8 . Note that these two curves and their corresponding values of $q_{1}^{*}$ and $q_{3}^{*}$ are very similar. In Figure 5.5(a), we plot the results of using the model calibrated with Drinking Episode 8 to deconvolve an estimated BrAC signal from the TAC signal from Drinking Episode 3. In Figure 5.5(b), we do the opposite and use the model calibrated with Drinking Episode 3 to deconvolve an estimated BrAC signal from the TAC signal for Drinking Episode 8. In these two plots, there appears to be reasonably close agreement between the estimated BrAC signal for the drinking episode and the BrAC signal obtained when the drinking episode is used to calibrate the model (i.e., when both the TAC and BrAC data are used in the deconvolution).

The fact that we can obtain reasonably good fits when each of the 11 drinking episodes is used to calibrate the model suggests that diffusion is the appropriate modeling paradigm. However, the fact that we observe variation in the models obtained from drinking episode to drinking episode suggests that a more sophisticated, possibly nonlinear, diffusion model with a higher dimensional parameterization may be more appropriate. For example, one might consider a nonlinear Fickian based diffusion law involving a diffusivity that is a function of ethanol concentration and/or the gradient of ethanol concentration. Of course in this case, strictly speaking, extracting an estimate of the BrAC signal from the field TAC signal can no longer be considered a deconvolution problem.

### 6.2 Deconvolution

For all three types of BrAC measures, the calibrated BrAC estimation did the best. Among the other methods, using the raw TAC data provided by the TAC sensor provides a reasonable, second best estimate of peak BrAC . This approach, however, provides a less accurate estimate of the area underneath the BrAC curves and a particularly poor estimate of the time of peak BrAC. The drinking diary method was good at capturing the time of peak BrAC , but was poorest at estimating the area under the BrAC curve. Our approach did almost as well as the calibrated BrAC method at estimating the time of peak BrAC . Although not as accurate as the calibrated BrAC method at estimating the area underneath the BrAC curves, our method was considerably better than the other three methods in this regard.

It is, of course, not surprising that deconvolution was more accurate when BrAC data from each individual drinking episode was used to calibrate the model before the deconvolution. Indeed, this approach is less blind. However, this requires subjects to not only continuously wear the TAC sensor, but to also provide at least some contemporaneous BrAC measurements from the field. Indeed, in comparing the data in Table 5.4 for the different methods used to obtain estimated BrAC curves, one must take into account the amount of field data the subject must provide. For example, estimates based on the raw TAC data, while less accurate, require no active participation by the subject in data collection. The drinking diary approach, on the other hand, requires the subject to maintain a detailed drink diary in the field. This increases subject burden and decreases the naturalism of the drinking environment. Our blind deconvolution approach requires an alcohol challenge session before sending the subject out into the field, but once in the field, no active participation by the subject in data collection is required. Thus naturalistic drinking behaviors should not be affected.

In general, our results indicate that our approach is a relatively effective tool for obtaining semi-quantitative measure of BrACs from TAC devices. It was able to produce relatively consistent measures of BrAC , and given the relatively low real-time subject burden, our approach appears to be an effective way to improve real-time objective measures of alcohol consumption.

## References

1. Swift RM. Direct measurement of alcohol and its metabolites. Addiction. 2003; 98S:73-80. [PubMed: 14984244]
2. Swift, RM.; Swette, LL. Assessment of ethanol consumption with a wearable, electronic ethanol sensor/recorder.. In: Litten, R.; Allen, J., editors. Measuring Alcohol Consumption: Psychosocial and Biological Methods. Humana Press; Totowa, NJ: 1992.
3. Labianca, Dominick A. The chemical basis of the breathalyzer, a critical analysis. Journal of Chemical Education. 1990; 67(3):259-261.
4. Okubo, A. Diffusion and Ecological Problems: Mathematical Models. Springer-Verlag; New York: 1980.
5. Anderson JC, Hlastala MP. The kinetics of transdermal ethanol exchange. Journal of Applied Physiology. 2006; 100:649-655. [PubMed: 16239611]
6. Dumett M, Rosen IG, Sabat J, Shaman A, Tempelman LA, Wang C, Swift RM. Deconvolving an estimate of breath measured blood alcohol concentration from biosensor collected transdermal ethanol data. Appl. Math. and Comp. 2008; 196:724-743.
7. Banks, HT.; Kunish, K. Estimation Techniques for Distributed Parameter Systems. Boston, Birkhauser: 1989.
8. Banks HT, Ito K. A unified framework for approximation in inverse problems for distributed parameter systems. Control Theory Advanced Technology. 1988; 4(1):73-90.
9. Bertsekas, DP. Nonlinear Programming. 2nd ed.. Athena Scientific; Nashua, NH: 1999.
10. Bradley, SP.; Hax, AC.; Magnanti, TL. Applied Mathematical Programming. Addison-Wesley; Reading, PA: 1977.
11. Brauer J, Gomez-Sorzano A, Sethuraman S. Decomposing violence: political murder in Colombia, 1946-1999. European Journal of Political Economy. 2004; 20(2):447-461.
12. Hodrick R, Prescott E. Postwar U.S. business cycles: An empirical investigation. Journal of Money, Credit and Banking. 1997; 29(1):1-16.
13. Ley; Eduardo. The Hodrick-Prescott Filter, Knowledge Brief for Bank Staff. The World Bank; Washington, DC: 2006.
14. Danthine, Jean-Pierre, Girardin, Michel. Business cycles in Switzerland, A comparative study. European Economic Review. 1989; 33:31-50.
15. Curtain RF, Salamon D. Finite dimensional compensators and infinite dimensional systems with unbounded input operators. SIAM J. Control and Optimization. 1986; 24(4):797-816.
16. Pritchard AJ, Salamon D. The linear quadratic control problem for infinite dimensional systems with unbounded input and output operators. SIAM J. Control and Optimization. 1987; 25(1):121144.
17. Gibson JS, Rosen IG. Approximation of discrete time LQG compensators for distributed systems with boundary input and unbounded measurement. Automatica. 1988; 24(4):517-529.
18. Banks HT, Ito K. Approximation in LQR problems for infinite dimensional systems with unbounded input operators, J. Mathematical Systems. Estimation and Control. 1997; 7(1):1-34.
19. Carey KB, Hustad JTP. Are retrospectively reconstructed blood alcohol concentrations accurate? Preliminary results from a field study. Journal of Studies on Alcohol. 2002; 63:762-766. [PubMed: 12529077]
20. Hustad JTP, Carey KB. Using calculations to estimate blood alcohol concentrations for naturally occurring drinking episodes: A validity study. J Stud Alcohol. 2005; 66(1):130-138. [PubMed: 15830913]
21. Matthews DB, Miller WR. Estimating blood alcohol concentration: Two computer programs and their applications in therapy and research. Add. Behaviors. 1979; 4:55-60.
22. National Highway Traffic Safety Administration. Computing a BAC Estimate. Department of Transportation; Washington, D.C.: 1994.
23. Hille, E.; Phillips, RS. Functional Analysis and Semi-Groups, Providence. American Mathematical Society; 1957.
24. Helmberg, G. Introduction to Spectral Theory in Hilbert Space. North Holland/American Elsevier; Amsterdam: 1975.
25. Pazy, A. Semigroups of Linear Operator and Applications to Partial Differential Equations. Springer; New York: 1983.
26. Kato, T. Perturbation Theory for Linear Operators. Second Edition. Springer; Berlin: 1976.
27. Levi AJ, Rosen IG. A novel formulation of the adjoint method in the optimal design of quantum electronic devices. Siam Journal on Control and Optimization. 2010; 48(5):3191-3223.
28. Najfeld, Igor; Havel, Timothy F. Derivatives of the matrix exponential. Advances in Applied Mathematics. 1995; 16(3):321-375.
29. Adams, Robert A. Sobolev Spaces. Academic Press; New York: 1975.
30. Wloka, J. Partial Differential Equations. Cambridge University Press; Cambridge: 1987.
31. Tanabe, H. Equations of Evolution. Pitman; London: 1979.
32. Showalter, RE. Hilbert Space Methods for Partial Differential Equations. Pitman; London: 1977.
33. Friedman, A. Partial Differential Equations of Parabolic Type. Prentice Hall; Englewood Cliffs: 1964.
34. Lions, JL. Optimal Control of Systems Governed by Partial Differential Equations. Springer Verlag; New York: 1971.
35. Schultz; Martin. Spline Analysis. Prentice Hall; Englewood Cliffs: 1971.


Figure 5.1.
Plot of TAC and BrAC data showing the 11 actual drinking episodes.



Figure 5.2.
(a) (left panel) Plot of trend component of TAC signal along with the automatically identified drinkingepisodes. (b) (right panel) Plot of trend and cyclical components of TAC signal produced by HP filter.



Figure 5.3.
(a) Estimated TAC signal as output of fit model for drinking episode 1 (top left panel) and estimated BrAC signal as deconvolved from TAC data using fit model for drinking episode 1 (lower left panel). (b) Convolution filters or impulse response functions obtained using each of the 11 different drinking episodes in Figure 5.1 to calibrate the model (right panel).


Figure 5.4.
(a) (left panel) Estimated BrAC signal for drinking episode 7 from Figure 5.1. (b) (right panel) Convolution kernel or impulse response functions obtained by calibrating model using drinking episodes 3 and 8 from Figure 5.1.


Figure 5.5.
(a) (left panel) Estimated BrAC for Drinking Episode 3 using model calibrated using Drinking Episode 8. (b) (right panel) Estimated BrAC for Drinking Episode 8 using model calibrated using Drinking Episode 3.
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Table 5.1
Automatically identified starting and ending hours for the 13 automatically identified drinking episodes.

| Event | $\mathbf{1}$ | $\mathbf{2}$ | $\mathbf{3}$ | $\mathbf{4}$ | $\mathbf{5}$ | $\mathbf{6}$ | $\mathbf{7}$ | $\mathbf{8}$ | $\mathbf{9}$ | $\mathbf{1 0}$ | $\mathbf{1 1}$ | $\mathbf{1 2}$ | $\mathbf{1 3}$ |
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| Start Hr | 0 | 16 | 66 | 87 | 114 | 135 | 160 | 185 | 210 | 231 | 257 | 282 | 328 |
| End Hr | 16 | 66 | 87 | 114 | 135 | 160 | 185 | 210 | 231 | 257 | 282 | 328 | 351 |

\footnotetext{
Converged values of the model and regularization parameters and various error values when calibrating on the 11 different drinking episodes．

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Table 5.3
Summary of data presented in Table 5.2.

| Summary | Minimum Value | Maximum Value | $\mu$ | $\sigma$ |
| :---: | :---: | :---: | :---: | :---: |
| $q_{1}^{*}$ | 0.294 | 2.350 | 1.038 | 0.721 |
| $q_{3}^{*}$ | 0.199 | 1.770 | 1.200 | 0.452 |
| $r_{1}^{*}$ | 0.100 | 0.210 | 0.130 | 0.040 |
| $r_{2}^{*}$ | 0.100 | 1.080 | 0.327 | 0.342 |
| TAC L $_{2}$ | $5 \%$ | $33 \%$ | $15 \%$ | $9 \%$ |
| TAC L |  |  | $32 \%$ | $20 \%$ |
| BrAC L 2 | $11 \%$ | $79 \%$ |  |  |
| BrAC L $\infty_{\infty}$ | $17 \%$ | $77 \%$ | $27 \%$ | $11 \%$ |
| Peak BrAC | $0 \%$ | $42 \%$ | $12 \%$ | $12 \%$ |
| Time Peak | $5 \%$ | $86 \%$ | $33 \%$ | $30 \%$ |
| Area | $0 \%$ | $15 \%$ | $6 \%$ | $5 \%$ |

Peak BrAC $\left(P_{i}\right)$ ，time at which peak BrAC occurs $\left(T_{i}\right)$ ，and area under the $\operatorname{BrAC}$ curve $\left(A_{i}\right), i=1,2,3,4$ ，and 5 ，computed five different ways for the 11 different drinking episodes shown in Figure 5．1．

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