On the genesis of spike-wave activity in a mean-field model of human brain activity

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Abstract

In this letter, the genesis of spike-wave activity - a hallmark of many generalized epileptic seizures - is investigated in a reduced mean-field model of human neural activity. Drawing upon brain modeling and dynamical systems theory, we demonstrate that the thalamic circuitry of the system is crucial for the generation of these abnormal rhythms, observing that the combination of inhibition from reticular nuclei and excitation from the external signal, interplay to generate the spike-wave oscillation. We demonstrate that this is a nonlinear phenomena and that linear stability analysis is not appropriate to explain such solutions.

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Epilepsy is a relatively common neurological disorder, with a life-time prevalence of approximately 1%. The generalized seizures (tonic-clonic and Absence) are defined as those associated with abnormal activity across most, or all, of the cortex. Several models have been proposed to explain the aggregated electrical activity of large scale neuronal populations, or mass action brain models. Pioneering work in this area was performed by Wilson and Cowan [1], which was generalized to account for functional activity within the brain by Nunez [2] and Freeman [3]. During the last decade, several groups have advanced mass-action neural models to incorporate a range of increasingly plausible neurophysiological processes [4, 5]. Robinson and co-workers explicitly incorporated thalamic circuitry and analytically described the propagation and stability of electrical activity within the cortex by means of a damped wave equation [6].

Absence seizures occur predominantly in children and are characterized by brief, intermittent interruptions to consciousness. Preliminary studies of seizures generated by the model [7] have demonstrated that it can correctly predict the occurrence of spike-wave morphologies ($\sim$3Hz paroxysmal oscillations) which are the hallmark of Absence seizures. In this model, the two main subdivisions of the thalamus, the reticular nucleus (RTN) and the specific relay nuclei (SRN), are both implicated in the generation of seizure waveforms. Other work points to a specific role of the SRN underlying the generation of oscillations. In particular, the SRN is widely accepted (both, through in-vitro and in-vivo experiments, and modelling) to play a pivotal role in the generation of spike-wave activity [8–11]. Consequently, the purpose of the present letter is to conduct a detailed examination of the role of the thalamic circuitry in the initiation of Absence seizure dynamics. This has important implications in understanding the pathophysiological mechanisms leading to seizure activity.

The model we consider [6] provides a unified description of both the EEG (Electroencephlogram) recorded at rest and the ERPs (Evoked Response Potentials) which occur following a sensory input. It incorporates a wide-range of neurophysiological processes, including excitatory and inhibitory neural populations, axonal and dendritic time lags, long range excitation, and the low-pass filter effect of dendritic integration on incoming impulses. Importantly, the model incorporates the main features of corticothalamic loop which are believed to be one of the mechanisms for epileptogenesis [10]. These include excitatory inputs between the cortex and the SRN, the excitatory influence of the cortex and the SRN on the RTN, and the inhibitory feedback from the RTN onto the SRN. One should note that this

description does not explicitly consider ionic currents. These currents are averaged out and fitted parametrically to the data.

In this letter, we consider a reduced formulation where the asymptotic temporal evolution is investigated. Further, only the thalamic circuitry driven by an external periodic signal is considered. The first motivation for this is associated with the fact that observations from the full model suggest that there is a phase shift in the dynamics of the *specific* neuronal populations when compared to both *cortical* and *reticular* populations. This feature is supported by both *in-vivo* and *in-vitro* experiments [8–11] that demonstrate spike-wave activity is first initiated in the *specific* neurons which then propagates to the *cortex* and finally induced in the *reticular*.

Secondly, in our preliminary study of the full model [7], we observed that in the absence of a cortical signal, the thalamic subsystem was quiescent and that spike-wave activity (a periodic signal with an extra spike per period) was generated via periodic dynamics from the cortex fed into both specific and reticular populations. The strength of modulation of this signal into the specific population was observed to be the crucial parameter for generation of such rhythms (see Figure 2 of [7]).

Thus, as an approximation to the full model, we consider only the thalamic circuitry driven by an external periodic signal. This reduced model is defined by

$$\begin{cases} \frac{1}{\alpha\beta}\left[\frac{d^2}{dt^2}V_s(t) + (\alpha+\beta)\frac{d}{dt}V_s(t) + \alpha\beta V_s(t)\right] = \nu_{sr}\sum[V_r(t)] + \nu_{se}\phi_{\text{external}} + \nu_{sn}\phi_n, \\ \frac{1}{\alpha\beta}\left[\frac{d^2}{dt^2}V_r(t) + (\alpha+\beta)\frac{d}{dt}V_r(t) + \alpha\beta V_r(t)\right] = \nu_{rs}\sum[V_s(t)] + \nu_{re}\phi_{\text{external}}. \end{cases} \tag{1}$$

where

$$\sum[V_a(t)] = \frac{Q_a^{\max}}{1+\exp\left(-\frac{\pi}{\sqrt{(3)}}\frac{V_a(t)-\theta_a}{\sigma_a})\right)}$$

is a unipolar sigmoidal function representing the relationship between the transmembrane potential V_a and the axonal firing rate. Descriptions and typical values of these parameters are provided in Table 1 of [7]. System (1) models the averaged postsynaptic activity at the cell soma. It relates the induced transmembrane voltage $V_a(t)$ with the incoming pulses $\phi_a(t)$ where $a = \{r, s\}$(*reticular* and *specific*). The perturbation in the induced transmembrane voltage propagates along dendrites and reaches the cell body with some attenuation and lag. Thus, α and β are constants representing the inverse rise and decay times parameterising the dendritic response to impulse.

This model is illustrated schematically in Figure 1. A similar model for the study of olfaction has been considered in [12] where linear stability analysis was performed and stability curves in the parameters space were derived.

As mentioned previously, in-vivo and in-vitro experiments from animal models [11], as well as our own extensive numerical simulations of both the full and reduced models suggest that the abnormal rhythms associated with Absence seizures originate in the specific relay nuclei. Subsequently, if the excitation between specific to reticular, or specific to cortex, is strong enough then these abnormal rhythms may also be observed there.

Simulations (see Figure 2) also indicate that the subthalamic input plays no part in the generation of abnormal rhythms. We further observe that the solutions to $V_r(t)$ are always periodic and that only the amplitude of these oscillations change when the parameters are varied.

Thus, for the purposes of understanding the genesis of abnormal activity in this reduced case, we make the following assumptions. First, we assume that there is no interactions between the *specific* and the *reticular* neuronal populations, i.e. $\nu_{rs} = 0$. Second, we assume that the subthalamic input is also zero, i.e. $\nu_{sn} = 0$.

In this case, the homogeneous solution for the individual modules is a combination of decaying exponentials. This can be seen by studying the roots of the characteristic polynomial derived from either of the differential operators in (1),

$$r^2 + (\alpha + \beta)r + \alpha\beta = 0,$$

the solution for which is given by $V_a^h(t) = Ae^{(-\alpha t)} + Be^{(-\beta t)}$. A further important point to note is that the dynamics of each individual system is overdamped; the damping factor in this case is $\zeta = \frac{(\alpha+\beta)}{2\sqrt{(\alpha\beta)}} > 1$. This demonstrates that spike-wave activity can not occur due to any intrinsic dynamics within the individual thalamic modules.

In the absence of the excitatory input from the specific, the solution for the reticular module when $\phi_{\text{external}} = \sin(\omega t)$ can be derived explicitly and is given by:

$$V_r(t) = K\sin(\omega t + \delta) \tag{2}$$

where $K = \sqrt{(C^2 + D^2)}$ and $\delta = \arcsin(D/K)$ with

$$C = \frac{(\alpha\beta - \omega^2)\nu_{re}\alpha\beta}{((\alpha+\beta)^2\omega^2 + (\alpha\beta - \omega^2)^2)(\alpha\beta - \omega^2)}$$

and

$$D = -\frac{\omega\nu_{re}\alpha\beta(\alpha+\beta)}{(\alpha+\beta)^2\omega^2 + (\alpha\beta-\omega^2)^2}$$

Consequently the behavior of the specific module, $V_s(t)$, is governed by the solution of the differential equation:

$$\frac{1}{\alpha\beta}\left[\frac{d^2}{dt^2}V_s(t) + (\alpha+\beta)\frac{d}{dt}V_s(t) + \alpha\beta V_s(t)\right] = \nu_{sr}\sum[V_r(t)] + \nu_{se}\phi_{\text{external}} \tag{3}$$

where $V_r(t)$ is given in equation (2).

Since Σ is a unipolar sigmoidal function, an explicit solution to this equation is not possible. However, a result from [13] shows that it is possible to relate the stability of the full system to that of a related piecewise linearized system. Essentially, we perform a piecewise linearization of the unforced system and then reapply the forcing term in each case.

In order to do this, we obtain steady-states for $V_r^\star$ and $V_s^\star$ of the system, using the numerical software package XPP [14]. Linearizing about these steady-state gives the following:

$$\frac{dx}{dt} = \mathbf{L}x + \mathbf{B}u, \tag{4}$$

where the vector $\mathbf{B}$ comes from the external drive,

$$\mathbf{B} = \begin{pmatrix} 0 \\ \alpha\beta\nu_{se}\sin(\omega t) \\ 0 \\ \alpha\beta\nu_{re}\sin(\omega t) \end{pmatrix},$$

and $\mathbf{L}$ is the piecewise linear vector field of the system,

$$\mathbf{L} = \begin{pmatrix} 0 & 1 & 0 & 0 \\ -\alpha\beta & -(\alpha+\beta) & \alpha\beta\nu_{sr}y_\sigma(V_r^\star) & 0 \\ 0 & 0 & 0 & 1 \\ \alpha\beta\nu_{rs}y_\sigma(V_s^\star) & 0 & -\alpha\beta & -(\alpha+\beta) \end{pmatrix}.$$

Essentially $\mathbf{L}$ is the Jacobian matrix of the unforced system on each considered segment of the sigmoidal function Σ. The first order Taylor approximation of this function at a point $\mathbf{x_0}$, is given by

$$y(v)|_{x_0} = \frac{Q^{max}}{1+e^{-\frac{\pi}{\sqrt{3}}(\frac{x_0-\theta}{\sigma})}} + (v-x0)\frac{\frac{Q^{max}\pi}{\sigma\sqrt{3}}e^{(-\frac{\pi}{\sqrt{3}}(\frac{x_0-\theta}{\sigma}))}}{[1+e^{(-\frac{\pi}{\sqrt{3}}(\frac{x_0-\theta}{\sigma}))}]^2} + H.O.T. \tag{5}$$

Hence, the specific piecewise approximation we consider is

$$y_\sigma(v) = \begin{cases} y(v)|_{V_s^\star} & -\infty \leq v < b, \\ y(v)|_{V_r^\star} & b \leq v < \infty, \end{cases} \tag{6}$$

where $b > 0$ is the intersection point of the lines (at this point the derivative loses continuity). Note that we could have considered more line segments in the whole domain of the function Σ. However, this would not change the conclusions, as the solution $V_r(t)$ is bounded and evolves around a steady state and consequently the solution for $V_s(t)$ will also be bounded. Considering more approximations will only smooth out the solutions obtained.

The composition of this piecewise linear approximation $y_\sigma(v)$ in (6) with the explicit solution for $V_r(t)$ given in (2) results in two regions of interest:

$$\text{Region}_{\text{I}} = \left\{ t \in \mathbb{R}, N \in \mathbb{Z} : \frac{\arcsin(\frac{b}{K}) - \delta + 2N\pi}{\omega} \leq t \leq \frac{\pi - \arcsin(\frac{b}{K}) - \delta + 2N\pi}{\omega} \right\}$$

$$\text{Region}_{\text{II}} = \left\{ t \in \mathbb{R}, N \in \mathbb{Z} : \frac{-\arcsin(\frac{b}{K}) - \pi - \delta + 2N\pi}{\omega} < t < \frac{\arcsin(\frac{b}{K}) - \delta + 2N\pi}{\omega} \right\}$$

It is now possible to solve explicitly this piecewise linear appoximation to (3) using the method of variation of parameters, taking care to ensure that the boundary conditions for each interval are satisfied. The resulting calculation is long and complex and for reasons of conciseness is omitted. However, a full discussion of the solution will be submitted elsewhere.

The spike-wave oscillation arises as a result of the interaction of the positive sinusoid due to the excitatory external input and the negative sinusoid-like function resulting from the composition of the piecewise linear approximation to Σ with $V_r(t)$. This composite function has the same total period as the external signal, however, it consists of two sinusoids of different amplitudes acting on each of the Regions I and II. The peaks of each bump correspond to the transition between regions. Noting that the area of Region_{I} is less than that of $\text{Region}_{\text{II}}$, this can technically be classed as a 'spike-wave' oscillation, since the area of the spike part of the solution is less than that of the wave. This phenomena is illustrated more clearly in Figure 3 and a comparison between the explicit solution and that numerically generated for the same case using XPP is given in Figure 4.

The fact that the solution of the two parts are opposite facing in each region is also crucial for the generation of the abnormal rhythm. Were both to point the same way, then

only a one-bump solution would be observed. These opposite facing solutions are due to the inhibitory effect of the reticular on the specific parameter and explains why no such solutions are ever observed in the reticular in the absence of the specific, since the synaptic interactions between specific and reticular are excitatory in nature. Finally, note that the gradient of the sigmoidal function Σ varies dramatically between the two regions and it is this marked difference in gradient that leads to the different amplitudes on each Region, which in turn gives the spike-wave solution. This illustrates the need for at least a piecewise linear approximation to Σ and explains why attempts to use linear stability analysis to explain this phenomena are doomed to failure.

A final point concerns time-delays in the system. The mechanisms responsible for generation of the abnormal rhythms elucidated in this letter do not require any time-delays, which is consistent with the work of [11]. However, the full model [6], from which this reduced model was obtained, has delays between cortex and thalamus. Thus, it is imperative to determine the precise role that these time-delays play in the full system and this work is currently underway.

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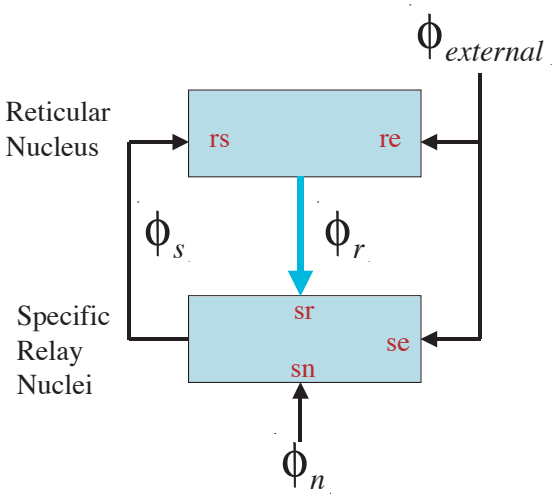

FIG. 1: COLOR ONLINE Schematic of the reduced Thalamic model considered. All interactions illustrated by black (thin) arrows are assumed to be excitatory. The one between reticular and specific illustrated by the blue (thick) arrow is inhibitory.

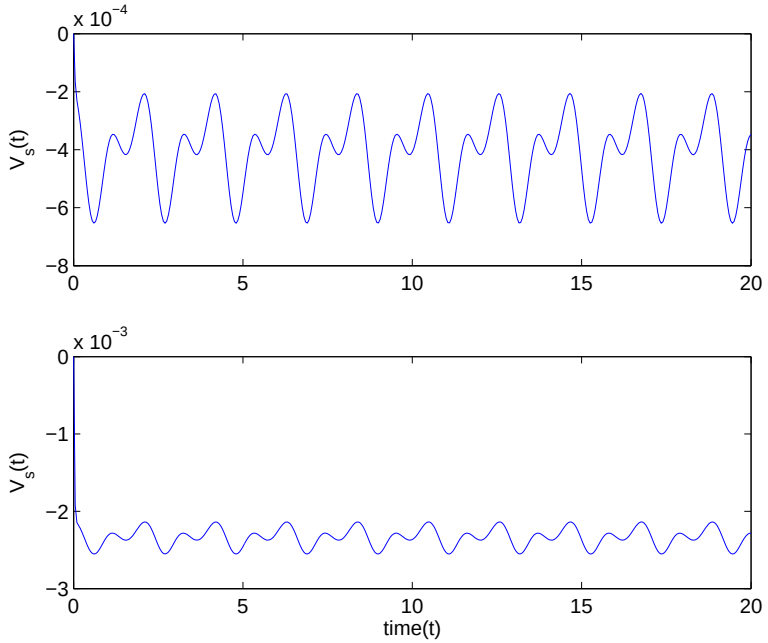

FIG. 2: In this Figure, we demonstrate that the subthalamic interactions have no effect on the occurence of spike-wave like activity. The two graphics are numerical simulations of system (1) using XPP. The top graphic shows $V_s(t)$ with ν_{sr} non-zero. The bottom graphic shows the same system with $\nu_{sr} = 0$. In both cases the abnormal rhythm persists, with the subthalamic input acting effectively as an amplifier.

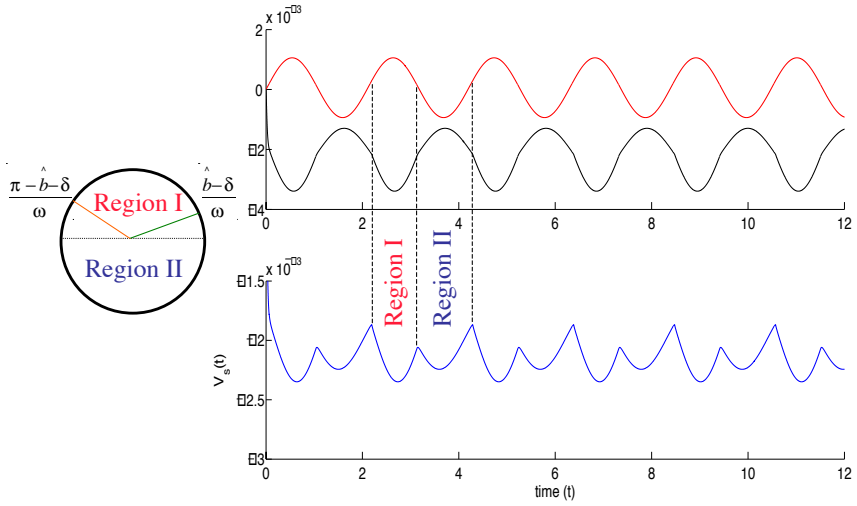

FIG. 3: COLOR ONLINE In the top graphic, the upper solution (in red) is the solution of the system when driven by the periodic forcing term $\nu_{se}sin(\omega t)$ and the lower solution, is that of the system when driven by the composition of the piecewise linear approximation $y_\sigma(v)$, and $V_r(t)$. The difference in amplitudes of the second solution on each of the regions, combined with Region I being less than half the period gives rise to the spike-wave activity, illustrated in the lower graphic. The length of these regions can be adjusted by varying the parameters $\hat{b} = \arcsin\left(\frac{b}{K}\right)$ and δ as indicated on the circle.

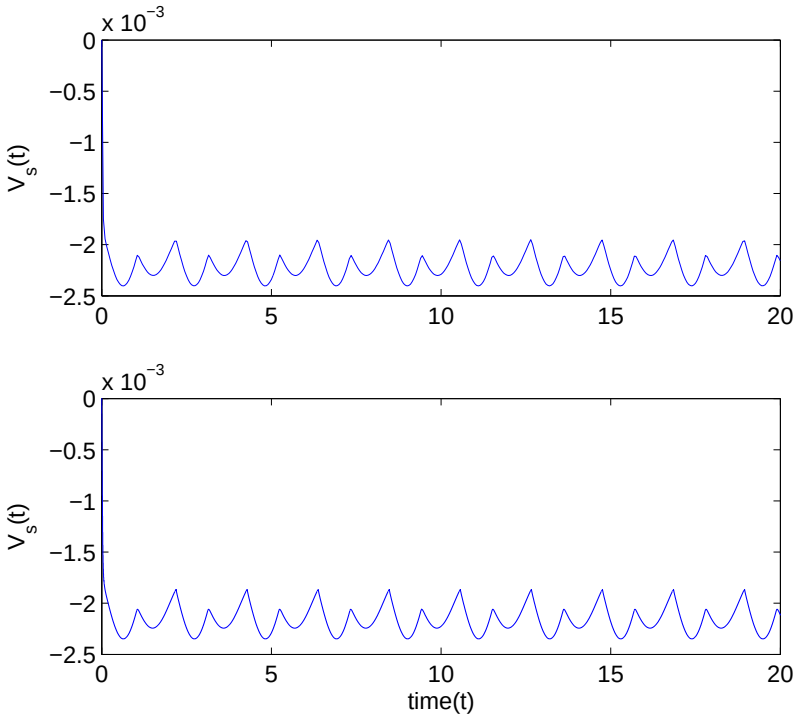

FIG. 4: The top graphic shows the solution of $V_s(t)$ from the numerical package XPP for the peicewise linear system in the absence of ν_{sn}. The bottom graphic shows the explicit solution obtained, demonstrating precise agreement between the numerics and our analysis.