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Analysis of a novel ODE mean-field model for studying clinically recorded epilepsy dynamics

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Abstract

In this letter we describe how an ordinary differential equation (ODE) model of cortico-thalamic interactions may be obtained from a more general system of delay differential equations (DDEs). We demonstrate that transitions to epileptic dynamics via changes in system parameters are qualitatively the same as in the original model with delay, as well as demonstrating that the onset of epileptic activity may arise due to regions of bistability. Hence, the model presents in one unique framework, two competing theories for the genesis of epileptiform activity. We demonstrate similarities between model transitions and clinical data and argue that statistics obtained from and parameter estimation of this new model may be a potential means of classifying and predicting the onset and offset of seizure activity.

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Electroencephalography (EEG) is a technique for recording the aggregated activity of populations of cortical excitatory neurons, via electrodes placed on the scalp. Close correlates between the dynamical activity patterns observed in EEG and the cognitive state of the subject have been inferred, and EEG is frequently used as a diagnostic tool in subjects with a variety of neurological disorders [1]. In the past few years, there has been increasing interest in the use of mathematical models of macroscopic brain activity to explain transitions between different dynamical states observed in EEG [2, 3], with a particular focus on understanding the transition between healthy and seizure states in epilepsy [4–8]. These recent works have focussed on a mean-field description of cortico-thalamic interactions, which have been implicated in detailed physiological studies [9] as being crucial in determining dynamical activity arising during sleep and epilepsy [10].

The focus of our research is a class of primary generalized seizures, absence seizures, which typically affect children and young adults. There is a classical waveform associated with such seizures, namely a 3Hz 'spike and wave' (SW) discharge, that appears approximately synchronously across all EEG channels. Closer inspection of such discharges reveals a much greater array of dynamical behaviour, such as poly-spike and wave, and wave-spike discharges (See Figure 1 of [11]), as well as graded onsets; in some seizures the spike appears immediately at the start of the seizure, whereas in others it evolves over a number of initial cycles of the seizure (see Figure 3 of [8]). These suggest that a number of different mechanisms may play a role in determining seizure dynamics and it is our desire to develop a unifying model that can capture the wide variety of such transitions.

In the present letter we discuss a neural mass model, which is based on our work in [11]. In this work, we used a delay differential equation (DDE) to simulate dynamics observed in patients with absence seizures. In the present letter we demonstrate how this model can be improved, by adding in a slow synaptic mechanism, leading first to a model with distributed delay. Moreover, we compare the past and present modelling approaches in terms of bifurcation structures, and show the existence of various transitions to SW-dynamics.

The model we propose arises as a result of amalgamating a number of different theoretical viewpoints; namely the work of Lopes da Silva [12] and Freeman [13], who first described the behaviour of large populations of neurons (neural masses), based upon the results of detailed experimental studies. The incorporation of the cortico-thalamic loop, shown in studies to be important in the generation of sleep-spindles and generalized seizure activity [14, 15]. Also, the use of a wave-like equation to describe the propagation of cortical activity, first introduced in [16]. Combining these approaches leads to the following cortico-thalamic model (depicted schematically in Fig 1):

$$\begin{cases} \frac{d}{dt}\phi_e(t) = y(t), \\ \frac{d}{dt}y(t) = \gamma_e^2\left[-\phi_e(t) + \varsigma(V_e(t))\right] - 2\gamma_e y(t), \\ \frac{d}{dt}V_e(t) = z(t), \\ \frac{d}{dt}z(t) = \alpha\beta\left[-V_e(t) + \nu_{ee}\phi_e(t) + \nu_{ei}\varsigma(V_e(t)) + \nu_{eTC}\varsigma(V_{TC}(t))\right] - (\alpha+\beta)z(t), \\ \frac{d}{dt}V_{TC}(t) = w(t), \\ \frac{d}{dt}w(t) = \alpha\beta\left[-V_{TC}(t) + \nu_{TCn}\phi_n + \nu_{TCe}\phi_e(t) + \nu_{TCRE}^A\varsigma(V_{RE}(t)) + \nu_{TCRE}^B\phi_B(t)\right] - (\alpha+\beta)w(t), \\ \frac{d}{dt}V_{RE}(t) = v(t), \\ \frac{d}{dt}v(t) = \alpha\beta\left[-V_{RE}(t) + \nu_{REe}\phi_e(t) + \nu_{RETC}\varsigma(v_{TC}(t))\right] - (\alpha+\beta)v(t). \end{cases} \tag{1}$$

Each of the neural masses (e = excitatory cortical neuron, RE = reticular nucleus, TC = thalamocortical neurons) is described by its average membrane potential $V_a(t)$ where $a = e$, RE, TC and a sigmoidal function $\varsigma(\cdot)$ describing the average firing rate. In addition, cortical excitatory neurons are described by a field variable $\phi_e(t)$ to take into account long-range cortico-cortical connections. In this investigation, we shall only consider spatially uniform solutions, leaving more general solutions as a next step in our research. The parameters ν_{ab} represent the weighting of inputs via synapses from population b onto population a. A more detailed description of these equations and the function $\varsigma(\cdot)$ appears in [11].

Inhibition of TC cells by RE neurons in the thalamus has been found to be a crucial component in the development of SW-activity [14] and thus we focus our attention on

modelling two important receptors GABA_A and GABA_B, which mediate this inhibition. In our previous work [11], we incorporated a time-delayed connection $\nu^B_{TCRE}\varsigma(V_{RE}(t-\tau))$ with a fixed delay τ from RE to TC populations. This served as a straightforward mechanism to account for a difference in timescales between GABA_A and GABA_B; the inhibitory post-synaptic potential (IPSP) mediated by GABA_B receptors has a much slower timescale than those mediated by GABA_A.

To account more appropriately for this discrepancy in time-scales we introduce a new firing rate $\phi_B(t)$, a slow variable governing the IPSPs of GABA_B. We obtain this by convolving the output firing-rate of the RE-population with a distributed delay kernel to account for the slow mediation of GABA_B receptors:

$$\phi_B(t) = \int_0^\infty k(\tau)\varsigma(V_{RE}(t-\tau))d\tau, \tag{2}$$

where the normalized kernel function $k(t)$ is given by:

$$k(t) \equiv k(t; a_1, a_2) = \frac{a_1 a_2(e^{-a_1 t} - e^{-a_2 t})}{a_2 - a_1}, \quad a_2 > a_1, \tag{3}$$

with a_1 and a_2 corresponding to rise and decay times respectively. Our choice is motivated by existing modelling approaches, which put emphasis on physiological GABA_B-models (see [15] for single cell GABA_B-models, and [5, 17] for neural population dynamics). These various models (linear and nonlinear) have one thing in common: if a sufficiently strong presynaptic input is given to activate GABA_B, the receptor responds with a current profile consisting of a steep rise and a slow decay (see Figure 5.9 of [15] for an illustration). The double exponential function $k(t)$ is chosen because it mimics this particular behaviour. Note that to keep our model simple, we do not use this approach to describe any other synapses (GABA_A, excitatory), we consider these faster timescales to be captured in the rise and decay time parameters (α,β) in (1).

An interesting comparison can be made with our previous work [11], where we effectively

used $\phi_B(t) = \varsigma(V_{RE}(t-\tau))$. Our present approach turns the cortico-thalamic model (1) into a distributed DDE. However, substituting the double exponential (3) as the kernel $k(t)$, enables us to employ the so-called 'linear chain trick' [18] (essentially noting that $\phi_B(t)$ then satisfies a second order ODE) to reformulate our model (1-3) as a set of 10 ODEs, as opposed to the set of 8 DDEs in our previous investigations. It should be noted that the particular choice of $k(t)$ to mimic the rise and decay profile is not unique (see [19] for details).

We perform a numerical bifurcation analysis of the system (1-3), using the continuation package MATCONT [20] and then compare these results with our past investigations with DDE-BIFTOOL, presented in [11]. To aid this comparison, we introduce a term relating the effective delay:

$$\tau_{\text{eff}} = \int_0^\infty \tau \cdot k(\tau) d\tau = \frac{a_1 + a_2}{a_1 a_2}. \tag{4}$$

Our motivation for this choice is our past work with DDE-BIFTOOL, where we used the single $GABA_B$ delay as one of the key parameters in continuation. Because our new model has a delay-distribution $k(t)$, we use this average timescale τ_{eff} (see Fig. 1) as a bifurcation parameter. To simplify our work, we will assume a fixed ratio $a_2/a_1 = 3$ (based on existing literature [17]), which ensures a one to one correspondence between a_1 and τ_{eff}. Further, the coupling ν_{TCe} from cortical excitatory neurons (e) to thalamic TC neurons has been used in past research [6–8, 11] to study the onset of SW-activity, and we employ it as a second bifurcation parameter in our present study.

The results of our bifurcation analysis in the two dimensional (ν_{TCe}, τ_{eff})-plane are shown in Fig. 2. Branches of bifurcations divide the plane into various dynamical regions, of which (III, IV) are bistable. We find that if the average delay τ_{eff} is made large enough (80-100 ms, a characteristic timescale for GABA_B) our model supports 2-3 Hz SW-activity. Interestingly, if $\tau_{\text{eff}} < 40$ ms the model supports 11 Hz Alpha-like activity (region VI). Decreasing τ_{eff} to this order of magnitude can be viewed as introducing a mismatch between GABAergic

receptors.

In Fig. 3 we present a comparison between our present model and previous model [11]. Here panel (a) is a simplified version of Fig. 2, where we left out parts of the branches H_1 and H_2, and put emphasis on the regions of parameter space that support SW-activity. We find that in both models, the parameter ν_{TCe} can be used to make a transition from a steady state region to a SW-oscillation (for example, fix $\tau_{\text{eff}} = 0.12s$ in Figure 3(a) and increase ν_{TCe}). An increase of (effective) delay leads to an increase of spikes in both models. Moreover, when the (effective) delay is decreased below a certain point, no SW-oscillations are generated in either case. Note however, that in Figure 3(b), it is still possible to have $\sim$3Hz oscillations without spikes for $\tau \leq 40$ ms, whereas in our present model, we find instead 11 Hz activity (resembling Alpha), which is in some sense more in keeping with clinical data.

In terms of modelling the onset of SW-activity, our present model captures two fundamentally different mechanisms: Firstly, a bifurcation from a pre-seizure state (such as region I) into SW-activity by changing a parameter. Secondly a noise-induced transition from an inter-ictal state to an SW-attractor, in a bistable region of our model. In Fig. 4 we show examples of these two transitions; in (a) we simulate an episode of SW-activity, by slowly ramping ν_{TCe} (see Fig. 3(c) of [6] for illustrations of ramping). In (b) we keep all model parameters fixed in a bistable region, and observe transitions arising due to the subthalamic noise term (ϕ_n, see equation 1). This leads to episodes of SW-activity, the precise statistics of which may be controlled by the levels of noise used.

An interesting analogy is found when considering real EEG-data from patients with absence epilepsy (see Fig. 1 of [21]); some seizures start abruptly with spikes occurring in the first cycle, whereas others gradually build up a $\sim$3Hz oscillation and develop a spike as time progresses. In terms of modelling, the first case can be viewed as either bistability, or a rapid change in system parameters. The second case however seems to point more clearly to a bifurcation mechanism. It is an important feature of the present model that both of

these scenarios can be explained and makes it worthy of further consideration.

In conclusion, we have shown how a neural mass model can be enhanced by introducing an additional slow synaptic term. Moreover, we have shown how the bifurcation structure of this model, containing a distributed delay, compares to a previously studied single-delay neuron model. The emphasis of our analysis was to simulate SW activity, as seen in human absence seizures. In our present model, transitions from fixed point attractors to SW-oscillations can arise not only via bifurcations, but also due to bistability.

Our findings lead to a variety of interesting directions for future work: (1) Investigation of the relationship between dynamical transitions to SW-activity demonstrated in the model and their clinical characteristics. (2) analyzing the mapping between neural mass-models, and conductance based models (see [19]), in order to understand dynamical mechanisms that lead to the onset of and offset of seizure-activity. (3) Fitting model parameters of inter-ictal epochs in human absence seizure EEG. This will aid our understanding of which parameters in our model vary most as a seizure develops, and may indicate if the model is in a bistable regime of parameter-space, or close to any bifurcation points near the onset/offset of seizure EEG. (4) Using the above schemes for developing early detection/prediction methods of epileptic seizures, based on deterministic models, and comparing them to statistical inferences of EEG data. Such an approach provides an exciting alternative approach to existing methods of seizure prediction based purely on data analysis techniques [22].

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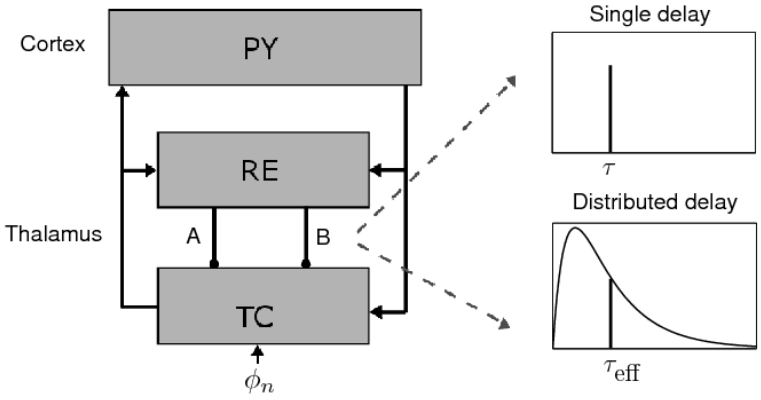

FIG. 1: Schematic of the thalamocortical model. Three neural populations (e, RE, TC) are linked together via synaptic interactions. Arrows represent excitatory synaptic connections, dots represent inhibitory GABA_A (label A) and GABA_B (label B) receptors. A comparision is drawn between modelling GABA_B with a single delay (as in our previous work [11]) or a distribution of delays $k(\tau)$ (as in the present study). We use the average of $k(\tau)$, τ_{eff} as a bifurcation parameter, to enable a comparison to be made.

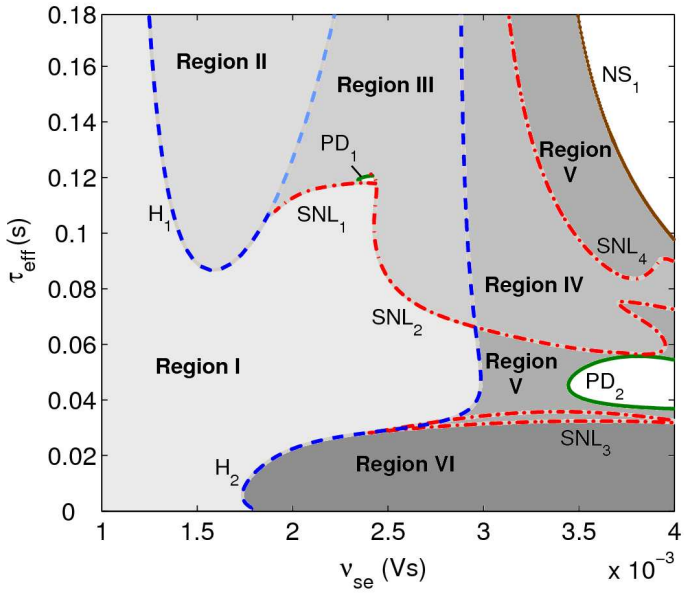

FIG. 2: Two parameter analysis of our present model in the (ν_{TCe},$\tau_{\rm eff}$)-plane. Curves of bifurcations (H=Hopf, SNL=saddle node of limit cycles, PD=period doubling and NS = Neimark Sacker) divide the plane into various dynamical regions. (I) contains only a steady state, (II) contains 2-3 Hz SW-oscillations, (III) contains both steady state and SW-oscillations, (IV) contains both SW-oscillations and a fast 20 Hz oscillation, (V) contains only the 20 Hz oscillation, (VI) contains an alpha-like 11 Hz oscillation. White regions contain more complex dynamics, and are beyond the scope of the present letter.

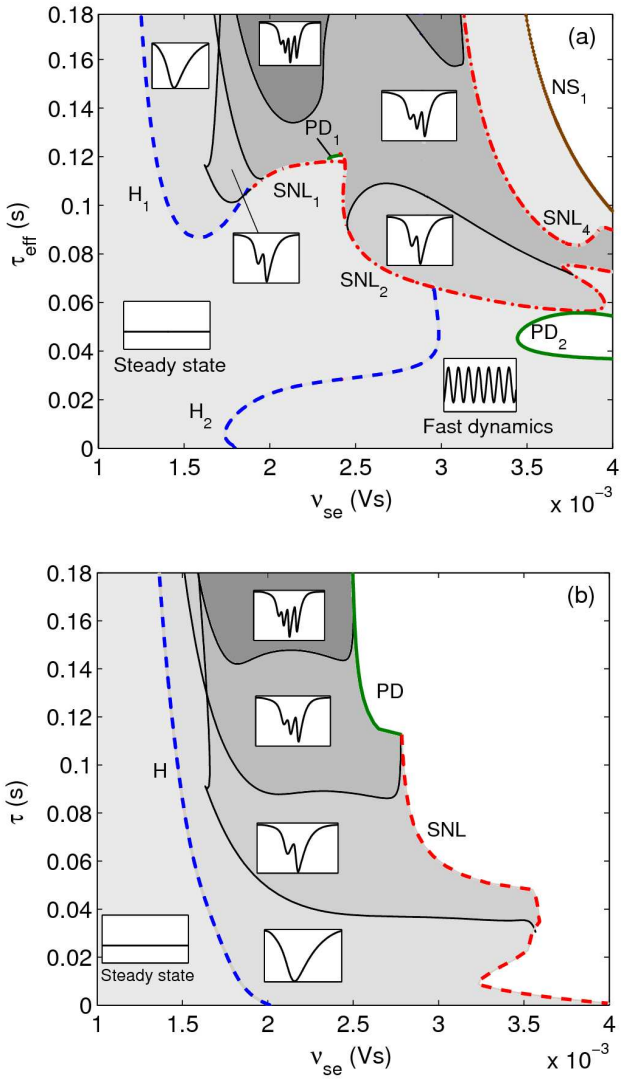

FIG. 3: Comparing bifurcations of: (a) our present ODE-model and (b) our previous DDE-model [11]. Black solid curves indicate the points where 2-3 Hz periodic solutions develop a spike (see Refs. [8, 11]) Note that in our previous work, the region of parameter space studied effectively corresponds to the top left quadrant of panel (a). In both panels (a) and (b), SW-oscillations only exist above a certain value of the (effective) delay.

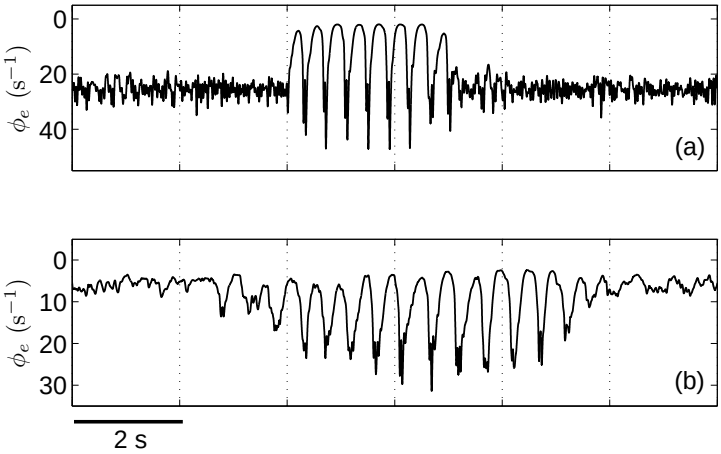

FIG. 4: Illustrating the two mechanisms for the onset of SW-activity; in panel (a) bistability obtained by keeping parameters fixed and injecting subthalamic noise causes a transition to a seizure-like state. In panel (b) the activity arises by ramping up a bifurcation parameter. Note that in the first case, the spike is already present at the onset of oscillation. This can be compared to human EEG data (see Ref. [21]) where some SW-patterns measured during absence seizures start abruptly, whereas others grow from a sinusoidal-like oscillation over the initial cycles of the seizure.