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Tracking and blind deconvolution of blood alcohol concentration from transdermal alcohol biosensor data: A population model-based LQG approach in Hilbert space

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Abstract

LQG control in Hilbert space, a novel approach for random abstract parabolic systems, and new transdermal alcohol biosensor technology are combined to yield tracking controllers that can be used to automate inpatient management of alcohol withdrawal syndrome and human subject intravenous alcohol infusion studies, and to blindly deconvolve blood or breath alcohol concentration from biosensor measured transdermal alcohol level. The approach taken is based on a full-body alcohol population model in the form of a random, nonlinear, hybrid system of ordinary and partial differential equations and its abstract formulation in a Gelfand triple of Bochner spaces. The efficacy of the approach is demonstrated through simulation studies based on laboratory collected drinking data.

Keywords

LQG tracking; Random abstract parabolic systems; Transdermal alcohol biosensor; Alcohol withdrawal syndrome; Deconvolution

1. Introduction

A transdermal alcohol biosensor measures alcohol excreted by the skin through perspiration. These devices function as fuel cells via an oxidation–reduction reaction that produces electrons in numbers proportional to the number of molecules of ethanol present (Swift, 2000). Using these newly developed devices, it is now possible for researchers and clinicians studying and treating people suffering from alcohol use disorder (AUD), to collect data passively, unobtrusively, and nearly continuously in the field and in naturalistic settings (Swift, 2000). In this brief paper, we consider two applications of this new biosensor technology formulated as linear quadratic Gaussian (LQG) tracking problems. The first is

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the in-patient management of alcohol withdrawal syndrome (AWS) (Bayard, Mcintyre, Hill, & Woodside, 2004; Dissanaike, Halldorsson, Frezza, & Griswold, 2006; Hansbrough et al., 1984; Hodges & Mazur, 2004) and the related problem of carrying out alcohol clamping studies (ACS) (O'Connor, Morzorati, Christian, & Li, 1998; Ramchandani et al., 2006) in the laboratory. As currently implemented, both of these rely on the manually controlled, open-loop, intravenous, infusion of ethanol. The second application is the estimation of the commonly accepted measures of alcohol intoxication, blood and breath alcohol concentration, BAC and BrAC, respectively, based on biosensor measured transdermal alcohol concentration or TAC (Dai, Rosen, Wang, Barnett, & Luczak, 2016; Rosen, Luczak, & Weiss, 2014; Sirlanci et al., 2018). A comprehensive survey of the literature on TAC, TAC biosensors, and the estimation of BAC or BrAC from TAC measurements can be found in Yao, Luczak, and Rosen (2022).

Over the course of the last two decades, our research team comprised of applied mathematicians, statisticians, psychologists, and psychiatrists, has developed high fidelity models for the metabolism and transport of ethanol from the blood or from either intravenous or oral ingestion, to its collection and measurement by a TAC biosensor. Once the parameters in the model have been fit, our models exhibit excellent agreement with clinical and laboratory data (Dai et al., 2016; Rosen et al., 2014). However, the use of these models (which take the form of, in general, nonlinear, abstract parabolic hybrid systems of PDEs and ODEs) in the design of controllers is confounded by the fact that the model parameters tend to vary across drinking episodes, subjects, placement location of the sensor, the manufacturer and calibration of the sensor itself, and environmental conditions such as ambient temperature and humidity. By collecting data from hundreds of subjects, we have been able to demonstrate that estimates for the distributions of these model parameters can be identified (Sirlanci et al., 2019, 2018). Consequently, in this treatment, we develop our control strategies based on what we shall refer to as a *population model*, that is, a model in which the parameters are assumed to be uncertain but with known distribution. We do this by relying on a novel treatment of random parabolic systems wherein the random parameters are effectively treated as additional spatial variables (Gittelson, Andreev, & Schwab, 2014; Schwab & Gittelson, 2011). The standard treatment of parabolic systems in a Gelfand triple of Hilbert spaces is extended to Bochner spaces and then, with the use of linear semigroup theory, we are able to obtain a state space model to which the LQG theory in infinite dimensional Hilbert space and its associated finite dimensional approximation and convergence results can be directly applied (Banks & Kunisch, 1984; Gibson & Rosen, 1988; Yao et al., 2022).

We solve the two TAC biosensor related problems mentioned earlier by using the novel framework developed in Gittelson et al. (2014) and Schwab and Gittelson (2011) (and described above) to extend LQG tracking control to parabolic systems with random parameters. This is an extension of our earlier effort (Yao et al., 2022) that focused on the development of LQG compensators (i.e. a combined regulator and observer) for problems of this type. In Yao et al. (2022) we also looked at the AWS and ACS problems, but the resulting designs could only track piece-wise constant reference signals as equilibrium solutions to the nonlinear state space models. With the approach we develop here, we are able to design nonlinear output feedback compensators that permit the tracking of an arbitrary reference signal. In particular, the deconvolution or estimation of BrAC from TAC would not be possible using the approach in Yao et al. (2022). While the LQG theory and its associated finite dimensional approximation and convergence results for both continuous and discrete time systems set in infinite dimensional Hilbert state spaces have been studied for nearly half a century (see, for example, Banks and Kunisch (1984), Gibson and Rosen (1988) and Lions (1971), for a more complete survey of the literature), to the best of our knowledge, this treatment is the first to look at sampled time LQG tracking in Hilbert space, its extension to a particular subclass of nonlinear systems, and the associated finite dimensional approximation and convergence theory.

The remainder of the paper is organized as follows. In the next section we describe our first principles physics based full-body alcohol model for the metabolism and transdermal transport of ethanol. In a third section we recast this model (in which we have now allowed the parameters to be random) in state space form. In the fourth section we discuss LQG tracking in Hilbert space and its associated finite dimensional approximation theory, and in a final fifth section we present the results of some of our numerical studies.

2. Modeling the metabolism and transdermal transport of alcohol:

We consider the one dimensional hybrid ODE/PDE semilinear reaction diffusion system given for $t > 0$ by

$$\begin{aligned} &\frac{\partial x}{\partial t}(t,\eta) = q_1 \frac{\partial^2 x}{\partial \eta^2}(t,\eta), \\ &\eta \in (0,1), \\ &\frac{dw}{dt}(t) = q_3 \frac{\partial x}{\partial \eta}(t,0) - q_4 w(t) + \omega_1(t), \\ &\frac{dv}{dt}(t) = -q_5 \frac{\partial x}{\partial \eta}(t,1) - q_6 v - \frac{q_7 v}{q_8 + v} + q_2 u(t) + \omega_2(t), \end{aligned} \tag{1}$$

with boundary conditions, controlled variable and observation given by $x(t,0) = w(t)$, $x(t,1) = v(t)$, $z(t) = v(t)(\text{or } w(t))$, $y(t) = w(t) + \zeta(t)$, for $t > 0$, respectively, where q_i, $i = 1, 2, \ldots, 8$ are all positive. In addition, ω_1, ω_2, and ζ denote uncorrelated, zeromean, stationary, Gaussian white noise processes with variances σ_1^2, σ_2^2, and σ^2, respectively. In the above system $x(t,\eta)$ is the concentration of ethanol at time $t \geq 0$ and depth $\eta \in [0,1]$ in the epidermal layer of the skin, $w(t)$ is the concentration of ethanol in the transdermal alcohol biosensor vapor collection chamber at time $t \geq 0$, $v(t)$ is the concentration of ethanol in either the dermal layer with an active blood supply or the blood at time $t \geq 0$, and at time $t \geq 0$, $u(t)$ is the flow rate of either an infused intravenous or oral dosing of a solution of ethanol or BAC. The initial conditions are given by $x(0,\eta) = \varphi_0(\eta) \geq 0$, $\eta \in (0,1)$, $w(0) = \theta_0 \geq 0$, and $v(0) = \chi_0 \geq 0$. Without loss of generality, we have normalized the thickness of the epidermal layer to be one.

The Michaelis–Menten (Mullen, 1977) nonlinear reaction term involving q_7 and q_8 in (1) models the liver's alcohol dehydrogenase enzyme-catalyzed metabolism of ethanol into aldehydes and ketones which are then either further processed, and used or excreted from the body through urine or breath. When $v \ll q_8$, we have first-order kinetics (i.e.

exponential decay) and when $q_8 \ll v$, we have zero-order kinetics. This is typical of enzyme catalyzed reactions where at higher substrate concentrations reaction rate saturates. At saturation, alcohol accumulates in the blood and crosses the blood–brain barrier resulting in intoxication. The term $-q_6 v$ represents all the other losses of ethanol from the blood; in general $q_6 v \ll \frac{q_7 v}{q_8 + v}$. A detailed description of the derivation of the model including the physical interpretation of the various parameters that appear in the model can be found in Yao et al. (2022).

The state is (w, v, x) and given a target trajectory reference signal, $\hat{v}$, (or $\hat{w}$), the tracking objective is to determine an output feedback law for u that forces $v(w)$ to track $\hat{v}(\hat{w})$ based on observations of w, with the caveat that only the distribution of $q = (q_1, q_2, q_3, q_4, q_5, q_6, q_7, q_8)$ is known.

3. A population model in Bochner space

Let Q be a compact subset of the positive orthant of $\mathbb{R}^8$, let $H = \mathbb{R}^2 \times L^2(0, 1)$ be endowed with the standard inner product and norm, and for $q \in Q$, let $H_q = \mathbb{R}^2 \times L^2(0, 1)$ with the inner product $\left\langle (\theta, \xi, \varphi), (\bar{\theta}, \bar{\xi}, \bar{\varphi}) \right\rangle_q = \frac{q_1}{q_3}\theta\bar{\theta} + \frac{q_1}{q_5}\xi\bar{\xi} + \int_0^1 \varphi(\eta)\bar{\varphi}(\eta)d\eta$. It is clear that for $\hat{\varphi}, \hat{\psi} \in H$ fixed, the map $q \mapsto \langle \hat{\varphi}, \hat{\psi} \rangle_q$ is continuous from Q into $\mathbb{R}$. Let V be the Hilbert space $V = \left\{ (\theta, \xi, \varphi) \in H : \varphi \in H^1(0, 1), \theta = \varphi(0), \xi = \varphi(1) \right\}$, $\langle (\varphi(0), \varphi(1), \varphi), (\bar{\varphi}(0), \bar{\varphi}(1), \bar{\varphi}) \rangle_V = \varphi(0)\bar{\varphi}(0) + \varphi(1)\bar{\varphi}(1) + \langle \varphi', \bar{\varphi}' \rangle_{L^2(0,1)}$, where $\langle \cdot, \cdot \rangle_{L^2(0,1)}$ denotes the standard inner product on $L^2(0, 1)$. Standard arguments (Tanabe, 1979) yield the dense and continuous embeddings $V \hookrightarrow H_q \hookrightarrow V^*$ and that the embeddings are uniformly bounded with respect to q for $q \in Q$. Define the bilinear form $a(q; \cdot, \cdot): V \times V \to \mathbb{R}$ by

$$
\begin{aligned}
&a(q; (\varphi(0), \varphi(1), \varphi), (\bar{\varphi}(0), \bar{\varphi}(1), \bar{\varphi})) = \frac{q_1 q_4}{q_3} \cdot \\
&\varphi(0)\bar{\varphi}(0) + \frac{q_1 q_6}{q_5}\varphi(1)\bar{\varphi}(1) + q_1 \int_0^1 \varphi'(\eta)\bar{\varphi}'(\eta)d\eta \,.
\end{aligned}
\tag{2}
$$

The assumption that Q is compact immediately yields that the form $a(q; \cdot, \cdot)$ given in (2) is uniformly (with respect to q for $q \in Q$) bounded and coercive, and it depends continuously on q for $q \in Q$ (see Banks & Ito, 1988; Dai et al., 2016; Rosen et al., 2014; Sirlanci et al., 2019; Yao et al., 2022).

Define $A(q): Dom(A(q)) \subset H \to H$ by: $\langle A(q)\hat{\varphi}, \hat{\psi} \rangle_{V^*, V} = -a(q; \hat{\varphi}, \hat{\psi})$, for $\hat{\varphi} \in Dom(A(q))$, and $\hat{\psi} \in V$, where $Dom(A(q)) = \left\{ \hat{\varphi} = (\varphi(0), \varphi(1), \varphi) \in V : \varphi \in H^2(0, 1) \right\}$ is independent of $q \in Q$. It is not difficult to show (Banks & Ito, 1988; Banks & Kunisch, 1984; Dai et al., 2016; Pazy, 1983; Tanabe, 1979) that for $\hat{\varphi} = (\varphi(0), \varphi(1), \varphi) \in Dom(A(q))$, we have $A(q)\hat{\varphi} = A(q)(\varphi(0), \varphi(1), \varphi) = (q_3\varphi'(0) - q_4\varphi(0), \quad -q_5\varphi'(1) - q_6\varphi(1), q_1\varphi'')$, and that the operator $A(q)$ is densely defined on H_q, regularly dissipative (see, for example Tanabe, 1979) and self-adjoint. Consequently $A(q)$ is the infinitesimal generator of a uniformly exponentially stable, self-adjoint, analytic semigroup of bounded linear operators, $\{T(q;t): t \geq 0\}$, on H_q (Banks & Ito, 1988; Banks & Kunisch, 1984; Pazy, 1983; Tanabe, 1979).

Formally the state variable is $\mathbf{x} = (w, v, x) \in H$ and we want to force either v or w to track the given reference signal. We define the controlled variable operator $D \in \mathscr{L}(H_q, \mathbb{R})$ by either $D(w, v, x) = \sqrt{\hat{v}}v$ or $D(w, v, x) = \sqrt{\hat{v}}w$, for some weight $\hat{v} > 0$. The observed state variable is w and therefore the observation or output operator $C \in \mathscr{L}(H_q, \mathbb{R})$ is given by $C(w, v, x) = w$. For $q \in Q$, the input operator $B(q) \in \mathscr{L}(\mathbb{R}, H_q)$ is given by $B(q)u = (0, q_2 u, 0)$, and the random noise influence operator $B_1 \in \mathscr{L}\left(\mathbb{R}^2, H_q\right)$ by $B_1\omega = (\omega_1, \omega_2, 0)$. We have $U = Y = Z = \mathbb{R}$, all of which are clearly finite dimensional.

The precise value of the parameter vector $q \in Q$ is uncertain. As in Gittelson et al. (2014), Schwab and Gittelson (2011) we assume $q = \mathscr{q}$ is a random vector with support Q and distribution described by the either known or fit (see, for example, Sirlanci et al. (2019, 2018) and Yao et al. (2022)) push-forward probability measure π (i.e. $\mathscr{q} \sim \pi$) with the assumption that all functions involving q are π-measurable. The state equation is formulated in weak form wherein the parameters q are treated as additional spatial variables; that is the spatial dimension of the state equation effectively now becomes $1 + \dim q = 9$ with the spatial variable given by $(\eta, q_1, q_2, \ldots, q_8)$.

Let $\mathscr{V}$ be the Bochner space $\mathscr{V} = L_\pi^2(Q; V)$ and let $\mathscr{V}^*$ be its dual. Let $\mathscr{H} = L_\pi^2(Q; H_q)$, and identify the Hilbert space $\mathscr{H}$ with its dual to obtain the Gelfand triple (Tanabe, 1979) $\mathscr{V} \hookrightarrow \mathscr{H} \hookrightarrow \mathscr{V}^*$. Define the bilinear form $\mathscr{a}(\cdot, \cdot)$ on $\mathscr{V} \times \mathscr{V}$ and the operator $\mathscr{A} \in \mathscr{L}(\mathscr{V}, \mathscr{V}^*)$ by:

$$
\begin{aligned}
&\mathscr{a}(\hat{\varphi}, \hat{\psi}) = \mathbb{E}_\pi\left\{a(q; \hat{\varphi}(q), \hat{\psi}(q))\right\} \\
&= \int_Q a(q; \hat{\varphi}(q), \hat{\psi}(q)) d\pi(q) = -\langle \mathscr{A}\hat{\varphi}, \hat{\psi} \rangle_{\mathscr{V}^*, \mathscr{V}},
\end{aligned}
$$

for $\hat{\varphi}, \hat{\psi} \in \mathscr{V}$. The operator $\mathscr{A}$ is regularly dissipative (see, for example, Tanabe (1979)) and self-adjoint and can be restricted to $Dom(\mathscr{A}) = \{\varphi \in \mathscr{V}: \mathscr{A}\varphi \in \mathscr{H}\}$ as the infinitesimal generator of a uniformly exponentially stable, analytic semigroup $\{\mathscr{T}(t): t \geq 0\}$ of bounded, self-adjoint, operators on $\mathscr{H}$.

Since our design will be based on LQ theory, we first consider the linear model (i.e. $q_7 = q_8 \equiv 0$). We will extend these ideas to the semilinear case later. We assume zero-order hold input and random noise with sampling time $\tau > 0$, and we formulate the discrete time tracking problem by considering the quadratic performance index

$$
\hat{J}(u) = \mathbb{E}_\pi\left\{\sum_{k = k_0}^{k_1 - 1} \left|\hat{D}\mathbf{x}_k - \xi_k\right|^2 + \hat{r}u_k^2 + \hat{\rho}\left|\hat{D}\mathbf{x}_{k_1} - \xi_{k_1}\right|^2\right\},
$$

where $\hat{r} > 0$, $\hat{\rho} \geq 0$, k_1 can be either finite or infinite (in the latter case, $\hat{\rho} = 0$), $\{\xi_k\}$ is the given reference signal to be tracked, and when $\mathscr{q} = q$, $\mathbf{x}_k$ is given by

$$\mathbf{x}_{k+1} = \hat{A}(q)\mathbf{x}_k + \hat{B}(q)u_k + \hat{B}_1(q)\omega(k\tau), \tag{3}$$

with $\mathbf{x}_0 = (w(0), v(0), x(0, \cdot))$, $\omega(t) = [\omega_1(t), \omega_2(t)]^T$, $\hat{A}(q) = T(q;\tau) \in \mathscr{L}(H_q, H_q)$ and, since $-A(q)$ is coercive, and hence either invertible or may be made so without loss of generality via a change of variable, that $\hat{B}(q) = A(q)^{-1}(\hat{A}(q) - I)B(q) \in \mathscr{L}(\mathbb{R}, H_q) = H_q$ with $\hat{B}(q) \in Dom(A(q))$, and $\hat{B}_1(q) = A(q)^{-1}(\hat{A}(q) - I)B_1 \in \mathscr{L}\left(\mathbb{R}^2, H_q\right) = H_q \times H_q$ with $\hat{B}_1(q) \in Dom(A(q)) \times Dom(A(q))$. Furthermore, it follows that $\hat{C} = C$ and $\hat{D} = D$, and we define $\hat{Q} = \hat{D}^*\hat{D} \in \mathscr{L}(H_q, H_q)$, $\hat{G} = \hat{\rho}\hat{D}^*\hat{D} \in \mathscr{L}(H_q, H_q)$, and $\hat{R} = \hat{r}$.

Define the operators $\mathscr{B} \in \mathscr{L}(\mathbb{R}, \mathscr{H})$, $\mathscr{B}_1 \in \mathscr{L}\left(\mathbb{R}^2, \mathscr{H}\right)$, and $\mathscr{C}, \mathscr{D} \in \mathscr{L}(\mathscr{H}, \mathbb{R})$ by $\langle \mathscr{B}u, f \rangle = \langle B(\cdot)u, f \rangle_{\mathscr{H}}, f \in \mathscr{H}, u \in \mathbb{R}$, $\langle \mathscr{B}_1\omega, f \rangle = \langle B_1\omega, f \rangle_{\mathscr{H}}, f \in \mathscr{H}, \omega \in \mathbb{R}^2$, $\mathscr{C}\hat{\varphi} = \mathbb{E}_\pi\{C\hat{\varphi}\}$, and $\mathscr{D}\hat{\varphi} = \mathbb{E}_\pi\{D\hat{\varphi}\}$, $\hat{\varphi} \in \mathscr{H}$, respectively. Then set $\widehat{\mathscr{A}} = \mathscr{T}(\tau) \in \mathscr{L}(\mathscr{H}, \mathscr{H})$, $\widehat{\mathscr{B}} = \mathscr{A}^{-1}(\widehat{\mathscr{A}} - \mathscr{I})\mathscr{B} \in \mathscr{L}(\mathbb{R}, \mathscr{H})$, $\widehat{\mathscr{B}}_1 = \mathscr{A}^{-1}(\widehat{\mathscr{A}} - \mathscr{I})\mathscr{B}_1 \in \mathscr{L}\left(\mathbb{R}^2, \mathscr{H}\right)$, $\widehat{\mathscr{C}} = \mathscr{C} \in \mathscr{L}(\mathscr{H}, \mathbb{R})$ and $\widehat{\mathscr{D}} = \mathscr{D} \in \mathscr{L}(\mathscr{H}, \mathbb{R})$, where $\mathscr{I}$ is the identity operator on $\mathscr{H}$. When we discuss the solution to the LQG tracking problem in the next section, we will also require the operators $\widehat{\mathscr{Q}}$ and $\widehat{\mathscr{G}}$ in $\mathscr{L}(\mathscr{H}, \mathscr{H})$ given by $\widehat{\mathscr{Q}} = \widehat{\mathscr{D}}^*\widehat{\mathscr{D}}$, and $\widehat{\mathscr{G}} = \hat{\rho}\widehat{\mathscr{D}}^*\widehat{\mathscr{D}}$, respectively.

With these definitions, we can now rewrite the performance index $\hat{J}$ given above and consider the equivalent discrete-time tracking problem in $\mathscr{H}$, Problem ($P1$), given by

$$\widehat{\mathscr{J}}(u) = \sum_{k=k_0}^{k_1-1} \left|\widehat{\mathscr{D}}x_k - \xi_k\right|^2 + \hat{r}u_k^2 + \hat{\rho}\left|\widehat{\mathscr{D}}x_{k_1} - \xi_{k_1}\right|^2 \tag{4}$$

$$\begin{aligned} x_{k+1} &= \widehat{\mathscr{A}}x_k + \widehat{\mathscr{B}}u_k + \widehat{\mathscr{B}}_1\omega(k\tau), \quad x_0 = \hat{\varphi}_0 \in \mathscr{H}, \\ y_k &= \hat{C}x_k + \zeta(k\tau), \quad k = k_0, k_0+1, k_0+2, \ldots, \end{aligned} \tag{5}$$

where $x = (w, v, \mathscr{X}) \in \mathscr{H}$ with all components now being functions of $q \in Q$. The quadratic performance index $\widehat{\mathscr{J}}$ given in (4) is equivalent to $\hat{J}$ and the solution to (5) agrees with the solution to (3), π almost surely on Q (Gittelson et al., 2014; Schwab & Gittelson, 2011).

Since we do not observe the full state in (5), and in particular, how it depends on q, our feedback tracking controller requires an observer or state estimator. In anticipation of this, we note that for $q \in Q$, the deterministic state covariance operator and output covariance matrix are given by $\tilde{Q}(q) = \hat{B}_1(q)\Sigma\hat{B}_1(q)^* \in \mathscr{L}(H_q, H_q)$ where $\Sigma = diag\left(\sigma_1^2, \sigma_2^2\right) \in \mathbb{R}^{2\times 2}$, and $\tilde{R} = \sigma^2 \in \mathbb{R}$, respectively. The population model version of the state covariance operator is given by $\widehat{\mathscr{Q}} = \widehat{\mathscr{B}}_1\Sigma\widehat{\mathscr{B}}_1^* \in \mathscr{L}(\mathscr{H}, \mathscr{H})$.

The system (5) is infinite dimensional requiring finite dimensional approximation. In anticipation of the semilinear case, let N denote the multi-index $N = (n, m_1, m_2, \ldots, m_8)$ and when we write $N \to \infty$ we mean $n \to \infty$ and $m_i \to \infty$, $i = 1, 2, \ldots, 8$. We assume that the random parameter q_i has support $[a_i, b_i]$, $i = 1, 2, \ldots, 8$, all assumed to be bounded. Let Q be the compact subset of $\mathbb{R}^8$ given by $Q = \times_{i=1}^{8} [a_i, b_i]$. For $i = 1, 2, \ldots, 8$, partition $[a_i, b_i]$ into m_i equal subintervals, and let $\chi_j^{m_i}$ denote the characteristic function of the jth subinterval, $j = 1, 2, \ldots, m_i$ For $n = 1, 2, \ldots$, let $\{\varphi_j^n\}_{j=0}^{n}$ denote the standard linear B-splines on [0, 1] with respect to the uniform mesh $\left\{0, \frac{1}{n}, \frac{2}{n}, \ldots, 1\right\}$ and set $\hat{\varphi}_j^n = (\varphi_j^n(0), \varphi_j^n(1), \varphi_j^n) \in V$. Let J denote a multi-index of the form $J = (j_0, j_1, \ldots, j_8)$ where $j_0 \in \{0, 1, 2, \ldots, n\}$ and $j_i \in \{1, 2, \ldots, m_i\}$, $i = 1, 2, \ldots, 8$. Then set $\Phi_J^N = \hat{\varphi}_{j_0}^n \Pi_{i=1}^{8} \chi_{j_i}^{m_i}$, let $\mathscr{V}^N = \mathrm{span}_J\{\Phi_J^N\}$, and let $\mathscr{P}^N : \mathscr{H} \to \mathscr{V}^N$ denote the orthogonal projection of $\mathscr{H}$ onto $\mathscr{V}^N$. Standard arguments from the theory of splines and piecewise constant approximation in L^2 can be used to argue that $\mathscr{P}^N$ converges strongly to the identity in both $\mathscr{H}$ and $\mathscr{V}$ (Banks & Ito, 1988; Rosen et al., 2014; Sirlanci et al., 2019).

Since $\mathscr{V}^N$ is a subspace of $\mathscr{V}$ (and therefore $\mathscr{H}$ as well), we simply set $\widehat{\mathscr{C}}^N = \widehat{\mathscr{C}}\mathscr{P}^N$ for all multi-indices N. We obtain $\mathscr{A}^N \in \mathscr{L}\left(\mathscr{V}^N, \mathscr{V}^N\right)$ via a standard Galerkin approach (Banks & Kunisch, 1984; Dai et al., 2016; Gibson & Rosen, 1988; Rosen et al., 2014; Sirlanci et al., 2018) and set $\widehat{\mathscr{A}}^N = \exp\left(\mathscr{A}^N \tau\right) \in \mathscr{L}\left(\mathscr{V}^N, \mathscr{V}^N\right)$. We then set $\widehat{\mathscr{B}}^N = \left(\mathscr{A}^N\right)^{-1}\left(\widehat{\mathscr{A}}^N - \mathscr{I}^N\right)\mathscr{P}^N\mathscr{B} \in \mathscr{L}\left(\mathbb{R}, \mathscr{V}^N\right)$. Similarly we set $\widehat{\mathscr{B}}_1^N = \left(\mathscr{A}^N\right)^{-1}\left(\widehat{\mathscr{A}}^N - \mathscr{I}^N\right)\mathscr{P}^N\mathscr{B}_1 \in \mathscr{L}\left(\mathbb{R}^2, \mathscr{V}^N\right)$, and then set $\widetilde{\mathscr{Q}}^N = \widehat{\mathscr{B}}_1^N \Sigma\left(\widehat{\mathscr{B}}_1^N\right)^* \in \mathscr{L}\left(\mathscr{V}^N, \mathscr{V}^N\right)$. We note also that $\widehat{\mathscr{Q}}^N = \mathscr{P}^N \widehat{\mathscr{Q}} \mathscr{P}^N = \left(\widehat{\mathscr{D}}^N\right)^* \widehat{\mathscr{D}}^N$, where $\widehat{\mathscr{D}}^N = \widehat{\mathscr{D}}\mathscr{P}^N$, and $\widehat{\mathscr{G}}^N = \hat{\rho}\left(\widehat{\mathscr{D}}^N\right)^* \widehat{\mathscr{D}}^N$.

The Trotter–Kato theorem from linear semigroup theory (Banks & Ito, 1988; Banks & Kunisch, 1984; Gibson & Rosen, 1988; Pazy, 1983; Rosen et al., 2014; Sirlanci et al., 2019) yields that for each $x \in \mathscr{H}$, $\mathscr{T}^N(t)\mathscr{P}^N x \to \mathscr{T}(t)x$ in the $\mathscr{H}$ norm for $t \geq 0$, uniformly in t on compact sub intervals. Then since $\widehat{\mathscr{A}} = \mathscr{T}(\tau)$ and $\widehat{\mathscr{A}}^N = \mathscr{T}^N(\tau)$, it follows that $\widehat{\mathscr{A}}^N \mathscr{P}^N \to \widehat{\mathscr{A}}$ strongly in $\mathscr{H}$ as $N \to \infty$. Note that since $\mathscr{T}(t)$ and $\mathscr{T}^N(t)$ are self adjoint, we have $\left(\widehat{\mathscr{A}}^N\right)^* \mathscr{P}^N \to \widehat{\mathscr{A}}^*$ strongly in $\mathscr{H}$ as $N \to \infty$. Standard arguments (see Yao et al., 2022) (making use of finite dimensionality where appropriate) can then be used to argue the convergence of $\widehat{\mathscr{B}}^N$, $\widehat{\mathscr{B}}_1^N$, $\widehat{\mathscr{C}}^N$, $\widehat{\mathscr{D}}^N$, and $\widehat{\mathscr{Q}}^N$ along with their adjoints to their infinite dimensional counterparts, either strongly, or in some cases in the uniform operator topology, as $N \to \infty$

We consider the finite dimensional approximating LQG tracking problems on either the finite (k_1 is finite) or infinite-time horizon ($k_1 = \infty$, $\hat{\rho} = 0$) of minimizing

$$\mathscr{J}^N\left(u^N\right) = \sum_{k=k_0}^{k_1-1} \left|\widehat{\mathscr{D}}^N x_k^N - \xi_k\right|^2 + \hat{r}\left(u_k^N\right)^2 + \hat{\rho}\left|\widehat{\mathscr{D}}^N x_{k_1}^N - \xi_{k_1}\right|^2,$$
$$x_{k+1}^N = \widehat{\mathscr{A}}^N x_k^N + \widehat{\mathscr{B}}^N u_k^N + \widehat{\mathscr{B}}_1^N \omega(k\tau),\ x_0^N = \mathscr{P}^N \hat{\varphi}_0,$$
$$y_k^N = \widehat{\mathscr{G}}^N x_k^N + \zeta(k\tau),\ k = k_0, k_0 + 1, \ldots$$

4. Sampled-time LQG tracking

Since in discrete time, all relevant operators are bounded (in particular, the state transition operator), the sampled time LQ tracking theory on both the finite and infinite time horizon in Hilbert space is entirely analogous to the finite dimensional case (Kwakernaak & Sivan, 1972) with the exception of the fact that the Riccati matrix equations, the expressions for the gains, and the matrices themselves are simply replaced by their operator counterparts. We briefly summarize the relevant results (see, for example, Gibson and Rosen (1988), Kwakernaak and Sivan (1972) and Lions (1971)) for both the infinite dimensional and finite dimensional approximating problems given in the previous section along with the corresponding convergence theory.

When $k_1 < \infty$, for every initial value, x_0, and reference signal, $\{\xi_k\}$, the optimal input for the problem ($P1$) is unique and generated by the following control law

$$\begin{aligned}\overline{u}_k &= -\widehat{\mathscr{F}}_k\overline{x}_k + \Theta_k \\ &= \left(\widehat{\mathscr{B}}^*\mathscr{K}_{k+1}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\left(-\mathscr{K}_{k+1}\widehat{\mathscr{A}}\overline{x}_k + \theta_{k+1}\right),\end{aligned} \tag{6}$$

where $\widehat{\mathscr{F}}_k = \left(\widehat{\mathscr{B}}^*\mathscr{K}_{k+1}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\mathscr{K}_{k+1}\widehat{\mathscr{A}} \in \mathscr{L}(\mathscr{H}, \mathbb{R})$ and $\Theta_k = \left(\widehat{\mathscr{B}}^*\mathscr{H}_{k+1}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\theta_{k+1} \in \mathbb{R}$ with $\mathscr{K}_k$, θ_k computed backward from k_1 to k_0 in the following way:

$$\mathscr{K}_k = \widehat{\mathscr{A}}^*\left[\mathscr{K}_{k+1} - \mathscr{K}_{k+1}\widehat{\mathscr{B}}\left(\widehat{\mathscr{B}}^*\mathscr{K}_{k+1}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\mathscr{K}_{k+1}\right]\widehat{\mathscr{A}} + \widehat{\mathscr{Q}}, \quad \mathscr{K}_{k_1} = \widehat{\mathscr{G}}$$

$$\theta_k = \widehat{\mathscr{A}}^*\left(I + \hat{r}^{-1}\mathscr{K}_{k+1}\widehat{\mathscr{B}}\widehat{\mathscr{B}}^*\right)^{-1}\theta_{k+1} + \widehat{\mathscr{D}}^*\xi_k,$$

with $\theta_{k_1} = \hat{\rho}\widehat{\mathscr{D}}^*\xi_{k_1}$. When $k_1 = \infty$, $\hat{\rho} = 0$. By Theorem 2.4 in Gibson and Rosen (1988) (see also Yao et al., 2022), $\widehat{\mathscr{A}}$ open loop stable, implies that the solution to the algebraic Riccati equation (ARE)

$$\mathscr{K} = \widehat{\mathscr{A}}^*\left[\mathscr{K} - \mathscr{K}\widehat{\mathscr{B}}\left(\widehat{\mathscr{B}}^*\mathscr{K}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\mathscr{K}\right]\widehat{\mathscr{A}} + \widehat{\mathscr{Q}}$$

exists, is unique, self-adjoint, and positive definite, and the efficacy of the tracking controller

$$\begin{aligned}\overline{u}_k &= -\widehat{\mathscr{F}}\overline{x}_k + \Theta \\ &= \left(\widehat{\mathscr{B}}^*\mathscr{K}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\left(-\mathscr{K}\widehat{\mathscr{A}}\overline{x}_k + \theta\right),\end{aligned} \tag{7}$$

is guaranteed, where $\widehat{\mathscr{F}} = \left(\widehat{\mathscr{B}}^*\mathscr{K}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\mathscr{K}\widehat{\mathscr{A}} \in \mathscr{L}(\mathscr{H}, \mathbb{R})$ and $\Theta = \left(\widehat{\mathscr{B}}^*\mathscr{K}\widehat{\mathscr{B}} + \hat{r}\right)^{-1}\widehat{\mathscr{B}}^*\theta \in \mathbb{R}$ with $\theta = \widehat{\mathscr{A}}^*\left(I + \hat{r}^{-1}\mathscr{K}\widehat{\mathscr{B}}\widehat{\mathscr{B}}^*\right)^{-1}\theta + \widehat{\mathscr{D}}^*\xi$.

Since the plant (5) is assumed to be corrupted by the random noise processes $\widehat{\mathscr{B}}_1\omega(k\tau)$ and $\zeta(k\tau)$, and since the state cannot be measured completely, the feedback controllers given in (6) and (7) cannot be implemented. Consequently, we introduce an observer or state estimator in the form of a Kalman filter into the feedback loop. The resulting control laws, are now output feedback and the combined feedback tracking controller and observer are known as a tracking compensator.

For $k \geq k_0$, the state estimator takes the form

$$\widetilde{x}_{k+1} = \widehat{\mathscr{A}}\widetilde{x}_k + \widehat{\mathscr{B}}u_k + \widetilde{\mathscr{L}}_k\left(y_k - \widehat{\mathscr{C}}\widetilde{x}_k\right), \widetilde{x}_{k_0} = x_0, \tag{8}$$

where $x_0 \in \mathscr{H}$ is arbitrary, the operators $\widetilde{\mathscr{L}}_k$ are given by $\widetilde{\mathscr{L}}_k = \widehat{\mathscr{A}}\Pi_k\widehat{\mathscr{C}}^*\left\{\sigma^2 + \widehat{\mathscr{C}}\Pi_k\widehat{\mathscr{C}}^*\right\}^{-1} \in \mathscr{L}(\mathbb{R}, \mathscr{H})$, with the operators Π_k, $k = k_0, k_0 + 1, \cdots$ given by the recurrence

$$\Pi_{k+1} = \widehat{\mathscr{A}}\left[\Pi_k - \Pi_k\widehat{\mathscr{C}}^*\left(\sigma^2 + \widehat{\mathscr{C}}\Pi_k\widehat{\mathscr{C}}^*\right)^{-1}\widehat{\mathscr{C}}\Pi_k\right]\widehat{\mathscr{A}}^* + \widetilde{\mathscr{Q}},$$

$k = k_0, k_0 + 1, \ldots$, with $\Pi_{k_0} = 0$. Then by the separation principle (see Theorem 5.3 in Kwakernaak and Sivan (1972)), the optimal controller $\widetilde{u}_k$ in the presence of noise is given by applying the deterministic tracking law (6) to the Kalman estimator $\tilde{x}_k$ generated by the recurrence relation (8). The optimal feedback tracking control law is now $\widetilde{u}_k = -\widehat{\mathscr{F}}_k\tilde{x}_k + \Theta_k$.

When $k_1 = \infty$, let $\widetilde{\mathscr{L}}_k = \widetilde{\mathscr{L}} \in \mathscr{L}(\mathbb{R}, \mathscr{H}) = \mathscr{H}$ be given by $\widetilde{\mathscr{L}} = \widehat{\mathscr{A}}\Pi\widehat{\mathscr{C}}^*\left\{\sigma^2 + \widehat{\mathscr{C}}\Pi\widehat{\mathscr{C}}^*\right\}^{-1}$, with Π being the positive semi-definite, self-adjoint solution to the ARE

$$\Pi = \widehat{\mathscr{A}}\left[\Pi - \Pi\widehat{\mathscr{C}}^*\left(\sigma^2 + \widehat{\mathscr{C}}\Pi\widehat{\mathscr{C}}^*\right)^{-1}\widehat{\mathscr{C}}\Pi\right]\widehat{\mathscr{A}}^* + \widetilde{\mathscr{Q}}.$$

By the separation principle, the optimal tracking controller $\widetilde{u}_k$ in the presence of noise is given by applying the deterministic tracking law (7) to the steady state Kalman estimator $\widetilde{x}_k$ generated by the steady state version of (8) (i.e. with $\widetilde{\mathscr{L}}_k = \widetilde{\mathscr{L}}$) to obtain $\widetilde{u}_k = -\widehat{\mathscr{F}}\widetilde{x}_k + \Theta$.

The approach just described can now be readily extended to our semilinear plant (1) since the nonlinearity is of the form $\widehat{\mathscr{B}}\frac{q_7 v}{q_2(q_8 + v)}$. A nonlinear feedback term that effectively cancels the plant's nonlinearity can be added to the linear compensator that forces the linear part of the plant to track the given reference signal $\{\xi_k\}$. To wit

$$\widetilde{u}_k = -\widehat{\mathscr{F}}_k\widetilde{x}_k + \Theta_k + \frac{q_7\widehat{\mathscr{D}}\widetilde{x}_k}{q_2\left(\sqrt{v}q_8 + \widehat{\mathscr{D}}\widetilde{x}_k\right)}, \tag{9}$$

where $\left\{\widehat{\mathscr{F}}_k\right\}$ and $\{\Theta_k\}$ are designed to have the linear part of the system track $\{\xi_k\}$. This controller can then be paired with the nonlinear observer given by

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$$
\begin{aligned}
\widetilde{x}_{k+1} = {} & \widehat{\mathscr{A}}\widetilde{x}_k + \widehat{\mathscr{B}}u_k + \widetilde{\mathscr{L}}_k\left(y_k - \widehat{\mathscr{C}}\widetilde{x}_k\right) \\
& - \widehat{\mathscr{B}}\frac{q_7\widehat{\mathscr{D}}\widetilde{x}_k}{q_2\left(\sqrt{v}q_8 + \widehat{\mathscr{D}}\widetilde{x}_k\right)} .
\end{aligned}
\tag{10}
$$

When $k_1 < \infty$, the corresponding equations for the approximating tracking compensator are given by

$$
\mathscr{K}_k^N = \left(\widehat{\mathscr{A}}^N\right)^*\left[\mathscr{K}_{k+1}^N - \mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N\left(\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N + \hat{r}\right)^{-1}\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\right]\widehat{\mathscr{A}}^N + \widehat{\mathscr{Q}}^N,
$$

$$
\theta_k^N = \left(\widehat{\mathscr{A}}^N\right)^*\left[I + \hat{r}^{-1}\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N\left(\widehat{\mathscr{B}}^N\right)^*\right]^{-1}\theta_{k+1}^N + \left(\widehat{\mathscr{D}}^N\right)^*\xi_k .
$$

with $\mathscr{K}_{k_1}^N = \widehat{\mathscr{G}}^N$ and $\theta_{k_1}^N = \hat{\rho}\left(\widehat{\mathscr{D}}^N\right)^*\xi_{k_1}$. The optimal tracking control, $\overline{u}^N$, is given by $\overline{u}_k^N = -\widehat{\mathscr{F}}_k^N\overline{x}_k^N + \Theta_k^N$, where $\widehat{\mathscr{F}}_k^N = \left[\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N + \hat{r}\right]^{-1}\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\widehat{\mathscr{A}}^N$ and $\Theta_k^N = \left[\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N + \hat{r}\right]^{-1}\left(\widehat{\mathscr{B}}^N\right)^*\theta_{k+1}^N \in \mathbb{R}$.

For the finite dimensional approximation scheme for the open-loop system given in Section 3 having the convergence properties stated there, it is shown in Gibson and Rosen (1988), that $\mathscr{K}_k^N\mathscr{P}^N$ converges strongly to $\mathscr{K}_k$, $k \in [k_0, k_1]$, and $\mathscr{F}_k^N\mathscr{P}^N$ converges in the uniform operator topology to $\mathscr{F}_k$, $k \in [k_0, k_1]$. In addition (Yao et al., 2022) $\left[I + \hat{r}^{-1}\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N\left(\widehat{\mathscr{B}}^N\right)^*\right]^{-1}$ in the definition of θ_k^N can be transformed into an expression involving $\left[\hat{r} + \left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}_{k+1}^N\widehat{\mathscr{B}}^N\right]^{-1}$, and therefore that $\theta_k^N \to \theta_k$ as $N \to \infty$. The approximating closed loop control, $\overline{u}^N$, and closed loop state, $\overline{x}^N$, converge to $\overline{u}$ and $\overline{x}$, respectively, in l^2, where the l^2 inner product and corresponding norm are defined by $\langle \mathscr{X}, y\rangle_{l^2} = \sum_{k=k_0}^{k_1}\langle \mathscr{X}_k, y_k\rangle_{\mathscr{H}}$ for any $\mathscr{X}$ and y in $l^2(k_0, k_1; \mathscr{H})$. The approximating cost functions $\widehat{\mathscr{J}}^N\left(\overline{u}^N\right)$ also converge to $\widehat{\mathscr{J}}^N(\overline{u})$ as $N \to \infty$.

When $k_1 = \infty$ and $\hat{\rho} = 0$, Theorems 3.9 and 3.10 in Gibson and Rosen (1988) yield that for each $N = 1, 2, \ldots$ a positive semi-definite self-adjoint solution, $\mathscr{K}$, to the ARE

$$
\mathscr{K}^N = \left(\widehat{\mathscr{A}}^N\right)^*\left\{\mathscr{K}^N - \mathscr{K}^N\widehat{\mathscr{B}}^N\left[\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}^N\widehat{\mathscr{B}}^N + \hat{r}\right]^{-1}\left(\widehat{\mathscr{B}}^N\right)^*\mathscr{K}^N\right\}\widehat{\mathscr{A}}^N + \widehat{\mathscr{Q}}^N,
$$

exists, the approximating tracking controller, $\overline{u}^N$, is

$$\overline{u}_k^N = -\widehat{\mathscr{F}}^N \overline{x}_k^N + \Theta^N$$
$$= \left[\left(\widehat{\mathscr{B}}^N\right)^* \mathscr{K}^N \widehat{\mathscr{B}}^N + \hat{r}\right]^{-1} \left(\widehat{\mathscr{B}}^N\right)^* \left(-\mathscr{K}^N \widehat{\mathscr{A}}^N \overline{x}_k^N + \theta^N\right),$$

where $\widehat{\mathscr{F}}^N = \left[\left(\widehat{\mathscr{B}}^N\right)^* \mathscr{K}^N \widehat{\mathscr{B}}^N + \hat{r}\right]^{-1} \left(\widehat{\mathscr{B}}^N\right)^* \mathscr{K}^N \widehat{\mathscr{A}}^N$,
$\Theta^N = \left[\left(\widehat{\mathscr{B}}^N\right)^* \mathscr{K}^N \widehat{\mathscr{B}}^N + \hat{r}\right]^{-1} \left(\widehat{\mathscr{B}}^N\right)^* \theta^N \in \mathbb{R}$, with

$$\theta^N = \left(\widehat{\mathscr{A}}^N\right)^* \left(I + \hat{r}^{-1} \mathscr{K}^N \widehat{\mathscr{B}}^N \left(\widehat{\mathscr{B}}^N\right)^*\right)^{-1} \theta^N + \left(\widehat{\mathscr{D}}^N\right)^* \xi,$$

and, analogous to the finite time horizon case, convergence of $\mathscr{K}^N$, $\mathscr{F}^N$, $\overline{u}^N$, $\overline{x}^N$, and $\widehat{\mathscr{F}}^N$ to their infinite dimensional counterparts, as $N \to \infty$, can be established (Gibson & Rosen, 1988; Yao et al., 2022). The approximating observers are

$$\widetilde{x}_{k+1}^N = \widehat{\mathscr{A}}^N \widetilde{x}_k^N + \widehat{\mathscr{B}}^N u_k^N + \widetilde{\mathscr{L}}_k^N \left(y_k^N - \widehat{\mathscr{C}}^N \widetilde{x}_k^N\right), k \ge k_0,$$

where $\widetilde{x}_{k_0}^N = x_0^N \in \mathscr{V}^N$ is arbitrary and the operators $\widetilde{\mathscr{L}}_k^N \in \mathscr{L}\left(\mathbb{R}, \mathscr{V}^N\right) = \mathscr{V}^N \subset \mathscr{H}$ are given by

$$\widetilde{\mathscr{L}}_k^N = \widehat{\mathscr{A}}^N \Pi_k^N \left(\widehat{\mathscr{C}}^N\right)^* \left[\sigma^2 + \widehat{\mathscr{C}}^N \Pi_k^N \left(\widehat{\mathscr{C}}^N\right)^*\right]^{-1}$$

with the operators $\Pi_k^N, k = k_0, k_0 + 1, \cdots$ given by

$$\Pi_{k+1}^N = \widehat{\mathscr{A}}^N \left[\Pi_k^N - \Pi_k^N \left(\widehat{\mathscr{C}}^N\right)^* \left(\sigma^2 + \widehat{\mathscr{C}}^N \Pi_k^N \left(\widehat{\mathscr{C}}^N\right)^*\right)^{-1} . \widehat{\mathscr{C}}^N \Pi_k^N\right] \left(\widehat{\mathscr{A}}^N\right)^* + \widetilde{\mathscr{Q}}^N,$$

$k = k_0, k_0 + 1, \cdots$, with $\Pi_{k_0}^N = 0$. The observer gain and the ARE for the steady state observer are analogous. The convergence results for the Riccati operators, and the filter gains for both the finite time horizon and the steady state observer are analogous to those given above for the control Riccati operators and feedback gains (Yao et al., 2022).

Both the infinite dimensional and approximating finite dimensional optimal compensator on both the finite time and infinite time horizon can be represented (and in the finite dimensional case, implemented) in terms of functional gains with the approximating finite dimensional functional gains converging to their infinite dimensional counterparts (Gibson & Rosen, 1988). For example, in the finite dimensional, finite time horizon case, for $k = k_0, k_0 + 1, \ldots$, the optimal compensator is given by

$$\widetilde{u}_k^N = -\widehat{\mathscr{F}}_k^N \widetilde{x}_k^N + \Theta_k^N = -\left\langle \widehat{f}_k^N, \widetilde{x}_k^N \right\rangle_{\mathscr{H}} + \Theta_k^N$$
$$= -\int_Q \left\{ \frac{q_1}{q_3} \widehat{f}_{1,k}^N(q) \widetilde{x}_{1,k}^N(q) + \frac{q_1}{q_5} \widehat{f}_{2,k}^N(q) \widetilde{x}_{2,k}^N(q) + \int_0^1 \widehat{f}_{3,k}^N(\eta, q) \widetilde{x}_{3,k}^N(\eta, q) d\eta \right\} d\pi(q) + \Theta_k^N,$$

where $\widehat{\ell}_k^N = \left(\widehat{\ell}_{1,k}^N, \widehat{\ell}_{2,k}^N, \widehat{\ell}_{3,k}^N\right) \in \mathscr{V}^N \subset \mathscr{H}$ with

$$\widehat{\ell}_k^N = \left(\widehat{\ell}_{3,k}^N(0,\cdot), \widehat{\ell}_{3,k}^N(1,\cdot), \widehat{\ell}_{3,k}^N(\cdot,\cdot)\right) = \left(\widehat{\mathscr{F}}_k^N\right)^* \\ = \left(\widehat{\mathscr{A}}^N\right)^* \mathscr{K}_{k+1}^N \widehat{\mathscr{B}}^N \left[\left(\widehat{\mathscr{B}}^N\right)^* \mathscr{K}_{k+1}^N \widehat{\mathscr{B}}^N + \hat{r}\right]^{-1} \in \mathscr{V}^N.$$

The other three cases are analogous (see Yao et al. (2022)).

5. Examples and numerical studies

Alcohol withdrawal syndrome (AWS) can cause symptoms ranging from headache, nausea and vomiting to hallucinations, grand mal seizures and death. AWS can pose a significant challenge when a patient with AUD requires general anaesthesia for surgery or inpatient treatment in for example, the burn unit or the ICU. Intravenous infusion of ethanol is used to prevent and alleviate the symptoms of AWS in AUD patients (Dillard, Welch, Abdul-Hamed, Kesey, & Dissanaike, 2016; Dissanaike et al., 2006; Hansbrough et al., 1984; Hodges & Mazur, 2004).

In Dillard et al. (2016) is a protocol for infusing prophylactic intravenous ethanol: Initiate a 10% alcohol drip at 0.4 ml/kg/hr. Measure BAC at 6, 24, and 72 h after infusion is started. If BAC exceeds 80 mg/dl (0.08%), halt for 2 h then decrease by 50%. The patient should be monitored for symptoms of AWS. If AWS symptoms are no longer present after 24 h, decrease infusion by 20% after 48 h, decrease further by 50% after 72 h, decrease further by 50% after 84 h, and then halt infusion. If the patient develops symptoms of AWS, increase infusion by 50%.

We demonstrate the efficacy of our approach by showing (via simulation) how a TAC biosensor and the controller developed here can be used to automate a treatment regimen like this one. We first fit the parameters $q \in \mathbb{R}^8$ appearing in the individual model, (1), using BrAC and TAC data from 267 drinking episodes collected (Saldich et al., 2020) in the Luczak Laboratory in the Department of Psychology at USC from 40 participants (50% female, ages 21–33 years, 35% BMI > 25.0). Each participant orally consumed the same alcohol dose in a number of drinking sessions on different days. The alcohol used was Vodka with an ethanol content of 40%, which was mixed with fruit juice and sugar-free carbonated soda so subjects were not drinking pure alcohol. During each session, participant BrAC was measured via breath analyzer (Intoximeters, Inc., St. Louis, MO), and two sets of TAC were measured at the upper arms via SCRAM-CAM TAC sensors (Alcohol Monitoring Systems, AMS, Littleton, CO). BrAC and TAC were obtained at 10-minute intervals. A more detailed description of the data collection and its use in validating both the individual and population models can be found in Yao et al. (2022).

The fit parameters were clustered into sub-populations so that the variance in each sub-population was smaller than that of the full population. Eventually, the appropriate cluster to use for a patient will be determined by a regression model whose predictor variables are patient, sensor, and environmental dependent covariates (which we have also collected) such as age, sex, race/ethnicity, body measurement data (e.g. BMI, waist to hip ratio, percent body fat, etc.), drinking behavior, ambient temperature and humidity, sensor manufacturer, etc.

One of the sub-populations and the method of moments (Casella & Berger, 2002) was then used to fit independent fourparameter Beta distributions to the parameters q_i, $i = 1, 2, 3$ yielding q_1~Beta$(1.53, 2.54)$ with support [0.25, 0.54], q_2~Beta$(7.52, 17.72)$ with support [0.18, 0.76], and q_3~Beta$(1.38, 1.59)$ with support [3.20, 10.91]. For the remaining parameters in the population model, since their variance across the population was relatively small, we simply used their sample means (this is equivalent to assuming a uniform distribution), $\bar{q}_4 = 1.63 \times 10^{-1}$, $\bar{q}_5 = 2.18 \times 10^{-4}$, $\bar{q}_6 = 4.88 \times 10^{-4}$, $\bar{q}_7 = 1.23 \times 10^{-2}$ and $\bar{q}_8 = 2.26 \times 10^{-5}$. Since the dimension of the population compensator is exponential in the number of random parameters, it is desirable to keep this number small if possible. We set the output and control penalties to be $\hat{\upsilon} = 1.0$, $\hat{\rho} = 1.0$ and $\hat{r} = 0.5$. We set the noise levels to be $\sigma_1 = 0.004\%$, $\sigma_2 = 0.004\%$, and $\sigma = 0.004\%$ (5% of the initial alcohol level in the signal to be tracked). For the approximation, we set $n = 4$ and $m_i = 6$, $i = 1, 2, 3$, which yielded an approximating compensator of dimension $5 \times 6^3 = 1080$. The simulation runs very quickly even when n is chosen significantly larger (e.g. $n = 8$, 12, or 16) but this had virtually no effect on performance. This was on either a desktop or a laptop machine even including the computation of either the finite or infinite time horizon solution to the control and observer Riccati equations, which in actual practice would be computed off-line. The sampling rate was set to 1/60 Hz for a sampling interval of 1 min. We simulated the system for 7200 cycles or 120 h or 5 days. The result is shown in Fig. 1. The left panel of Fig. 1 shows the trajectory of the output feedback tracking controller and the right panel shows the controlled BAC along with the target trajectory. We generated these plots by simulating the plant (1) using a 65 dimensional spline based Galerkin scheme with the fit values for the eight parameters that appear in the model for each of the patients in the population cohort we used to construct the population model. We then used the approach described in the previous sections and our population model (which assumes knowledge of the fit distributions of the parameters only) to design an output feedback tracking compensator (9), (10). The two plots in Fig. 1 show the population mean (at each time, taken over the simulations for all of the patients in the cohort) control and BAC trajectories (recall, that it is the plant TAC that is observed, not the plant BAC) along with one and two standard deviations taken across all the plants in the cohort. One of the advantages of our scheme that treats the unknown parameters as additional spatial variables is that the state, output, and their estimators (and if desired, feedback and observer gains and the control as well) are obtained as functions of the unknown parameters q. By simply generating samples from the q distributions and then evaluating these functions at those samples, (to borrow a term from Bayesian estimation; although our approach here is not, strictly speaking, Bayesian) we obtain a conservative credible band or region (the shaded region in the BAC plot); that is, conditioned on the population cohort data, there is a 95% probability that the actual controlled BAC trajectory lies in the shaded region.

Both the individual and population linear models are open loop coercive (actually, elliptic) and therefore the corresponding semigroups are stable. The state transition operator is self-adjoint; thus both the steady state control and estimator AREs admit unique solutions with the closed loop compensator being stable with spectrum that is the union of the closed loop control and estimator spectra. Since the nonlinear feedback controller is designed to simply cancel the nonlinearity in the state equation, the relatively mild nonlinearity of the Michaelis–Menten term and a Gronwall estimate yield that the closed loop nonlinear system inherits the stability properties of the linear system. Now with that said, when the population model is used to design a compensator for the individual model together with the potential for spillover effects resulting from a finite dimensional approximation-based control design, it is certainly possible that the closed loop system could now exhibit instabilities. In practice, as is the case with any closed loop medical device (e.g. an artificial pancreas, etc.), one would certainly want to incorporate fault detection and safety guard rails into the design. With regard to enforcing constraints and optimizing performance, this is achieved by tuning the penalty weights $\hat{r}$, $\hat{\rho}$ and $\hat{v}$. In addition, in practice, the noise variances, σ_1^2, σ_2^2 and σ^2 are in general, unmeasurable and unknowable. Consequently, they can be considered to be design tuning parameters as well. The only way we are aware of to tune them is via simulation studies like the one presented here. Finally, we note that it is possible to introduce constraints into the LQ theory (Lions, 1971), but this would be at the cost of the elegant, closed form, feedback structure of the unconstrained solution presented here. In practice, we have observed that the control and state remain well within safe levels so long as the signal to be tracked does not have jump discontinuities or change too rapidly (i.e. so long as its first derivative remains within reasonable bounds that can also be determined via simulation.)

In a second example, we illustrate how our approach can be used to blindly (since the forward convolution filter or kernel is uncertain) deconvolve an estimate of BAC from TAC with regularization. This is a strictly linear problem wherein the compartment at $\eta = 1$ is now the dermal layer of the skin and the input, u, is now BAC. The nonlinear Michaelis–Menten reaction term describing the metabolic processes in the liver is no longer present in the model. The output is TAC, and the plant is now the population model and we are able to observe the full state (since the plant exists in the computer), thus making an observer unnecessary. The control objective is to determine an input (i.e. BAC) signal that causes the population model to track a given TAC signal. To wit, $D \in \mathscr{L}(H_q, \mathbb{R})$ is given by $D(w, v, x) = \sqrt{\hat{v}}w$ and ξ_k is the given TAC signal to be tracked. In addition, since this is in general an ill-posed inverse problem, it is desirable to include regularization in the form of a penalty on both the magnitude and rate of change of BAC so as to mitigate over-fitting and non-physical oscillations in the BAC estimate.

We introduce regularization by augmenting the state with the BAC signal, u_k, defining a new control variable, δu_k, and adding an additional state equation of the form $\Delta u_k = \delta u_k$ with initial condition $u_0 = 0$. The state is now given by the vector $\mathbf{x_k} = [x_k, u_k]^T$, with the magnitude of u being regularized by the quadratic state penalty term and any undo oscillations being mitigated by the control penalty term involving δu_k. The output variable to be tracked, $y_k \in \mathbb{R}^2$, has the given TAC signal as its first component and zero as its second. Once the optimal δu_k is determined, the estimated BAC, u_k is obtained from $u_k = \sum_{j=0}^{k-1} \delta u_j$.

We set the sampling rate at $\tau = 1/60$, we let $q_1 \sim \mathrm{Beta}(3,2)$ with support [0, 1], $q_2 \sim \mathrm{Beta}(7,9)$ with support [0, 3], $q_3 = 3.99$, $q_4 = 0.05$, $q_5 = 0.086$, $q_6 = 0.85$, $\hat{\rho} = 100$, $\hat{\upsilon} = 0.80$, the penalty weight on u_k (now part of the $\widehat{\mathscr{D}}$ operator) to be .01 and the control penalty on δu_k to be $\hat{r} = 100$. We set $n = 4$, and $m_1 = m_2 = 16$. For data, we used TAC collected by one of the co-authors (S. E. L.) (Dai et al., 2016; Rosen et al., 2014) using a WrisTAS 7™ transdermal alcohol biosensor manufactured by Giner, Inc. of Waltham, MA. Simultaneous BrAC data was also collected so we could evaluate the efficacy of our approach. The target TAC signal to be tracked along with the resulting tracking TAC and the estimated or deconvolved and true BrAC signals are plotted in Fig. 2. We are able to use the steady state Riccati operator, $\mathscr{K}$ and control gains, $\widehat{\mathscr{F}}$, which can all be pre-computed off-line, even though the TAC reference signal to be tracked is time dependent. Then estimating BAC or BrAC from TAC can be done in real time directly on a mobile device since now only relatively simple calculations are required at each sample time to obtain u_k, to wit, the backward integration of θ_k and the forward integration of x_k as the solutions of non-homogeneous linear recurrence relations with forcing terms depending on the TAC signal being tracked.

We are currently looking at combining the ideas from the first example involving the full body model with the objective of the second example to not only estimate BAC or BrAC, but to also use TAC tracking to estimate an oral alcohol ingestion profile. Such a tool has the potential to significantly enhance an alcohol researcher's ability to investigate drinking behavior outside of the lab or clinic in a naturalistic setting in the field. In addition, we are investigating how we might incorporate fault detection and safety guardrails into our design and we are exploring collaborative opportunities for a clinical trial of our design methodology, most likely in the form of an alcohol clamping study (O'Connor et al., 1998; Ramchandani et al., 2006; Yao et al., 2022).

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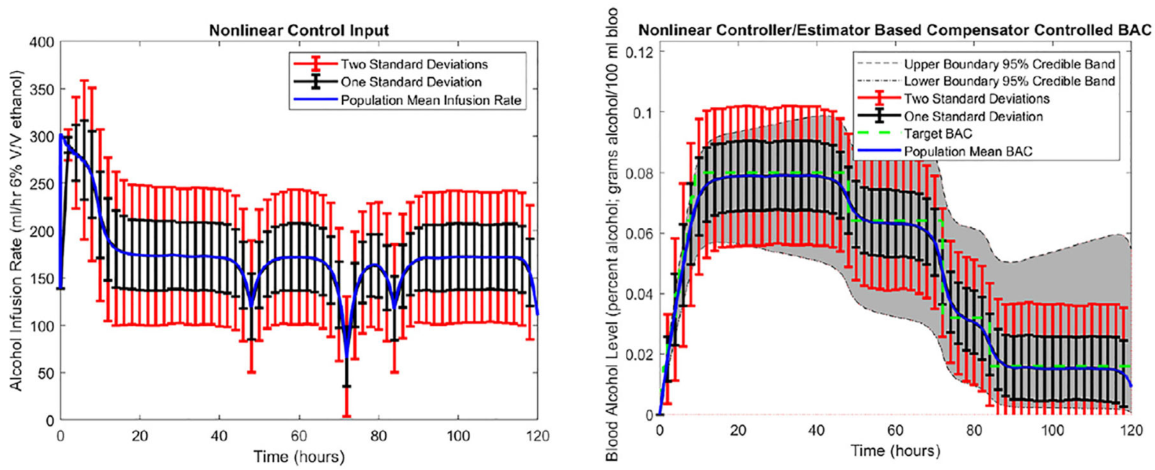

Fig. 1.

Intravenous AWS therapy: Left panel: Output feedback control, Right panel: Controlled BAC with error bars and 95% credible band.

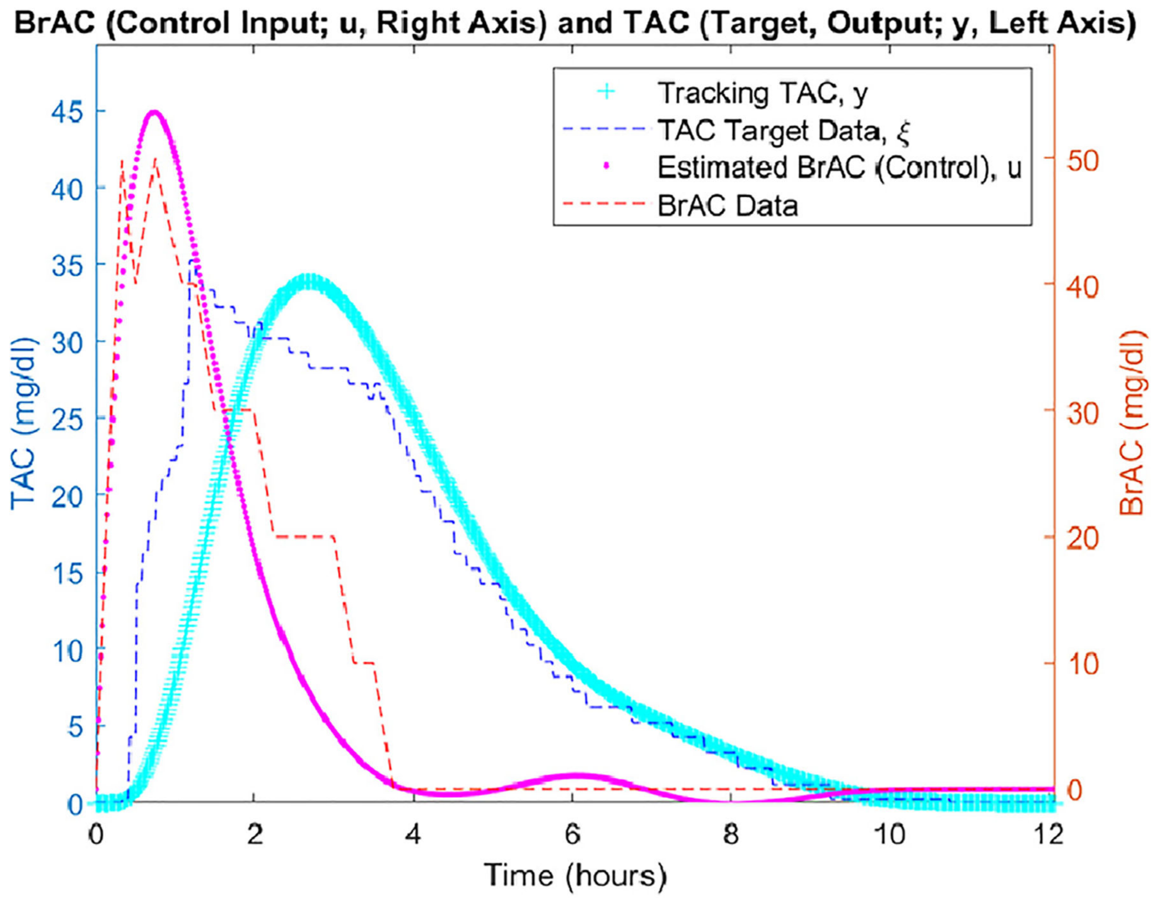

Fig. 2.
Tracked TAC and tracing control, or estimated BrAC.