Instabilities of the Cortex during Natural Sleep

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Introduction

The electrical signals generated by the human cortex during sleep have been widely studied over the last 50 years. The electroencephalogram (EEG) observed during natural sleep exhibits structures with frequencies from 0.5 Hz to over 50 Hz and complicated waveforms such as spindles and K-complexes. Understanding has been enhanced by comprehensive intra-cellular measurements from the cortex and thalamus such as those performed by Steriade et al [1] and Sanchez-Vives and McCormick [2].

Models of the cerebal cortex have been developed in order to explain many of the features observed. These can be classified in terms of individual neuron models or collective models. Since we wish to compare predictions with gross features of the human EEG, we choose a collective model, where we average over a population of neurons in macrocolumns. A number of models of this form have been developed recently; that developed at Waikato draws from a number of different sources to describe the temporal and spatial dynamics of the system.

The Sleep Model

Our sleep model follows the mean-field approach introduced by Freeman [3], with developments by Wright et al [4], Robinson et al [5] and Liley et al [6]. Many parameters are assigned values similar to those used by Rennie et al [7], but include modifications appropriate for the dominant neuromodulator effects associated with natural sleep (see Hasselmo [8] for a review). The model has been used previously to investigate the effect of anaesthetics on the cortex [9].

The time-variation excitatory (e) and inhibitory (i) soma potentials V_e and V_i are each modelled with a first-order equation in time t. Synaptic inputs arising from both e and i neurons contribute to each. These synaptic fluxes Φ_{ab}, meaning the flux *from* type a *to* type b neuron, are described in the model with second-order differential equations. These model the rise and fall of the e and i post-synaptic potentials (EPSPs and IPSPs). Inputs ϕ_a from neighbouring macrocolumns are represented by damped wave equations.

$$\tau_a \frac{dV_a}{dt} = V_a^{\text{rest}} - V_a + \rho_e \psi_{ea} \Phi_{ea} + \rho_i \psi_{ia} \Phi_{ia} \tag{1}$$

$$\left(\frac{d^2}{dt^2} + 2\gamma_{ea} \frac{d}{dt} + \gamma_{ea}^2 \right) \Phi_{ea} = \gamma_{ea}^2 \left(N_{ea}^\alpha \phi_{ea} + N_{ea}^\beta Q_e + \phi_{ea}^{\text{sc}} \right) \tag{2}$$

$$\left(\frac{d^2}{dt^2} + 2\gamma_{ia}\frac{d}{dt} + \gamma_{ia}^2\right)\Phi_{ia} = \gamma_{ia}^2\left(N_{ia}^{\beta}Q_i + \phi_{ia}^{\text{sc}}\right) \tag{3}$$

$$\left(\frac{\partial^2}{\partial t^2} + 2v\Lambda_{ea}\frac{\partial}{\partial t} + v^2\Lambda_{ea}^2 - v^2\nabla^2\right)\phi_{ea} = v^2\Lambda_{ea}^2 Q_e \tag{4}$$

where a can take on the labels e and i. In these equations V_a^{rest} are the neuron's resting potentials, ρ_e and ρ_i are the magnitudes of the EPSP and IPSP and ψ_{ab} are weighting functions dependent upon the soma potentials. The firing rates Q_a are described by sigmoidal functions of V_a. The N represent numbers of cortico-cortical connections and the ϕ_{ab}^{sc} sub-cortical input.

The terms τ_e and τ_i describe the time constants for the e and i neurons. The γ terms are synaptic rate constants; their reciprocals give the time-scales over which the EPSPs and IPSPs occur. Finally the terms $1/v\Lambda_{ea}$ give time scales for the propogation of the signals at velocity v through macrocolumns of size $1/\Lambda_{ea}$.

The somnogen adenosine is included in the model through a term ΔV_{rest} added to the excitatory resting potential—this encourages sleep. The neuromodulator acetylcholine (ACh), which is absent in slow-wave sleep but abundant in REM-sleep, acts against adenosine, but at the same time reduces the strength of the EPSP. A scaling of the EPSP with a factor λ_{ACh} is therefore introduced, and we map out a sleep domain with the parameters λ_{ACh} and ΔV_{rest}.

The homogeneous stationary states of the system have been found by Steyn-Ross et al [10]. In most cases there is a single stationary state. However, at $\Delta V_{\text{rest}} < 0.8$ mV there is a region of the sleep space where three states can be obtained.

Stability of Stationary States

We proceed using a simple eigenvalue analysis. First we decompose the second-order equations into pairs of first-order equations, giving a total of 14 coupled first-order differential equations in time. Then we perform a first-order series expansion in time about the stationary state. We assume a plane-wave perturbation of the system in two-dimensional space. Writing our fourteen-dimensional state vector as $\vec{y}$, we obtain:

$$\vec{y} = \vec{y}_{\text{eqm}} + \Delta\vec{y}\exp(i\vec{q}\cdot\vec{r})$$

$$\Delta\dot{\vec{y}} = A\Delta\vec{y} \tag{5}$$

where $\vec{y}_{\text{eqm}}$ is the stationary state of the system and A is a sparse 14×14 matrix.

The ∇^2 term of equation (4) generates a $-q^2$ term under the substitution (5). We then use row operations to reduce the problem to an 8×8 determinant giving a fourteenth-order polynomial equation for the eigenvalues. Introducing physiologically plausible symmetries into the parameters allows us to reduce the size of the determinant further. Assuming $\gamma_{ee} = \gamma_{ei}$, $\gamma_{ie} = \gamma_{ii}$, $N_{ee}^{\alpha} = N_{ei}^{\alpha}$, $N_{ee}^{\beta} = N_{ei}^{\beta}$, $N_{ie}^{\beta} = N_{ii}^{\beta}$ and $\Lambda_{ee} = \Lambda_{ei}$, we can reduce the problem to a 5×5 determinant with an eighth-order polynomial equation. In doing this, we obtain six eigenvalues; all have negative real parts and therefore do not lead to instabilities. The remaining eighth-order polynomial is solved with MATLAB, for a range of q-values over the sleep domain.

Results

For physiologically plausible parameters the stationary states are usually stable—i.e., all the eigenvalues of *A* have negative real parts. Increasing *q* leads to smaller eigenvalues (i.e., a more negative or less positive real part). However, there is a region of the domain, shown in Figure 1, that gives an instability for low values of *q* (i.e., positive eigenvalues).

Simulations of the equations show that if the system is started close to a stationary state in this region, it will approach a limit cycle, characteristic of a Hopf bifurcation. The frequency of oscillation is similar to the imaginary part of the highest eigenvalue; in the case of Figure 1 this is about 5 Hz.

The region of instability in the sleep domain is found to be particularly dependent on the inhibitory synaptic rate constants γ_{ia}. A reduction in the constant, corresponding to smearing out the IPSP in time, leads to a greater region of instability. The unstable area can spread into the region where there are multiple stationary states, leading to a region of three unstable stationary states. We have simulated the time-dependence of the system in this case; results are plotted in Figure 2. We see that the firing rates exhibit a squarewave-like variation in time, with a frequency of around 1 Hz. Notably the *e* and *i* firing rates are nearly in phase; the cortex exhibits times of quiescence followed by times of rapid firing. This low-frequency bursting phenomenon is observed experimentally during slow-wave sleep [1].

Simulations also show that the cortex synchronises in space. In other words, the behaviour at two spatially separated points on the cortex is very similar. During the course of simulations we have not found any clear evidence of spatially organised states.
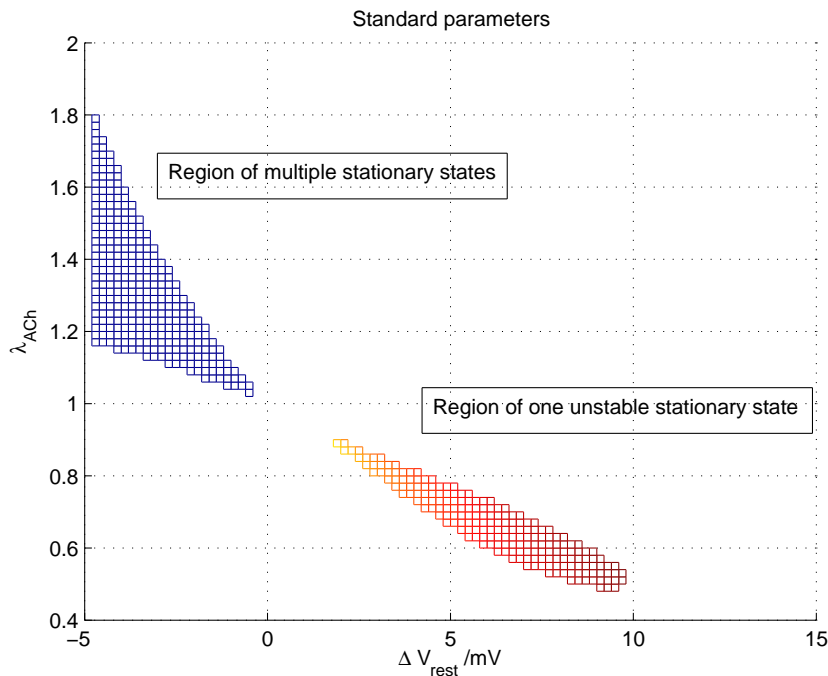

Figure 1: A plot of the stability of the sleep domain for a physiological set of parameters. At low ΔV_{rest} there can be three states (upper and lower stable, middle unstable). At mid-values of ΔV_{rest} there is the possibility of a single *unstable* state. Otherwise, a single stable state exists.
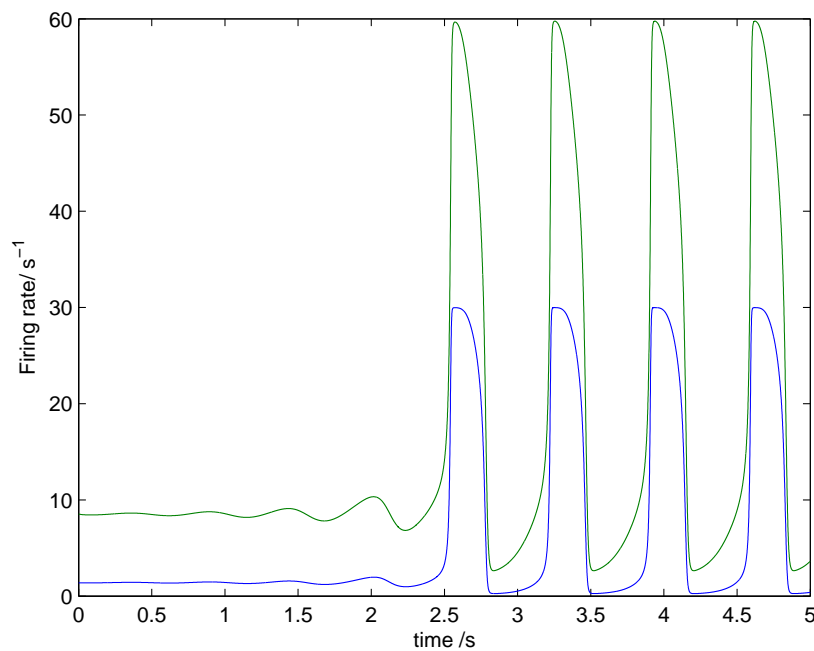
Figure 2: Time variation of excitatory (bottom) and inhibitory (top) firing rates, when there are three unstable stationary states. This trace has similarities with slow-wave bursting.

Conclusions and Further Work

An analysis of the linearised sleep model indicates that there are regions where the homogeneous stationary states can be unstable. The extent of the instability depends particularly on the inhibitory synaptic time constant. Simulations show that a system in the unstable region approaches a limit cycle. In some cases the cycle has similarities with the phenomenon of slow-wave bursting.

We will continue this work by carrying out a more comprehensive search of the parameter-space, looking particularly for evidence of spatial structures. We propose to extend the cortical model by introducing a model of the thalamus into the system.

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