IMAGINE going about your day doing normal, everyday activities. You work. You go home to relax. Cook dinner. Pet the dog. Perhaps watch a bit of television. Nice. Normal. Comfortable. The brain storm strikes without warning – a grand mal seizure. You black out and crumple to the floor. You stop breathing. Your body shudders and thrashes in a sequence of uncontrollable spasms. The spasms continue for agonizing moments. When the seizure subsides, you awake without any recollection. But you collapse exhausted and sore, feeling as if you had just staggered through a marathon.

MICHAEL HAGELBERG ILLUSTRATION

Forecasting Mind Storms

Epilepsy patients develop an insidious sense of dread from not knowing when their next seizure will strike. The storms in their minds are unpredictable; on any given day, blue skies become calamitous cloudbursts.

Many of the world's 50 million epilepsy sufferers live this daily fear. Powerless to control neither time nor place of their brain attacks, they must abandon thoughts of ever driving a car or earning a living as a firefighter, police officer, machine operator, or any other number of professions.

Leon Iasemidis wants to unravel the mysteries of these uncontrollable brain attacks. Iasemidis (pronounced Yah-si-me-dees), is a bioengineering professor at Arizona State University. His research group at the brain dynamics laboratory is the first in the world to accurately forecast epileptic seizures before they take place. The ASU engineer and his colleagues are on the cusp of developing treatments that may finally bring relief to the electrical storms in the epileptic mind.

Iasemidis was born in Athens, Greece, the ancient crucible of philosophy, democracy, and mythology. It is also where the term "epilepsy" originated, the cause of the illness assumed to be "delivered by the Gods."

After earning a degree in electrical engineering from the National Technical University of Athens in 1982, Iasemidis set his sights on the most complex biological signaling system known, the human brain. At the time, respectable programs for graduate studies in biomedical engineering had not been developed in Greece, so he headed to the University of Michigan to pursue a doctorate in biomedical engineering.

"I wanted to do something in research that was very challenging—to have my Ph.D. research lead to a discovery," says Iasemidis. When he began his graduate school project, physicians had already assembled a rich catalogue of the clinical symptoms and brain regions associated with epilepsy, yet the exact cause of the disease was still debated.

Scientists know quite a bit about the anatomy of the disease. Seizures are thought to begin in the limbic system and the area of the temporal lobes, Iasemidis says. The prevailing view holds that epilepsy results from an overexcitation in the electrical chatter from the brain's communication cells, called neurons. With a maze of over 100 billion individual neurons making up the brain, however, scientists weren't sure which path would lead to the source of the aberrant pulses that produce seizures.

One of the hallmarks in the diagnosis of epilepsy is a dramatic change in the shape of electroencephalographic (EEG) wave recordings. Physicians use the EEG as a means to listen to the jumbled conversations from hundreds of thousands of neurons. The readout on the EEG recording resembles the output on a heart monitor. Eating, reading, or dreaming each produce different patterns, or spikes, in the EEG. Doctors knew that rapid changes in the sharpness of the peaks and valleys produced by the EEG always accompanied the onset of a patient's seizure.

"I wanted to see if there was some kind of warning signal hidden in the EEG long before the seizure occurs," Iasemidis says. "No one had thought about this. Seizures were considered random and abrupt events."

Some epilepsy patients experience auras, a vague warning of an impending seizure that engages a variety of senses. Patients describe feeling light-headed, having a bad taste or smell, bright flashes of light and blurred vision, queasiness in their stomach, or an uncomfortable feeling of déjà vu, knowing that today will be a "seizure day."

Auras, however, vary from patient to patient. Only a small percentage of epilepsy patients will ever experience these feelings in connection with seizures, according to Iasemidis.

The conventional scientific wisdom concluded that Iasemidis' approach would never work. First, scientists believed the EEG recordings reflected random brain signals that could never be predictable. Second, they thought the change in the EEG was so abrupt during a seizure that one wouldn't be able to predict the event far enough in advance to provide any relief to the sufferer. In fact, when Iasemidis went to the literature to find papers to support his research project, he couldn't find any publications on the topic. He had to invent methods to carry out his research.

"Feasibility was up in the air," says Iasemidis. "It was a risky decision."

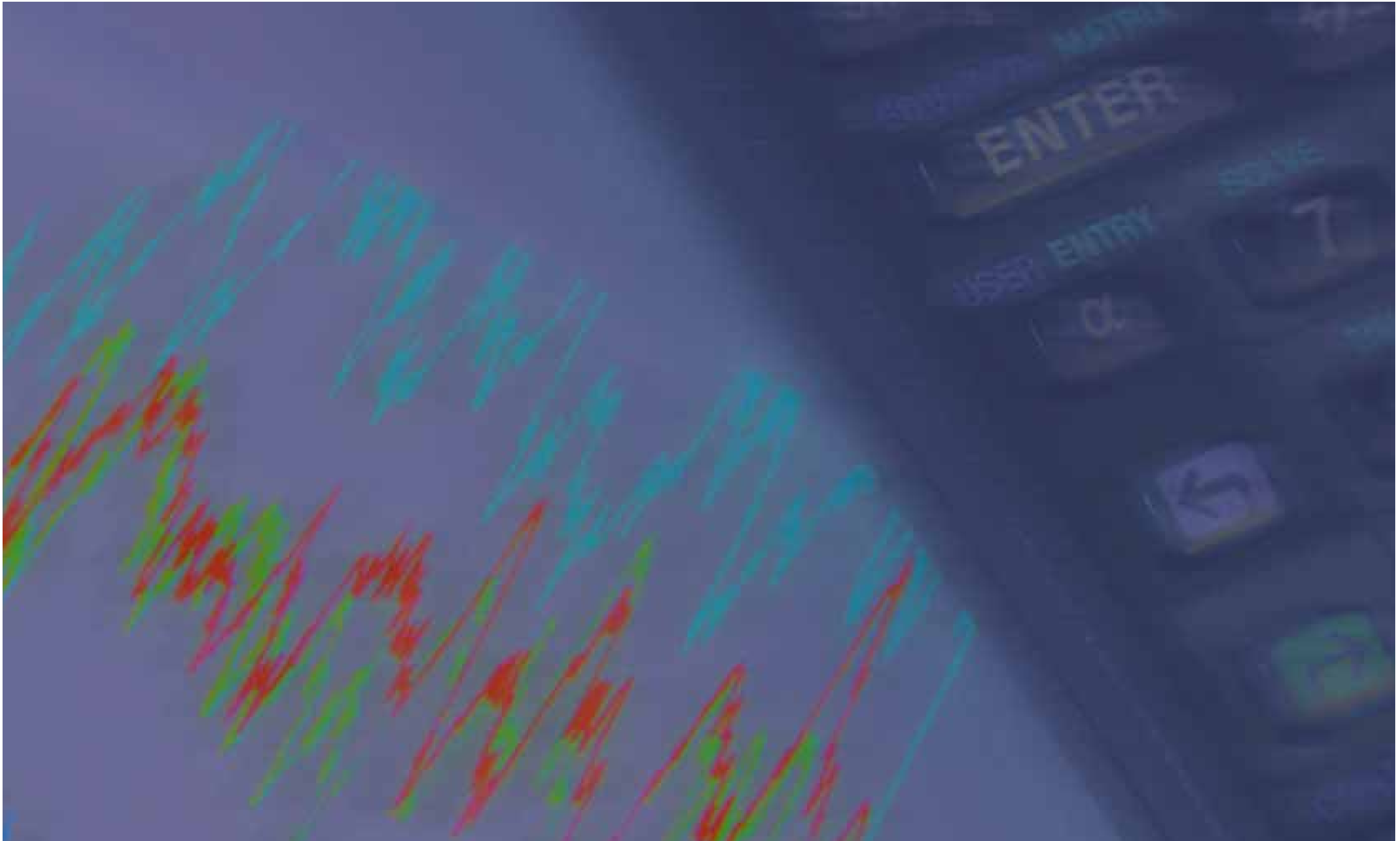
There was no shred of evidence to even hint that finding an early warning for seizures was a possibility. But Iasemidis had to play his hunch.

Iasemidis did his graduate work at the University of Michigan at great professional risk. But his decision to try would eventually make him the world leader in a new field he created.

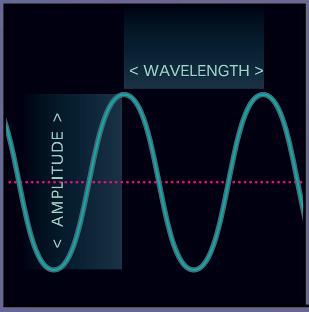
Professor William Williams, an electrical engineer, and Dr. J. Chris Sackellares, a neurologist, served as his dissertation advisors.

"As his advisor, I had no choice," says Sackellares. "Leon's combination of intelligence, confidence, dedication, and sheer will power combined to create an unstoppable force of nature. He was truly driven." >>

by Joe Caspermeyer

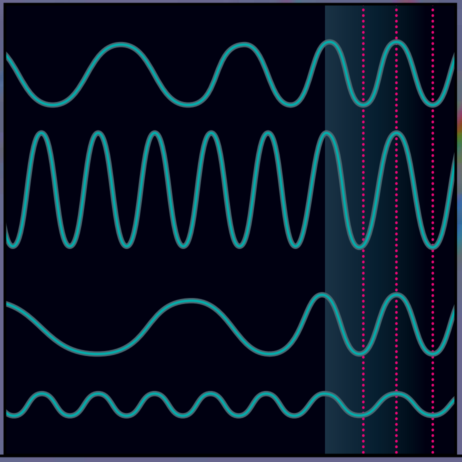


WAVE



Engineers use similar mathematics to describe any cyclic action, such as waves of the ocean or the electrical fluctuations of the human brain. Basic wave characteristics include amplitude, or the strength of the wave activity, and frequency, the number of full wave cycles per unit time.

ENTRAINMENT



Researchers know that the human brain is full of electrical wave activity. Individual nerve cells in the brain are always active with rhythmic electro-chemical cycles. Groups of cells produce larger electric currents which are detected by electroencephalagraphs (EEG). Seizures occur when wave activities through large regions of brain become synchronized.

MULTIPLE DIMENSIONS

Entrainment can occur over time in one area of the brain or over time between different locations. Researchers try to detect correlations of activity in both time and space dimensions.

MICHAEL HAGELBERG ILLUSTRATION

“Feasibility was up in the air. It was a risky decision.”

Being the pioneer in a new field of research can drive any ambitious graduate student, but relying on intuition and no real data meant that there would be no funding sources from government grant agencies. Iasemidis had to support himself by teaching and doing other research on the side.

“There was no money for this research. It was a difficult time,” says Iasemidis.

“He had no one to help him,” Sackellares says. “I don’t think anyone really understood what Leon was doing. We had faith in him because he had aced all of his course work—always scoring at the top of his class on tests.”

Iasemidis held true to his hunch. He realized that if he did develop a reliable method to predict epileptic seizures, it would be the first significant breakthrough towards helping epileptic patients resulting from the application of engineering methods to medicine.To get started, Iasemidis needed a large and well-defined group of epilepsy patients with continuous EEG recordings to study. The largest groups were hospital patients afflicted with focal epilepsies, which are caused by an isolated region of the brain. That isolated region is called the focus.

Such patients are monitored around-the-clock with EEG recordings. If the area in the brain is small enough and not located in any vital cognitive regions, often, focal epilepsy patients are good candidates for surgical removal of the focus. They have good odds—about 60 to 70 percent—of being seizure-free after the surgery.

Before removing the focus, surgeons implant electrodes underneath the scalp and either on the surface or deep within the patient’s brain. They want to pinpoint the focus, the area of the brain responsible for the seizures.

Next, the surgeons attach grapevines of electrical sprouts to the patient’s scalp. “This array of electrodes functions like an antenna,” says Iasemidis.

The surgeons try to capture the signals produced from the focus of the seizure. Instead of moving through the air like a radio station signal broadcast to your home, the seizure signals must first pass through dense brain tissue before reaching the electrodes.

“That’s why most of the time this fails,” says Iasemidis. “But it gave me an idea. Forget about locating the focus, I thought. Let’s concentrate on the problem of the dynamics of the phenomenon. Let’s find a method that can actually predict when this transition to a seizure is going to happen.”

The ASU scientist poured over piles of EEG data, for years. But those years of work were not in vain.

Iasemidis and his colleagues developed a method that proved promising. He devised a means to measure the amount of chaos in the brain determined by a complex mathematical quantity called the Lyapunov exponent.

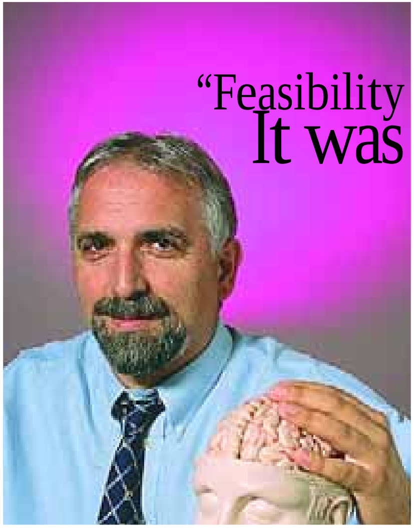
“In chaos theory, when the Lyapunov exponent becomes low, the system studied becomes less chaotic and more ordered,” says Iasemidis.

Iasemidis used this method to examine the patients with focal epilepsy seizures. When he did, he saw an emerging pattern.

At the moment a seizure begins, there is a rapid transition within the epileptic brain from chaos to order. Quite different than what a lay person might envision when hearing terms such as “brain storms” and “fire in the mind.”

Iasemidis looked even closer. In a process he calls dynamical entrainment, the ASU researcher saw that order begins long before the onset of a seizure. Starting from the region where the seizure initiates, the order then spreads rapidly throughout the brain.

The brain eventually becomes stuck, kind of like music played from a scratched CD in your stereo.



JOHN C. PHILLIPS PHOTO

LEON IASEMIDIS

“By measuring the degree of chaos over time, we were able to identify seizure susceptible periods, and to issue warnings when the brain becomes susceptible to a seizure,” Iasemidis explains.

Remarkably, after applying his new mathematical methods to five patients with focal epilepsy, he found that he could predict a seizure up to 85 minutes before the seizure occurred.

Iasemidis holds the first U.S. patent for this new forecasting ability. He hopes to reach an agreement with an EEG manufacturer to include his epilepsy warning system in their machines.

The ability to forecast seizures can go a long way toward improving the quality of life for people who suffer from epilepsy. By knowing up to an hour and a half ahead of time when the next seizure will occur, patients could be given drugs or an electric pulse to help minimize the severity of, or completely abort, an upcoming seizure.

Iasemidis is recognized by his peers as the worldwide leader in his field. Iasemidis and Sackellares, his former advisor and longtime collaborator, now at the University of Florida, have received more than $10 million in grants since 1993 to conduct their pioneering work.

Within the next two years, Iasemidis hopes to put his warning system into an implantable computer chip. When a seizure is looming, the chip will send out an alarm signal from the patient’s brain. The early warning will give doctors enough time to intervene with drugs and provide relief from the impending brain attack.

Iasemidis also envisions linking the chip to a brain stimulator device that would work like a heart pacemaker. When an attack is imminent, the device would send a small charge to the brain in order to reset its dynamics before the seizure occurs. “The idea is to control dynamical properties of the epileptic brain by stimulating the brain at just the right time and just the right way,” says Sackellares. One such device, called a vagal nerve stimulator, has already been used to shock nerves in the neck to relieve the suffering of some epilepsy patients.

For Iasemidis, the years of hard work are only the beginning. He plans to apply his patented chaos analysis to other brain disorders.

“This method is general enough to apply to any other system,” he says.

Iasemidis’ techniques could help medical researchers to better understand other brain disorders, such as migraine headaches, Parkinson’s disease, and stroke. They might even prove useful for predicting the impending chaos of the world’s number one killer, heart disease and heart attacks.

IASEMIDIS’ EPILEPSY RESEARCH IS SUPPORTED BY THE NATIONAL INSTITUTES OF HEALTH, THE VETERAN’S ADMINISTRATION, WHITAKER FOUNDATION, AND THE DEFENSE ADVANCED RESEARCH PROJECTS AGENCY. FOR MORE INFORMATION, CONTACT LEON IASEMIDIS, PH.D., BIOMEDICAL ENGINEERING, IRA A. FULTON SCHOOL OF ENGINEERING, 480.965.9134. SEND E-MAIL TO LEON.IASEMIDIS@ASU.EDU

Knowing the Beast

Chaos theory was a novel idea in the late 1980s. That was when Leon Iasemidis first began his work on a method to predict epileptic seizures. The ASU biomedical engineering professor was a doctoral student at the University of Michigan at the time. Scientists and engineers were just beginning to apply chaos theory to a variety of problems. “There were no ‘real world’ biological applications of chaos theory at that time,” says University of Florida neurologist J. Chris Sackellares, a former advisor and longtime collaborator with Iasemidis.

The human brain includes more than 100 billion neurons firing back and forth at different rates at different times. The brain represents perhaps the ultimate chaotic system. In the case of epileptic seizures, scientists say that chaos does not refer to a “random” event. A seizure may appear to be a random event, but it is not.

Chaos in this case is more like the behavior of the ball whirling around a roulette wheel. When the ball drops onto the wheel, players know that it will obey the law of gravity. What they don’t know is exactly where the ball will land. If they did, casinos around the country would go broke.

Scientists say that the goal of chaos theory is to interpret and predict such randomly appearing complex behavior. At the root of chaos theory are a predictable group of mathematical equations that generate an unpredictable behavior over time.

Iasemidis’ idea was to apply of chaos theory to epilepsy. He thought that it might provide a means to predict seizures.

He and his colleagues studied thousands of electroencephalograms (EEG). “We were able to see the brain get into an ordered state and then, within seconds to a couple of minutes, come right back out of it,” says Iasemidis. “That’s what was really fascinating to me.”

Once an epileptic seizure is complete, patients usually return to a relative state of calm. Iasemidis thought the role of epileptic seizures might be to reset the brain, much like rebooting a network of computers. He and his group have used mathematics to prove that idea.

Seizures are innate for each epilepsy patient. As a result, Iasemidis didn’t have to worry about the influence of external factors clouding the interpretation of his results.

“We had an ideal setting for study. We could look at real patients under real conditions,” he explains “The hallmarks of epilepsy are seizures and the existence of epileptic spikes in the EEG. The coming and going of seizures appears to work randomly, so, in that sense, epilepsy is a dynamic disorder.”

Since the 1960s, doctors have used continuous videotape recording and simultaneous EEGs to help diagnose epilepsy. They study the EEG activity from electrodes that monitor different portions of the brain.

“We’ve known for decades that there is a synchronization of different brain areas during the seizure itself,” Iasemidis says. Unlike the patterns seen on a heart monitor, the wave patterns seen on an EEG are irregular.

“The traditional view is that seizures occur randomly. We have proven that seizures are not random events,” he continues. “We are able to define mathematically the existence of a long-term pre-seizure period.”

Iasemidis and his colleagues took a very close look at the pre-seizure period. That is where what he calls a “dynamical entrainment” of critical brain areas occurs. When drawn on paper, an EEG signal is viewed as a one-dimensional line of valleys and peaks. The ASU researchers analyze each signal. They use mathematics to convert the one-dimensional signal into an image that covers seven dimensions. The result is what mathematicians call a fractal.

Fractals are characterized by rough geometric shapes. Fractals are abundant in Nature. They can be seen in the natural shapes of mountains and clouds, even lightning.

“We can see the ‘fractal creature’ during an epileptic seizure. We can mathematically prove it to be a fractal,” Iasemidis says. “Whenever there is order in the system, our fractal beast appears on the scene, much like Beowulf’s nemesis, Grendel.”

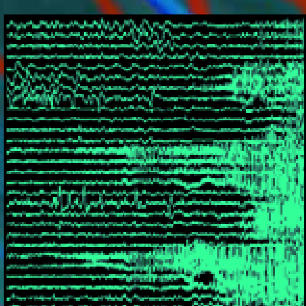
Iasemidis and his team examined lots of EEGs. They saw the pattern emerge within the data. Every time a seizure occurred, the fractal beast progressively appeared. When there was no seizure, the beast disappeared and the brain’s neurons fired away in chaotic bliss. When the next seizure began, the fractal appeared again.

Iasemidis and his colleagues now view epileptic seizures as a recurring cycle of chaos, order, chaos, order, and so on. They have seen the beast. They know when it is about to arrive.

Iasemidis says this knowledge will be valuable to physicians and patients. Physicians can intervene in many ways if they have an early warning of an impending seizure. They can use a variety of treatments to lessen the severity of a seizure or even help to fend it off entirely. Patients who suffer from epileptic seizures may get a tool that can help restore some semblance of order to their lives.

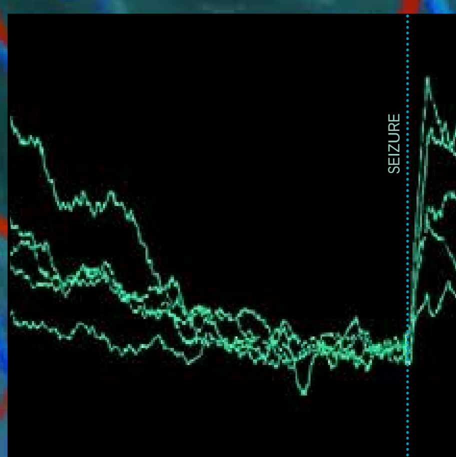
Joe Caspermeyer

EEG



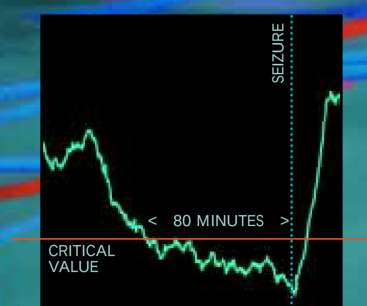
Electrodes record electrical activity at multiple locations in the brain. This chart shows the beginning of a seizure recorded by EEG.

STABILITY MEASURE



The wave signals from individual electrodes are mathematically analyzed to determine a measure of disorder—chaotic behavior. Signals that are more stable, that show less disorder, occur during seizures.

T-INDEX



Other calculations reveal the total measure of stability between multiple electrode locations over time. When the T-index reduces to a critical value, at a high rate, a seizure will follow.

MICHAEL HAGELBERG ILLUSTRATION