An in silico approach for pre-surgical evaluation of an epileptic cortex

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Abstract—Clinical evidence indicates that a third of patients with epilepsy are refractory to anti-epileptic drug treatment. For some of these patients better seizure control can be achieved by surgical treatment in which the seizure focus is localised and resected while avoiding injury to crucial cortical tissues.

In this paper, non-seizure (interictal) epoch of electrographic recording was used to calculate the functional synchrony between different cortical regions. This synchrony measure was then used as the connectivity parameter in a computational model of transitions to a seizure like state.

The seizure focus was localised using this model and the surgical intervention procedure was simulated. It was shown that the in silico removal of a subset of seizure focus can decrease the likelihood of a seizure in the model. The in silico results were also compared with the clinical surgical outcomes and a convincing agreement was shown for five out of six patients; sixth being a counter-example.

These methods may aid in the identification of the seizure onset zone using the interictal electrographic data. Moreover, it may facilitate neurosurgeons to investigate alternative cortical tissues to operate on if the seizure focus cannot be operated.

I. INTRODUCTION

The World Health Organisation reports that approximately 50 million people have epilepsy and more than 50% of such patients have localisation related epilepsy (i.e., there is thought to be a focally abnormal area leading to seizures). Unfortunately, for 30% of these patients uncontrolled seizures prevail even after maximal pharmacological therapy using anti-epileptic drugs (see, e.g., [1], [2]). Often these medically intractable patients undergo surgery where the abnormal ‘focus’ is resected to achieve better seizure control.

In order to accurately delineate the seizure onset zone (and consequently the abnormal ‘focus’), clinicians mostly rely on electrocorticography (ECoG) recordings of seizure (ictal) activity. This requires enough seizures to be captured (typically between 3 to 5) during the recording period. Since seizures do not always occur frequently, this often requires a long hospitalization time, sometimes with invasive electrodes placed on the patient’s cortex which involves substantial risk, discomfort and cost. Studies by [3], [4] and [5] show that non-seizure interictal EEG contains relevant information about the location of the epileptic brain area. However, these techniques for aiding seizure focus delineation are not routinely used clinically. Furthermore, these measures are not typically used to give a prediction of whether the surgical outcome will be successful.

Mathematical models allow an exciting opportunity to make predictions, based on the model dynamics, when using certain parameter values. Changes in these parameter values have been shown to be capable of inducing seizure-like dynamics in these models [6], [7], [8]. Similarly, it should therefore be possible to prevent (or reduce the likelihood of) seizures through alterations to parameters too. In previous studies, the connection strengths between different brain areas have been considered to be model parameters [9], [10], though those studies did not investigate the impact of removing connections with a view to simulating the impact of surgery. [11], [12] have investigated the impact of lesions using a model in conjunction with cortical connectivity, however, those studies were not with application to epilepsy.

In this study we infer model connectivity parameters from the clinically obtained ECoG data of epileptic patients. Using a model capable of transiting to a seizure-like state we first predict that nodes which transit to a seizure-like state are located in the clinically determined seizure focus. Secondly, we hypothesise that the removal of these nodes will lead to a greater reduction of seizures than the removal of random nodes. Ultimately, we propose the use of the model for prediction of the likelihood of surgical success.

II. METHODS

A. ECoG data and Preprocessing

We investigated interictal ECoG data of 6 patients with intractable localised epilepsy who had undergone intracranial investigation using intracortical electrodes (depth) and subdural surface electrodes (grid). In each case, 1-hour segment of data, at least 24 hours separated from seizure activity, were examined. The data was band-pass filtered between 4 and 30 Hz, and each ECoG signal was then normalised (mean subtracted and divided by standard deviation). A common reference was used for data analysis. The reference electrode in each case was located far from the area of recording. No further pre-processing was performed; the channels were not selected based on any pre-existing knowledge, except that clearly dysfunctional channels were discarded.

To infer the functional synchrony between different cortical regions, pairwise Pearson correlation coefficient between the ECoG signals were computed and its absolute value was taken. In the temporal correlation analysis of ictal and interictal ECoG data, [13], [14], [15] suggests that linear measures perform similar to nonlinear measures. Thus for the sake of conciseness, we limit ourselves to linear measure instead of more sophisticated measures. Moreover, our results will
also suggest that linear measures suffice for our purposes. The ECoG signal was first segmented in non-overlapping consecutive segments of 5s, in total 720 segments per 1-hour ECoG signal. The functional synchrony was calculated for each 5s segment and the average value was obtained for that 1 hour ECoG signal. These methods were described in detail elsewhere [4]. This gives a functional connectivity matrix $M$.

B. Model

To investigate the role of network topology in seizure initiation, [9] suggested a mathematical model which can display focal onset of episodes of high-amplitude oscillations. These oscillations can be identified with seizure. This model hypothesises seizure initiation to be a noise driven process in a bistable system. Bistability means the model can exhibit coexisting normal (non-seizure) and abnormal (seizure) dynamics. Our implementation of this model considers the cortex under each ECoG electrode to be divided into discrete set of regions with bidirectional connectivity. Individually, each region is modelled to be bistable, which is then extended to multiple regions. The resulting dynamics of seizure initiation are governed by a stochastic differential equation as follows:

$$dz_j(t) = \left( f(z_j) + \beta \sum_{k \neq j} M_{kj}(z_k - z_j) \right) dt + \alpha dw(t),$$  \hspace{1cm} (1)

where

$$f(z_j) = (\lambda - 1 + i\omega)z_j + 2z_j|z_j|^2 - z_j|z_j|^4,$$

and $\omega$ is the parameter which controls frequency of oscillation; $\lambda$ determines the possible attractor of the system; $\beta$ determines the coupling strength of cortico-cortical connectivity; $M$ is the aforementioned subject-specific connectivity matrix; $w(t)$ is Laplace distributed random noise, with zero mean and standard deviation scaled by $\alpha$. Model solutions were computed numerically using a fixed step Euler-Maruyama solver in MATLAB.

Bistability in this model in the deterministic dynamics (i.e. where $\alpha = 0$) depends on the parameter $\lambda$, shown in figure 1 (upper right panel) which is in accordance with [9]. To place the model in bistable region, we use the parameter values as $(\lambda, \beta, \alpha, \omega) = (0.7, 0.01, 3.6, 1)$. Including noise causes the model to exhibit occasional transitions between the two states. The simulated model output for one of the ECoG electrodes is shown in figure 1 (lower panel).

C. Escape time and in silico seizure onset zone

We investigate the phenomenon of seizure initiation in the model, with an objective of reducing its likelihood. Let $E := \{E_1, E_2 \cdots E_N\}$ and $N$ is the number of surface electrodes. Seizure initiation of a node $E_i$ can be quantified using its escape time, $\tau_{E_i}$, which is defined as follows:

$$\tau_{E_i} := \min \left\{ t > 0 \mid x_{E_i}(t) \in B(L), x_j(0) \in B(F) \forall j \right\}, \hspace{1cm} (2)$$

where $x_{E_i}$ is the trajectory of $i^{th}$ node; $B(F)$ and $B(L)$ are the basin of attraction of the fixed point (non-seizure) state and the oscillating (seizure) state respectively.

Hypothesising that the nodes with minimum escape time should form the seizure focus we define the seizure onset zone, in this modelling framework as follows:

$$S_K = \arg \min \{ T(A) \mid A \in \mathcal{P}(E_K) \},$$  \hspace{1cm} (3)

where $S_K$ is the set of nodes forming the seizure onset zone; $T(A)$ is the mean escape time of nodes whose labels are in $A$; $\mathcal{P}(E_K)$ is the collection of subset of $E$ containing exactly $K$ elements. In this paper, to find the number of nodes comprising the seizure onset zone, we calculate $K$ as follows:

1) The model being stochastic was simulated with 2000 different noise vectors and mean escape time was calculated for each channel, i.e., $\mathbb{T}_i = \{ \tau_{E_i}(m) \mid m = 1, 2 \cdots 2000 \}$ for $i = 1, 2 \cdots N$.
2) $p$-values were calculated using two sample $t$-test between $\mathbb{T}_i$ and $\min \{ \{ \mathbb{T}_j / |\mathbb{T}_j| \} \mid i = 1 \cdots N \}$. To obtain $\mathbb{P} = \{ p_i \mid i = 1, 2 \cdots N \}$.
3) $K$ was calculated as the cardinality of $\{ p \mid p \in \mathbb{P} \text{ & } p < 0.1 \% \}$.

The surgical intervention procedure has been simulated in this mathematical model of epileptic cortex. A node $E_p$ can be resected in silico by setting $M_{pi} = M_{ip} = 0$ with $i = 1, 2 \cdots N$ in the connection parameter $M$ of the model. This process isolates the cortical region, thus inhibiting it from contributing in the overall dynamics of the network topology.

III. RESULTS

In this section, we describe the results obtained after analysing the non-seizure intracranial ECoG data (cf. Section II).
A. In silico seizure localisation and simulating surgical intervention

We delineate the seizure onset zone, $S_K$, in silico for all the six patients. Using the methods described in section II, we calculate $K$ and find the set of nodes which satisfy (3). These nodes have been shown in green in the first column of Fig. 2 for five patients and in Fig. 3 for the sixth patient.

In silico surgical simulations were performed to ascertain that the nodes in $S_K$ are more likely to go into seizure state as compared to other nodes. Figure 2 shows the relative shift between the histogram of the mean escape time prior to surgical intervention of $S_K$ (in green) and after its surgical intervention (in red). This indicates that after the (simulated) surgical resection it takes more time for all the nodes to go into the seizure state. Finally, to verify if this result is consistent, 30 sets chosen randomly from $P_{S_K}$ were resected. It is evident that the shift in the histogram shown in red is still larger than that in blue. Therefore, these results suggest that the elements in $S_K$ are the optimally delineated seizure focus which is also evident from $\bar{\tau}_{pre} < \bar{\tau}_{rand} < \bar{\tau}_{post}$.

B. Correlation with clinical results

The second column in figure 2 shows the seizure onset areas, localised by trained electroencephalographers from seizure data (blinded to the results of this analysis) marked in grey. With the exception of patient 6, figure 3, the in silico seizure onset zone either overlaps or clusters around the same cortical region as determined clinically in all patients.

In the case of patient 6 (figure 3) some depth electrodes were also implanted. By analysing those depth electrodes, it became clear that seizures actually started deep inside the brain, and then propagated towards the centre of the grid. Thus there is an offset between the clinically obtained seizure onset zone and in silico seizure focus. This case may be considered as a counterexample of the analysis presented. In future, we will investigate cases of this nature on a more fundamental basis. Despite this, the regions which were identified by our method with shorter escape times are all located near the centre of the grid. It is indeed possible that resection of these surface areas may have led to a reduction of seizures both in silico and in vivo.
C. Outlook: clinical application

The methods presented above may be utilised in cases where seizure focus is in the eloquent cortex [16]. Since the eloquent cortex can not be operated, we suggest an investigative method of iterative in silico resection. This method may aid neurosurgeons in locating potential alternative cortical locations where surgery may be performed.

In the first iteration of this procedure, few nodes which do not form a part of eloquent cortex but have low values of mean escape time are resected. This resection would change the dynamics of remaining set of nodes whose mean escape time should be recalculated. The nodes with low mean escape time, not forming a part of the eloquent cortex, should then be delineated and resected again. With every iteration this process will result into a set of nodes, outside the eloquent cortex, whose resection will cause maximal seizure reduction in the model.

IV. DISCUSSIONS AND CONCLUSION

In this study we have developed in silico methods using only the non-seizure EEG epochs to delineate the seizure onset zone in a mathematical model of an epileptic cortex. We calculated the functional connectivity between different cortical regions and used it in the model proposed by [9] to investigate the dynamics leading to seizure initiation. This model has previously been used to highlight the importance of connectivity between brain areas in the context of epilepsy [10]. We showed that the change in mean escape time provides a quantitative measure to elucidate the effect of seizure reduction when a node is resected in silico.

An increase in functional synchrony leads to a stronger effective input to the model. This causes the dynamics of the model to cross the basin of the attractor more frequently, and hence seizures are more frequent. The conjuncture of the computational model and functional synchrony, provides an interesting method to simulate the surgical procedure by varying the parameters in the model. Therefore, this may be used in prediction of the likelihood of a surgical success.

The methods presented here may aid clinicians to effectively use both ictal and interictal epochs of EEG to delineate the seizure focus. Moreover, we have suggested a procedure of iterative in silico resection that may be helpful to neurosurgeons to locate alternate cortical regions, which may be further be investigated for surgery if the seizure focus is found to be in the eloquent cortex. However, it remains for clinical/experimental results to validate this method.

We have also shown a case for which this in silico method fails and thus should be used carefully. In particular we found that functional synchrony at the grid electrodes do not allow us to infer the depth at which seizures are generated; we can obtain that information only from the depth electrodes. We aim to expand these in silico methods to cases where depth electrodes are used and the seizure onset zone lies deep inside the brain.

REFERENCES