- RESEARCH STATEMENT -

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I. RESEARCH STATEMENT

RESEARCH FOCUS

Goal: Our *primary* goal is to design and implement novel methodology and advanced signal processing techniques to monitor, process and model the electrical and magnetic activity recorded from the brain for the purpose of diagnosis, differential diagnosis, evaluation of treatment, timely warning and intervention to avert catastrophic state transitions like epileptic seizures. The *secondary* goal is to interface the developed products with existing devices in biomedical industry used for monitoring and real-time treatment of the respective disorders, diseases and emergencies, for example, vagus nerve stimulators (VNS), deep brain stimulators (DBS), transcranial magnetic stimulators (TMS) and/or other neuromodulation devices based on timely in situ cooling of the brain or in situ administration of medication.

Significance: Abrupt disruptions of the normal electrical activity of the brain result into devastating medical conditions that may require immediate treatment. About 1% of the world's population develops epileptic seizures in a lifetime due to genetic or acquired insults to the brain. Epileptic seizures are manifestations of epilepsy, a serious brain dynamical disorder second only to strokes. Of the world's ~70 million people with epilepsy, fully 1/3 have seizures that are not controlled by anti-convulsant medication. The field of seizure prediction, in which engineering technologies are used to decode brain signals and search for precursors of impending epileptic seizures, holds great promise to elucidate the dynamical mechanisms underlying the disorder, as well as to enable implantable devices to intervene in time to treat epilepsy. There is currently an explosion of interest in this field in academic centers and medical industry with clinical trials underway to test potential prediction and intervention devices for FDA approval. Therefore, development of algorithms and devices that, based on early detection of precursors to such apparently abrupt episodes, could **issue on-time warnings and trigger on-demand interventions is of emerging importance.** We are one of the leading research groups in the world in this effort. I first presented results on the predictability of epileptic seizures from analysis of the electroencephalogram (EEG) in 1988 [1]. Over the years, and through our publications and continuous support from NIH and the VA, we have developed the field of epileptic seizure prediction, that has flourished over the years with the collaboration of Neurologists, Bioengineers and scientists from diverse areas like Physics, Mathematics, Chemistry and Statistics (see [2] for a review). Results from prospective, real-time, long-term (in the order of tens of minutes) prediction of epileptic seizures have been generated [3]. This research provides the answer to the question of "when to intervene". However, answers to the questions of "how" and "where" to intervene are needed for complete control of these transitions in the brain, and constitute part of our ongoing research effort (real-time on-line seizure prediction and control schemes in computer simulations, animal models and patients), supported by NIH [4] and more recently by NSF [4] and Cyberonics Inc. [4]. Subsequent implementation of the algorithms into implanted devices in the brain, controlling an actuator (e.g. electromagnetic stimulator or drug release device), is anticipated to provide the bioengineering solution to these medical crises (emergencies). **Future applications of the research** to the following areas are conceived, tested and some of them already validated: **a)** diagnose epilepsy from interictal periods in patients, in an outpatient setting (e.g. identification and localization of an epileptogenic focus), as well as provide differential diagnosis in the emergency room and intensive care unit (e.g. epilepsy versus metabolic encephalopathy), **b)** evaluate treatment of seizures by anti-epileptic drugs (of critical importance in status epilepticus cases, which exhibit the most severe and life-threatening form of epilepsy), **c)** develop seizure susceptibility indices that can monitor the susceptibility of patients to seizures over days, so that they can be warned on a regular basis to increase or decrease their medication accordingly, **d)** based on resetting of brain dynamics, predict which patients with traumatic brain injury need to be treated with anti-epileptic drugs early, so that they do not develop epilepsy in the future (supported by a recent grant by DoD), and **e)** evaluate the efficacy of rehabilitation schemes and propose directions for improvement of the treatment itself in patients with other brain disorders than epilepsy (e.g. stroke survivors and patients with Parkinson's disease). This research direction is currently supported by an NSF IGERT grant and is conducted in collaboration of our Brain Dynamics Lab with the Arts, Media and Engineering Lab at ASU.

Approach: The foundation of this research is the application of nonlinear systems and control theory to biological systems and signals. Advanced signal processing concepts, like spatio-temporal bifurcations and measure of complexity and stability profiles over time and critical brain sites automatically and adaptively selected by global optimization techniques, are used to quantify the human or animal brain's intermittent transitions into and out of epileptic seizures. The generated results have led us to postulate and pursue three novel hypotheses. A process we have called "dynamical entrainment" characterizes the convergence of the aforementioned profiles of critical brain sites with the epileptogenic focus over time long before the occurrence of seizures, and it is the basis of the seizure prediction hypothesis. Dynamical resetting (disentrainment) of the brain sites occurs right after these seizures [5-8]. It is this observation (in rodents and humans) that has led us to the brain resetting hypothesis that may explain why seizures occur when they do, and provide some very important insight into schemes for seizure control and understanding of crises (e.g. we have shown that seizures that do not reset the brain may eventually lead it to status epilepticus). According to this hypothesis, seizures occur to reset a pathological situation of long entrainment of the dynamics of normal sites with the epileptogenic focus. In this sense the problem in epilepsy is not the seizures themselves, but what precedes them. Actually, counter-intuitively and contrary to the common belief, seizures may then be seen as a solution, or defense mechanism, or the last resort for the brain to counteract the pathology in its function. Accordingly, it is the pathology of the dynamics that develops prior to seizures than the seizures themselves a successful treatment for epilepsy should address. This is another reason why a seizure prediction software could be invaluable in the treatment of ictogenesis. Experimentation also with mathematical models of coupled nonlinear and chaotic oscillators [9-10] provided us with clues that we further pursued and tested on our real EEG data. A novel control scheme based upon stimulation of the brain by anti-epileptic drugs and/or electromagnetic stimuli at the onset of the dynamical entrainment, that is, long prior to a seizure, as well as upon the level of entrainment of the brain dynamics, has been devised and tested on our simulation models and rodent animal models with excellent preliminary results. We have called this new control scheme **"feedback decoupling control".** The external feedback provided by the actuator disentrains the entrained dynamics very efficiently and effectively and "seizures" do not then have to occur, and they do not occur [11-14]. Applications of the above findings to diagnosis and differential diagnosis of epilepsy have followed [15-20]. **This research is currently supported by the following 3 grants:**

1. **Vagus Nerve Stimulation: A Bioengineering Approach to Assess its Effect on Resetting the Epileptic Brain Dynamics** (03/09-03/12) (NIH *R21 NS061310-01A2*, in collaboration with BNI; PI: Dr. L.D. Iasemidis, Co-PI: Dr. D. Treiman; Total amount: $414,714; ASU: GES0118).
2. **Epileptogenic Focus Localization and Closed-Loop Control of Brain Dynamics in Epilepsy** (09/11-09/14) (NSF, ECCS Division, Cyber Systems ECCS-1102390, PI: Dr. K. Tsakalis, Co-PI: Dr. L.D. Iasemidis; Total amount: $360,000).
3. **Development of a closed-loop detect-and-treat system using transcranial direct current stimulation (tDCS) for epilepsy** (01/11-01/12) (CIMIT: The Center for Integration of Medicine and Innovative Technology in Boston; PI: Felipe Fregni, Department of Neurology, Harvard University; Co-PI: Dr. L.D. Iasemidis).

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[2] L.D. Iasemidis, "Epileptic seizure prediction and control", *IEEE Trans. Biomed. Eng.,* **50** (5), 549-558, 2003.
[3] L.D. Iasemidis et al., "Adaptive epileptic seizure prediction system", *IEEE Trans.Biomed. Eng.,* **50** (5), 616-627, 2003.
[4] **NIH-NINDS** RO1 NS39687 BRP grant: "Bioengineering Research Partnership for Brain Dynamics"; **NIH** *R21 NS061310-01:* Vagus Nerve Stimulation: A Bioengineering Approach to Assess its Effect on Resetting the Epileptic Brain Dynamics; **NSF** Cyber Systems grant: "Closed-loop control of brain dynamics in epilepsy"; **Epilepsy Research Foundation** grant: "Seizure Control by Closed Loop Feedback in a Rat Model of Chronic Temporal lobe Epilepsy"; **Science Foundation of Arizona:** "Optimizing Multidimensional Time Series Classification: Spatio-Temporal Data Mining in Epileptic Brain

Dynamics"; **Cyberonics Inc.** grant: "Characterization of Novel Vagus Nerve Stimulation (VNS) Parameters' Efficacy, Based on Desynchronization of Brain Dynamics, in Open and Closed-Loop Configurations: A Study in an Animal Model of Chronic Epilepsy"; **DoD** Concept grant: "A new quantitative EEG technique for prediction of post-traumatic epilepsy (PTE) in individual subjects after traumatic brain injury (TBI)"

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Related Press:

Local

- o "Forecasting Mind Storms", *ASU Research magazine*, pp. 24-29, Summer 2003.
- o "*ASU Bioengineer presents evidence of forecasting epileptic attacks*", **ASU Engineering web page** (www.eas.asu.edu/ceas/news/)
- o *"Professors find way to predict epileptic seizures"* in the **State Press**, March 1, 2001
- o "*ASU Bioengineer presents evidence of forecasting epileptic attacks*", **ASU Research magazine**, March, 2001.

National / International

- o "Predicting a storm in the brain", *IEEE Spectrum,* pp. 45, July 2003
- o *"Doctors look ahead to pacemakers for the brain"* in **The New York Times,** science section page D5, February 18, 2003. (http://nytimes.com)
- o "*Fire in the Brain*", **Discover magazine,** May issue 2002, pp. 50-53 (*www.discover.com*)
- o *"Epileptic seizures could be predictable"* in **The New York Times**, by Reuters, February 20, 2001. (http://nytimes.com)
- o "*Chaos theory sheds light on pre-seizure transition period*", Vanguard, **U.S. Department of Veterans Affairs**, pp.13, February 2000.
- o "*Chaos theory helps researchers predict epileptic seizures*", Friday Evening Post, **The University of Florida Health Science Center**, December 17, 1999.

Publications: This research has enjoyed a lot of publicity in the local and national press (see above). To date, the current research has cumulatively generated 46 journal papers, 27 book chapters, 29 conference papers and 83 abstracts of presentations; 4 patents have been awarded and 6 more are under review.

Patents: This research is protected by the following patents: *Seizure warning and prediction* (awarded 10/16/01 - US Patent and Trademark Office – No. 6,304,775); *Multi-Dimensional Multi-Parameter Time Series Processing for Seizure Warning and Prediction* (awarded 08/28/07 - US Patent and Trademark Office – No. 7,263,467); *Optimization of Multi-dimensional Time Series Processing for seizure warning and prediction* (awarded 05/13/08 - US Patent and Trademark Office – No. 7,373,199); *Pacemaker for treating physiological system dysfunction* (awarded 06/12/12 – US Patent and Trademark Office No. 8,197,395).

Funding Mechanisms: This research thrust area has been funded over the years by NIH, NSF, DARPA, not-for-profit organizations (Epilepsy Foundation of America, Whitaker Foundation, Science Foundation Arizona), for-profit organizations (Cyberonics Inc.) and seed grants from ASU. Details of the major grants are given below. New proposals to NIH and NSF are under way. Use of the STTR and SBIR mechanisms for collaboration with new or existing companies is also under way.

Funding History (Major Grants only):

Cyberonics Inc.	VNS Closed-Loop	01/11-06/12	$100,000
NSF (Cyber Systems)	Epileptogenic Focus Localization and Closed-Loop Control of Brain Dynamics in Epilepsy	09/11-09/14	$360,000
DoD (Concept grant)	A new quantitative EEG technique for prediction of post-traumatic epilepsy (PTE) in individual subjects after traumatic brain injury (TBI)	10/10-04/13	$300,000
Cyberonics Inc.	Characterization of Novel Vagus Nerve Stimulation (VNS) Parameters' Efficacy, Based on Desynchronization of Brain Dynamics, in Open and Closed-Loop Configurations: A Study in an Animal Model of Chronic Epilepsy	6/10-12/11	$560,000

NSF (IGERT)	NSF Integrative Graduate Education and Research Traineeship Program (IGERT) on Experiential Media: Analysis of EEG for evaluation of rehabilitation in stroke patients	09/05-09/12	$3,000,000
NIH R21	Vagus Nerve Stimulation: A Bioengineering Approach to Assess its Effect on Resetting the Epileptic Brain Dynamics	4/09-4/11	$410,000
SFAz	Optimizing Multidimensional Time Series Classification: Spatio-Temporal Data Mining in Epileptic Brain Dynamics	7/08-7/09	$267,000
NSF	Closed-loop control of brain dynamics in epilepsy	4/06-3/09	$435,000
Research Epilepsy Foundation of America	Seizure Control by Closed Loop Feedback in a Rat Model of Chronic Temporal lobe Epilepsy	7/05-6/06	$100,000
NINDS R01	On-line Real-Time Seizure Prediction	7/05-6/10	$2,523,000
NIH RO1	Bioengineering Epilepsy: Dynamical Analysis of Scalp EEG	4/04-4/09	$3,670,000
NIH BRP R01 NS39687	Bioengineering Research Partnership for Brain Dynamics	5/01-5/06	$4,600,000
DARPA MDA972-00-1	Advanced Neural Implants and Control	7/00-7/03	$6,249,999
VA Merit Grant	Dynamical mechanisms initiating temporal lobe seizures	4/97-4/00	$195,600
NIH-NINDS R01 NS31451-05	Dynamical studies in temporal and frontal lobe epilepsy	6/97-6/01	$715,974
NIH-NINDS R01 NS31451	Dynamical studies in temporal lobe epilepsy	8/93-8/97	$539,466

OTHER ONGOING RESEARCH

i) Epileptic Brain

Goal: Further development of the nonlinear dynamical and global optimization techniques to completely characterize the brain's spatiotemporal dynamics during the transition to epileptic seizures in humans and rodent models: i) at the macroscopic (EEG and field potential) level; ii) at the microscopic (AP trains) level using in vitro hippocampal slices and measuring individual firing of neurons under various conditions (e.g. low-Ca^{2+}). This research will involve scientists from Basic Neuroscience, Clinical Neurophysiology and Signal Processing (including pattern recognition, system modeling and optimization), Circuitry and Instrumentation.

Research Approach:
a) Identification of seizure precursors in "status epilepticus" (in collaboration with Dr. Treiman at Barrow Neurological Institute (BNI) (animal and human models) and hyperthermia induced febrile seizures (in collaboration with Dr. Wu at BNI (hippocampal slices).
b) Modeling of the epileptic transition via nonlinear chaotic models and biologically-plausible neural networks of the brain that exhibit "seizures". Candidate models are: i) Silnikov coupled attractors; ii) Kohonen networks; iii) generalized feedforward neural network topologies and iv) recurrent neural network topologies. This branch of the research has already resulted to a Ph.D. dissertation (Niranjan Chakravarthy) and several publications, one noteworthy on "Homeostasis of brain dynamics".

c) Control of the epileptic transition (in collaboration with Dr. Tsakalis at ASU). We have found that seizures represent a phase transition in a nonlinear, chaotic system. Therefore, properly timed (early in the preictal state), low-intensity perturbations may be the most effective means in averting an impending seizure. The hypothesis is that such interventions could stop the epileptogenic focus from entraining critical cortical or subcortical sites, a process that we now know progressively leads into a seizure. Results will be produced from: i) control simulation studies with the models developed in (b); ii) stimulation control studies in animal models. The effects of intensity, frequency, duration, and onset time of various modes of neural stimulation (e.g. vagus nerve, thalamic or cortical stimulation) aimed at aborting an impending seizure will be tested. iii) stimulation control studies in humans. The first pre-clinical studies using the Cyberonics vagus nerve stimulator in epileptic rats have just started.

d) Design and development of a microdevice to intervene and abort epileptic seizures in real time. Such a device could be implanted subcutaneously and used to trigger the release of an anticonvulsant drug or an electric/magnetic stimulator in time to abort an impending seizure. Such devices may be practical in the near future. For example, chronically implanted thalamic stimulators are currently in use for treating the tremor of Parkinson's disease. A vagus nerve stimulator (VNS) is being used to reduce the frequency of seizures in epilepsy. The (VNS) is implanted subcutaneously on the chest and a wire is extended to the vagus nerve in the neck. The stimulator is programmed to generate an electrical stimulus intermittently at a fixed intensity, rate, and duration. The stimulation parameters have been set empirically, with no theoretical basis. Based on our findings, we expect that vagus nerve stimulation delivered at a critical time during the preictal transition, would be more effective in preventing seizures. Such devices might be particularly useful for patients whose seizures cannot be controlled with medication and are not candidates for removal of the epileptogenic focus. **This research is currently supported by the following grant:**

1. **Characterization of Novel Vagus Nerve Stimulation (VNS) Parameters' Efficacy, Based on Desynchronization of Brain Dynamics, in Open and Closed-Loop Configurations: A Study in an Animal Model of Chronic Epilepsy** (06/10-06/12) Cyberonics Inc.; Total amount: $760,000.

ii) Normal Brain

Normal brain does not experience seizures without external stimulation. According to our findings from the epileptic brain, and since seizures do not occur spontaneously in the normal brain, the normal brain itself should be able to reset any observed entrainment of dynamics, in a short time and without any seizure occurrences. It is very reasonable to assume that communication inside the normal brain occurs via instantaneous dynamical synchronization (or dynamical entrainment) of pertinent cortical sites (however, this synchronization should last for a very short time so that the involved sites can then participate in other tasks). We hypothesize that this can occur only if the feedback circuits for desynchronization of dynamics of the involved sites do operate properly. We plan experiments with normal subjects to test exactly this hypothesis. We expect that analysis of their EEG would reveal entrainment of their brain dynamics accompanied by fast disentrainment. Taken together, these results would signify that the degree of resetting for the normal brain would be much higher than the epileptic one. These experiments have started in the Arts Media and Engineering Lab with students as normal subjects.

iii) Other Biodynamical Disorders

Brain dynamical disorders other than epilepsy exist and may also be characterized by intermittent neurophysiologic transitions from normal to abnormal states (e.g. strokes, narcolepsy, migraine attacks, abrupt changes in anesthesia, depression). Also, catastrophic cardiovascular transitions (e.g. heart attacks, fibrillation attacks) exist, and every year about 1.1 million Americans suffer a heart attack, out of which 460,000 are fatal. In both areas, the overall goal will be to explore the utility of similar approaches

to the ones we have used in epilepsy to further characterize and understand the dynamical mechanisms underlying the involved dynamical transitions, and to possibly develop and test novel and more effective approaches than the existing ones in the diagnostic, prediction and treatment (intervention / control) domain.

iv) Research in Genomic Signal Processing

This has been an emerging field for signal processing. We expect that insights and advanced techniques developed from processing of brain signals would be helpful in the analysis of the DNA signals. Towards this goal, since 2002, I started a collaboration with Dr. Spanias (Electrical Engineering, ASU) and TGen Inc. (Phoenix) for the application of modern signal processing techniques to the identification of exons and introns of genes in long DNA sequences from prokaryotic and eukaryotic cells. To date, a Masters thesis, a conference proceedings' paper, and a journal paper are the initial results of this collaboration (see N. Chakravarthy et al. in my CV). Entropy-based methods from information theory and nonlinear dynamics (Kolmogorov entropy, Transfer entropy, Lyapunov exponents and Cross-Lyapunov exponents), that are used to characterize our EEG signals (see Veeramani et al., Sabesan et al. in my CV), will be implemented to provide enhanced similarity measures between different DNA segments. Last, but not least, we have started working with Phoenix Children's Hospital and TGen (Translational Genomics Institute) towards a project on autism and epilepsy. We expect to correlate our findings from the EEG dynamics of autistic brain (e.g. seizure susceptibility) to the DNA abnormalities related to epilepsy found by genome analysis in these patients.

v) Research in the Rehabilitation of Stroke

Patients who suffer strokes and Parkinson's disease must undergo extensive physical therapy to relearn use of their limbs. To assist patients with their physical therapy a cutting-edge computerized Mixed Reality Rehabilitation system is utilized in conjunction with recording and analysis of EEG from the subject's brain for objective evaluation of the therapy and to propose future improvements in the therapy itself. Patients engage with audiovisual scenes, enabling them to practice physical movements that expedite their recoveries. They are positioned in front of a video screen and a set of sound speakers. Sensory equipment tracks their movements in real time and connects them to interactive images and sounds. For instance, patients learn to move their arms efficiently to make puzzle-like images converge on the screen. The image convergence is accompanied by an interactive music composition that helps patients improve the timing of their movement. The system's digital and physical aspects are algorithmically adapted to each individual patient's needs and progress. The future goal is to get the Mixed Reality Rehabilitation system into an adaptable, portable low-cost platform that patients can use in their homes. The home system will give the patients freedom to continue their rehabilitation training on their own on a daily basis, between sessions with trained medical professionals. Trained professionals also will be able to remotely monitor a patient's work with the home system. This can help reduce the number of trips a patient needs to take to a hospital for physical therapy. Not all patients have ready access or transportation to rehabilitation facilities at hospitals, clinics and medical centers to help them recover quickly. This research is at the leading edge of today's trend of employing virtual-reality technology in medical rehabilitation **and is currently supported by the following grant:**

1. **NSF Integrative Graduate Education and Research Traineeship Program (IGERT) on Experiential Media: Analysis of EEG for evaluation of rehabilitation in stroke patients**. $3,000,000 (09/05-09/12)

vi) Research in Post-Traumatic Brain Injury

A great percentage of patients who have suffered severe traumatic brain injury (TBI) develop epilepsy over time. The diagnosis of such a possibility beforehand is extremely difficult and usually delays the treatment with anti-epileptic drug therapy for a long time, probably enough to render it ineffective. Based

on nonlinear dynamical analysis of EEG, we have developed specific measures of seizure susceptibility that we will apply to the EEG recorded regularly from patients and rodents after TBI. These measures will be used to predict the development of post-traumatic epilepsy in specific individuals. Identification of those candidates long before the appearance of any clinical symptoms will allow for a timely intervention and treatment, and probably early seizure control and therapy. **This research is supported by the following DoD grant:**

1. **A new quantitative EEG technique for prediction of post-traumatic epilepsy (PTE) in individual subjects after traumatic brain injury (TBI)** (10/10-04/13) (Dept. of Defense - Concept grant; PI: David Treiman; Direct cost: $300,000)

INFRASTRUCTURE: BRAIN DYNAMICS LABORATORY (BDL)

Goal: I developed this Laboratory at ASU 10 years ago as a research Lab for investigations in the dynamics of signals (electrical or magnetic) recorded from the surface or interior of the human and animal brain, as well as from simulations of coupled, spatially extended physical systems (e.g. nonlinear oscillators). We have so far been particularly successful in the prediction and control of epileptic seizures, as well as very instrumental in the development of novel measures of information transfer in the brain for localization of abnormal brain activity (see press reports and publications).

Mathematical and Technical Tools:
- Mathematical analysis of brain electrical and magnetic activity within the framework of nonlinear spatiotemporal dynamics (Individual Lyapunov exponents, Cross-Lyapunov exponents, Transfer of Entropy, dynamical coupling/entrainment)
- Use of Global Optimization techniques in signal processing. Recent application of such methods to EEG analysis has resulted to a deeper understanding and improvement of epileptogenic focus localization and seizure prediction.
- Theory of chaos for strongly coupled and spatially distributed mathematical, physical and biological systems (e.g. coupled nonlinear maps, coupled laser arrays and networks of neurons respectively). Identification of the critical parameters and controllability of the phase transitions of these systems.
- Development of fast digital signal processing algorithms for real time estimation of indices of chaoticity and complexity of complex signals.
- Advanced multi-dimensional digital signal processing techniques for analysis of nonstationary signals and images (e.g. Time-Frequency and Wavelet transforms, Kalman filtering, KL transform, Independent Component Analysis / Blind Source Decomposition).
- Analysis of single-trial evoked potentials and event responses of the nervous system to visual, auditory, electrical and mechanical stimuli at the macroscopic and microscopic level. Issue of nonstationarity
- Design of biomedical (implanted or portable) devices (BioMEMS) for: a) measurement, b) amplification, c) analysis of biological and clinical signals of interest (e.g. EEG, MEG, MRI, ultrasound) and d) control and intervention for therapeutic purposes (e.g. via electromagnetic stimulators).

Equipment: The Laboratory physically occupies an area of 1,400 sqft. It is divided into two parts, one third for scalp EEG recordings and the rest for office space and mathematical analysis of signals. The recording function is supported by two portable Neuroscan EEG/EP machines of 32 channels each, with 0-20KHz per channel sampling rate capability, also capable to work in an fMRI environment. The analysis function is supported by 12 state-of-the-art computer stations connected in a LAN network, protected by a firewall, and connected to the outside world through high speed internet connections. Two color laser printers, 3 regular laser printers, server, web cameras, CD burners and scanners, fax machine, copier and three telephone lines are among the available peripherals devices. Access to ASU's high speed computing facilities and storage is in place.

Personnel: Currently 1 Research Scientist, 5 PhD graduate students, 2 MS graduate students and 4 undergraduate students from the departments of Electrical Engineering and Bioengineering.
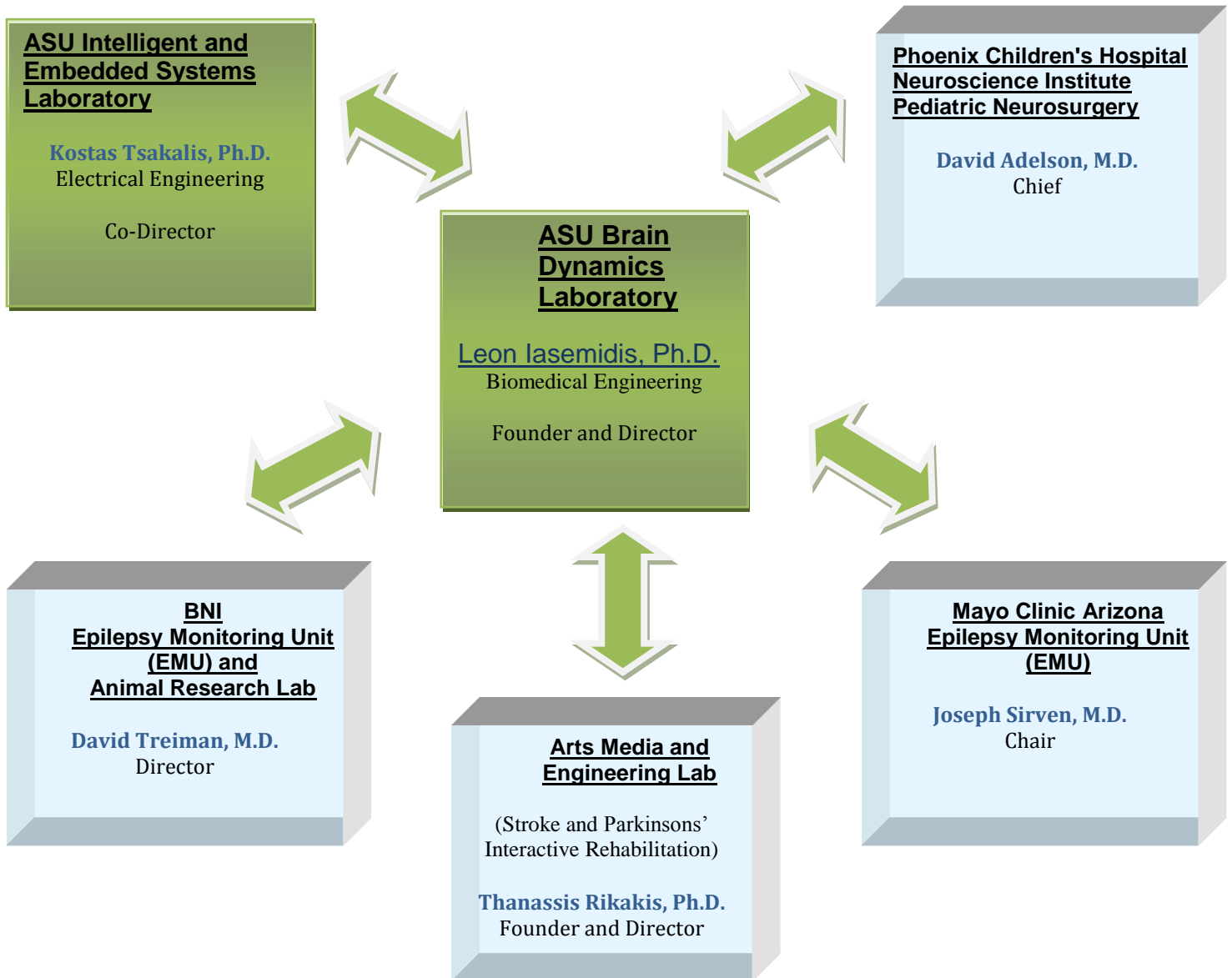
Prof. Iasemidis' Local Collaborators

ASU Intelligent and Embedded Systems Laboratory

Kostas Tsakalis, Ph.D.
Electrical Engineering

Co-Director

Phoenix Children's Hospital Neuroscience Institute Pediatric Neurosurgery

David Adelson, M.D.
Chief

ASU Brain Dynamics Laboratory

Leon Iasemidis, Ph.D.
Biomedical Engineering

Founder and Director

BNI Epilepsy Monitoring Unit (EMU) and Animal Research Lab

David Treiman, M.D.
Director

Arts Media and Engineering Lab

(Stroke and Parkinsons' Interactive Rehabilitation)

Thanassis Rikakis, Ph.D.
Founder and Director

Mayo Clinic Arizona Epilepsy Monitoring Unit (EMU)

Joseph Sirven, M.D.
Chair

Figure 1: Diagram for Collaborative Relations of BDL with entities in the valley

➢ **ASU Brain Dynamics Laboratory (BDL) (Dr. Iasemidis, Founder and Director)**

This Laboratory was developed 10 years ago as a research (recording and computational) facility for investigations into the dynamics of signals (electrical or magnetic) recorded from the surface or interior of the human and animal brain. The computational algorithms used toward this goal include conventional signal processing techniques and software (ARMA and linear filters, principal components, time-frequency and wavelet transforms), as well as innovative ones (nonlinear modeling, nonlinear measures of stability and complexity). MATLAB, Mathematica, MatCad, Labview, C++, visual C, Fortran are the programming languages currently used. The Lab has so far been particularly successful in the modeling

and prediction of epileptic seizures, as well as in the development of novel measures of nonlinear dynamics to quantify and decode the information transfer inside the brain. The Lab has dedicated powerful computing facilities with ten 2 to 3GHz computer stations, running Windows XP and Linux in LAN configuration, with ultra-fast Internet connection and protected by firewall. Laplink Software gives members of the lab the ability to dial-in to a Workstation, and work from remote locations The Lab extends to a 1,256 sqft facility with conference and reception rooms, 12 computer stations, 1 scanner, 1 digital camera, 1 copy machine, 2 colored laser printers, back up CD burners and tape drivers and large data storage units, an EEG recording room and two portable NEUROSCAN 32 channel EEG machines (0-20KHz per channel sampling rate capability, capable to work in an MRI environment). High performance clustering (HPC) service is rented from the ASU's HPC facility. The Lab currently supports 2 undergraduate students, 3 graduate students and 1 post-Doc fellow, and physically is located in the center of the Arizona State University central campus (next to the Nobles Engineering Library and the ASU. The Brain Dynamics Lab collaborates with key national and international players. A detailed list of these players is provided above. This list currently includes investigators at Harvard Medical School, MIT, Stanford U, U Rhode Island, Rutgers U, Holland, Germany, Norway, Poland, and Greece. The Founder and Director of this laboratory is Dr. Iasemidis.
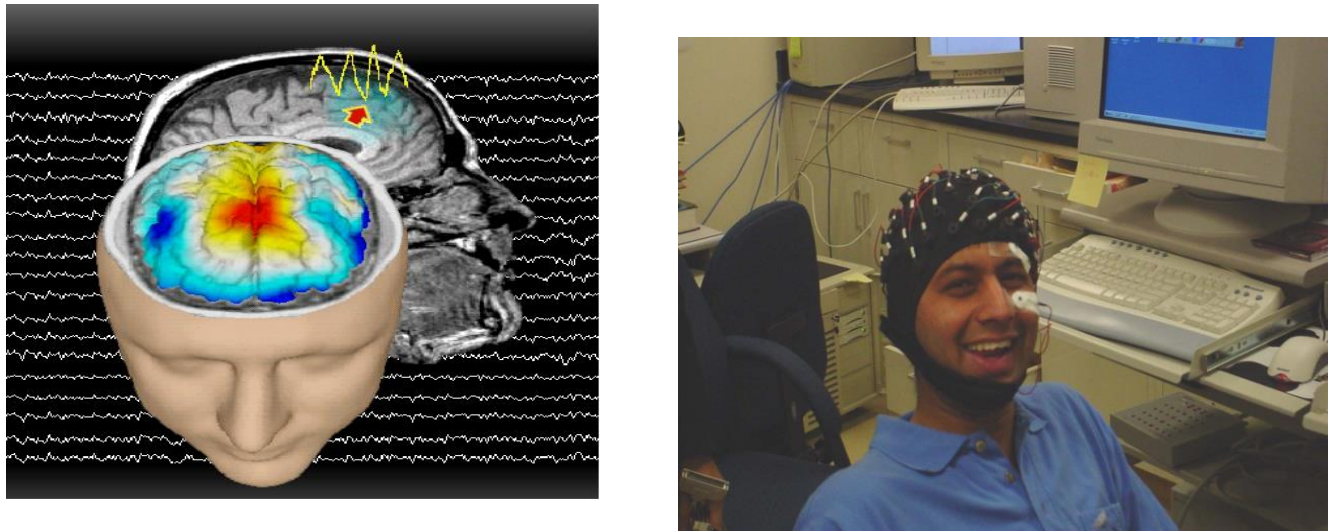

Figure 2: (a) EEG Recording and Analysis at BDL. (b) A happy graduate student at BDL.

> **ASU Intelligent and Embedded Systems Laboratory (Dr. K. Tsakalis, Co-Founder and Co-Director)**

The Intelligent and Embedded Systems Laboratory (IESL) is located on the 3rd floor of the Goldwater Building, with approximately 8,000 square feet of contiguous space for faculty, staff, and graduate offices, a state-of-the-art conference/media room, and large laboratory spaces. Three major laboratories are included: 1) a Control Systems Lab dedicated to teaching undergraduate and graduate students on the subject of feedback systems, signals and systems, and rapid prototyping using embedded systems; 2) a research Lab dedicated to state-of-the-art research on Machine Learning and Intelligent Systems; and 3) a computer Lab that consists of many high end PC servers and a Unix Enterprise4500 server, dedicated for Applied Computational research purposes. Dr. Tsakalis is the Co-Founder and Co-Director of this laboratory.
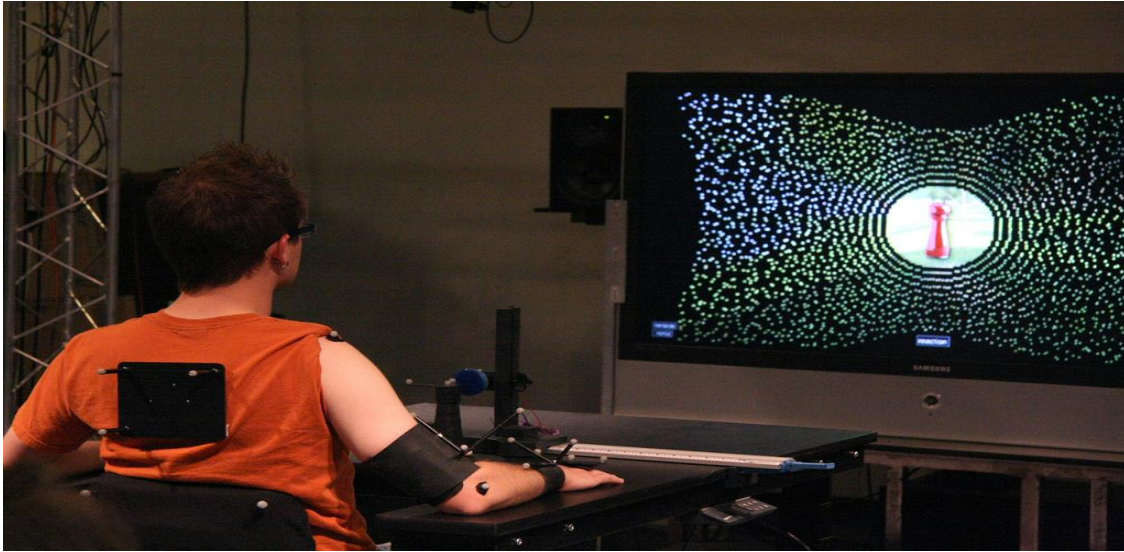
➢ **ASU Arts Media and Engineering Laboratory (Dr. Rikakis, Founder and Director)**

The Motion Analysis Lab/Intelligent Stage is a research lab and performance space dedicated to motion analysis and interactive, multimodal feedback development. The lab has two sections, each with two independent high end and standard motion-capture systems. The facility has sound and projection systems, lighting, and a pressure-sensitive floor developed at the School of Arts, Media and Engineering that is integrated to the motion-capture system (in partnership with Motion Analysis Corporation). The lab is part of the Interdisciplinary Research Environment for the Motion Analysis (IREMA) initiative, which offers a unique and powerful palette of perspectives to address existing research questions in motion capture and analysis. IREMA also helps create new approaches and tools, and identify new areas of inquiry. The latest addition to the Lab are two portable EEG machines from the Brain Dynamics Lab. They are used to simultaneously record scalp EEG from the subjects undergoing motion analysis. This initiative was awarded an NSF infrastructure grant in 2005, which allowed for its continued expansion. (http://ame.asu.edu/facilities/)

➢ **BNI Epilepsy Center (Clinical Facility and Research Labs) (Drs. D. Treiman and N. Wang)**

The Epilepsy Center at Barrow Neurological Institute (St. Joseph Hospital) offers a comprehensive program for the diagnosis and treatment of children and adults with epilepsy. In addition, the Epilepsy Center manages special populations of people with epilepsy, including patients with refractory epilepsy, elderly patients, and pregnant women. Every year the Epilepsy Center evaluates and treats thousands of people with epilepsy and seizure disorders from the US and around the world. The highly experienced Barrow epilepsy team includes neurologists, neurosurgeons, neuropsychologists, neuroscience nurses, and clinical and basic researchers who focus exclusively on epilepsy and seizure disorders. Some of Barrow's neurologists and other clinical staff specialize in treating infants and children, while others specialize in treating only adults. Barrow is recognized as a leader in the development of new epilepsy-related treatments and surgical procedures, making it one of the foremost epilepsy programs in the United States. The U. S. News & World Report named Barrow Neurological Institute (BNI) at St. Joseph's Hospital and Medical Center (SJHMC) as one of the top 10 hospitals for neurology and neurosurgery in 2006. The BNI Epilepsy Program faculty at St. Joseph's Hospital and Medical Center (SJHMC) in Phoenix, AZ consists of nine clinical epileptologists (five adult, four pediatric) and two experimental epileptologists. There are 180 – 200 outpatient visits each week in the adult epilepsy clinic and a similar number in the pediatric epilepsy clinic.

BNI Clinical Neurophysiology and EMU
The Clinical Neurophysiology unit at SJHMC has a total of 24 EEG technologists, 16 of whom are ABRET certified. The unit has eight new Nihon-Kohden EEG machines (sampling frequency of up to 1 kHz, Low filter cutoff up to 159 Hz (-6dB/oct), High filter cutoff up to 300 Hz (-18dB/oct), and up to 199 channels for recording, and the capacity to simultaneously record five prolonged outpatient EEGs. Approximately 5000 EEGs and 250 evoked potentials are recorded annually. In addition, the clinical neurophysiology unit has "Stat" EEG capability with 24/7 on-call neurophysiologist and EEG technologist. The epilepsy monitoring unit (EMU) is a 15 bed unit, with separate pediatric EMU, and has approximately 600 epilepsy admissions annually. The average hospital stay for patients in the EMU ranges between four and seven days. The EMU are open 24 hours a day, seven days a week. These monitoring units are hospital-based, so that medication can be reduced if necessary to record a seizure. EEGs are recorded and subsequently downloaded to a central server for permanent secure storage.

BNI Data Collection
A review of the Barrow Neurological Institute EEG database, which records all patients' ectroencephalographic findings, was recently performed for a period of 14 months, from June 1, 2007 through September 31, 2008. EEG records that demonstrated definitive SE were identified and the electronic medical records were reviewed for correlation with their hospital admission records. Data abstracted included demographic variables such as age, length of stay, medications used for treatment and 30- and 60-day mortality rates. Etiology of SE was also determined. Over this 14 month period of time, 36 unique patient (adult and pediatric) admissions for status epilepticus were identified and confirmed. The 36 patients included 66% females (24 female, 12 male) with an average age of 49 years (range between 1 and 84 years of age). The average length of stay for SE patients was 8.2 days with a range between 1 and 30 days. Sixteen of the total patients were either admitted or transferred to BNI with SE, while the remainder were admitted for other reasons and developed SE during their hospital admissions. The Epilepsy Monitoring Unit also had patients who developed SE during their presurgical evaluation, accounting for 3 of the status cases. Twenty eight of the 36 patients required more than two medications to manage their status epilepticus and therefore were deemed refractory. The overall 30-day mortality was 50% and 60-day mortality was 55%. Long-term EEG will be recorded with scalp and depth electrodes from epileptic patients with focal epilepsy (e.g. temporal, frontal, occipital lobe) admitted to the Epilepsy Monitoring Unit (EMU) at BNI, developed SE and enrolled in this study. Also, scalp EEG will be recorded from epileptic patients with Status Epilepticus (SE) admitted to the Emergency Room (ER) and/or the Intensive Care Unit (ICU) for treatment and monitoring of their SE.

BNI Animal Research Lab
The facility includes three dedicated laboratories: a) The monitoring lab is a faraday-shielded room (300 sq ft) used for acute and chronic video/EEG monitoring. b) The surgery lab (150 sq ft) is dedicated for small animal surgery. c) The third dedicated lab is the animal behavioral testing lab (120 sq ft.). These three labs are in close proximity to each other and the vivarium. A 600 sq. ft. biochemistry lab is built and houses HPLC equipment for AED assays.
The monitoring lab contains two recently purchased Grass-Telefactor Beehive® Millennium long-term EEG monitoring stations, each capable of recording up to 128 channels of EEG. Currently there are two 32-Channel CTE amplifiers configured to record 64 channels of EEG chronically on one of the stations and one 32-Channel CTE amplifier configured to record 32 channels of EEG acutely. The monitoring lab also contains the Rat Epilepsy Monitoring Unit (Rat EMU) that allows for individual housing and free range of motion video/EEG monitoring for up to 20 rats. The Rat EMU consists of 20 low light video cameras, two video multiplexers, 20 commutator wiring systems and 20 Plexiglas cages. A Pentium IV data analysis computer also resides in this room for EEG review and processing.

Figure 3. Rat EMU: Shows low light CCTV video camera multiplexed system, Grass-Telefactor Beehive® Millennium EEG monitoring stations, Plexiglas cages and commutator wiring systems.

The surgery lab is dedicated to the preparation and implantation of electrode and connector systems in small animals. It is equipped with four Kopf stereotaxic frames and a full array of surgical instruments. An area within the surgery lab is also set aside for the construction of electrode and head connector systems that includes a soldering station and electrical tools.

The behavioral testing room is dedicated to testing small animals in a Morris Water Maze. It includes a five-foot diameter circular water tank with video camera mounted overhead and uniform lighting. The video is captured directly to computer through a Real Networks Osprey 210 video capture board.
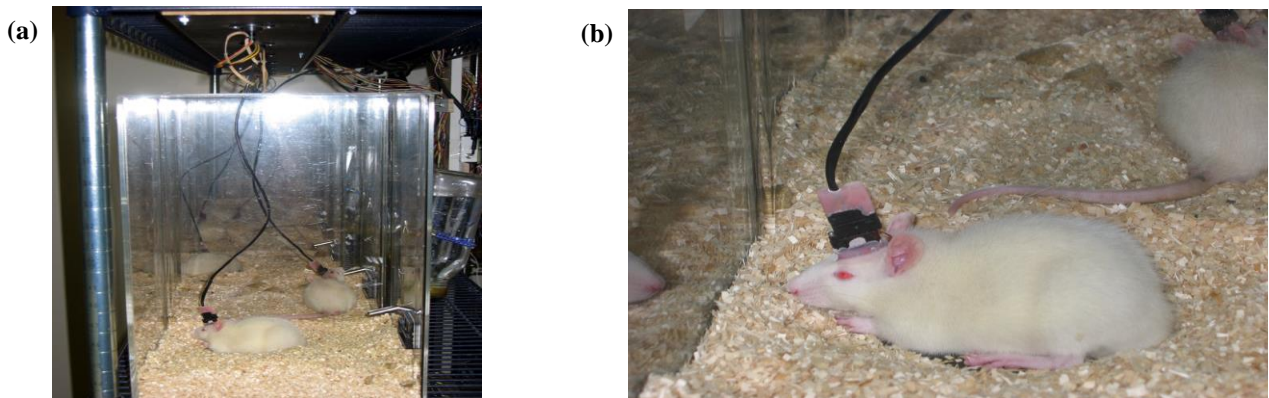
(a)   (b)

Figure 4. Rat EMU: (a) Plexiglass cage with commutator wiring systems allowing free range of motion and free access to food and water within the cage during EEG monitoring. (b) Close-up view of rat head-piece connected to commutator for EEG recording

A five-client 1-Terabyte data server was recently purchased that allows the networking and data storage of all the computers and Grass-Telefactor EEG machines. This allows the EEG data to be accessed for analysis and review from any computer within the three laboratories.

Fully equipped and accredited vivarium, with ample space to house rats prior to surgery and monitoring. Vivarium is directed by a veterinarian, who is available for technical advice.

We have access to a nearby histology laboratory which is fully equipped with cryostat capability, staining equipment, and microscopes for review of brain sections. Dr. Treiman is the Founder and Director of this Laboratory.

➢ **Mayo Clinic Epilepsy Division** (**Dr. J. Sirven, Chief**)

The Mayo Epilepsy Clinic in Scottsdale and Mayo Hospital, Phoenix campus, Arizona offer patients with epilepsy a wide array of services provided by an expert staff of neurologists, neurosurgeons and psychologists dedicated to the latest treatment options and research. The Mayo Clinic offers complete outpatient care using both standard and investigational drugs, a full range of diagnostic services including a 6-bed video EEG monitoring unit (EMU) at Mayo Clinic hospital, the latest brain imaging techniques, neuropsychological evaluations and community education. There are 4 portable EEG machines at the Mayo Clinic Outpatient laboratory and 6 portable EEG machines at the Mayo Hospital. Four EEG technologists and one instrumentation engineer are in the Hospital side, while four EEG technologists are in the Clinic side of the campus. The majority of epileptic seizures are successfully controlled by medications. Patients with seizures can benefit from an array of anti-seizure medications. In addition, the Epilepsy Clinic also offers Vagal nerve stimulation, epilepsy surgery, ketogenic diet planning and hormone therapy and are currently involved in research protocols for responsive neurostimulation via direct cortical stimulation.

The Epilepsy faculty at Mayo Clinic consists of **3** clinical epileptologists on the Phoenix campus and 1 combined electroencephalographer and movement physiologist. Based on the enrollment figures over the last four years, an average of 200 to 250 adult patients are admitted into EMU each year for clinical assessment of their neurological condition (phase I – scalp EEG). Around 30% of these patients are diagnosed with some form of a non-epileptic manifestation (e.g. pseudoseizures). From the remaining 70% of the patients, only 15% undergo phase II (intracranial EEG) recordings for pre-surgical evaluation and 80% of them undergo surgery for focus ablation. In addition, the hospital gets at least one case of life-threatening emergency such as status epilepticus (SE), encephalopathies etc per month (for SE it is more like 1 patient bimonthly). Thus, there should be no difficulty in identifying the 72 EMU patients and 18 SE patients over the span of 3 years we propose in this study.

Mayo Epilepsy Monitoring Unit

The EMU at Mayo Clinic, Phoenix campus, is a 6-bed facility of 4000 square footage, attended by 3 neurologists, 20 nurses, 4 technologists and 1 engineer. The average hospital stay for patients in the EEG monitoring unit ranges from four to seven days. The EEG monitoring units are open 24 hours a day, seven days a week. The monitoring units are hospital-based, so that medication can be reduced if necessary to record a seizure. The laboratory has six new Nihon-Kohden EEG machines (sampling frequency of up to 1 kHz, Low filter cutoff up to 159 Hz (-6dB/oct), High filter cutoff up to 300 Hz (-18dB/oct), and up to 199 channels for recording) that have the capacity to simultaneously record six prolonged EEGs from patients. In addition, the unit has two 4 new ambulatory systems with the capacity to simultaneously record prolonged EEGs in an outpatient setting (ER, ICU, Mayo Clinic at Scottsdale). EEGs are downloaded to a central server for permanent secure storage.

Figure 5. Mayo's EMU

Mayo Emergency Room and Intensive Care Unit

Patients with acute seizures are admitted to Mayo Clinic Hospital via the Mayo Clinic Hospital emergency room. In the emergency room, the patient is stabilized if there are concerns about respiratory or circulatory compromise. Patients often spend anywhere from 1 hour to 6 hours in the ER depending on the clinical circumstance. If the patient is stabilized, the individual may be transferred to the epilepsy monitoring unit for further care. If the patient cannot be stabilized, they are transferred to the Intensive care unit (ICU). Patients must stay in the ICU until they are stable for transfer to the epilepsy monitoring unit. Typically, this occurs when the patient no longer requires mechanically assisted ventilation or other circulatory support.

Mayo Clinic Data Collection

A review of the Mayo Clinic Arizona EEG database, which records all patients' electroencephalographic findings, was recently performed for the period from January 1, 2005 through December 31, 2007. EEG records that demonstrated definitive status epilepticus (SE) were identified and the electronic medical records were reviewed for correlation with their hospital admission records. Data abstracted included demographic variables such as age, length of stay, medications used for treatment and 30- and 60-day mortality rates. Etiology of SE was also determined. Over this 3 year period of time, 43 unique patient admissions for SE were identified and confirmed. The 43 patients included 81% females (35 female, 8 male) with an average age of 56 years (range between 12 and 84 years of age). Around 47% of these patients were over the age of 60. The average length of stay for status was 11.8 days with a range between 1 and 59 days. Twenty-one (49%) of the total patients were either admitted or transferred to Mayo Clinic Arizona with SE, while the remainder were admitted for other reasons and developed SE during their hospital admissions. The Epilepsy Monitoring Unit also had patients who developed SE, accounting for 3 of the total SE cases. Twenty-six of the 43 patients required more than two medications to manage their status epilepticus and therefore were deemed refractory. The overall 30-day mortality was 42% and 60-day mortality was 44%. In light of the undergoing expansion of our neurology resources, we expect that the target of 60 SE patients over 4 years set in this study for the Mayo site will be easily reached. Long-term EEG will be recorded with scalp or depth electrodes from epileptic patients with SE. Only patients in phase II at EMU, who develop SE while undergoing presurgical evaluation for localization of the epileptogenic focus, may have depth electrodes. Scalp EEG will be recorded from epileptic patients with SE admitted to the Emergency Room (ER) and/or the Intensive Care Unit (ICU) for treatment and long-term monitoring of their SE respectively.

Mayo Clinic Standard EEG Recording procedures
The long-term scalp and depth EEG recordings are part of the clinically diagnostic evaluation of the patients admitted to EMU (phase I and phase II patients) whereas, only long-term scalp EEG is typically recorded from patients admitted to the ER and/or ICU. Patients who are admitted to the EMU undergo evaluation for potential epilepsy surgery. During this time, patients have their antiseizure medications tapered in order to provoke and record their typical seizures. A minimum number of 4 seizures is recorded in order to insure adequate information for anatomical localization of the epileptogenic focus. Once 4 seizures are recorded, the patient's medication is restored until therapeutic serum levels of the antiepileptic drug are achieved. The average hospital stay for patients in the EEG monitoring unit ranges from four to seven days. On the other hand, patients with acute seizures, such as SE, are admitted to Mayo Clinic Hospital via the Mayo Clinic Hospital emergency room. In the emergency room, the patient is first stabilized if there are concerns about respiratory or circulatory compromise. If the patient is stabilized, the individual may be transferred to the EMU for further care. If the patient cannot be stabilized, he/she is transferred to the intensive care unit (ICU). Patients must stay in the ICU until they are stable before they are transferred to the EMU. Typically, this occurs when the patient no longer requires mechanically assisted ventilation or other circulatory support. Per protocol, all patients with SE are monitored with 21 channels of EEG throughout the duration of the condition. EEG monitoring occurs in the ICU, ER and EMU. The EEG data are viewed several times throughout the day and formally dictated on a daily basis. The available EEG recording machines at Mayo Clinic are six new Nihon-Kohden Neurofax EEG-9100 and 9200 EEG machines (sampling frequency of up to 1 kHz, Low filter cutoff up to 159 Hz (-6dB/oct), high filter cutoff up to 300 Hz (-18dB/oct), and up to 199 channels for recording) that have the capacity to simultaneously record six prolonged EEGs from patients.

> ➢ **Phoenix Children's Hospital / Neuroscience Institute (Dr. D. Adelson, Chief)**

Laboratory: 5,000 square feet of laboratory space.
Clinical:
Phoenix Children's Hospital is a 325 bed facility. It is one of the top ten largest pediatric hospitals in the country. The expansion of the facility will expand the 5 bed pediatric epilepsy monitoring unit (EMU), to a 12 bed one, with XLTek EEG equipment to provide state-of-the-art continuous EEG monitoring. In addition, there is an outpatient EEG lab and advanced Neuro Imaging Center with MRI, FMRI, DTI, MRS, PET, SPECT capabilities. Dr. Adelson has ample office space at the Children's Neuroscience Institute at Phoenix Childrens' Hospital. He is supported by a full-time administrator, a full-time secretary and full-time research staff. The Institute has 10,000 square feet of office and clinic space. It will quadruple when the new hospital opens to include an EEG diagnostic center, neurodiagnostic center, gait analysis, and clinical research. Dr. David Adelson is the Director of the Neuroscience Institute, the PI of a multi-million multi-site brain trauma NIH grant, Fellow of the American College of Surgeons (FACS), Fellow of the American Academy of Pediatrics (FAAP) and the current President of the Congress of Neurological Surgeons.