The Dynamics of Epilepsy in Relation to the Application of Anti-Epileptic Drugs

Aaron Huus, Rebecca Rodenkirch, and Theoden Netoff
Department of Biomedical Engineering, University of Minnesota

Introduction

The general purpose of this project is to understand how neurons in a network interact during a seizure. This knowledge would allow for a better comprehension of seizures, as well as the improvement of current treatment options. To accomplish this, Phase Response Curves (PRCs) are used to measure how a periodically firing neuron is perturbed by synaptic inputs. By understanding how a single neuron responds to these inputs, it can be predicted whether a network of neurons will synchronize or not.

Currently in the medical field it is accepted that anti-epileptic drugs work, but no one understand why they work the way they do. The preliminary results for this project indicate that some anti-epileptic drugs increase synchrony. This finding is contrary to the general belief that epilepsy is caused by hyper-synchrony, in which case increasing synchrony should cause more seizures.

This project examines how the anti-epileptic drug, Phenytoin affects the PRC and thusly the synchrony of the neuronal network. Once it is known whether Phenytoin increases or decreases synchrony, people can use this knowledge to increase the efficiency of anti-epileptic drugs which will be beneficial for individuals with epilepsy.

Phase Response Curve Theory

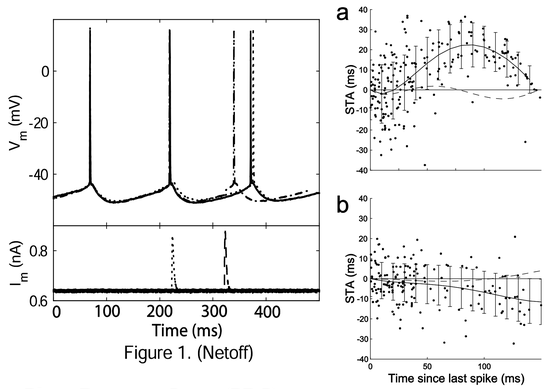
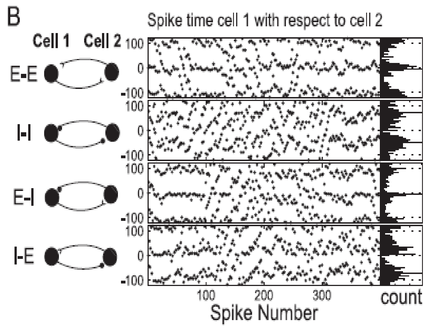


Figure 1. (Netoff)

Phase Response Curve (PRC): Synaptic input applied at different phases of a periodically firing neuron have different effects. A PRC is a measure of the sensitivity of the neuron as a function of phase.

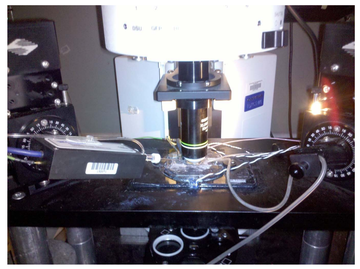


Netoff et al., Figure 2

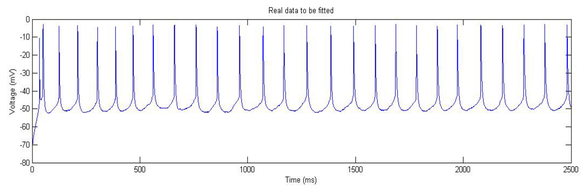
Methods

Experiments were performed in 15-day-old rat hippocampal neurons using patch clamping, a standard neuroscience experimental technique. Patch clamping is a method of studying voltage and current levels through an ion channel of a neuron in a prepared brain slice. In this technique, suction is used to attach the tip of a metal electrode to the cell membrane and create a high-resistance seal. Then, the metal electrode conducts the electrical changes from the membrane to a patch clamp amplifier which provides electrical measurements through computer software (MultiClamp Commander 700B and RTXI – Realtime Experimental Interface).

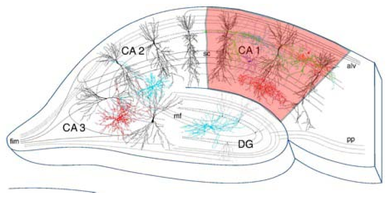
Dynamic clamp is a special type of patch clamping that allows the researcher to control the current input and period of the firing rate of a neuron. This technique is used to measure and record PRCs by simulating controlled synaptic inputs into the neurons. For each neuron, we recorded a PRC before the addition of the drug, when the neuron was exposed only to ACSF (Artificial Cerebrospinal Fluid). Then a prepared solution of Phenytoin was introduced to the cell and a second PRC recorded. The comparison of these PRCs reveals the effect of Phenytoin on the firing rate of the neuron, and thus network synchrony.



Experimental setup. The slice is placed in the center underneath the microscope, with the electrode mounted in the holder on the left. The image is projected onto a television screen (not shown) for better view.



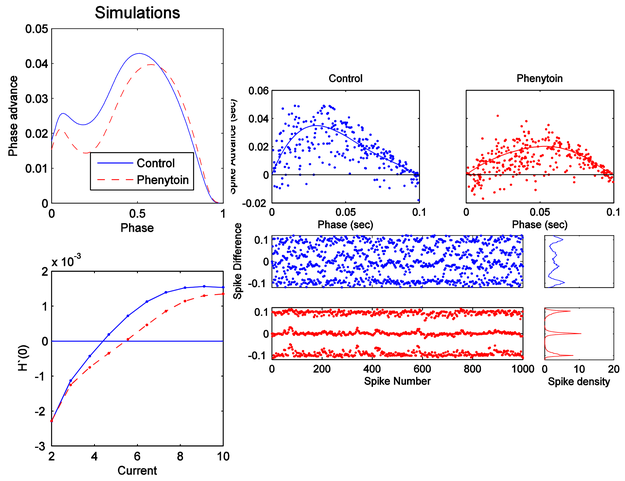
Example of a voltage trace of a patched cell. The voltage readings show a series of periodic action potentials of the firing neuron.



Basic map of the hippocampus. Neurons studied were located in the hippocampal region CA1.

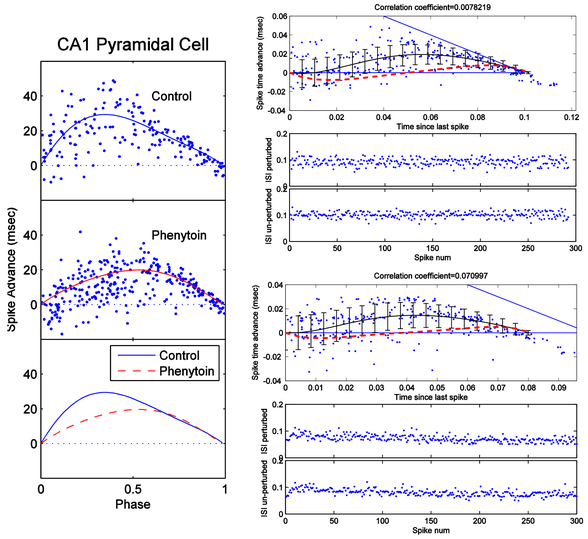
Theoretical Results

Phenytoin is a common anti-epileptic drug that effects the SCN1A channel. It works by stabilizing the inactive state of this voltage gated sodium channel due to a shift in the inactivation curve. This project measures, both in simulation and in a Dynamic clamp experiment, how Phenytoin effects the shape of the PRC and infers the effect on neural network synchrony.



Experimental Results

The experimental results modeled the theoretical results as expected. It can be seen that there was a decrease for the subsequent spike time once the Phenytoin had been washed on. These cells were patched in the CA1 region of the hippocampus. The application of Phenytoin shows a trend that allows inferences that the network would tend to synchronize even in the presence of an anti-convulsant.



Conclusions

During an epileptic seizure, it is currently accepted that the neurons in the brain increase in synchrony. Counter intuitively however, the theoretical and experimental results both show that the anti-epileptic drug, Phenytoin, causes a decreased sensitivity at the beginning of the phase which relates to the increased synchrony. This finding is in direct opposition to the general notion that destroying synchrony should prevent epileptic seizures from occurring, while hyper-synchrony should cause more seizures.

Future research may be built on this initial knowledge by obtaining more data and see if the control and Phenytoin PRCs are statistically different. It is possible that our initial fundamental concept that seizures occur due to an increased synchrony in the brain my be incorrect. If this is true, this would open up many other possibilities for causes of a seizure and how to properly treat it. As more is understood about how anti-epileptic drugs function, a more efficient anti-epileptic drug may emerge.

In summary, the Phenytoin caused an initial decrease in the sensitivity of the PRC and allowed for the network to begin to synchronize. This is the opposite of the previously accepted concept that seizures were due to an increase in synchrony. As more data is obtained, this will have a greater impact on the information behind epileptic seizures.

References

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