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A Brain-Machine Interface for Control of Burst Suppression in Medical Coma

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Abstract— **Burst suppression is an electroencephalogram (EEG) marker of profound brain inactivation and unconsciousness and consists of bursts of electrical activity alternating with periods of isoelectricity called suppression. Burst suppression is the EEG pattern targeted in medical coma, a drug-induced brain state used to help recovery after brain injuries and to treat epilepsy that is refractory to conventional drug therapies. The state of coma is maintained manually by administering an intravenous infusion of an anesthetic, such as propofol, to target a pattern of burst suppression on the EEG. The coma often needs to be maintained for several hours or days, and hence an automated system would offer significant benefit for tight control. Here we present a brain-machine interface (BMI) for automatic control of burst suppression in medical coma that selects the real-time drug infusion rate based on EEG observations and can precisely control the burst suppression level in real time in rodents. We quantify the burst suppression level using the burst suppression probability (BSP), the brain's instantaneous probability of being in the suppressed state, and represent the effect of the anesthetic propofol on the BSP using a two-dimensional linear compartment model that we fit in experiments. We compute the BSP in real time from the EEG segmented into a binary time-series by deriving a two-dimensional state-space algorithm. We then derive a stochastic controller using both a linear-quadratic-regulator strategy and a model predictive control strategy. The BMI can promptly change the level of burst suppression without overshoot or undershoot and maintains precise control of time-varying target levels of burst suppression in individual rodents in real time.**

I. Introduction

Medical coma is a drug-induced state of profound brain inactivation and unconsciousness that is used to help recovery after traumatic and hypoxic brain injuries and to treat epilepsy that is refractory to conventional drug therapies. In medical coma, the electroencephalogram (EEG) pattern, termed burst suppression, consists of bursts of electrical activity alternating with periods of suppression. The state of coma is achieved by the intensive care unit (ICU) staff manually adjusting the drug infusion rate to achieve a desired level of burst suppression on the EEG. Since the state of coma for such treatments is often required for days, it is usually infeasible for the ICU staff to continuously monitor the EEG and adjust the drug infusion rate to achieve tight control. Hence developing an automated brain to pump interface system or a brain-machine interface (BMI) that continuously monitors the brain's EEG activity in real time, calculates the burst suppression level based on the EEG, and determines the appropriate real-time rate of the infusion pump to target a desired level would offer significant benefit.

BMI systems for control of anesthesia are often referred to as closed loop anesthesia delivery (CLAD) systems. There has been considerable work and success in the last 60 years on developing these systems for control of sedation and general anesthesia [1], [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [8], [20], [21], [22], [23], [24], [25]. For the management of medical coma, however, no CLAD system has been developed to date. To develop a framework for testing new anesthetics, Vijn and Sneyd [26] implemented a CLAD system for non-model based control of burst suppression in a rat model. Cotten and colleagues [27] tested new etomidate-derived anesthetics in a rat model using that framework. Both these studies controlled a constant level of burst suppression rather than time-varying levels as needed in medical coma, and reported only average control results over animals rather than results for individual animals.

Here we develop a BMI for control of time-varying target burst suppression trajectories in individual rodents. We demonstrate that the BMI can accurately achieve and maintain multiple target levels in a single session, can enable prompt transitions of burst suppression level between the target levels while avoiding overshoot or undershoot, and can explicitly impose various constraints over the infusion rates and vital states. Our BMI uses the burst suppression probability (BSP) [28], the brain's instantaneous probability of being in the suppressed state, as the control signal and represents the effect of the anesthetic on BSP using a linear two-dimensional compartment model that we fit in experiments prior to BMI control. We build the BMI using a stochastic optimal control framework that we have also developed for the design of motor BMIs [29], [30], [31], [32], [33]. We derive a two-dimensional recursive Bayesian estimator of the BSP from the EEG segmented into a binary time-series. We then derive controllers using both a linear-quadratic-regulator strategy and a model predictive control strategy that use the BSP estimate as feedback to adjust the drug infusion rate and achieve a target BSP level.

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II. METHODS

Our goal is to design a BMI that can maintain the burst suppression level at any desired target level and that can reliably change the burst suppression level in response to a change in the target level. We first present the problem formulation and then derive the BMI estimator and controllers.

A. Problem Formulation

We define BSP as our measure of the burst suppression level by identifying the EEG activity in small time intervals as a burst or a suppression event after filtering and thresholding it (Figure 1a). We define BSP, denoted by p_t, as the brain's instantaneous probability of being in the suppressed state at an interval and use a hyperbolic transform to relate it to a measure of the brain's anesthetic concentration, denoted by $x_e(t)$. This transform maps the drug concentration to a BSP value between 0 and 1 as

$$p_t = \frac{1-\exp(-x_e(t))}{1+\exp(-x_e(t))}. \quad (1)$$

The BMI aims to control the BSP or equivalently the brain's anesthetic concentration using the EEG as input (Figure 1a). To develop the BMI, we build a two-dimensional state model for the dynamics of the anesthetic concentration in response to propofol infusion. For this state model, we adapt a simple two-compartment linear pharmacokinetic model whose compartments are the central plasma compartment and the brain or effect-site compartment. Hence our state is two-dimensional and is denoted by $\mathbf{x}_t = [x_c(t), x_e(t)]'$, where as before, $x_e(t)$ is the brain's anesthetic concentration and $x_c(t)$ is the central plasma concentration. Denoting the anesthetic infusion rate by u_t, the state model is given by

$$\mathbf{x}_{t+1} = \mathbf{A}\mathbf{x}_t + \mathbf{B}u_t \quad (2)$$

with

$$\mathbf{A} = \begin{bmatrix} 1-\Delta(k_{ce}+k_{c0}) & \Delta k_{ec} \\ \Delta k_{ce} & 1-\Delta k_{ec} \end{bmatrix}$$
$$\mathbf{B} = \begin{bmatrix} \Delta \\ 0 \end{bmatrix}.$$

Here Δ is the discretization time step, and k_{ce}, k_{ec}, and k_{c0} are parameters of the two-compartment model (Figure 1b). We parameterize and estimate this model from the EEG response to boluses of propofol administered in a preliminary experiment prior to initiating real-time control. We do this by first estimating the BSP from the EEG using a one-dimensional version of our estimator derived in Section II-B and then using the method of nonlinear least-squares to minimize the sum-squared-error between the model predicted BSP and the estimated BSP.

B. Estimator Design

We derive a recursive Bayesian estimator for the brain concentration state (or equivalently for the BSP) based on the EEG observations. Since the anesthetic concentration states are positive, we estimate their logarithm $\mathbf{z}_t = \log(\mathbf{x}_t)$.

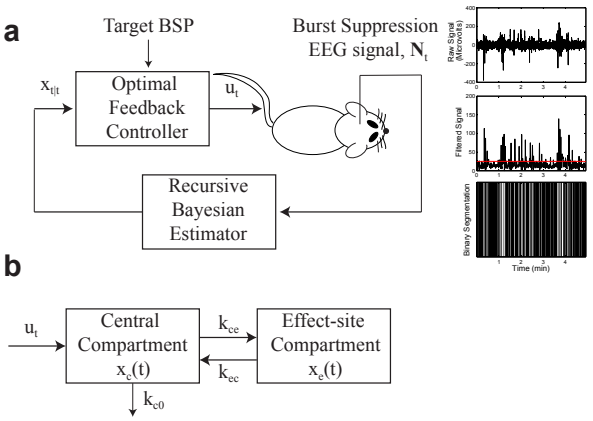

Fig. 1. The BMI system. (a) The BMI records the EEG, estimates the effect-site concentration, and uses this estimate as feedback to control the infusion rate. Right panel shows a sample burst suppression EEG signal (*top*), the absolute value of the low-pass filtered EEG signal in black and the threshold used to detect the suppression events in red (*middle*), and the corresponding binary time-series with black indicating the suppression and white indicating the burst events (*bottom*). (b) The two-compartmental model used by the BMI to characterize the effect of propofol on the EEG.

The goal of the estimator is to find the minimum mean-square error (MMSE) state estimate at each time. The MMSE state estimate is given by the mean of the posterior density, $p(\mathbf{z}_t|N_{1:t})$, where N_t denotes the number of observed suppression events in the tth interval of length Δ, assuming at most N possible suppression events in this interval.

A recursive Bayesian estimator consists of a prior model on the concentration states and an observation model relating the EEG signal to these states. We construct the prior model on $\mathbf{z}_t$ based on the two compartment model in (2) with additive Gaussian noise $\mathbf{w}_t$ of covariance $\mathbf{W}$

$$\mathbf{z}_{t+1} = \log(\mathbf{A}\exp(\mathbf{z}_t) + \mathbf{B}u_t) + \mathbf{w}_t = f(\mathbf{z}_t) + \mathbf{w}_t \quad (3)$$

where $\exp(\mathbf{z}_t)$ denotes component-wise exponentiation of the elements in $\mathbf{z}_t$. The observation in the estimator is the binary time-series of the burst suppression events obtained by thresholding the EEG (Figure 1a). To construct the observation model, we assume that the number of suppression events N_t in a given time interval of length Δ, which can at most exhibit N suppression events, is binomially distributed with burst suppression probability p_t.

Both the prior state model and the binomial observation model above are non-linear functions of the state $\mathbf{z}_t$. We thus use two approximations at each time step to derive the estimator recursions – a linear approximation to the prior model at that step and a Gaussian approximation to the posterior model. Using these two approximations, the Bayes' rule, and the Chapman-Kolmogorov equation, we derive the recursions of the estimator. We omit the derivation of the estimator for compactness. The derived estimator recursions consist of a prediction step and an update step. Denoting the MMSE estimate or equivalently the posterior mean $E(\mathbf{z}_t|N_{1:t})$ by $\mathbf{z}_{t|t}$ and its covariance matrix by $\mathbf{W}_{t|t}$, and the mean of the one step prediction density $p(\mathbf{z}_t|N_{1:t-1})$ by $\mathbf{z}_{t|t-1}$ and its covariance matrix by $\mathbf{W}_{t|t-1}$, the estimator

recursions are given by

$$\mathbf{z}_{t|t-1} = f(\mathbf{z}_{t-1|t-1}) \tag{4}$$

$$\mathbf{W}_{t|t-1} = \tilde{\mathbf{A}}\mathbf{W}_{t-1|t-1}\tilde{\mathbf{A}}' + \mathbf{W} \tag{5}$$

as the prediction step and

$$\mathbf{z}_{t|t} = \mathbf{z}_{t|t-1} + \mathbf{W}_{t|t}\left[\begin{matrix}0\\ \frac{c_t}{p_t(1-p_t)}(N_t - Np_t)\end{matrix}\right]_{\mathbf{z}_{t|t-1}} \tag{6}$$

$$\mathbf{W}_{t|t}^{-1} = \mathbf{W}_{t|t-1}^{-1} + \left[\begin{matrix}0 & 0\\ 0 & \gamma_t\end{matrix}\right]_{\mathbf{z}_{t|t-1}} \tag{7}$$

as the update step. The notation $[\cdot]_a$ indicates the evaluation of the inside expression at value a, $\tilde{\mathbf{A}} = [\frac{\partial f}{\partial \mathbf{z}}]_{\mathbf{z}_{t-1|t-1}}$ and

$$c_t = \frac{x_e(t)\exp(x_e(t))}{1+\exp(x_e(t))}(1-p_t) \tag{8}$$

$$\gamma_t = \frac{Nc_t^2}{p_t(1-p_t)} - \frac{N_t - Np_t}{p_t(1-p_t)}\left[\frac{\partial^2 p_t}{\partial z_e^2(t)} - \frac{1-2p_t}{p_t(1-p_t)}c_t^2\right] \tag{9}$$

$$\frac{\partial^2 p_t}{\partial z_e^2(t)} = c_t\left[1 + x_e(t) - (1-p_t)x_e(t)\exp(x_e(t))\right]. \tag{10}$$

C. Controller Design

The controller uses the estimated brain anesthetic concentration as feedback to determine the drug infusion rate in real time. We derive the controller using an optimal feedback control framework. Once a target BSP level, or equivalently a target brain concentration level is specified, the goal of the controller is to take the brain concentration state close to this target value using as little drug as possible, while satisfying any required constraints on the control variables. We quantify this goal as a quadratic cost function for the controller as

$$J = \sum_t (x_e(t) - x^*)^2 + w_r u_t^2 \tag{11}$$

where $x^* = \log\left((1+p^*)/(1-p^*)\right)$ is the non-zero effect-site concentration for the desired non-zero target BSP level p^* (see (1)), and w_r is a positive quantity chosen depending on the desired system response. The controller then selects, at each time, the infusion rate u_t that minimizes this cost function. Using the standard linear-quadratic-regulator (LQR) solution and by transforming the origin of the state-space to x^* [34], we find a closed-form linear-quadratic-regulation control strategy. Omitting the details for compactness, we find the solution as $u_t = -\mathbf{L}(\mathbf{x}_t - \mathbf{x}^*) + u^*$ where $\mathbf{x}^* = [\frac{k_{ec}}{k_{ce}}x^*, x^*]'$, $u^* = \frac{k_{c0}k_{ec}}{k_{ce}}x^*$, and $\mathbf{L}$ is the steady-state LQR feedback matrix given by the well-known solution to the discrete form of the famous algebraic Riccati equation [34].[1] The value of $\mathbf{x}_t$ at each time step is provided by the estimator. We impose any infusion rate constraints by bounding this unconstrained optimized rate.

We also implement a model predictive controller (MPC) [35] that explicitly enforces the drug infusion rate constraints, such as positivity, by solving a constrained optimization problem at each time step to minimize the cost function. The bounded LQR and MPC strategies perform similarly in our experiments since we do not require any constraints on the state variables. However, our estimator combined with the implemented MPC can solve problems in which constraints are required on the state variables as well as the drug infusion rates, and can extend our paradigm to the joint control of the anesthetic state and other vital states such as blood pressure using joint administration of multiple drugs.

[1]The steady-state solution in our problem exists since we can show using the experimental fits that the state model, $[\mathbf{A}, \mathbf{B}]$, is controllable.

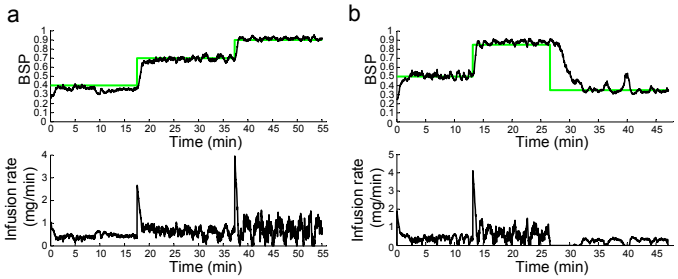

Fig. 2. Real-time BMI control of burst suppression in individual rats in two experiments. In each subfigure, the top panel shows the closed-loop controlled BSP trace in black and the desired time-varying target level in green, and the bottom panel shows the corresponding drug infusion rate administered by the BMI.

III. Results

We implemented our BMI in real-time rat experiments. Surface EEG recordings were collected using intra-cranial electrodes at 4 stereotactic coordinates relative to lambda. The EEG signal was low-pass filtered (below 5Hz) and thresholded to convert it into a binary time-series (Figure 1a). This binary EEG signal was then used as input to the BMI that controlled a Physio 22 syringe pump (Harvard Apparatus, Holliston, MA) to deliver propofol using a 24-gauge IV catheter placed in a lateral tail vein. At the start of each experiment, multiple boluses of propofol were administered to the rat and the resulting BSP signals were used for offline fitting of the two-compartment model (see Methods). The real-time BMI experiments followed this system identification. The aim in the real-time BMI experiments was to acquire, maintain, and transition between at least three target BSP levels (low, medium, high) in randomized order.

To characterize the performance of the BMI at steady state, we compute the error between the target BSP at each time, $p^*(t)$, and the controlled BSP, $p_{t|t}$, i.e., $e_t = p^*(t) - p_{t|t}$. We then calculate two standard metrics of performance [36], the median prediction error (MDPE) given by MDPE $=$ median$(e_t/p^*(t))\times 100$ and the median absolute performance error (MDAPE) given by MDAPE $=$ median$(|e_t|/p^*(t)) \times 100$. The MDPE is a measure of bias at steady state and the MDAPE is a measure of normalized error.

In each animal and experimental session, the BMI successfully and promptly transitioned between levels and accurately maintained the BSP at a desired target level. The results for two experimental sessions in two rats are shown in Figure 2. The BMI was especially successful in increasing

or decreasing the level of BSP promptly and reliably, while avoiding overshoot or undershoot. At steady-state, the BMI could accurately maintain a desired BSP level in these experiments (Figure 2) with a median performance error, MDPE, of 3.57% and a percent bias, MDAPE, of -0.13% .

IV. Conclusions

We investigated the feasibility of automatic control of medical coma by developing a BMI to control burst suppression in a rodent model. Our BMI reliably and accurately controlled burst suppression in individual rodents across dynamic time-varying target trajectories. Our results demonstrate that automatic control of medical coma is highly feasible using a BMI.

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