Electrorhythmogenesis and anaesthesia in a physiological mean field theory

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Abstract

We solve eight partial-differential, two-dimensional, nonlinear mean field equations, which describe the dynamics of large populations of cortical neurons. Linearized versions of these equations have been used to generate the strong resonances observed in the human EEG, in particular the α-rhythm (8-13 Hz), with physiologically plausible parameters. We extend these results here by numerically solving the full equations on a cortex of realistic size, which receives appropriately "colored" noise as extra-cortical input. A brief summary of the numerical methods is provided. As an outlook to future applications, we simulate the effects of GABA-enhancing general anaesthetics.

Key words: electroencephalogram; alpha rhythm; cortical mean field theory

1 Introduction

Rhythmic cortical activity has been observed with the electroencephalogram (EEG) for 74 years. The EEG has become a standard tool for examining brain function in a clinical setting [1]. One recent clinical application is monitoring the progress of anaesthesia by its effect on the EEG. Nevertheless, the underlying physiological mechanisms of even prominent EEG features, like the α-rhythm at 8-13 Hz, remain poorly understood. We demonstrate here that the model of Liley *et al.* [2,3] produces stable α-rhythms and qualitatively accounts for the effects of GABA-enhancing general anaesthetics. Physically, the EEG is generated by current flowing in response to synaptic activity in the apical dendrites of pyramidal neurons perpendicular to the cortical surface [4].

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Electrodes sample the electric activity of this two-dimensional, cortical current dipole layer. On the scalp, they average over the potential of more than 1 cm^2 of the cortex, or $\sim 10^7$ neurons. Thus the recorded electrode voltage will vary smoothly across the cortex, even though the activity of individual neurons may fluctuate strongly.

Similarly, the electric activity of macrocolumns, defined by the typical size 0.5-3 mm of the axon collateral systems, varies smoothly over the cortex. One can define the average over the $\sim 10^5$ neurons of a macrocolumn as one "spatially averaged neuron". A two-dimensional mean field model can describe the collective actions of such large ensembles of neurons, just like the *macroscopic* effects of large numbers of gas atoms can be described by thermodynamics. Liley *et al.* [2,3] have suggested such a model and they and others [5] have shown that even simplified versions of it can reproduce typical EEG features. Here we go further by numerically solving the full model:

$$\tau_k \frac{\partial h_k(\vec{x}, t+\xi)}{\partial t} = -\left[h_k(\vec{x}, t+\xi) - h_k^{\rm rest}\right] + \sum_l \psi_{lk}(h_k) I_{lk}(\vec{x}, t) \quad , \tag{1}$$

$$\psi_{lk}(h_k) = \left[h_{lk}^{\rm eq} - h_k(\vec{x}, t+\xi)\right] / \left|h_{lk}^{\rm eq} - h_k^{\rm rest}\right| \quad , \tag{2}$$

$$\left(\frac{\partial}{\partial t} + \gamma_{lk}\right)^2 I_{lk}(\vec{x}, t) = \exp(1)\Gamma_{lk}\gamma_{lk}\left[N_{lk}^{\beta} S_l(h_l) + \Phi_{lk}(\vec{x}, t) + p_{lk}(\vec{x}, t)\right] \quad , \tag{3}$$

$$S_k(h_k) = S_k^{\rm max} / \left\{1 + (1 - r_{\rm abs} S_k^{\rm max}) \exp\left[-\sqrt{2}\,\frac{h_k(\vec{x}, t+\xi) - \overline{\mu}_k}{\hat{\sigma}_k}\right]\right\} \quad , \tag{4}$$

$$\left[\left(\frac{\partial}{\partial t} + v\Lambda_{ek}\right)^2 - \frac{3}{2}v^2\nabla^2\right]\Phi_{ek}(\vec{x}, t) = v^2\Lambda_{ek}^2 N_{ek}^{\alpha} S_e(h_e) \quad , \tag{5}$$

$$\Phi_{ik}(\vec{x}, t) \equiv 0 \quad , \tag{6}$$

with $k, l = e$(xcitatory), i(nhibitory) denoting the two distinct types of spatially averaged sub-populations. The subscripts lk means $l \to k$, i.e., type l acting on type k. EEG voltage is expected to be linearly related to h_e, the spatially averaged excitatory soma membrane potential [2,4].

In this model the mean soma membrane potentials h_k of Eq. (1) relax to their resting values $h_k^{\rm rest}$ with characteristic time constants τ_k, in the absence of any synaptic input. The factor ψ_{lk} of Eq. (2) takes into account the reversal (Nernst) potentials $h_{lk}^{\rm eq}$ associated with excitation and inhibition. Although this is basic membrane physiology, it is a new feature in mean-field models and crucial for avoiding unphysiological solutions. The postsynaptic activations I_{lk} in Eq. (3) are taken to have the impulse response $\Gamma_{lk}\gamma_{lk}t\exp(1-\gamma_{lk}t)$, based on "fast" excitatory (AMPA/kainate) and inhibitory (GABA$_A$) neurotransmitter kinetics, respectively. Presynaptic activity in Eq. (3) has three sources: short-range via *intra-cortical* connections N_{lk}^{β} with mean firing rates $S_l(h_l)$, long range *cortico-cortical* activity Φ_{lk}, and *extra-cortical* input p_{lk}. Since the

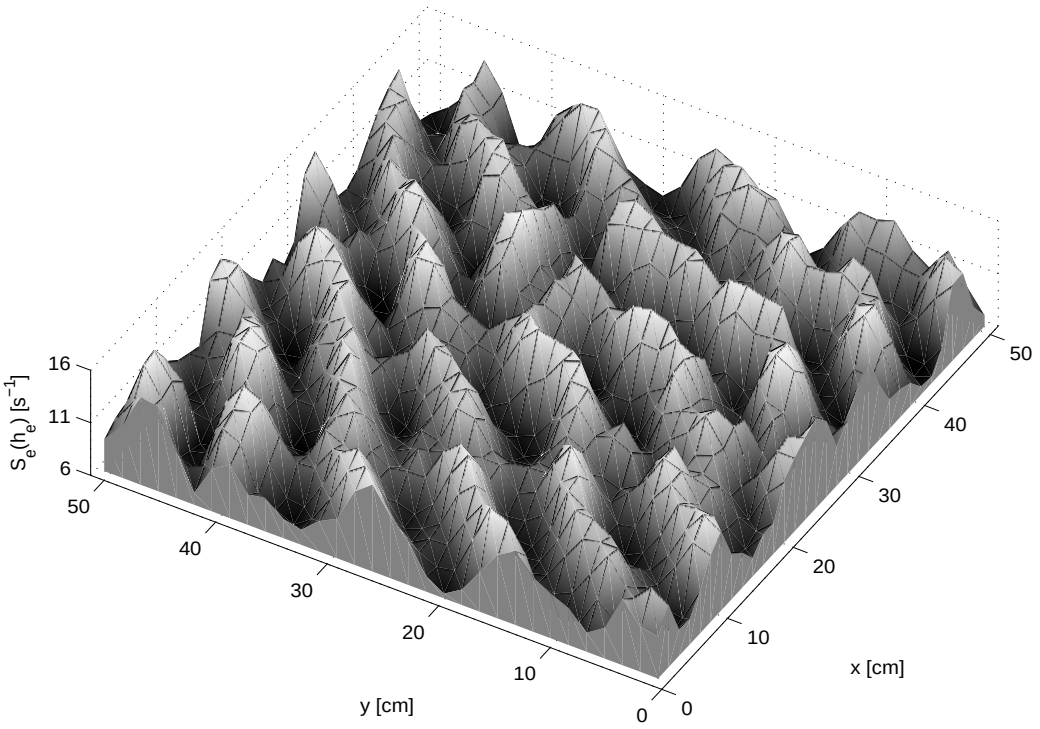

Fig. 1. Mean firing rate $S_e(h_e)$ frame with standard parameters (but $v = 2$ m/s) after 15 s. Maximum and minimum h_e are -62.2 mV and -65.5 mV, respectively.

α-rhythm is attenuated or blocked by sensory stimuli, alerting, mental concentration, or drowsiness, one can speculate that it is the natural rhythm of the awake cortex in the absence of *structured* extra-cortical input. This motivates using *noise* for p_{lk}, as specified below. Mean firing rates are given by the sigmoid of Eq. (4). Finally, one can derive Eq. (5) by assuming homogeneous, isotropic connectivity functions that fall off $\sim \Lambda_{ek}^2 \exp(-\Lambda_{ek}\Delta x)$. The mean cortico-cortical conduction velocity enters via the the conduction time delay $\Delta x/v$ and the Laplacian represents a first order approximation. It is assumed that cortico-cortical fibers are exclusively excitatory, see Eq. (6).

All 36 parameters in Eqs. (1)-(6) can be related to physiological or anatomical data. However, available experimental constraints are generally weak, see Ref. [2] for further discussion. In the following we will set ξ and $r_{\rm abs}$ to zero. Our canonical choice for the other parameters is: ($h_k^{\rm rest}$, $h_{ek}^{\rm eq}$, $h_{ik}^{\rm eq}$, $\overline{\mu}_k$, $\hat{\sigma}_k$, Γ_{ek}, Γ_{ik}) = (-70, 45, -90, -50, 5, 0.18, 0.37) mV, (N_{ek}^{α}, N_{ek}^{β}, N_{ik}^{β}) = (2000, 3034, 536), (γ_{ek}, γ_{ik}, $S_k^{\rm max}$) = (300, 65, 500) $\rm s^{-1}$, and $\Lambda_{ek} = 0.4$/cm for both $k = e$ and $k = i$; $v = 300$ cm/s, and (τ_e, τ_i) = (0.1, 0.02) s. Shaping noise for the extra-cortical input p_{lk} is computationally expensive. Since thalamocortical connections to pyramidal cells in the cortex are mainly excitatory, we fill only p_{ee} and set the other $p_{lk} = 0$. The noise is distributed normally (mean 5000 $\rm s^{-1}$, variance 1000 $\rm s^{-1}$), but its variation over grid and time steps is low-pass filtered (cutoffs: $k_c = 2\pi/5$ mm, $f_c = 75$ Hz) to avoid unphysiologically rapid changes. Note that in Ref. [5] all p_{lk} were filled with unshaped white noise.

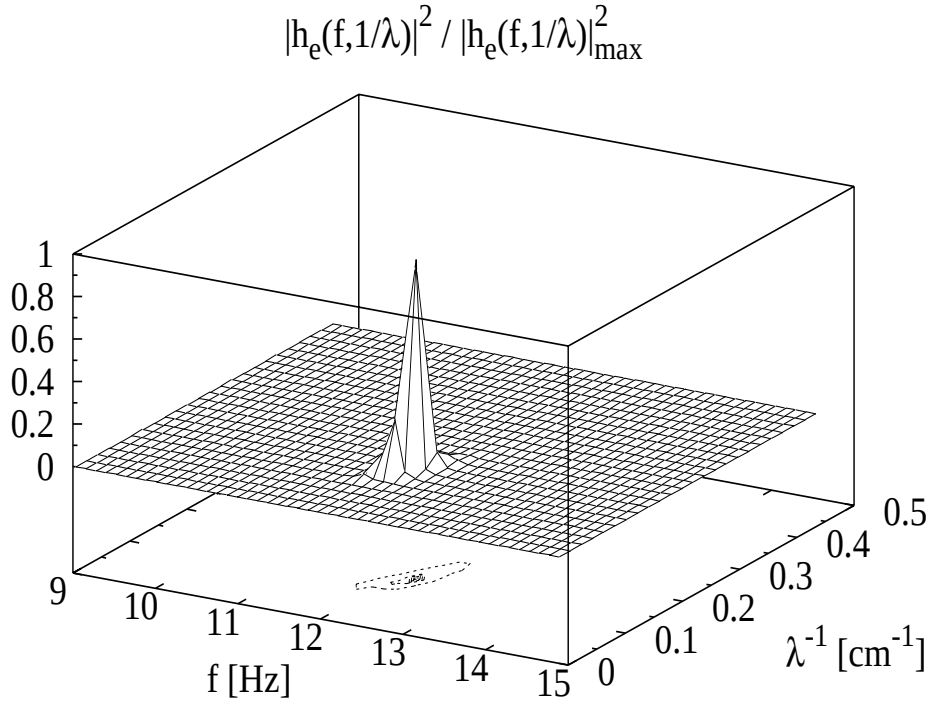

Fig. 2. Normalized maximum "radial" power in h_e for the run of Fig. 1. The last 8.192 s have been sampled. A clear α-peak is seen at $f = 12.2$ Hz and $\lambda = 7.31$ cm in the spectrum. Contour lines $0.01 + (0, 1, \ldots) \cdot 0.2$ are shown at the base.

2 Implementation and Results

The model is solved numerically by discretizing it in time and space. Eqs. (1)-(4) are transformed to a set of first order differential equations and solved by forward Euler iterations. Eq. (5) is iterated directly with three point time derivatives and a five point Laplacian. A full size cortex is simulated by employing a 512×512 toroidal space grid with a grid spacing of 1 mm. Time steps of 50 μs are sufficient to obtain stable and convergent solutions at this grid spacing up to the highest tested conduction velocities of $v = 1000$ cm/s. It is tempting to view the numerics as a cellular automaton with macrocolumns as cells. However, the local rules encode large range behavior, like cortico-cortical interactions at scales of $1/\Lambda_{ek} = 2.5$ cm. The program writes "frames", the grid values of a chosen state variable, at regular time intervals, typically every 2 ms. It can tile the whole grid, averaging over each tile, and output only these averages. On one hand this simulates sampling by regularly spaced electrodes, on the other hand this is a simple form of data reduction. In the following, tiles of 16×16 grid points (1.6 cm $\times$ 1.6 cm) are used. Frames then contain only 32×32 values, reducing the output by a factor of 256. The program code has been parallelized using `MPI Fortran` [6]. On 34 Pentium IV (2 GHz) machines, one run with 7500 frames (15 s) takes about three hours to complete. A typical frame is shown in Fig. 1.

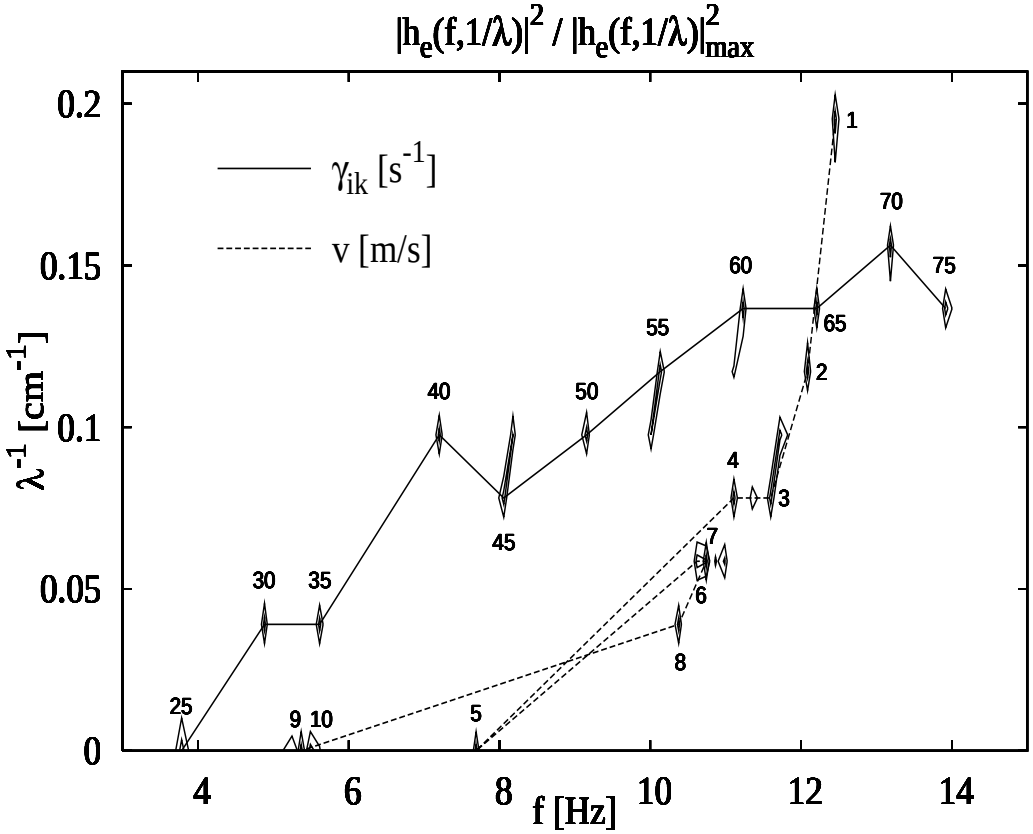

Fig. 3. Normalized maximum "radial" power in h_e for scans of γ_{ik} and v. Contours are drawn for 0.7 and 0.9. Labels indicate the variations: $\gamma_{ii} \equiv \gamma_{ie}$ from 25 to 75 s^{-1} and v from 1 to 10 m/s. Lines connecting maximum power guide the eye.

We analyze the frames by applying either two- (space) or three-dimensional (space and time) fast Fourier transforms (FFT). The three-dimensional power spectrum displays the dispersion relation between the frequency f (or $\omega = 2\pi f$) and the wavenumber $\vec{k}$. Since we are not interested in the direction of the waves, we bin the maximum "radial" power in $k \equiv |\vec{k}|$, with wavelength $\lambda = 2\pi/k$. Fig. 2 shows such a normalized maximum "radial" power spectrum from the run that produced Fig. 1. The spectrum is essentially zero for all frequencies not shown. A strongly dominant peak has developed. It is important to note that the result in no way resembles the extra-cortical p_{ee} noise. A plot of that noise would be entirely flat over the shown range, as the noise attenuates only above 50 Hz and its 5 mm spatial correlations are averaged out by the 1.6 cm "electrodes".

In Fig. 3 we show the results of varying the inhibitory postsynaptic potential rate constant γ_{ik} from 25 to 75 s^{-1} and the mean cortico-cortical conduction velocity v from 1 to 10 m/s. The difference between the runs $\gamma_{ik} = 65$ s^{-1} and v =2 m/s indicates typical uncertainties, as they have the same parameters. In order to keep the figure uncluttered, sub-dominant peaks at other "dispersion" locations have been suppressed by showing only normalized power > 0.7.

Conduction velocity is scanned as an example of a *global* parameter and one finds two broad regions of dominant α-rhythm: 1 to 4 m/s and 6 to 8 m/s. The jump at 5 m/s remains unexplained, but has been confirmed with more detailed scans. Variations of the rate constant, a *local* parameter, are motivated by the supposed action of GABA-enhancing general anaesthetics, like propofol or benzodiazepines. By keeping chloride-ion channels open longer, they *increase* the duration of the inhibitory impulse response. This can be simulated in the model by *decreasing* the appropriate decay rate constant, γ_{ik}. The result is an almost linear shift of the strongest resonance from high to low frequencies and from short to large wavelengths. A scan of γ_{ik} with $v = 7$ m/s has shown the same behavior. Often a measure for the "strength" of the EEG in a specified frequency band $[f_1, f_2]$ is adopted, e.g., integrated power. Upon lowering γ_{ik} with anaesthetics, our model qualitatively predicts first an increase and then a decrease of "strength", as the resonance moves through the chosen frequency band. Experiments have been observing such "biphasic" behavior, for example in the aperiodic analysis amplitude in Ref. [7].

3 Conclusions

The full mean field theory of Liley *et al.* [2,3] has been solved numerically on a "cortex" of realistic size for the first time. Like in previous simplified analyses, EEG resonances like the α-rhythm can be generated with physiologically plausible parameters. The impact of anaesthesia has been simulated by changing one parameter systematically and the experimentally observed "biphasic" response was qualitatively reproduced without further tuning. Comparisons with experimental EEG data and other model tests are in preparation.

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