Epilepsy in Small World Networks

(Extended Abstract)

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Epilepsy is a disease characterized by two electrographic behaviors: short inter-ictal bursts of activity that last on the order of 100 ms, and longer seizures that last on the order of seconds to minutes. Slice models of epilepsy have shown that bursts and seizures can be elicited in different regions of the hippocampus (Hpc) bathed in 4-aminopyridine (4-AP). Bursts originate in the CA3 region of the Hpc (Chesnut and Swann, 1988) while seizures originate in the CA1 (Barbarosie and Avoli, 1997). 4-AP causes the neurons to be slightly more excitable and the synaptic strengths to be increased (Perreault and Avoli, 1989); however epileptiform behavior can be induced in the slice through a variety of methods (Traub and Miles, 1991), suggesting that the cause of these behaviors is not unique to 4-AP but rather a general property of the network.

Traditionally, epilepsy is viewed as a disease of "hyper-synchronous" neuronal activity (Penfield and Jasper, 1954). Evidence from hippocampal slice experiments supports the hypothesis that bursts are caused by neuronal activity that is synchronous on a fine time scale (< 100 ms). However, this work suggests that the neuronal activity during seizures are not "synchronous" (Netoff and Schiff, 2002; Van Drongelen et al., 2003). The most notable difference between the hippocampal regions is that the CA3 has many more recurrent synaptic connections than the CA1. Staley et al. (Staley et al., 1998) hypothesized that bursts originate in the CA3 because recurrent excitation causes the network to activate quickly, simultaneously depleting the neurons' primary glutamate stores. The depletion results in the network activity shutting down. Our operating hypothesis for CA3 bursts is similar to that of Staley et al. (Staley et al., 1998), except that we suggest that neuronal refractoriness, rather than synaptic depression, terminates bursting activity. In contrast, we hypothesize that seizures occur in the CA1 because it has less recurrent excitation, preventing the activity from spreading too quickly. In this

hypothesized mechanism, an excitable pool of CA1 neurons is always available, leading to sustainable, seizure-like activity.

To study the range of epileptiform behaviors and how they relate to the connectivity of the networks that generate them, we devised model networks of neurons and simulated them. A "small-world network" connection topology was used because the Hpc is neither a lattice of connections nor completely randomly connected (Mountcastle, 1997; Gonzalez-Burgos et al., 2000; McCormick and Contreras, 2001). Because the number of "local" versus long distance connections are unknown in Hpc, we use the proportion of random connections in the network as an explicit free parameter. Computational experiments have shown that networks of neurons coupled in a small-world fashion can synchronize and produce similar behaviors seen in the brain slice experiments. It has been shown that networks with few long distance connections require stronger coupling between the elements to synchronize than networks with more long distance connections (Hong et al., 2002). The ability of a network to synchronize also depends on the refractory time and the synaptic delay and firing frequency (Wiedemann and Luthi, 2003). It has also been shown that networks of integrate and fire neurons go through a phase transition of sustained high activity and bursting like activity as long distance connections are added to the network (Roxin et al., 2003). These simulations suggest that the same rewiring of two networks with different local connectivity may result in one bursting, and one with sustainable high amplitude activity resembling a seizure.

As we changed the connectivity properties of our simulated network, we observed behaviors that resemble the epileptiform behaviors seen in slice models and are consistent with our hypothesized mechanisms of bursting and seizing. These behaviors were independent of the specific neuronal model (Poisson, integrate-and-fire, Hodgkin-Huxley) used in the simulations. In the simulations, seizure activity in the CA1-like networks is temporally disordered, allowing the activity to be sustained. The same model supported the view that bursts in CA3 are caused by "synchronous" rapid recruitment of neuronal activity. Simulation results did not depend on the particular cellular models used, indicating that the proportion of long-distance connections more important than the details of individual neurons in determining the network's epileptiform properties.

From observations made from the simulations and slice models, we derived a reduced mathematical description of the network behavior. This describes the average activity in the network as a "birth-death process" in discrete time, and is valid in a low-activity regime. The reduced model accurately predicted transitions from bursting to seizing found in the full network simulations as free parameters were varied. These transitions were described as a loss of stability of an equilibrium in the reduced model. The reduced model highlights the qualitative roles of physical parameters that could underlie the different epileptiform behaviors observed in CA1 versus CA3. While this model is too simplified to yield more than a heuristic description of the slice behavior, it leads to broad predictions about the dependency of the behaviors on particular physical parameters.

The small world network model and our mathematical description of it are highly reduced compared to the hippocampal slice. Therefore, we simulated the networks with only excitatory activity and overestimated the number of recurrent excitatory connections in the CA1. The purpose of this model was not to calculate the exact transition of the network behavior, or to derive physiological values for these transitions, but to give an intuitive feel for why these transitions occur. The exact parameter values where the networks transition between behaviors may differ as we change the form and constituents of the network, but we expect that these transitions will remain qualitatively the same. Nevertheless we feel that our simple network is useful as one approximation to the qualitative properties of collective behavior in the hippocampus, and as a guide to further study.

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