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A hidden semi-Markov model for estimating burst suppression EEG

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Abstract—Burst suppression is an electroencephalogram (EEG) pattern associated with profoundly inactivated brain states characterized by cerebral metabolic depression. This pattern is distinguished by short-duration band-limited electrical activity (bursts) interspersed between relatively near-isoelectric periods (suppressions). Prior work in neurophysiology suggests that burst and suppression segments are respectively associated with consumption and regeneration of adenosine triphosphate resource in cortical networks. This indicates that once a suppression (or, burst) segment begins, the propensity to switch out of the state gradually increases with duration spent in the state. Prior EEG monitoring frameworks that track the brain state during burst suppression by tracking the estimated fraction of time spent in suppression, relative to bursts, do not incorporate this information. In this work, we incorporate this information within a hidden semi-Markov model (HSMM) wherein two states (burst & suppression) stochastically switch between each other using sojourn-time dependent transition probabilities. We demonstrate the HSMM’s utility in analyzing clinical data by estimating the state probabilities, the optimal state sequence, and the brain’s metabolic activation level characterized by parameters governing sojourn-time dependence in transition probabilities. The HSMM-based approach proposed here provides a novel statistical framework that advances the state-of-the-art in analyzing burst suppression EEG.

I. INTRODUCTION

Burst suppression is a characteristic feature of electroencephalogram (EEG) signals associated with states of profound unconsciousness in patients, such as those under general anesthesia or in coma [1]. This pattern comprises bursts of high amplitude electrical activity interspersed between isoelectric or quiescent suppression periods. Prior neurophysiological modeling studies indicate that the alternating burst and suppression epochs are respectively associated with adenosine triphosphate (ATP) depletion and regeneration [2]. In each cycle, the recovery of rhythms within bursts is associated with recovery of basal dynamics at the neuronal circuit level caused by transient increases in energy reserves. As the level of unconsciousness deepens, such as in general

anesthesia, the brain’s metabolic activation level characterizing the transient ATP dynamics progressively decreases. The fraction of time spent in the suppression periods within a local time window is regarded as an index of the level of brain’s inactivation. The real time monitoring of this index in patients provides valuable information about a patient’s anesthetic state during surgery or in medically-induced coma.

Early research efforts in quantitative description of burst suppression led to the burst suppression ratio (BSR) [3]. BSR is a value between 0 to 1 where $BSR = 0$ and $BSR = 1$ respectively correspond to epochs with no suppressions and no bursts. Building upon the BSR, while addressing the limitations posed by the BSR-based analyses, an earlier work proposed the burst suppression probability (BSP) index which has better dynamical performance relative to BSR [4]. To estimate the BSP, the burst suppression EEG time series is viewed as a binary sequence which takes values of 1 when the EEG amplitude is below a user-specified threshold (data point belonging to a suppression segment) and 0 otherwise (data point belonging to a burst segment). This binary observation sequence allowed the authors to use a point process state-space (SS) model, where the binary observations were assumed to be realizations of a non-stationary binomial process, to estimate the BSP within a sequential Bayesian estimation framework [4].

The earlier BSP work did not incorporate mechanistic insight based on aforementioned ATP-dynamics from prior neurophysiological modeling work [2]. Utilizing this insight, a previous work posited a SS model with a nonlinear first order Markovian process describing the evolution of a continuous-valued latent state variable [5]. The binary observations were assumed to evolve as Markovian switchings between burst and suppression states where the transition probability depended on both the aforementioned latent state as well as the length spent in current burst or suppression state. Owing to the complexity induced by the nonlinear SS model, the model parameters were approximated by fitting a parametric distribution to the empirical distribution on the joint space of the smoothed BSP estimate and length of state epochs.

In the current work, we propose a novel, principled statistical modeling framework based on a hidden semi-Markov model (HSMM) [6], while preserving two key conceptual elements from the prior work [5], (1) the sojourn-time (time spent in the current state since entering that state) dependence of the transition probabilities governing the fast time-scale Markovian state switching and (2) the use of parameters that characterize this sojourn-time dependence as metrics

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to track the brain's metabolic activation level. One of the main advantages of our estimation paradigm over [5] is that the HSMM-based approach can estimate the metabolic activation level directly from the binary data without requiring the intermediate dependence on the BSP estimate, thus simplifying the estimation procedure. Another key advantage is that the HSMM formulation enables usage of standard sequential state estimation tools available in HMM literature [7] to track the unobserved burst/suppression states and their sojourn-times. It also provides an analytically tractable and computationally feasible framework to learn the sojourn-time dependence of the state switching probabilities from data. We regard the parameters describing the sojourn-time dependence as indicative of the current metabolic activation level. Additionally, we use a Bayesian paradigm for HSMM model estimation to compensate for the finiteness of the data. We prescribe prior probability distributions on the model parameters and calculate the maximum a posteriori (MAP) estimates of these parameters using an Expectation Maximization (EM) framework.

II. THEORY

A. Binary observation sequence

We consider an EEG time-series data sampled at F_s Hz that is converted to a binary time series by using an amplitude threshold such that any data point lying below the threshold is marked as 1 (suppression) and 0 (burst), otherwise. We view this binary sequence in non-overlapping time-windows of size Δ each containing $n(= F_s \Delta)$ binary observations. We denote the number of 1's in the k -th time bin of size Δ as y_k where $0 \leq y_k \leq n$. A sequence of length K , denoted by $y_{1:K} \triangleq \{y_1, y_2, \dots, y_K\}$, is considered as the observation input to the HSMM model under consideration.

B. HSMM observation model

We assume that for the k -th time-bin of size Δ , the observation y_k is sampled from one of two binomial distributions.

$$P(y_k | s_k = i) = \binom{n}{y_k} (p_i)^{y_k} (1 - p_i)^{n - y_k} \quad (1)$$

where, $i \in \{1, 2\}$ and s_k represents a discrete-valued random process such that $s_k = 1$ (or, $s_k = 2$) corresponds to a burst (or, suppression) state.

C. HSMM state evolution model

We assume that the hidden (unobserved) random process s_k is evolving stochastically, such that the probability to transition out of the current state depends on the time-spent in the same state since entering that state. To characterize this, we define an integer-valued random processes τ_k , such that a realization of $\tau_k \Delta$ is the sojourn-time for the realization s_k . We assume a finite sample space $\tau_k \in \{1, 2, \dots, \tau_{\max}\}$ where $\tau_{\max}$ is set to a value that is high enough to include all possible sojourn-times in either state; a candidate value is $\tau_{\max} = K$. Using intuitions based on prior work [2], we assume that the propensity to switch out is lowest when a state switching occurs and gradually increases

with time [2]. We model the sojourn-time dependence in the transition probabilities as follows,

$$\begin{aligned} P(s_{k+1} \neq s_k, \tau_{k+1} = 1 | s_k, \tau_k) &= 1 - e^{-\lambda_{s_k}(\tau_k - 1)\Delta}, \quad (2) \\ P(s_{k+1} = s_k, \tau_{k+1} = \min(\tau_k + 1, \tau_{\max}) | s_k, \tau_k) &= e^{-\lambda_{s_k}(\tau_k - 1)\Delta}, \end{aligned}$$

where the first and second equations correspond to switching and continuation events, respectively. For all the other transition events, beyond the ones accounted for in Eq. (2), the transition probabilities are always zero. Note that $\tau - 1$ in the exponent ensures that when the process enters a given state, it tends to remain in that state for at least two Δ time-bins. We assume that over the time-window of size $\Delta_B = K\Delta$ the time-constant parameters λ_1 and λ_2 are constant.

D. Likelihood

We can write the joint distribution of $y_{1:K}$ as,

$$P(y_{1:K}) = \sum_{s_K, \tau_K} P(s_K, \tau_K, y_{1:K}) \quad (3)$$

and evaluate the likelihood using the following recursion,

$$\begin{aligned} P(s_k, \tau_k, y_{1:k}) &= P(y_k | s_k) \sum_{s_{k-1}, \tau_{k-1}} P(s_k, \tau_k | s_{k-1}, \tau_{k-1}) \\ &\quad \cdot P(s_{k-1}, \tau_{k-1}, y_{1:k-1}) \end{aligned} \quad (4)$$

where, the observation and state transition probabilities are calculated per Eq. (1) and Eq. (2), respectively. The recursion in Eq. (4) begins with, $P(s_1, \tau_1, y_1) = P(y_1 | s_1)\pi$, where $\pi \triangleq P(s_1, \tau_1)$, is the unconditional probability of the hidden states at $k = 1$. Therefore, for the HSMM, the model parameter set includes $\Psi \triangleq \{\Theta, \Delta, \tau_{\max}\}$ where $\Theta \triangleq \{\pi, p_1, p_2, \lambda_1, \lambda_2\}$.

E. Estimating states from observations

Given a prescribed Ψ we seek to estimate $P(s_k, \tau_k | y_{1:K}, \Theta)$ where the conditioning on Θ is indicated as it is estimated from data while the dependence on rest of the parameters in Ψ is implied. We implement the HSMM as an extended state HMM [8] that enables us to use standard sequential Bayesian estimation procedure, *Forward-Backward* algorithm, to estimate the posterior state probabilities [7]. Using this same framework, we also calculate $P(s_k, \tau_k, s_{k+1}, \tau_{k+1} | y_{1:K}, \Theta)$ which is essential for the EM procedure. Furthermore, we use the *Viterbi* algorithm from HMM literature to estimate the MAP state trajectory [7],

$$\{\hat{s}_{1:K}, \hat{\tau}_{1:K}\} = \operatorname{argmax} P(y_{1:K}, s_{1:K}, \tau_{1:K} | \Theta). \quad (5)$$

F. MAP estimation of Θ from observations

Given a prior probability, $P(\Theta)$, we determine point-estimates $\hat{\Theta}$ of Θ by maximizing the logarithm of the posterior probability,

$$\hat{\Theta} = \operatorname{argmax} \ln P(\Theta | y_{1:K}) \quad (6)$$

This optimization problem can be solved using the iterative EM procedure [9]. Taking a similar approach as [10], we maximize $R(\Theta, \hat{\Theta})$ defined as,

$$R(\Theta, \hat{\Theta}) \triangleq Q(\Theta, \hat{\Theta}) + \ln P(\Theta), \quad (7)$$

in the M-step within an EM iteration where $\hat{\Theta}$ refers to the optimal estimate from the previous M-step. $Q(\Theta, \hat{\Theta})$ denotes the expected total data log-likelihood and defined as

$$Q(\Theta, \hat{\Theta}) \triangleq \sum_{s_{1:K}, \tau_{1:K}} \ln P(y_{1:K}, s_{1:K}, \tau_{1:K} | \Theta) \cdot P(s_{1:K}, \tau_{1:K} | y_{1:K}, \hat{\Theta}) \quad (8)$$

We assume statistically independent gamma priors on λ_1 and λ_2 , beta priors on p_1 and p_2 , and Dirichlet prior on π as these are conjugate priors to exponential, binomial and multinomial distributions, respectively. These priors are represented as,

$$P(\lambda_i) \propto \lambda_i^{a_i-1} e^{-b_i \lambda_i}, \quad a_i > 1, b_i > 0, \quad (9)$$

$$P(p_i) \propto (p_i)^{c_i-1} (1-p_i)^{d_i-1}, \quad c_i, d_i > 0, \quad (10)$$

$$P(\pi) \propto \prod_{s=1}^2 \prod_{\tau=1}^{\tau_{max}} (\pi_{s,\tau})^{e_{s,\tau}-1}, \quad e_{s,\tau} \geq 0. \quad (11)$$

where, $i \in \{1, 2\}$ and $\{a_1, b_1, a_2, b_2, c_1, d_1, c_2, d_2, \{e_{s,\tau}\}_{s=1, \tau=1}^{2, \tau_{max}}\}$ is the set of hyper-parameters that parameterize $P(\Theta)$. The combined prior is, $P(\Theta) = P(\lambda_1)P(\lambda_2)P(p_1)P(p_2)P(\pi)$, which follows from the statistical independence assumption. Differentiating the expression $R(\Theta, \hat{\Theta})$ (Eq. (7)) with respect to each of the individual terms in Θ and equating the result to zero leads to the analytical representations of equations to solve for the updated $\hat{\Theta}$. While implementing each EM iteration, we perform the E-step to evaluate $P(s_k, \tau_k | y_{1:K}, \hat{\Theta})$ and $P(s_k, \tau_k, s_{k+1}, \tau_{k+1} | y_{1:K}, \hat{\Theta})$ using procedure discussed in Sec. II-E. Incorporating this information in the analytical expressions for the optimal Θ , we solve for the new $\hat{\Theta}$ in the M-step.

III. RESULTS

We have analyzed our HSMM framework by applying it to de-identified EEG recordings from surgical patients under general anesthesia at Massachusetts General Hospital (MGH). The data was collected as a part of the MGH Human Research Committee-approved protocol. Each EEG dataset, sampled at a rate of $F_s=250$ Hz, is detrended over sliding windows of 2 seconds each, and then band-pass filtered from 1 Hz to 55 Hz. After this preprocessing, each EEG data sequence is converted to a binary time series using an existing binary classification algorithm that is parameterized by a forgetting factor, β , and a classification threshold, θ , on the instantaneous EEG variance [5]. We label time points with variance values lying below θ as 1's and all others as 0's. We use $\beta = .9534$ (the globally optimal forgetting factor in [5]) and $\theta = 0.1 \mu V^2$, uniformly across all 3 patient datasets used here. We convert each of these binary sequences to a count sequence by summing the 1's in non-overlapping intervals, $\Delta = 0.5 s \Rightarrow n = F_s \Delta = 125$. In the

subsequent analyses, unless otherwise prescribed, the default configuration for the MAP EM algorithm implementation will comprise $\Delta_B = 30 s \Rightarrow K = 60$ within which we have assumed stationarity of sojourn-time dependence in transition probabilities and $\tau_{max} = 60$.

For the beta priors on p_i we choose $c_1 = 1.1, d_1 = 20, c_2 = 20, d_2 = 1.1$ such that suppression (or, burst) segments will have a higher $P(y_k | s_k = 2)$ (or, $P(y_k | s_k = 1)$) when y_k 's are close to n (or, 0) and lower when y_k 's are close to 0 (or, n). The highly skewed beta priors ensure that states $s_k = 1$ (and $s_k = 2$) will correspond to bursts (and suppressions). For the gamma priors on λ_i , we specify $a_1 = 10 = a_2$ and $b_1 = 90 = b_2$ such that the distribution, $P(\lambda_i)$, has a mode ($= (a_i - 1)/b_i$) at $1/10$ and a wide spread around this mode. For the Dirichlet prior on π we use $e_{s,\tau} = 1 \forall s = \{1, 2\}, \tau = \{1, 2, \dots, \tau_{max}\}$. For the example cases analyzed here, an upper limit of 30 EM iterations was found to be sufficient for $R(\Theta, \hat{\Theta})$ to converge.

To demonstrate the HSMM analyses' outputs on a single Δ_B segment, we analyze 0.5 min segments of a patient's EEG data. Comparing across the three segments in Fig. 1, we note that as the average duration of the suppression segments become shorter, the relative ratio $\hat{\lambda}_2/\hat{\lambda}_1$ tends to increase. This agrees with our intuition that shorter suppression segments in a given Δ_B will lead to higher λ_2 such that the switching probability approaches 1 more quickly.

Fig. 1. HSMM estimated from three (A, B, C) 0.5 minute segments in a single recording session. Sub-panels, from top to bottom, represent the EEG data, observations y_k , the MAP estimate of state trajectory $\hat{s}_{1:K}$ (where the suppression segments are filled as black rectangles) given the converged $\hat{\Theta}$, $P(s_k = 2 | y_{1:K}, \hat{\Theta})$, and switching probability ($P(\hat{s}_{k+1} \neq \hat{s}_k | \hat{s}_{1:K}, \hat{\Theta})$) given the MAP sequence, all as a function of time. The 4-tuple $(\hat{\lambda}_1, \hat{\lambda}_2, \hat{p}_1, \hat{p}_2)$ for each case: A (0.0751, 0.0523, 0.0208, 0.7920), B (0.0313, 0.0940, 0.0321, 0.7331), C (0.0576, 0.1220, 0.0018, 0.3719).

To analyze the properties of the HSMM parameter estimator, we present a brief analyses in Fig. 2 based on data simulated using a ground truth HSMM similar to the one estimated in Fig. 1(A). Figs. 2(B) and 2(C) demonstrate that that our estimator for $\hat{\lambda}$ and $\hat{p}$ has desirable asymptotic properties; with increasing length of data, the posterior estimates become closer to the true value and the uncertainty reduces. This also agrees with our understanding that with more data, the posterior estimates will have relatively more contribution from the likelihood than the prior. To further explore the behavior of how λ_1 and λ_2 vary with duration

Fig. 2. Panel A - Random realization of length $K = 60$ for an unobserved state $s_k^{(G)}$ and observation $y_k^{(G)}$ using a ground truth HSM ($\lambda^{(G)} = [\lambda_1^{(G)}, \lambda_2^{(G)}] = [0.07, 0.05]$ and $p^{(G)} = [p_1^{(G)}, p_2^{(G)}] = [0.02, 0.80]$). We generate such $y_k^{(G)}$ for 10 values of $K \in [60, 1200]$, and for 20 replicates for each K . We run MAP HSM estimation on each realization of $y_k^{(G)}$ (similar to rows 3 to 5 of Fig. 1), and then plot the median (black circles, joined by dashed line) and 25th and 75th percentiles of e_λ (Panel B) and e_p (Panel C) versus K where, $e_x = 100\|\hat{x} - x^{(G)}\|_2/\|x^{(G)}\|_2$.

of suppressions within fixed length Δ_B window, we apply HSM to non-overlapping Δ_B windows on long recording sessions. In Fig. 3, by observing the MAP sequence of $\hat{s}_{1:K}$ we can see that time-points where the y_k 's are close to zero (or, n) for prolonged time are classified as burst (or, suppression) segments. From each HSM corresponding to every Δ_B window, we calculate the mean suppression probability as, $\bar{P}_S \triangleq \frac{1}{K} \sum_{k=1}^K P(s_k = 2 | y_{1:K}, \hat{\Theta})$. The $\bar{P}_S$ metric, like the BSR, is an estimate of the fraction of time spent in suppression state in the Δ_B bin, but more informed than BSR since it is based on conditional probability of suppression state given all data in Δ_B window and the MAP estimate of Θ . Comparing across the three datasets, we note that wherever the black bars in the second row $\hat{s}_{1:K}$ grow denser we see increase in $\bar{P}_S$. The information on lengths of continuous suppression and burst segments is contained in $\hat{\lambda}_1$ and $\hat{\lambda}_2$ estimates. By visual examinations of $\hat{\lambda}$ time-series, we note that for longer suppressions (or, bursts) the $\hat{\lambda}_2$ (or, $\hat{\lambda}_1$) is smaller, provided the analyses window has enough suppression events to move the MAP estimate of λ_2 away from the mode of the prior. This explains why we see $\hat{\lambda}_2$ stagnate at a high value when there are negligible or no suppression event in the epoch. To track the brain's metabolic activation state based on these time-constants, and inspired by [5], we define another metric, the *relative duration index*, $RDI \triangleq \hat{\lambda}_2^{-1}/(\hat{\lambda}_1^{-1} + \hat{\lambda}_2^{-1})$, that encapsulates information of average duration of suppressions relative to bursts. The analyses presented in Fig. 3 indicates that on the slower time-scale (across Δ_B time-windows) dynamics in $\bar{P}_S$, RDI and BSP may be similar.

IV. CONCLUSION

In this work we have developed a novel, neurophysiology-informed HSM framework to model the stochastic switchings between EEG burst and suppression patterns. The estimated HSM states can track the fast dynamics in state evolution (s_k, τ_k) evolving at Δ time-intervals. The HSM model parameters (λ_1, λ_2) can be used to track the changes in transition probability dependence on sojourn-time which is representative of dynamics in the brain's metabolic activation level. A key advantage of the MAP HSM framework over previous works is that it provides an integrated inference framework for estimating state trajectories and their sojourn-times, as well as the sojourn-time dependence on state transitions. The latter aspect allows us to analyze duration statistics of the bursts and/or the suppressions across multiple Δ_B time-intervals. The sequential Bayesian inference

Fig. 3. HSM analyses on 3 sessions of data (A, B, C). The rows, from top to bottom, indicate the observations y_k , the MAP estimate of state trajectory $\hat{s}_{1:K}$ (where the suppression segments are filled as black rectangles) given the converged $\hat{\Theta}$, the mean suppression probability $\bar{P}_S$, the MAP estimates of $\hat{\lambda}_1$ and $\hat{\lambda}_2$, the RDI , and BSP estimate. The HSM estimates are calculated from each of the sliding windows of size Δ_B . Linear regression of RDI (or, BSP) vs. $\bar{P}_S$ for each of three recordings A, B and C yields $R^2 = 0.90, 0.85$ and 0.95 (or, $= 0.88, 0.66$ and 0.95), respectively.

framework of the HSM makes it suitable for efficient real-time tracking of the aforementioned dynamical metrics. Although we have focused on a particular parametric form of sojourn-time dependence in transition probabilities (an exponential decay in continuation probability with sojourn-time), our framework has scope for incorporating alternative descriptions and thus has potential as a statistical paradigm to compare across different models of sojourn-time dependence in transition probabilities.

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