A computational model of the influence of depolarization block on the initiation of seizure-like activity

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Seizure-like activity can be triggered in a network of excitatory and inhibitory neurons when excessive excitation is not balanced by inhibition. Recent experimental studies report that, prior to propagation of ictal discharges, inhibitory neurons, receiving a barrage of excitatory input, become functionally impaired due to depolarization block [1]. In this study, we used a mean field model and network simulations to investigate different types of network dynamics emerging from the interaction of excitatory and inhibitory neurons when the latter is prone to depolarization block. We modified the Wilson-Cowan equation [2] such that the output firing rate of inhibitory population decreases monotonically given sufficiently strong input. Specifically, we analyzed the solutions of following equation:

$$\frac{dr_e}{dt} = -r_e + \phi_e(w_{ee}r_e - w_{ei}r_i + I_e), \qquad \tau\frac{dr_i}{dt} = -r_i + \phi_i(w_{ie}r_e - w_{ii}r_i + I_i),$$

where the activation functions are defined as follows

$$\phi_e(x) = \frac{1}{1+e^{-k_1(x-\theta_e)}}, \qquad \phi_i(x) = \frac{1}{1+e^{-k_2(x-\theta_i)}} \cdot \frac{1}{1+e^{k_3(x-\beta_i)}}. \tag{1}$$

Note that, for the activation function of inhibitory population, ϕ_i, the standard sigmoidal function is multiplied by a monotonically decreasing function to capture the effects of depolarization block.

Numerical bifurcation analysis of the mean field model predicts that the transition to pathological state occurs around Bogdanov-Takens bifurcation point. In other words, the network may reach the pathological state, in which inhibitory neurons enter depolarization block and excitatory neurons fire at high rate, via a saddle-node bifurcation or a homoclinic bifurcation.

We performed a large scale simulation of networks of conductance-based excitatory and inhibitory neurons to verify the predictions from the mean field analysis. Pathological state can be reached via a saddle-node bifurcation if the recurrent excitation is not too strong or via a homoclinic bifurcation, preceded by a Hopf bifurcation, if recurrent excitation is increased. In the case of homoclinic bifurcation, the coexistence of oscillatory and pathological states allows one to produce tonic to clonic phase transition observed in epileptic brain slices when extracellular potassium concentration is modulated.

We also discuss the effects of second order network motifs on pathological dynamics [3]. The convergent motifs from excitatory neurons onto inhibitory neurons, which may be observed in mossy fiber sprouting, facilitates depolarization block of inhibitory neurons such that the network enters the pathological state more easily. A mean field model accounting for the second order network structure allows one to predict the effects of this network motif. Specifically, we analyze the stability of

$$\frac{dS_e}{dt} = -S_e + \int y_e\rho(x,y)\phi_e(w_{ee}x_{ee}S_e - w_{ei}x_{ei}S_i + I_e)dxdy$$
$$\tau\frac{dS_i}{dt} = -S_i + \int y_i\rho(x,y)\phi_i(w_{ie}x_{ei}S_e - w_{ii}x_{ii}S_i + I_i)dxdy,$$

where x and y are the normalized in- and out-degree of each neuron, respectively, $\rho(x,y)$ is their distribution, and $S_a = \int yr_a(x,y)dxdy$ is the synaptic drive of population $a \in \{e,i\}$. The prediction of the mean field model is verified by large scale simulations.

References

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