Dichter, Marc A.

Progress Report - Bioengineering Research Partnership Grant

An Implantable Device to Predict and Prevent Seizures

Progress Report Period: September 2002 - May 2003

Aim 1: Predicting electrographic onset of seizures: Dr. Brian Litt, University of Pennsylvania and Dr. George Vachtsevanos Georgia Institute of Technology

Progress Report Engineering Efforts: UPenn (Litt Lab) and Georgia Tech (Vachtsevanos Lab)

I. Seizure Prediction, Seizure Precursors and Algorithm Development

Overall, the past year has seen great progress in perfecting methods for identifying, detecting and tracking seizure precursors in mesial temporal and now neocortical epilepsy. In one of our most exciting findings this year, in a paper under review at the journal ***Brain***, Greg Worrell M.D., Ph.D. from our lab describes high frequency epileptiform oscillations in the gamma range that appear to localize the ictal onset zone and predict seizures in neocortical epilepsy. We found this highly localized activity both before and between seizures only in the region of seizure onset in all 7 patients with neocortical epilepsy investigated. We also found that these quantitative precursors in neocortical seizures may evolve in a way analogous way to those described in mesial temporal epilepsy. These findings have the potential to not only target devices for treating neocortical epilepsy, but also to direct current epilepsy surgery methods, which have only a 50% seizure-free rate in non-lesional cases, perhaps in part due to poor ability to localize regions of seizure onset. A copy of this manuscript is attached to this report. Intense investigation is under way in this area, and Dr. Worrell has now opened a strong collaboration between UPenn and Mayo to jointly collect, process and analyze clinical data. In addition, Dr. Worrell has submitted a training grant application to the NIH, in collaboration with our laboratory, to reduce his clinical practice time to pursue this work as part of our team, now that he has returned to the Mayo Clinic staff.

Equally exciting, Eric Marsh, M.D., Ph.D., a neurophysiologist and pediatric neurology fellow in our laboratory, has identified these precursors in neocortical seizure onsets in regions of cortical dysplasia children, and is in the process of analyzing complete, multi-channel recordings from 9 children with neocortical epilepsy, a number of them who appear to have multifocal onsets, collected from the Children's Hospital of Philadelphia (CHOP) as part of this project. As part of our new collaboration with The Mayo Clinic, we will also pool recordings obtained from CHOP and pediatric epilepsy at Mayo, for analysis. In this way we hope to drive basic research in seizure generation, and device research and implementation into pediatric epilepsy, which has been largely neglected in these areas in Bioengineering to date.

As outlined in the grant proposal, in the second year of our BRP we have focused on continuing to refine our understanding of seizure precursors, but also on automating algorithms, distilling

them to run in real time, and employing them in the animal laboratory. In two papers published this year by Maryann D'Alessandro and Joel Niederhauser from our laboratory, we describe rapid algorithms for detecting and characterizing seizure precursors, and methods for taking in multichannel data and multiple features, and distilling them down to a few critical electrode sites and quantitative methods for each individual patients, so that they can be monitored in real time by a low-power implantable device. Principles derived from this research are already being applied in clinical research in early trials of intelligent devices in humans (see below). Development continues on an automated system for processing seizure precursors in real time from human and animal recordings, and we are in the process of deploying this system in the animal laboratory. Additional work continues on analyzing state of consciousness from intracranial EEG, as this is necessary to calibrate energy measures employed in tracking seizure precursors. Perry Betterton, a graduate student in the laboratory, presented these methods in a peer-reviewed conference paper at an international engineering conference in Austria this year (see Betterton below). A more comprehensive study at Mayo and Penn is currently under way to validate and further refine these methods.

II. Translating Lab Discoveries into Clinical Trials

This year has also seen exciting developments in pilot clinical trials of devices for epilepsy. In particular, NeuroPace Inc., a company that has licensed 3 patents from our laboratory, recently presented results from bedside testing of an externalized prototype of an intelligent implantable device for epilepsy based upon principles developed under this proposal. The device fuses 3 features for detecting seizure onsets and precursors, and triggers reactive stimulation through intracranial contacts. In this presentation of 34 patients on which the device was tested, results were significantly improved, compared to when stimulation responded to seizure detection, when stimulation was triggered on rhythmic seizure precursors described by our research group (Pless, Cayman Epilepsy Conference, session on Brain Stimulation for Epilepsy, St. Georges, Grand Cayman, April 2003). Our research group, is currently analyzing over 1400 detections and stimulations from this pilot trial, amassing statistics and focusing on methods for determining characteristics of successful stimulations, as opposed to stimulations which did not prevent seizures. This effort is primarily taking place at Georgia Tech, in close collaboration with Penn Neuroengineering. While this work has not yet been published, and is in its early stages, results from this line of experimentation can be rapidly applied to clinical testing as it evolves, a very unique aspect of our collaboration. This research is the main focus of Perry Betterton's Ph.D. dissertation, at the Georgia Institute of Technology. He is co-advised by Drs. Vachtsevanos and Litt, which has been made possible by this grant. In related research, our group is analyzing data from these human trials in an attempt to discern where it is possible to stimulate to interfere with seizure generation, and whether stimulation must be applied in the ictal onset zone, or if it is sufficient to stimulate in more remote functionally connected areas.

III. Research Using Animal Models

This area has been more challenging in the second year of the grant, as efforts near conclusion on finalizing procedures and the experimental setup to acquire round the clock, continuous video-

EEG data from animals with spontaneous seizures. In initial work we tested intracranial EEG for seizure precursors in four animal models of epilepsy: systemic pilocarpine (Coulter lab, UPenn), intrahippocampal kainite (Bragin Lab, UCLA), sustained electrical status epilepticus (Bertram lab, U. Virginia) and Neuro-D knockout animals (Noebels lab, Baylor). We found that though many spontaneous animal models of epilepsy have only intermittent clinical seizures, these animals frequently have a very large burden of subclinical seizures that can appear as subclinical partial status epilepticus, without clear visual findings. Though further discussion with the laboratories above indicated that titration with the agents inducing status epilepticus can greatly space out electrical and clinical seizure activity, these findings indicated that all experiments with animal models should be conducted with continuous, round-the-clock video EEG monitoring. We found that the pilocarpine model used by Dr. Coulter in the animal core had acceptable seizure frequency and discrete electrical as well as clinical events, which are sufficient for this study. Initial animal recordings of Dr. Coulter's animals were noisy, with high electrode impedance, cable capacitance and comutator noise. Most of these problems have been solved, and we are currently finalizing a system with a staged amplifier on the rat head, to actively drive down noise in the collection apparatus. Initial recordings appear to show seizure precursors that evolve prior to spontaneous seizures in pilocarpine treated animals, but larger-scale, continuous recording and stimulation experiments are slated to begin by summer's end. In an interesting related experiment, recording from the induction of status epilepticus in these animals demonstrates a series of changes in the EEG over 1-4 weeks after induction of status epilepticus, which may be important markers for epileptogenesis in these animals. Recording during this period results in a high failure rate, due to animal death and electrode loss, but further experiments are planned. We are slated to purchase more recording equipment for the animal laboratory and are in the process of hiring a post doctoral fellow to spearhead these animal recording efforts. In addition, we have been promised implantable devices from NeuroPace for use in experiments in these animals, to proceed in parallel with more anatomically specific stimulation experiments in Dr. Dichter's laboratory.

IV. Mechanisms Underlying Seizure Generation and Guiding Stimulation

In two papers submitted this year Landi Parish, a research associate/ MIT graduate in our laboratory, and Gregory Worrell have published findings indicating that seizure generation in the temporal lobe has quantitative characteristics in common with critical systems, such as volcanoes, earthquakes and avalanches. In these systems, events of energy release occur in an inverse logarithmic relationship between the number of events and their amplitude. For example, in an avalanche prone area, many more very small events occur than large events. We are currently investigating quantitative measures of the critical state of the system that might guide controlled, very focal stimulation as seizures build, in the hope of controlling the amount and timing of energy release in order to prevent large electrical or clinical seizures. In this system, focal electrical stimulation might be applied in a way similar to how changes are exploded in avalanche-prone areas, in order to reduce the risk of a large, catastrophic event taking place. In a second paper on "long term correlations," we demonstrate that circuits in the epileptic temporal lobe have more persistent long-term correlations than on the non-epileptic side, which may reveal characteristics of network physiology related to epilepsy (See Worrel and

Parish below). This work complements research in this project performed on computational models and epilepsy in Leif Finkel's area, where we are building realistic, multi-compartment cellular network models of the dentate gyrus, CA1, CA3 regions, as well as thalamocortical interactions, to understand how seizures are generated and may be ameliorable to interventions to stop them.
Additional: Dr. Litt developed and co-hosted the first international collaborative workshop on Seizure Prediction, April 24-28, 2002, in Bonn Germany. Dr. Litt is also co-editor of special edition of IEEE Transactions on Biomedical Engineering devoted to seizure prediction. A second international collaborative workshop is being planned for Paris in 2004. Dr. Litt is also planning an IEEE-sponsored conference on implantable devices for the nervous system

Aim 2: **Mechanisms underlying ictogenesis**

Aim 2, Subaim A. Test the hypothesis that the stages of ictogenesis detected in Aim 1 correspond to specific changes in cellular and network behavior – Dr. Diego Contreras:

As part of the global strategy to detect specific cellular and network behaviors underlying ictogenesis, we have continued to concentrate our efforts during the past year in three fronts:

1. Developing multisite recordings of local field potentials and units from neocortex, thalamus and hippocampus, in order to detect the evolution of events during ictogenesis, simultaneously among these three structures.
2. Developing recordings of units in chronically implanted animals using tetrodes.
3. Determining particular susceptibility to seizures among different genetic mouse models.

By combining the three points above, we have been using genetic mouse models and multisite recordings (fields and cells) to explore the role of channelopathies, targeted to different structures, in the susceptibility and progression of ictogenesis. In particular we have performed recordings using arrays of 8 to 16 bipolar electrodes placed in different areas of cortex, thalamus and hippocampus in three types of genetically manipulated animals:
1. Mice lacking the potassium channel Kv 3.2. This is a voltage dependent channel with extremely fast kinetics and capable of carrying large currents, it opens at very depolarized membrane potential and is responsible for the fast repolarization of the action potential causing a sharp and short afterhyperpolarization. This channel exists only in the parvalbumin positive GABAergic interneurons of infragranular layers of neocortex, and is responsible for the fast spiking phenotype. Absence of the channel in the knockout mouse causes these interneurons to loose their ability to fire high frequency trains of spikes and weakens intracortical inhibition. The result is a lower threshold for electrically and chemically (PTZ) induced seizures and an altered background EEG.

2. Congenic animals with genetic background of C57BL/6 strain and a distal portion of DBA/2 strain chromosome 1. This portion of chromosome 1 is rich in potassium channels, of particular importance is the inward rectifier, Kir 1.4. Previous studies documented a lower seizure threshold in DBA/2 (D2) as compared to C57BL/6 (B6) mice and suggested a seizure-related

locus on distal chromosome 1. Using arrays of bipolar electrodes, we characterized the cortical, thalamic, and hippocampal EEG activity in response to different methods of seizure induction across three strains of mice: D2, B6, and a congenic B6.D2 (characterized by a distal portion of D2 chr.1 on a B6 background). Under ketamine/xylazine anesthesia, all strains of mice manifested a slow (<1Hz) oscillation in the EEG as described similarly in cats and humans. This background activity varied between strains, with D2 mice exhibiting multiple high-amplitude sharp waves during the depth-negative portion of the slow oscillation. These sharp waves were rarely observed in B6 mice. Furthermore, EEG activity following seizure-induction correlated with the known behavioral response of the different strains. After PTZ injection, B6 mice typically evolved an EEG pattern consisting of single interictal spikes, either in isolation or superimposed on the slow oscillation, but rarely progressed to electrically identified seizures. In contrast, D2 mice exhibited repetitive bursts of interictal spikes often progressing to fast runs of activity and electrically identified tonic-clonic seizures. Preliminary results suggest that the EEG activity of the congenic strain is similar to that seen in D2 mice. These findings demonstrate that the varying susceptibility to seizures observed between D2 and B6 mice correlates with variations in baseline EEG and may be mediated in part by a gene(s) on distal chr.1.

3. Mice lacking the cationic channel Pkdl. This is a mixed calcium/sodium channel located mostly in hippocampus and neocortex. It is not clear yet how excitability is enhanced but we have demonstrated that the $Pkdl^{-/-}$ mouse has a lower threshold for seizure induction as well as an altered background EEG. $Pkdl^{-/-}$ mouse also shows enhanced thalamocortical transmission as demonstrated by an increase in a form of short term plasticity termed augmenting. Augmenting consists in the facilitation of the second stimulus during pair pulse electrical stimulation of the thalamus.

These three models have shown that different types of specific cellular and network manipulations may cause enhanced susceptibility to seizures and that the three structures studied will entrain each other via different mechanisms which will certainly require different strategies in order to prevent the evolution of ictogenesis.

Future work on these and other models aims at demonstrating the differential role in ictogenesis of these three main structures (cortex, thalamus and hippocampus) in the generation of seizures. Simultaneous recordings will also shed light on the relationships and interdependencies established during ictogenesis. Such knowledge is critical to design the stimulating protocols which block seizure generation that are the ultimate goal of this BRP.

Subaim B: Study the circuit and cellular biophysical mechanisms operative during generation of the PIC using high resolution patch clamp recordings of principal cells and interneurons combined with simultaneous field potential analyses in hippocampal slices – Dr. Douglas Coulter:

Significant progress in the construction and implementation of the animal core occurred over the past year. Progress was in three main areas: improvements to the facility; animal monitoring; and analysis.

We have expanded and improved our monitoring facility in several ways. First we have added an additional 2 cages to now allow us to monitor 8 animals simultaneously. In addition we have purchased 4 new commutators that provide for recording from 2 additional bipolar channels, now bringing the number of recording sites to 4. This latter modification is critical in predicting seizure onset from within the various limbic sites known to be involved in temporal lobe epilepsy. We have also spent extensive time networking our computers in the rat/mouse epilepsy monitoring unit, to facilitate downloading and analysis of EEG.

We have conducted 24 hour continuous EEG/video recordings from rats during the month following status epilepticus (SE)-induced brain damage. During this period, animals have no overt behavioral seizures, so this time period has been termed the 'latent' or 'silent' period. Our preliminary studies have provided intriguing evidence that the period immediately following SE is anything but a 'silent period'. Based on extensive analysis of hippocampal and amygdala EEG, the time between SE-induction and the occurrence of spontaneous behavioral seizures is a dynamic period that eventually culminates in an epileptic state. EEG signature events during this time period resemble events described during the preictal cascade in humans with temporal lobe epilepsy, including long-term energy bursts and subconvulsive seizures. This suggests that progressive alterations preceding the onset of behavioral seizures during disease development may be recapitulated during the interictal progression to the next seizure in humans with full expression of temporal lobe epilepsy.

We have implemented EEG power analysis of recordings from rats together with Steve Cranstoun and Brian Litt. We have had some initial problems in utilizing our rat recordings with the algorithms developed from human data. These problems are primarily induced by differences in electrode impedence and fabrication between our animal studies, and electrodes utilized to record human data. Rat electrodes are much higher in impedence, resulting in increased noise levels, which in turn complicates analysis. Despite this limitation, Steve and Brian have still been able to analyze several long stretches of recordings, providing the results described above. However, we are working to optimize our recording strategy to further facilitate EEG analysis. We are in the process of testing multiple electrode types, and reducing electrode impedence as much as possible, in collaboration with Diego Contreras, who has extensive extracellular recording experience. This will be absolutely necessary to optimize in order to be able to facilitate implementation of an automated seizure prediction/intervention device in future years.

In the past year, we have conducted an extensive overhaul of our recording system to facilitate application of the human seizure detection algorithms to our rat recordings. In our initial recordings in Years 1 and 2, we were able to identify many of the seizure precursor events described in man by Litt and colleagues in our epileptic rats. This looked extremely promising, but required a laborious, manual analysis of the EEG. In order to implement an intervention strategy, we absolutely require automated, on-line analysis of depth EEG to trigger an intervention at appropriate times, designed to prevent the impending seizure. However, the differences in electrode characteristics between the human and animal recordings precluded

automated analyses in our initial studies, a concern echoed by many colleagues throughout the world conducting similar studies in different laboratories. The noise associated with animal movements, and the higher electrode resistance combined to make the recordings different enough to render the human derived algorithms inoperative.

This year has primarily focused on optimizing our electrographic recording system in the animal core. To minimize artifacts we implemented a design with pre-amplifiers directly incorporated in the cable system. These amplifiers were small enough so as to not impede the normal movements and sturdy enough so that they could not be destroyed by the rats. We have also conducted intensive studies designed to improve our electrode characteristics, and now routinely carry out extensive tests on the impedance characteristics of all electrodes prior to implantation, with a set of rigorous selection criteria further improving the quality of recordings.

In additional studies recording baseline EEG with this system in a number of animals, we found that these improvements have significantly decreased the unwanted artifact and have allowed much more detailed analysis of our electrographic recordings. Investigators in Litt's laboratory are now using these control recordings to evaluate whether these extensive improvement efforts will now allow us to apply human seizure prediction algorithms to our recordings.

We have also begun development of two distinct intervention strategies to implement once the human algorithms come on line. We have modified two of our commutators to allow for focal, triggered stimulation of various brain areas in our monitored rats. This is our primary intervention strategy proposed in the grant, and now is poised to be implemented once our prediction algorithms are implemented. We also have modified one of our commutators to allow coupled electrical recording and triggerable cannula-mediated infusion of drugs. This could allow us to directly infuse various substances (e.g. muscimol or lidocaine) into the seizure focus during epochs of impending seizure onset as an alternate strategy to preemptively terminate seizures.

Aim 2, Subaim C. Application of Gene Transcription Assays as a Predictive Strategy in Ictogenesis - Dr. Peter B. Crino:

Over the past year, Dr. Crino's laboratory has isolated total RNA from control rat brains from the animal core funded through the BERP grant and have generated biotinylated cDNA probes for the Affymetrix rat oligonucleotide chip. In addition, amplified radiolabeled mRNA has been used to probe lab-generated arrays containing candidate genes of interest. These animals include control and sham surgical controls. We have preliminary data in which rat hippocampi have been immunolabeled with MAP2, NeuN or GFAP antibodies in preparation for single cell microdissection and gene expression analysis. It is critical that we devote a significant amount of time to defining the baseline levels of gene expression in the control animals so that changes in gene transcription following pilocarpine induced seizures can be analyzed as a function of ictogenesis. The primary focus of Crino's lab is to define gene expression changes in a variety of human epilepsy syndromes and in several animal epilepsy models. We have implemented this approach in several recent papers that are listed below.

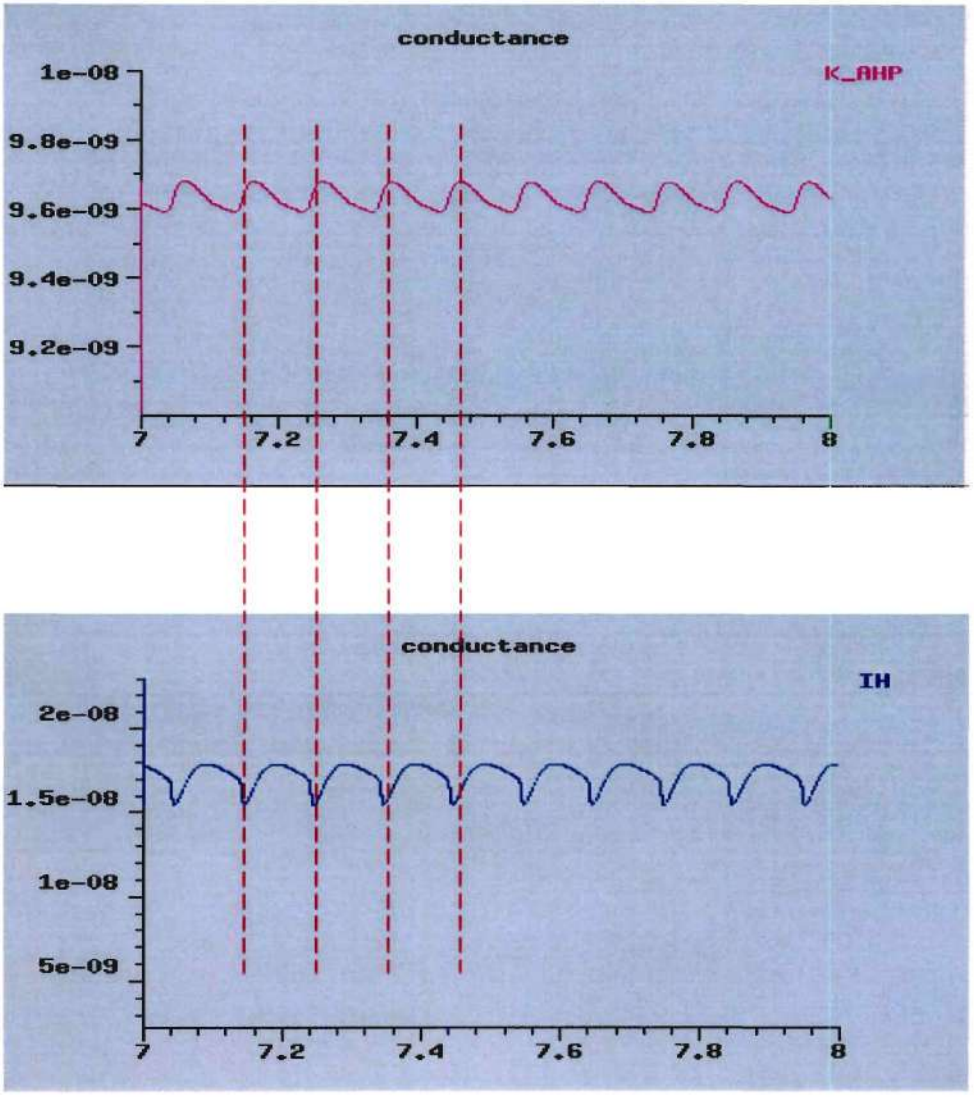
Aim 2, Subaim D. Network Mechanisms of Seizure Progression: Computational Modeling and Simulations – Dr. Leif Finkel:

The objective of the computational studies remains to develop biophysical-level network models of hippocampus, focusing on dentate and CA3, and to investigate proposed mechanisms of seizure activity induced by pathological changes at the neuronal and network level. We are nearing completion of the dentate and CA3 models, testing them against published physiological data on cell firing, and have carried out initial studies of the effects of carbachol and other agents on network activity.

CA3 Model

A CA3 network consisting of 100 pyramidal cells and 10 interneurons has been constructed using the Pinsky and Rinzel (1994) pyramidal cell model and the Wang and Buzsaki (1996) interneuron model. Tiesinga and Sejnowski (2001) have recently shown that the 2-compartment Pinsky-Rinzel model possesses neuronal properties sufficient to generate theta and gamma rhythms. Our pyramidal cell model includes the repertoire of currents used by Tiesinga and Sejnowski but with some updatings. The persistent Na^+ current (N_{aP}) and persistent K^+ current (K_O) used by Tiesinga were replaced by the hyperpolarization-activated non-specific cation current (I_H) and a non-specific calcium-sensitive cation (I_{CAT}) current. Tiesinga assumed that N_{aP} and K_O are present in the carbachol-induced model of theta oscillation whereas based on current information, it is unclear if I_{NaP} is present in the CA3 (although it is present in CA1) and there have been no reports of the I_{KO} existing in the hippocampus. In contrast, recent data suggest that in the in-vitro carbachol model of hippocampal oscillations, I_H is upregulated (Fisahn et al 2002) and the muscarinic action of carbachol also induces the I_{CAT} in CA3.

The temporal interaction of I_H with the calcium-dependent potassium current I_{KAHP} gives rise to a theta rhythm. I_{KAHP} has a time constant of ~1sec. However, I_{CAT} has a depolarizing effect, so that the cell recovers from its hyperpolarized state with a time constant of about 100 msec. As I_{KAHP} increases, the (pyramidal) cell hyperpolarizes and this activates I_H. As I_H increases, it depolarizes the cell and this switches off I_{KAHP}. As the cell becomes more depolarized, I_H is turned off, consequently, the cell becomes less depolarized or more hyperpolarized. This activates the I_{KAHP} and as I_{KAHP} rises, the cell hyperpolarizes and this activates I_H. The cycle then repeats. Figure 1 below shows the interaction of the time and voltage dependent conductances of I_H and I_{KAHP}, giving rise to the theta rhythm. Note that this is similar to the mechanism for theta generation proposed by Hasselmo and colleagues (2002) in entorhinal cortex. Figure 2 is a raster plot that shows the theta rhythm generated by the CA3 pyramidal cell network. Each dot represents an action potential from a pyramidal neuron. Initial entrainment of the network is observed within the 1st second of simulation.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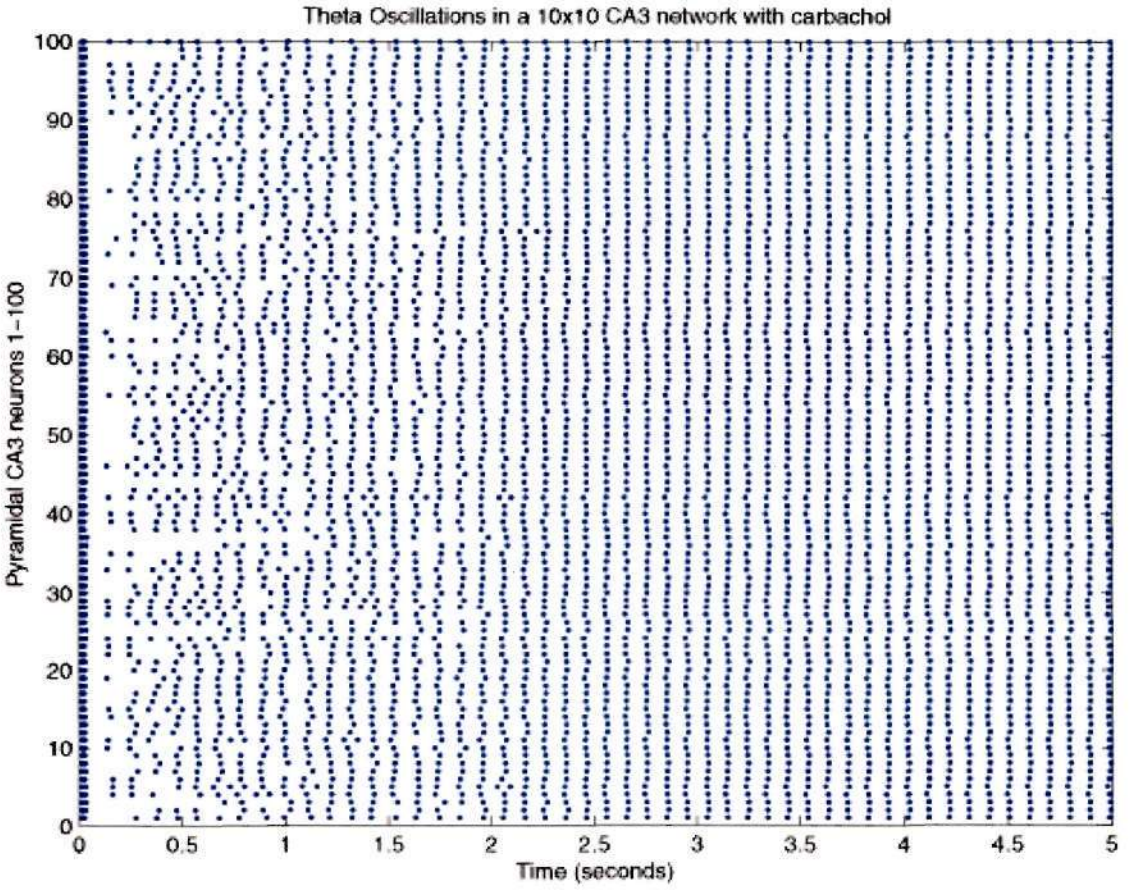
Figure(1)



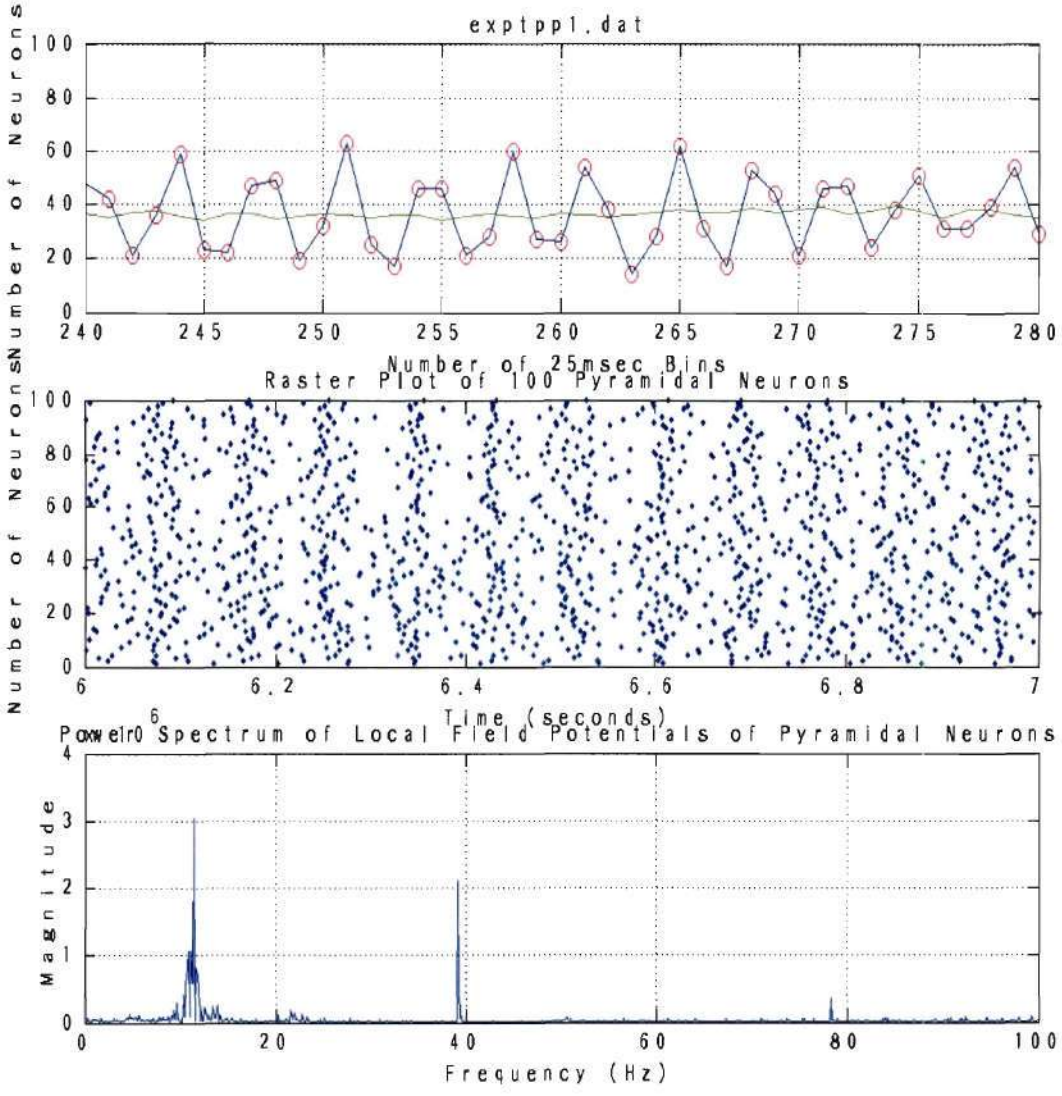
Figure(2)

Gamma Oscillations:

Interneurons play the key role in generating gamma oscillations in the hippocampus. In the CA3 model, the interneurons form a separate network that provides feedforward inhibition to the pyramidal cells. With mutual inhibition, the interneuronal network synchronizes at 40Hz, and imposes 40Hz IPSCs or gamma windows on the pyramidal cells. These gamma windows gave the CA3 pyramidal cells a temporal structure, dictating that these pyramidal cells can only fire action potentials during the gamma windows.

Figure (3) shows theta and gamma oscillations generated by the CA3 network. Figure (3b) shows a raster plot of the CA3 pyramidal cell network between the 6^{th} and 7^{th} second of simulation time. The majority of the cells are seen to oscillate at about 11 Hz which is the dominant frequency of oscillation. Riding on the theta frequency oscillation is the faster gamma oscillation. At the peak of each theta cycle, the majority of the cells fire action potentials, gated by the gamma windows. In between the theta cycles, fewer cells fire but when they do, they

would fire in periods dictated by the gamma windows. Figure (3a) displays the histogram of the raster plot using a gamma period bin. The average number of cells firing is approximated by the green line. Figure (3c) displays the frequency spectrum of the CA3 network and the spectrum peaks represent the theta and gamma oscillations present in the network.



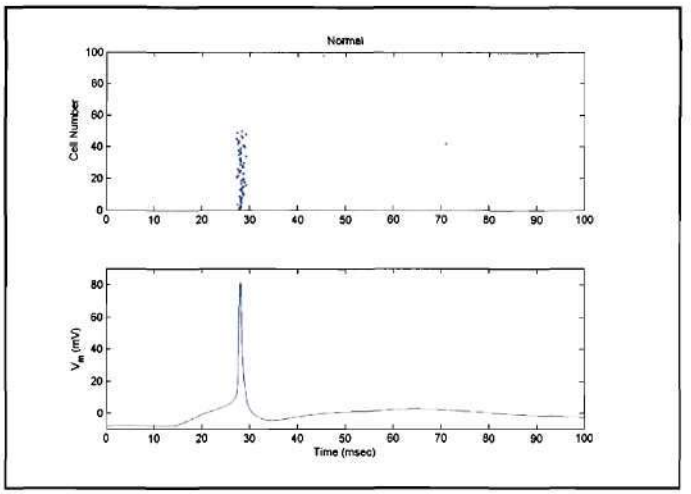
Figure(3)

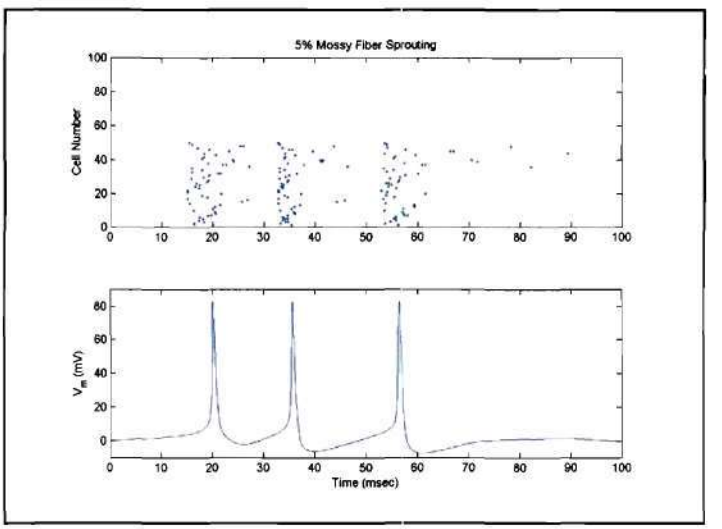
Dentate Gyrus (DG) Model

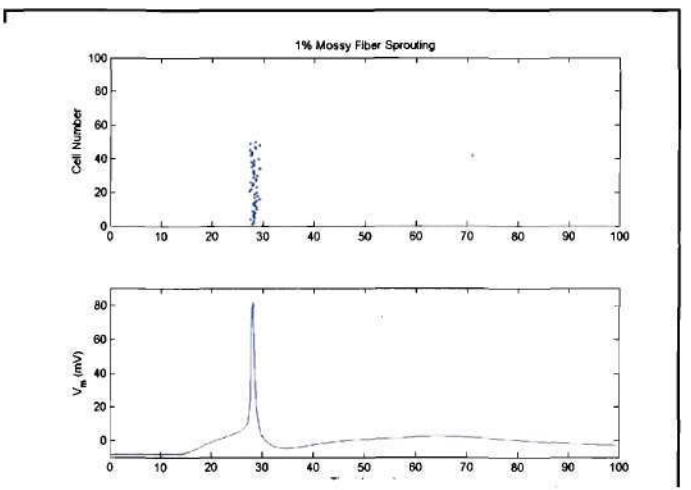
Our dentate model is an extension of the model proposed by Lytton et al. (1998) which in turn makes use of the connectivity matrix constructed by Patton and McNaughton (1995). Lytton and colleagues used their model to study the effects of mossy fiber sprouting and recurrent excitation. The Lytton model uses the Pinsky-Rinzel CA3 pyramidal cell model to model both granule (GC) and mossy cells (MC). As such, the neuronal model does not reproduce firing rate

properties with somatic current injection. The first renovation was to replace the GC with the model of Aradi and Holmes (1999). We are currently modifying this model of GC to include up-to-date information on ion channels, and to use channel kinetics specific to the adult rat. In particular, the Aradi model uses ion channel kinetics from a variety of species and cell types including CA3 and CA1 pyramidal cells, granule cells and motor neurons. This diversity makes difficult the task of modeling particular ion channelopathies found in animal models of epilepsy. In addition, more recent evidence has shown the existence of a hyperpolarization-activated non-specific cation current, I_H, and extra-synaptic $GABA_A$ receptors in the GC dendritic tree. Both of these currents contribute to a tonic shunting inhibitory current, which may contribute to the inability of the GC to show burst firing under normal conditions. We are fortunate to have as a collaborator Heinz Beck who is generously providing us with voltage clamp data from various rat GC ion channels in both normal and epileptic animals, so that we may more accurately portray channel kinetics.

As an initial test of the updated model we have reproduced the findings of Lytton et al (1998) on mossy fiber sprouting. The network consists of 50 granule cells, 2 mossy cells and 2 interneurons, randomly connected with convergenc and divergence in ratio similar to that given by Patton and McNaughton (Patton and McNaughton, 1995). %MFS represents the probability of connection between two granule cells. The network is stimulated with a short pulse to the perforant path inputs at t = 0 (the delay to firing is because the "perforant path" is another cell, with a somatic current injection, which synapses with the granule cells). Three conditions are shown: Normal, 1% and 5% MFS.







Aim 3: Developing therapeutic strategies to prevent seizure onset - Dr. Marc Dichter and Dr. Diego Contreras

Subaim 1: Seizure suppression by brain stimulation in animals with seizures

In order to implement this part of the research a new small animal electrophysiological recording station was established with capabilities for recording from both mice and rats. Initial experiments on creating animal models of spontaneous epileptic seizures is ongoing in Dr. Douglas Coulter's core animal facility, but we are also obtaining data from various mouse models with both spontaneous and acquired epilepsy. Future studies are likely to focus on both species, rats because they are larger and somewhat easier to work with from the electrophysiological perspective and because acquired focal epilepsy is better characterized, mice because of much more common spontaneous epilepsy, especially in various genetic models, and because any future interest in understanding genetic susceptibility to seizures is more likely to occur in mice.

In order to facilitate the maximum progress on the research for this grant in the face of a rather severe reduction in our original budget request, Drs. Dichter and Contreras have combined much of their early efforts into one laboratory project. This allows sharing of equipment and focusing the research on the seizure suppression project . The network analysis project originally proposed as part of Specific Aim 2 is being implemented by separate research in Dr. Contreras' laboratory.

A postdoctoral fellow, Dr. Kyle Kirkland, was recruited to participate in these studies. He has experience in systems and computational neuroscience and spent the first year becoming skilled at recording seizure activity from mice. An acute electrophysiology rig was constructed, computer hardware and software was purchased, and additional equipment was designed and built for recording seizures and stimulation of the brain. The utilization of mice for these experiments, while still considered very valuable, involved more significant technical problems than originally anticipated. During year 2 of the grant, Dr. Kirkland has moved to Dr. Contreras' laboratory to continue the mouse work and a second postdoctoral fellow was recruited to the Dichter lab to continue the acute seizure recording and seizure suppression stimulation in Dr. Dichter's laboratory. These experiments will continue to utilize acute focal seizure models, as human data emerging from other laboratories suggests that brief direct electrical stimulation of the seizure focus at the onset of the seizure can abort the incipient seizure. We hope to reproduce this work in the rat model to determine optimal seizure suppression parameters, experiments that cannot be done with human patients. In addition, we hope to develop additional rat epilepsy models to complement those being developed in the core laboratories. Two of particular interest are the perforant path stimulation model which can produce very localized hippocampal damage that mimics that seen in patients with mesial temporal lobe sclerosis, and the focal kainic acid injection model which similarly mimics the human pathology. Both of these have much less extensive neocortical damage than the pilocarpine model currently being used and my be more suitable for local stimulation paradigms.

Publications resulting from research supported by this grant:

Journal Articles

Betterton P, D'Alessandro M, Vachtsevanos G and Litt B. Determining State of Consciousness from the Intracranial Electoencephalogram (IEEG) for Seizure Prediction. Proceedings of the 22nd IASTED Conference on Modeling Identification and Control (MIC'2003), Innsbruck, Austria, 2003.

Cranstoun S, Ombao H, von Sachs R, Guo W, Litt B. Review of Time-Frequency Spectral Estimation Of Multi-channel EEG Using the SLEX Method. IEEE Transactions on Biomedical Engineering 49:988-996, 2002.

Cranstoun, S.D., Worrell, G., Echauz, J., Litt, B.; Self-organized criticality in the epileptic brain [Proceedings of the Second Joint Engineering in Medicine and Biology, 2002. 24th Annual Conference and the Annual Fall Meeting of the Biomedical Engineering Society] EMBS/BMES Conference, 2002., Volume: 1 , 23-26 Oct 2002 Page(s): 232 -233.

Crino PB, Miyata H, Vinters HVV. Neurodevelopmental disorders as a cause of seizures: neuropathologic, genetic, and mechanistic considerations. Brain Pathol 2002;12:212-33

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