Effects of sprouting and excitation-inhibition imbalance on seizure-like activity

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Human patients and animal models of mesial temporal lobe epilepsy exhibit pronounced mossy fiber sprouting in dentate gyrus and imbalance of excitation-inhibition (EI) in surrounding regions [1]. In this study, we considered a computational model of recurrently connected excitatory and inhibitory neurons to investigate the effects of mossy fiber sprouting and EI imbalance on the network dynamics. Mossy fiber sprouting was modeled by allowing a subpopulation of excitatory neurons to produce additional recurrent connection to itself. The effects of EI imbalance on the network dynamics was examined by changing the inhibitory synaptic strength onto sprouting and nonsprouting excitatory neurons. We derived a self-consistent equation for the stationary rate of the subpopulations from Fokker-Planck formalism and used XPPAUT to visualize the global properties of the solution. Network simulations were performed to verify the predictions from the theory.

Main results of the study are that (1) the network becomes bistable when recurrent connection or EI imbalance is increased within sprouting population, (2) promoting activity in *nonsprouting* neurons by either reducing inhibitory synaptic strength or applying external input can suppress oscillatory activity, and (3) when situated near the saddle-node bifurcation point, the network exhibits intermittent transition to seizure state purely due to noise, and the frequency of seizure events depends on the heterogeneity of inhibitory synaptic projections onto sprouting neurons.

We simulate a network of leaky integrate and fire neurons to demonstrate that injecting transient input to sprouting neurons shifts the network beyond the saddle-node bifurcation point, resulting in synchronized activity. Subsequently, we stimulate *nonsprouting* excitatory and inhibitory neurons simultaneously to suppress the oscillations. When the input to sprouting neurons is tuned to a critical value predicted from the theory, the network state can be placed near the saddle-node bifurcation point, at which the network stochastically switches between two modes: low firing rate and synchronized oscillations. The analysis of distribution of inter-seizure-interval shows that the frequency of seizure events can be reduced by promoting heterogeneity in the inhibitory projections onto sprouting neurons.

References

[1] Marx, M., Haas, C., Haussler, U. Differential vulnerability of interneurons in the epileptic hippocampus *Front. in Cellular Neuro.* 7. 2013.