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2012

MIMS EPrint: **2012.74**

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ISSN 1749-9097

State transitions in a model of intermittent seizure dynamics

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Abstract

We present a neural mass model of intermittent transitions into electroencephalographic (EEG) seizure rhythms in epilepsy. The route to intermittent dynamics is identified as Type 1 and state transition statistics are explored. It is demonstrated that a single framework can give rise to different distributions for seizure and non-seizure lengths in line with variability observed clinically. Further investigation of this model can give insight into the possible mechanisms underlying spontaneous seizure transitions in the epileptic brain.

PACS numbers: 87.19.xm, 87.19.le, 05.45.-a

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I. INTRODUCTION

Epilepsy is one of the most prevalent neurological disorders and is characterised by the occurrence of periods of abnormal neuronal activity in the brain, i.e. seizures. During seizures the electroencephalogram (EEG) displays state transitions into abnormal (epileptic) rhythms concomitantly with clinical signs and symptoms. Understanding the mechanisms of epilepsy is therefore aided by mathematical models accounting for epileptic EEG rhythms [1–6].

One of the issues raised by modelling studies is how to characterise the dynamic regime underlying recurrent state transitions. For absence epilepsy, characterised by recurrent brief episodes of EEG spike-wave discharges, both noise driven bistability [2, 7] and on-off intermittency [8, 9] have been proposed. Although the former has been explored in modelling studies [10], a mechanistic model for intermittent transitions has only recently been proposed, and as yet has not been extensively explored [5]. One of the limiting factors was the high dimensionality of the model of [5].

In this communication we study a reduced dimension model of [5] which preserves intermittent transitions. We demonstrate that intermittency arises in this model via a Type 1 route [11] and that the model is capable of producing consistent seizure dynamics but different seizure transition statistics depending upon its parameterisation. We propose the model as a framework for the study of complex and variable seizure transition characteristics in epilepsy.

II. METHODS

Neural mass models represent the dynamics of interacting populations of excitatory and inhibitory neurons in the brain (see e.g. [12–14]) and have been used extensively to understand EEG rhythms in epilepsy [1–6]. [5] presented a neural mass model which displayed a bifurcation between low amplitude background and high amplitude, spike-wave seizure rhythms. The authors demonstrated that introducing coupling between heterogeneous neural masses within this framework led to intermittent transitions between background and seizure states.

Each neural mass or node (given by superscript, i) of the network is governed by the following 8 ordinary differential equations:

$$\begin{aligned}
\dot{y}_0^i(t) &= y_4^i(t) \\
\dot{y}_4^i(t) &= AaS[EEG^i] - 2ay_4^i(t) - a^2y_0^i(t) \\
\dot{y}_1^i(t) &= y_5^i(t) \\
\dot{y}_5^i(t) &= Aa\{I + P^i + C_2S[C_1y_0^i(t)]\} - 2ay_5^i(t) - a^2y_1^i(t) \\
\dot{y}_2^i(t) &= y_6^i(t) \\
\dot{y}_6^i(t) &= B_f b_{f_i} \{C_4S[C_3y_0^i(t)]\} - 2b_{f_i}y_6^i(t) - b_{f_i}^2y_2^i(t) \\
\dot{y}_3^i(t) &= y_7^i(t) \\
\dot{y}_7^i(t) &= B_s b_s \{C_4S[C_3y_0^i(t)]\} - 2b_sy_7^i(t) - b_s^2y_3^i(t)
\end{aligned} \tag{1}$$

where $EEG(t)^i = y_1^i(t) - 0.5y_2^i(t) - 0.5y_3^i(t)$ is the model output of a single node. P^i describes the coupling between nodes, $P^i = \sum_{j=1, j \neq i}^N \frac{R}{N-1} S[EEG^j]$. The model output, M , representative of the EEG is given by the average over nodes $M = \frac{1}{N} \sum_{i=1}^N EEG^i$. $S[v] = 2e_0/(1 + \exp(r(v_0 - v)))$ is a sigmoid transfer function common to neural mass models [15].

For the extraction of state changes in the intermittent regime, we use the fact that the seizure rhythm of this model has large power in the 2-4Hz range. States were extracted from M by filtering in the band 2-4Hz and Hilbert transforming to extract instantaneous amplitude. Applying a threshold to the maxima of the resulting time series allowed good segmentation of states as verified by visual inspection.

III. RESULTS

Three compartments ($N = 3$) can generate salient state transitions on the mean field (M) when the parameter b_{f_i} is inhomogeneous across compartments. We therefore study the case with $N = 3$ as a lower dimensional prototype for the intermittent dynamics described in [5]. Intermittency can arise for different combinations of b_{f_i} and R . For simplicity we fix $b_{f_1} = 95, b_{f_2} = 97$ and $b_{f_3} = 102.5$ throughout this study. A one-dimensional bifurcation scan for changing R is shown in Figure 1.

For $R \gtrsim 29$ all compartments are phase locked in the seizure rhythm, though the waveforms of each compartment differs slightly due to parameter heterogeneity. As R is decreased

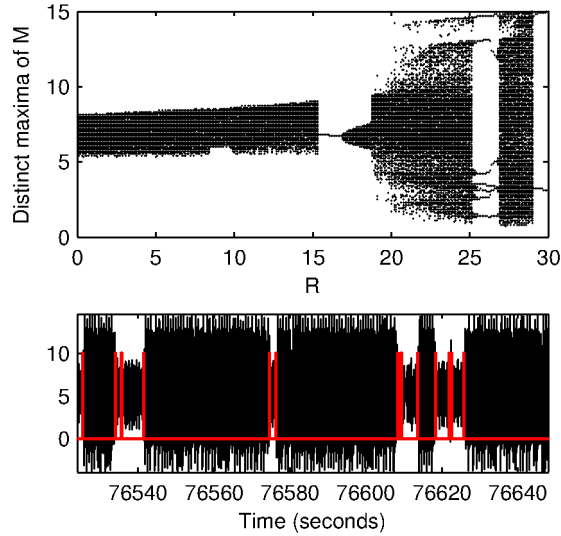


FIG. 1. Top: Unique maxima of the dynamics of equation 1 with $N = 3$ over changes in the coupling strength, R . The plot shows distinct maxima of M (see Methods). There is a small region of bistability around $R = 15$ (not shown). Bottom: Example time series with $R=25$. Extracted seizure states are delimited by vertical red bars. All parameters as default from [5] except $b_{f1} = 95$, $b_{f2} = 97$ and $b_{f3} = 102.5$.

a window of intermittent dynamics emerges. Figure 2 shows a first return map at the onset of these dynamics and indicates a proximate tangent bifurcation of the seizure limit cycle. Figure 2 also demonstrates a “U” shape in the distribution of seizure event lengths. Together these findings provide evidence for a Type 1 route into intermittency [11, 16].

At the onset of intermittency for large R the model resides predominantly in the periodic (laminar) seizure state with intermittent deviations into a lower amplitude, irregular (turbulent), background oscillation. This regime is therefore not relevant for most state transitions in epilepsy, in which the brain resides predominantly in the normal working state. However, persistent seizures can be seen in severe cases such as absence status epilepticus. A relevant regime of the model, more closely resembling typical absence seizure dynamics, can be seen for $20 \leq R \leq 25$. Example time series for $R = 25$ and $R = 21$ are shown in Figures 1 and 3, respectively. We therefore seek to characterise the nature of state transitions in this region. For comparison with previous studies [2, 10], we extract the distributions of seizure and non-seizure durations and use a gamma distribution fit in order to quantify the extracted shape. The gamma distribution probability density function, $p(x) = \frac{1}{\Gamma(\alpha)\beta^\alpha} x^{\alpha-1} e^{-\frac{x}{\beta}}$,

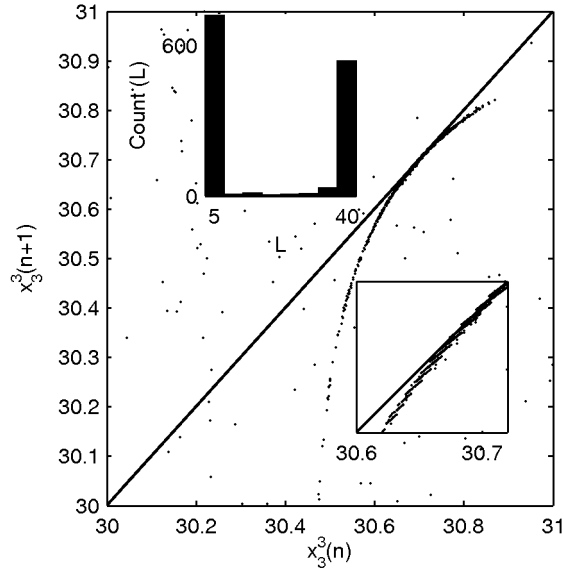


FIG. 2. Demonstration of Type 1 intermittency in the model close to the synchronisation regime at $R = 29.112$. The main figure shows a section of the first return map of the variable x_3^3 extracted at the peaks of x_3^3 during the laminar (seizure) phase. The bottom right inset is a close up of this map showing higher dimensional structure in the approximate tangent bifurcation. The top left inset shows the shape of the distribution of laminar phases of compartment 3. All parameters as default and $R = 29.112$.

is parameterised by a shape parameter, α and a scale parameter, β .

Although the characteristic waveform of seizure events is roughly preserved for changing R , the length of seizure and non-seizure intervals varies depending upon R . For $R=21$, most seizure events are small and consist of approximately integer repetitions of the seizure rhythm (Figure 3). Thus a gamma distribution fit can clearly be rejected, though may appear relevant if the data is coarsely binned. Figure 4 shows that increasing R leads to decreasing non-seizure and increasing seizure durations. α extracted from non-seizure durations is also shown in Figure 4. For $R \leq 21$ the gamma distribution fit cannot be rejected by a Kolmogorov-Smirnov test ($p > 0.05$).

The cumulative distribution of state lengths for $R = 21$ is shown in Figure 5. Here the extracted shape parameter $\alpha = 0.9$ lies close to the case of an exponential distribution ($\alpha = 1$), which is suggestive of Poissonian transition dynamics. In order to clarify this finding we investigated the sequences of non-seizure and seizure durations using tools from Random Matrix Theory (RMT) (see e.g. [17, 18]). These techniques have in the past

been applied to investigate spacing distributions in traffic [19] as well as between periodic neurophysiological events [20]. After unfolding our data by fitting a polynomial of degree 15 to the cumulated event density, the null hypothesis that the non-seizure durations are exponentially distributed could not be rejected ($p=0.34$). In addition, the event number variance $\Sigma^2(L)$ followed the Poissonian prediction for values up to $L \approx 20$ very closely (data not shown).

We postulate that state transitions arise due to the chaotic regime induced by coupling. This causes excitation of each of the three compartments, which reside in the vicinity of a saddle node bifurcation (see [5]). The compartment nearest the bifurcation (compartment 1, $b_{f1} = 95$) is more easily excited and, when spiking, can induce a response in the other two compartments depending on their phase of oscillation and the strength of perturbation. It is therefore interesting to examine the case of increased influence of compartment 1 on the other compartments. In Figure 5 we provide an example of this effect. In this regime, the connectivity $1 \rightarrow 2$ and $1 \rightarrow 3$ have been increased from 10.5 ($R/(N - 1)$) to 15. The effect of this change of parameters is to decrease the mean non-seizure duration and increase the mean seizure duration. However, the shape of the respective distributions have also changed, with a decrease in α for non-seizures ($\alpha=0.65$). This resulting combination of shape parameters closely resembles that observed in a previous study of seizure transitions in experimental models [10].

IV. DISCUSSION

In this study we identified Type 1 intermittency in coupled neural mass models leading to autonomous transitions between non-seizure and seizure rhythms. Intermittency has previously been suggested to underpin seizure transitions in *in vivo* animal models of absence epilepsy [8, 9]. In these studies, data analysis of transition statistics led to the observation of a power law in non-seizure periods and the suggestion of on-off intermittency as the underlying mechanism. A different study suggested that gamma distribution fits are appropriate for seizure and non-seizure durations [10]. Our current study reconciles the mechanism of intermittency with the transition statistics observed in [10]. In particular, our intermittent model can reproduce the finding of gamma distribution shape parameters of $\alpha \leq 1$ for non-seizure durations. However, we note that in several instances a K-S test of significance rejects the gamma fit, and so the extracted α provides a value for comparison rather than

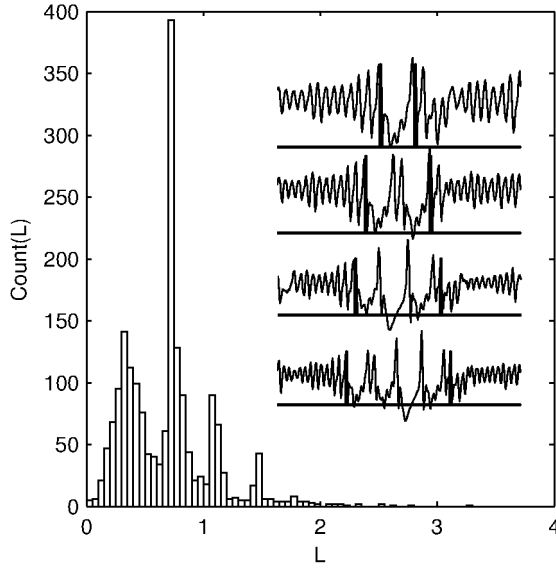


FIG. 3. Histogram of seizure durations for $R=21$. Insets show example time series for each peak in the distribution with vertical black lines indicating automated state extraction.

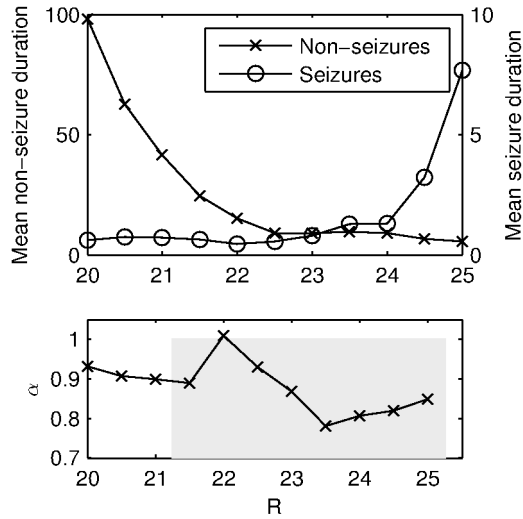


FIG. 4. Effect of R on the mean seizure and non-seizure durations (top) and on the extracted gamma shape parameter, α (bottom). The grey shaded region represents significant deviations from the gamma distribution.

evidence for the gamma distribution in these cases. Interestingly a change in α can arise due to a network rearrangement from the case of homogeneous coupling, in which statistics were indicative of Poissonian transitions, to the case in which the most excitable compart-

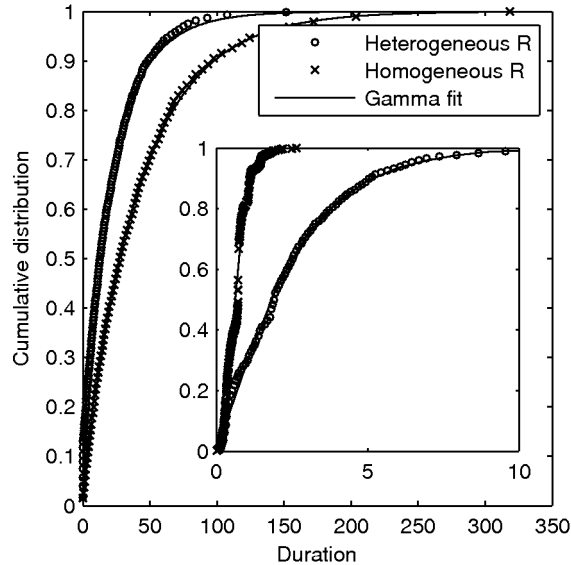


FIG. 5. Statistics of non-seizure (main) and seizure (inset) durations. Cumulative distributions are shown for the case of homogeneous $R = 21$ (marker “x”) and heterogeneous coupling (marker “o”, see text). The best fitting gamma distribution is given by a solid line in each case. α for non-seizure durations in the heterogeneous case is 0.65 and in the homogeneous case is 0.9. All parameters as default from [5] except $b_{f1} = 95$, $b_{f2} = 97$ and $b_{f3} = 102.5$.

ment more strongly drives the others. This demonstrates that different transition statistics can arise due to the same fundamental mechanisms, namely coupled, heterogeneous neural masses near a bifurcation.

Although we did not find on-off intermittency or power law distributions of events in our model it is not currently known whether such a regime is possible in alternative parameter settings. However, the finding of Type 1 intermittency raises several interesting points. Firstly, this regime identifies “laminar” states with the previously stable periodic seizure attractor and “turbulent” states with a low amplitude, irregular chaotic regime. In contrast, association with low dimensional prototypes of on-off intermittency (e.g. [21]) may suggest to identify laminar states with a quasi-stable fixed point that is interrupted by intermittent chaotic, seizure bursts [8]. Although it is unclear which of these descriptions is more appropriate, we find the former more appealing due to the regular, periodic nature of spike-wave discharges in absence epilepsy and the stereotypic evolution of seizures in general [22]. However, on-off intermittency can equally account for this by assuming a seizure orbit in an invariant manifold, to which the trajectory of the system intermittently approaches. It

will therefore be of interest to explore these possibilities in mechanistic models of epilepsy.

Data regarding long term seizure transitions in humans is difficult to acquire, especially in the case of absence seizures, which are not often subject to long-term monitoring. However, the question of when seizures will arise is of paramount importance to patients, in the field of seizure prediction and for the development of closed-loop therapeutic interventions. A long-standing problem of interest is therefore whether seizure occurrence is driven by a random process or not. Though evidence for Poissonian statistics have been found [23], it is also observed that seizures follow clustering patterns, leading to preferred periods of time at which seizures occur [24]. Clearly clustering does not rule out mechanisms such as Poissonian transitions. Rather these mechanisms could be operating in conjunction with slower underlying parameter modulations. This can be appreciated in the current model, for example, by periodically modulating the coupling parameter, R , making certain periods of time more prone to generating seizures. In order to further distil the mechanisms underlying transitions it will be appropriate to gather very long term recordings (presumably from animal models in the first instance) and to analyse both clustering tendencies and period-matched transition statistics. Such analysis can then be compared to our model taking into account slow modulations in the nature of intermittent dynamics.

An alternative dynamic regime suggested for absence epilepsy is bistability [2], in which noise perturbations move the system between stable attractors. In the bistable model, noise perturbations presumably contain a contribution from ongoing stochastic neuronal firing. Since large regions of the brain are engaged in stereotyped bursting dynamics during absence seizures [25], it is perhaps reasonable that the nature of ongoing neuronal noise may change during seizure, thus complicating the bistable route to seizure termination. In contrast, intermittency incorporates self-contained transition mechanisms. In our model, chaotic dynamics induced by coupling cause susceptible nodes to spike, which can entrain large transients in the remaining network. Seizure termination arises due to the instability of the trajectory on to which the system is perturbed. In the current model this is an emergent property due to coupling between heterogeneous regions.

The model presented in this study is lower in dimension than that of [5] and therefore offers the opportunity to further analyse intermittency as a model for the epileptic brain. Furthermore, the coupled neural mass approach allows the study of seizure dynamics to be placed into the context of interacting neuronal populations of varying degrees of excitability and therefore allows transition dynamics to be brought more closely into line with network

theories of epilepsy [26].

ACKNOWLEDGMENTS

We acknowledge financial support from BBSRC, EPSRC and The University of Manchester. KS and CR acknowledge support by the Swiss National Science Foundation (project # SNF 320030_122010). MG thanks Hil Meijer for discussion.

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