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Hidden Markov Chain modeling for epileptic networks identification

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Abstract— **The partial epileptic seizures are often considered to be caused by a wrong balance between inhibitory and excitatory interneuron connections within a focal brain area. These abnormal balances are likely to result in loss of functional connectivities between remote brain structures, while functional connectivities within the incriminated zone are enhanced. The identification of the epileptic networks underlying these hypersynchronies are expected to contribute to a better understanding of the brain mechanisms responsible for the development of the seizures. In this objective, threshold strategies are commonly applied, based on synchrony measurements computed from recordings of the electrophysiologic brain activity. However, such methods are reported to be prone to errors and false alarms. In this paper, we propose a hidden Markov chain modeling of the synchrony states with the aim to develop a reliable machine learning methods for epileptic network inference. The method is applied on a real Stereo-EEG recording, demonstrating consistent results with the clinical evaluations and with the current knowledge on temporal lobe epilepsy.**

Index Terms— **Temporal Lobe Epilepsy, Stereo-EEG, Network Inference, Bayesian Approach, Hidden Markov Chain**

I. Introduction

Recent studies have put forward evidence that partial epilepsies are occurring due to the hyper-excitable nature of a focal brain area, known as the epileptogenic zone [1]. The set of structures constitutive of this area is assumed to be organized in an epileptic network responsible for the genesis of paroxystic (ictal) events. This network takes successive configurations throughout the evolution of the crisis [2], and their identification would be helpful in understanding the role of each of the incriminated structures in the development of the epileptic process. The strength in connectivity between two structures is evaluated from their electrophysiologic activities provided by the EEG or by the Stereo-EEG (SEEG[1]). A wide range of quantification methods can be found in the literature [3], and the resulting quantities can be used to infer the connections in the network [4]. In this paper, a bivariate cross-correlation quantification using MODWT (Maximum Overlap Discrete Wavelet Transform) has been chosen to evaluate time-delayed relations between SEEG channels. The efficiency of such frequency-dependent quantifications has been demonstrated in the case of epilepsy [5], [6].

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[1]The SEEG modality, observed on bipolar montage, provides local measurements of targeted brain structures activity by invasively placing electrodes very near from the brain generators suspected to be involved in the epileptic process.

Various thresholding strategies can be used to infer graphs [7], [4]. The choice of the threshold has a high impact on the resulting graph as it is very sensible to concurrent activities and to the background noise correlation effect. The robustness of such inference methods has to be improved, with the objective to provide reliable and systematic network identifications. In this paper, we take advantage of the time persistence of the synchrony states, which is modeled using a hidden Markov chain (HMC). HMC is a well known model for robust signal segmentation and learning of data sequences, and will be helpful in identifying stable synchrony states during an epileptic event. A Bayesian framework is adopted, in which the model parameters can be estimated from the data. The method is here illustrated on a Temporal Lobe Epilepsy (TLE) event recorded by means of SEEG at the Neurology Unit of Nancy Hospital (France).

II. Connectivity measurement and likelihood

A. Synchrony quantification

Depending on the phenomena that are to be emphasized, the quantification method has to be chosen carefully, each having their specificities in capturing particular kind of relations in the electrophysiologic data. In the case of TLE, linear correlation-frequency dependent methods are eligible [5]. Indeed, these events are characterized by well identified oscillating activities in particular frequency bands, from beta rhythm to very fast oscillations, and usually show increased frequency-dependent synchronies as the seizure progress [4]. Such behavior is illustrated in figure 1, where the harmonic nature of the signal can be observed. On this figure, a phase switching occurs between the two signals, a feature having its importance as it is an indicator of a reconfiguration within the epileptic network. Such delays in synchrony are to be taken into account in the measurement method.

The synchrony quantification is carried out using the maximal overlap discrete wavelet transform (MODWT) [6]. Let w_m^j and w_n^j be the j^{th} level MODWT coefficients of two stochastic processes with zero-mean, called s_m and s_n. The MODWT estimator of the cross-correlation at scale j considering a delay value of τ writes:

$$\rho^{\tau}(t) = \frac{\text{cov}(w_m^j[t], w_n^j[t-\tau])}{\sqrt{\text{var}(w_m^j[t])\text{var}(w_n^j[t-\tau])}} \qquad (1)$$

where cov(.) and var(.) refer to the empirical estimations of covariance and variance respectively, $[t]$ denotes the considered time window, and the delay τ is allowed between fixed bounds ($-\tau_b \leq \tau \leq \tau_b$). Let $\tau_{\max}$ be the vector containing the delays for which the cross-correlation is

maximized for each time window. The associated maximum cross-correlation values will be stored in the vector $\rho^{\tau_{\max}}$. The delay τ is commonly assumed to bear an information on the causality of the activity of a structure on the second one [6].

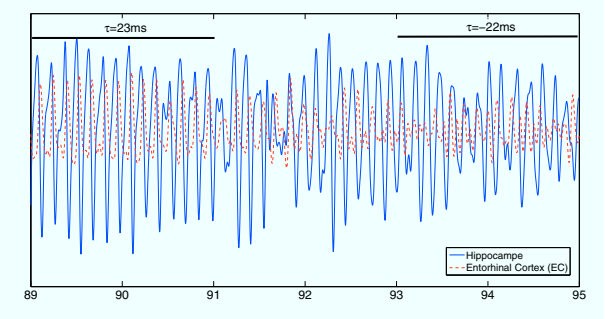

Fig. 1. A jitter in synchronization appearing during the paroxystic ictal event between hippocampus and entorhinal cortex (EC). Two phases in synchrony can be observed: a first on where the hippocampus is leading the EC with $\tau = 23$ms, and a second phase where the EC is leading the hippocampus with $\tau = 22$ms.

B. Connectivity likelihood

From our experiments, the Beta distribution has shown to provide well adapted bell shapes to fit the histograms of MODWC cross-correlation of real SEEG recordings (see fig. 2(a)&(b)). It can be noticed that such modeling is indeed well appreciated to model various correlations quantities [8], given the wide range of shapes that this distribution is able to provide. The beta distribution is given by:

$$g(y) \quad = \quad \frac{(1-y)^{\alpha-1}y^{\beta-1}}{B(\alpha,\beta)} \qquad (2)$$

where $B(\alpha,\beta) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)+\Gamma(\beta)}$. Crossing-values of the resulting distributions can be seen as an estimation of the threshold ρ_{thr} between synchrony and dyssynchrony cross-correlation values. A thresholding strategy is however not adequate in this context of uncertain biological data, since it is reported to lead to false alarms and omissions [7], [4]. In this work, we introduce a *prior* constraint of the synchrony time persistence, modeled by a HMC.

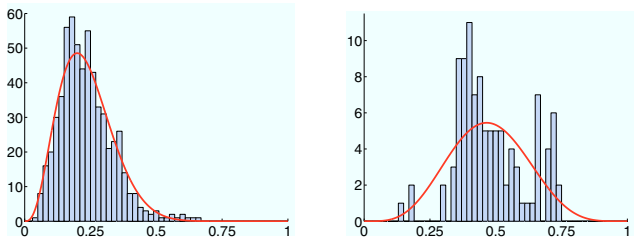

Fig. 2. Cross-correlations likelihoods: (a) shows the histogram of cross-correlation values in absence of synchrony (state λ_0), while (b) shows the histogram of the values related to the synchrony states $\lambda_{i,\ i>0}$, with fitted beta distributions.

III. Network Inference

Even though epilepsy is a chaotic event of hyper excitability and hyper synchronizations between distant brain structures, it can be reasonably assumed that some stable pathways are followed by the flow of information from a structure to another. A finite number of stable synchrony configurations (and delays) between two brain regions will be considered during an epileptic occurrence.

A. Hidden Markov Chain

Let $\mathbf{X} = (X_t)_{1\leq t\leq T}$ be the stochastic process modeling the state of synchrony between a couple of recorded channels. $\mathbf{X}$ is said to be *hidden* and takes its values in a finite set $\Lambda = \{\lambda_0, ..., \lambda_K\}$, λ_0 being associated with the state of dyssynchrony, and each $\lambda_{k_{1\leq k\leq K}}$ being associated to a state of synchrony with a delay τ_k. $\mathbf{Y}$ stands for the observation process, with realization $\mathbf{y} = \{(\mathbf{y_t})\}_{1\leq t\leq T}$, here given by the synchrony measurements ρ^τ (eq. 1), so that we have $\mathbf{y_t} = \{y_t^0, y_t^1, ..., y_t^K\} = \{\rho^{\tau_{\max}}(t), \rho^{\tau_1}(t), ..., \rho^{\tau_K}(t)\}$. $\mathbf{X}$ is supposed to be Markovian and we wish to retrieve these hidden states from the observation $\mathbf{Y}$. The *priors* on $\mathbf{X}$ are given by the initial probability $\pi_k(x_1) = p(x_1 = \lambda_k)$ and by the $(K+1)\times(K+1)$ square transition matrix $a_{ij} = p(x_t = \lambda_j | x_{t-1} = \lambda_i)$.
X is supposed to be homogeneous, and the i.i.d assumption is made on the process Y conditionally on X. The *posterior* probabilities at each time site $P(x_t|\mathbf{y})$ can then be computed [9], and the decision on $\mathbf{X}$ is finally obtained through the Maximal Posterior Mode criterion: $\hat{x}_t = \arg\max_{x_t} P(x_t|\mathbf{y})$

B. Parameter Estimation

The parameters of the model are estimated using the ICE procedure [10]. The set of parameters to estimate can be drawn as: $\theta = \{\pi_k, a_{ij}, \alpha_k, \beta_k, \tau_k\}$.

1) Initialization:

• The initialization of the number of synchrony classes K and of the related delay values $\tau_k^{[0]}$ is a critical issue. Indeed, this step might greatly influence the resulting networks. Depending on the pathological context and the incriminated structures, the neurologists expertise is likely to be helpful in setting relevant thresholds and delay boundaries. In this work, these values are initialized empirically from the vector $\tau_{\max}$ associated to the maximal cross-correlation delay values (see section II-A). If a time delay brings *sufficiently* high correlation quantifications over a *sufficient* length of time (*e.g.* over $1s$ in this work), then it is set *a priori* as an eligible synchrony state. An observation vector $\mathbf{y_t}$ is then computed from the equation (1) for each selected synchrony class λ_k.

• Prior parameters on X are initialized empirically as, *e.g.*, $\pi^{[0]}(i) = \frac{1}{K+1}$, $a_{ii}^{[0]} = \frac{9}{10}$ and $a_{ij}^{[0]} = \frac{1}{10(K)}$ for $i \neq j$.

• $K+1$ set of beta distribution parameters $\{\alpha_k, \beta_k\}_{k\in\{0,..,K\}}$ are to be initialized: an initial threshold value $\rho_{\text{thr}}^{[0]}$ is computed, being the mean plus twice the standard deviation of the maximum cross-correlation observations $\rho^{\tau_{\max}}$. Using this rough threshold, the full set of observations $\mathbf{y}$ is classified in two arrays $\{\mathbf{y_l}\}_{l\in\{0,1\}}$: $y_t^i \in \mathbf{y_0}$ if $y_t^i < \rho_{\text{thr}}^{[0]}$ and $y_t^i \in \mathbf{y_1}$ if $y_t^i > \rho_{\text{thr}}^{[0]}$. Empirical mean $\{\mu^{[0]}\}_{l\in\{0,1\}}$ and variance $\{\sigma^{[0]}\}_{l\in\{0,1\}}$ of these set are computed. We then get preliminary estimated versions of the Beta distribution parameters [11]:

$$\alpha_l^{[0]} = \mu_l^{[0]}\left(\frac{\mu_l^{[0]}(1-\mu_l^{[0]})}{\sigma_l^{[0]}} - 1\right) \quad (3)$$

$$\beta_l^{[0]} = (1-\mu_l^{[0]})\left(\frac{\mu_l^{[0]}(1-\mu_l^{[0]})}{\sigma_l^{[0]}} - 1\right) \quad (4)$$

The dyssynchrony beta distribution is then initialized with the parameters $\{\alpha_0, \beta_0\} = \{\alpha_0^{[0]}, \beta_0^{[0]}\}$, while the K synchrony beta distributions are initialized with the set of parameters $\{\alpha_k, \beta_k\}_{k>0} = \{\alpha_1^{[0]}, \beta_1^{[0]}\}$.

2) ICE estimation: For each q in $\mathbb{N}^*$, $q \leq Q$ (Q is the number of iteration set by the user), we compute the following ICE estimation for the parameters update:

• Computation of the *posterior* probabilities:
$\xi_t^{[q]}(k) = P(x_t = \lambda_k|Y)$ and $\Psi_t^{[q]}(i,j) = P(x_t = \lambda_i, x_{t+1} = \lambda_j|\mathbf{Y})$ using the forward-backward probabilities. Computation of a realization $\hat{\mathbf{X}} = \{\hat{x}_t\}_{1\leq t\leq T}$ using these *posterior* parameters [10].

• Equation for the maximization step:
- Estimation of the *prior* parameters:

$$\pi^{[q]}(k) = \xi_1^{[q]}(k), \qquad a_{ij}^{[q]} = \frac{\sum_{t=1}^{T-1}\Psi_t^{[q]}(i,j)}{\sum_{t=1}^{T-1}\xi_t^{[q]}(i)} \quad (5)$$

- Stochastic estimation of $\{\alpha^{[q]}, \beta^{[q]}\}$: $\{\mu_k^{[q]}, \sigma_k^{[q]}\}_{k\in\{0,K\}}$ are estimated using the stochastic realization $\hat{\mathbf{X}}$:

$$\mu_k^{[q]} = \frac{\sum_{t=1}^{T}\mathbf{1}_{(\hat{x}_t=\lambda_k)}y_t^{k,[q]}}{\sum_{t=1}^{T}\mathbf{1}_{(\hat{x}_t=\lambda_k)}} \quad (6)$$

$$\sigma_k^{[q]} = \frac{\sum_{t=1}^{T}\mathbf{1}_{(\hat{x}_t=\lambda_k)}(y_t^{k,[q]} - \mu_k^{[q]})^2}{\sum_{t=1}^{T}\mathbf{1}_{(\hat{x}_t=\lambda_k)}} \quad (7)$$

We then get the estimated versions of the Beta distribution parameters at iteration q from equations (3) and (4)
- Similarly, it is possible to compute a stochastic readjustment of the delays $\tau_k^{[q]}$ from the realization $\hat{\mathbf{X}}$:

$$\tau_k^{[q]} = \frac{\sum_{n\in J^k}\tau_{\max}[n]}{N_k} \quad (8)$$

where $J^k = \{t|\hat{x}_t = \lambda_k\}$, and N_k the cardinal of this set.

IV. Results and Discussion

The method has been applied on a SEEG recording of a patient suffering from partial TLE, sampled at Fs=512Hz. The considered intracranial recordings are related to the electrodes implanted in the incriminated regions of the temporal lobe: the hippocampus (B1-2), the entorhinal cortex (TB1-2), the amygdala (A1-2) and the temporal pole (P1-2). The observed activities lie mostly in the frequency band $[8, 16]$Hz (wavelet level $j = 5$), thus being the chosen frequency band for the identification task. A length of 3s has been chosen for the MODWT cross-correlation sliding window analysis, with an overlapping of 0.25s. The segmentation has been performed on a time window of length $[0-200]$s, containing approximately 75s of ictal activity in the time segment $[52-128]$s. The results are given on figure 3 for the 4 channels considered, zoomed on the most informative part between 40s and 140s, few significant synchronies being found outside these bounds. Corresponding values of delays are given in table I. By selecting a synchronization window simultaneously on each of these 6 segmentation maps, a connectivity graph is derived, reflecting the configuration of the epileptic network for this specific time window. Three time-dependent graphs associated to three well identified phases of the seizure are given on figure 4.

TABLE I
Delays (in ms) estimated for each synchrony states vs couple of channels.

	λ_1	λ_2	λ_3
P1-2 - A1-2	29	-	-
P1-2 - B1-2	−31	25	-
P1-2 - TB1-2	−11	-	-
A1-2 - B1-2	0	33	-
A1-2 - TB1-2	−42	−15	-
B1-2 - TB1-2	−27	0	23

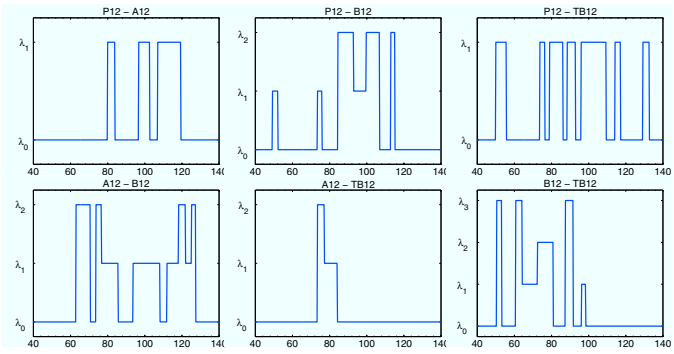

Fig. 3. Results of segmentation for the 6 couples of channel.

Very few significant synchronies are observed before or near after the ictal event. Some isolated short-term ($< 3s$) time range synchronies are appearing between the analyzed structures, mainly between temporal pole, amygdala and hippocampus. This is relevant with the common observation that the activity existing in the temporal lobe area are severely attenuated at the proximity of a seizure [1]. This also tends to prove the capacity of the method in bringing in light the effective synchronies.

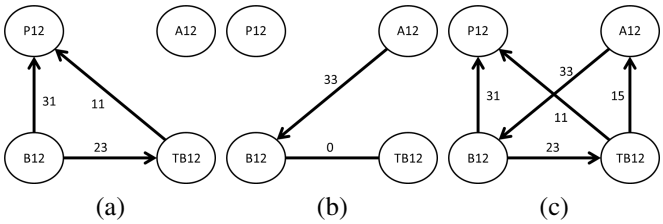

Fig. 4. Connectivity graphs derived from the segmentation results. (a) pre-ictal spikings ($[49-53]$s). (b) end of rapid discharge ($[64-72]$s). (c) paroxystic event onset ($[72-76]$s).

Around time instant 50s, high amplitudes pre-ictal spikings are observed in the signal, resulting in the identification of connectivities between hippocampus, entorhinal cortex and temporal lobe, while amygdala seems to have no role in this event (see fig. 4(a)). At the very beginning of the following rapid discharge ($[55-60]$s), no synchronies are observed, a property already demonstrated in a previous work [2] (however based on a non-linear connectivity quantification). While this rapid discharge activity progressively evolves toward the paroxystic ictal event, gaining in amplitude while decreasing in frequency, synchronies are mainly observed between hippocampus and EC, as well as from amygdala toward EC ($[64-72]$s, see fig. 3 (B1-2 - TB1-2) and fig. 4(b)), then generalizing to the whole set of structures. Fully connected graphs are thus obtained at the onset of the paroxystic event ($[72-76]$s, see fig. 4(c)). Along this highly energetic event ($[72-120]s$), multiple reconfigurations of the network then appear, in which the hippocampus is highly involved. Such synchronies tend to disappear quickly as the epileptic event reaches its term. Another interesting feature, however having to be interpreted with caution, are the estimated delays. Both the hippocampus and the EC seem to have a major role in the development of the event during the rapid discharges and in its evolution toward the paroxystic event, as these structures show high connectivity with mainly leading delays toward amygdala and temporal pole during these ictal phases.

These observations are concordant with the conclusions of the pre-surgical (electro-clinical) analysis of this specific seizure, which also reports that these four structures are found to be involved in the epileptic process, with an ictal behavior typical of a medial temporal lobe seizure [12] (early elementary gestual and oro-alimentary automatisms). Such visual analysis of the rough SEEG signals however do not allows for identification of the relation between structures, thus of the underlying network. The method presented is then likely to bring a higher refinement to the electro-clinical evaluation. However, while being consistent by many aspects with previous studies on partial epilepsy networks [2], the process must be applied on a larger data set to further evaluate its reliability. The fact that very few significant synchronies are obtained outside the ictal event and the epileptic zone can be taken as a first evidence of its relevance. A second validation procedure will be to rely on the high reproducibility of the TLE [13], by evaluating the capacity of the method to reproduce a similar succession of network patterns from an epileptic event to another within a given patient.

Since the current knowledge on brain connectivity pathways are still partial, it is very difficult to establish if connections identified from the data are physiologically effective. This issue may be tackled by exploiting in vitro/in vivo studies along with tractographic data, bringing quantitative information on the connections between distant cortical regions. Some studies already confirmed the relation between enthorinal cortex and the hippocampus region [14]. These information could be advantageously introduced as *priors* in the Bayesian framework described in this paper.

Finally, it has to be emphasized that the Bayesian approach presented in this paper is not dependent of the chosen synchrony quantification. Any (*e.g.* non-linear) quantification of connectivity can be derived in this framework, offering a general and systematic method for network inference whatever are the pathological/functional relations to be highlighted.

REFERENCES

[1] F. Bartolomei, P. Chauvel, and F. Wendling, "Epileptogenicity of brain structures in human temporal lobe epilepsy: a quantified study from intracerebral eeg," *Brain*, vol. 131, no. 7, pp. 1818–1830, 2008.

[2] F. Wendling, P. Chauvel, A. Biraben, and F. Bartolomei, "From intracerebral eeg signals to brain connectivity: identification of epileptogenic networks in partial epilepsy," *Frontiers in systems neuroscience*, vol. 4, 2010.

[3] E. Pereda, R. Quiroga, and J. Bhattacharya, "Nonlinear multivariate analysis of neurophysiological signals," *Progress in neurobiology*, vol. 77, no. 1-2, pp. 1–37, 2005.

[4] M. Kramer, E. Kolaczyk, and H. Kirsch, "Emergent network topology at seizure onset in humans," *Epilepsy research*, vol. 79, no. 2, pp. 173–186, 2008.

[5] K. Ansari-Asl, J. Bellanger, F. Bartolomei, F. Wendling, and L. Senhadji, "Time-frequency characterization of interdependencies in non-stationary signals: application to epileptic eeg," *Biomedical Engineering, IEEE Transactions on*, vol. 52, no. 7, pp. 1218–1226, 2005.

[6] L. Amini, C. Jutten, S. Achard, O. David, H. Soltanian-Zadeh, G. Hossein-Zadeh, P. Kahane, L. Minotti, and L. Vercueil, "Directed differential connectivity graph of interictal epileptiform discharges," *Biomedical Engineering, IEEE Transactions on*, vol. 58, no. 4, pp. 884–893, 2011.

[7] S. Ponten, F. Bartolomei, and C. Stam, "Small-world networks and epilepsy: graph theoretical analysis of intracerebrally recorded mesial temporal lobe seizures," *Clinical neurophysiology*, vol. 118, no. 4, pp. 918–927, 2007.

[8] Y. Ji, C. Wu, P. Liu, J. Wang, and K. Coombes, "Applications of beta-mixture models in bioinformatics," *Bioinformatics*, vol. 21, no. 9, pp. 2118–2122, 2005.

[9] L. Baum, T. Petrie, G. Soules, and N. Weiss, "A maximization technique occurring in the statistical analysis of probabilistic functions of Markov chains," *The Annals of Mathematical Statistics*, pp. 164–171, 1970.

[10] W. Pieczynski, "Champs de Markov cachés et estimation conditionnelle itérative," *Traitement du Signal*, vol. 11, no. 2, pp. 141–153, 1994.

[11] M. Evans, N. Hastings, and B. Peacock, *Statistical distributions*. Wiley-Interscience, 2000, ch. 5: "Beta distribution".

[12] L. Maillard, J. Vignal, M. Gavaret, M. Guye, A. Biraben, A. McGonigal, P. Chauvel, and F. Bartolomei, "Semiologic and electrophysiologic correlations in temporal lobe seizure subtypes," *Epilepsia*, vol. 45, no. 12, pp. 1590–1599, 2004.

[13] F. Wendling, J. Badier, P. Chauvel, and J. Coatrieux, "A method to quantify invariant information in depth-recorded epileptic seizures," *Electroencephalography and clinical neurophysiology*, vol. 102, no. 6, pp. 472–485, 1997.

[14] M. Witter and F. Wouterlood, "The parahippocampal region, organization and role in cognitive function," *Oxford University Press*, 2002.