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Treating epilepsy with physics

Millions of people with epilepsy live in dread of unpredictable seizures from this medical condition. **Louis Nemzer** describes how novel approaches to predicting and treating these events are being developed thanks to advances in our understanding of the physics of the brain

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Epilepsy is the world's most common chronic neurological disorder, affecting one in 100 people. It is characterized by recurrent seizures that often have no apparent external trigger but are the result of neurons in the brain behaving irregularly. The affliction was in fact one of the first medical conditions to be recognized in the ancient world. There is a 2600-year-old Babylonian cuneiform tablet that distinguishes between various type of seizures, while Roman emperor Julius Caesar was said to have "the falling sickness".

Despite the Greek physician Hippocrates proposing in the fifth century BC that epilepsy was a medical condition that originated in the brain, for a long time many people mistakenly thought it was caused by spirits. This superstition continued to be believed until the 17th century when it was finally accepted that the brain was indeed the site of the problem. However, no-one really knew how to treat epilepsy, with remedies including everything from prescribed diets and special living conditions, to medicinal herbs. Some people with epilepsy even had holes drilled in their skulls or were subject to bloodletting – but these surgical techniques were far from effective.

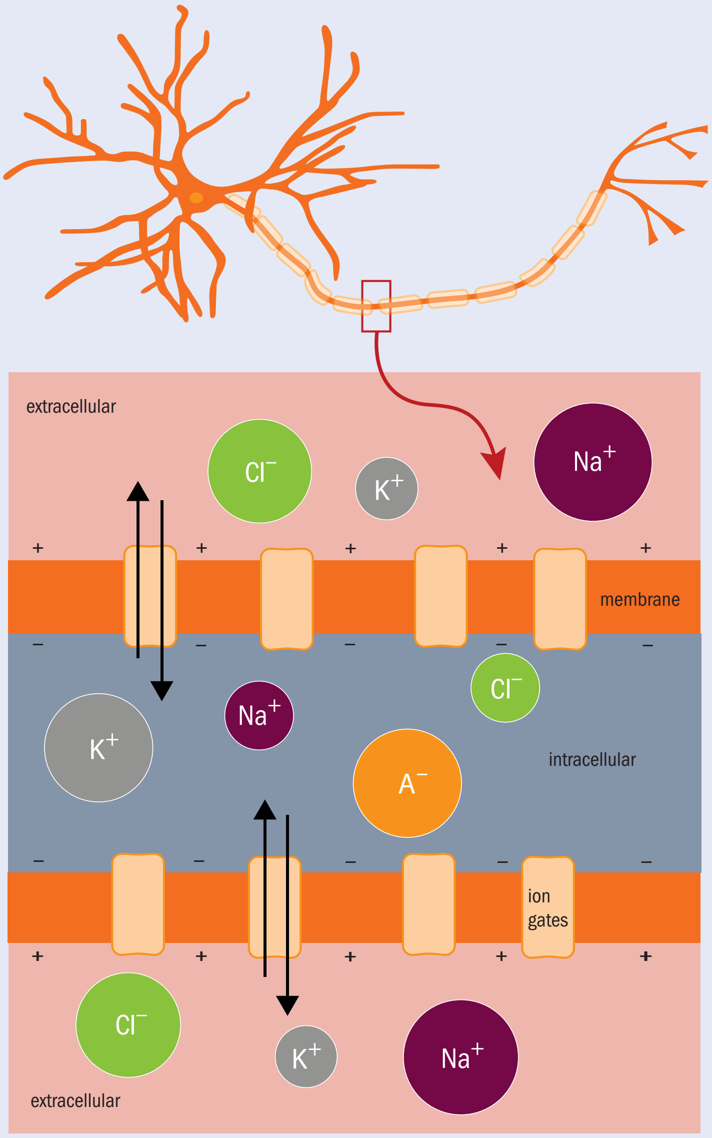
Modern medicine has thankfully made huge progress since then, but there are still millions of people who live with unpredictable seizures that are – for reasons we don't completely understand – not well controlled by medication or even surgery. Indeed, for the 30% of people with epilepsy who have symptoms that cannot be treated, the unpredictable onset of seizures can greatly hamper their daily lives, as they are, for example, prohibited from driving, swimming or operating machines – activities we usually think are commonplace. Some people have been seriously injured – or even died – as a direct result of sudden, unexpected seizures. An early warning system that would allow these patients to take the necessary precautions to prepare for or even avert the seizures entirely, would obviously be highly desirable.

So, what can physics say about this challenge?

It's all a phase

The brain is an incredibly complex network consisting of tens of billions of neurons forming hundreds

1 Firing neurons



Neurons are cells in our nervous system that receive and send information via electrochemical signals. (Adapted from *Noba textbook series: Psychology* 2019 DEF publishers "Neurons" chapter.)

of trillions of connections, which makes the task of prediction seem daunting. However, each neuron is still a physical object that obeys the laws of physics.

The fundamental equations that describe the electrical voltages inside neurons were discovered by Alan Lloyd Hodgkin and Andrew Fielding Huxley in 1952, for which they received the Nobel Prize for Physiology or Medicine in 1963. The Hodgkin–Huxley equations are considered the gold standard for understanding the intricate dance of sodium and potassium ions as they rush in and out of neurons. Their movement depends on changes in voltage that control specialized ion gates – proteins that open and close pores in the membrane to allow the passage of ions. Solving this system of coupled mathematical equations allows researchers to keep track of the voltage of each neuron over time.

One of the key processes that can be modelled is the rapid rise and fall of the voltage each time a neuron fires. When a neuron has been sufficiently stimulated by its neighbours, ion gates that were locking sodium ions out suddenly open. A massive influx of these charged particles ensues, causing the interior voltage to spike. In this way, a signal can quickly propagate along the length of the neuron, and then to other connected brain cells. As part of our research at Nova Southeastern University in Fort Lauderdale, US, we have carried out computer simulations of the behaviour of small networks of neurons using the Hodgkin–Huxley equations. This work has let us monitor the effects of slight changes to individual parameters, such as the threshold for each neuron to fire, or the "stickiness" of ion gates, which makes them stay open longer than they should. All of these may have a significant impact on the excitability of each neuron.

Understanding the behaviour of individual neurons is only a starting point. Complex systems like the brain show collective or emergent behaviour, in which the whole acts very differently from the sum of its parts. This can include sudden, marked changes caused by smooth alterations in external conditions, rather like the phase transition that occurs when you pull an ice cube out of your freezer. It remains frozen solid right until you raise its temperature to the critical point, 0 °C, whereupon it promptly melts into liquid water. This transition is due to complicated interactions between water molecules that you'd never guess no matter how long you studied a single water molecule in isolation.

Similarly, an epileptic seizure occurs when the normal functioning of the brain is interrupted by neurons locked into a single rhythm, and it's likely that this is also a kind of phase transition. In this case, a group of hyperexcitable neurons at a specific location – the seizure focus – start firing in unison. This recruits other neurons to synchronize with them, which in turn recruits other neurons, setting off a synchronization avalanche. In this picture, the seizure focus acts much like a seed crystal that, when dropped into a pot of sugar dissolved in hot water, causes the whole thing to crystallize into rock candy.

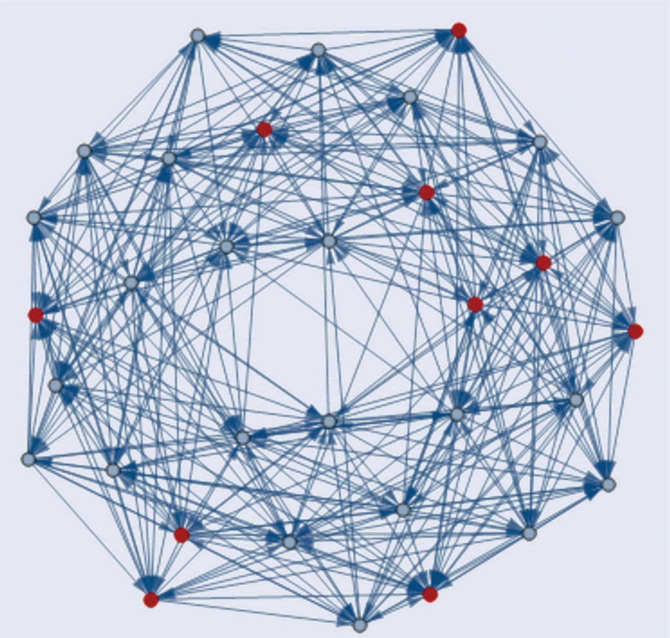
Edge of chaos

Clearly, the brain must be finely tuned between too much excitation, which can lead to chaos or runaway synchronization, and too much inhibition, which leads to stasis and inactivity. In fact, many scientists believe that healthy brain function is perched right on the edge of chaos. In our simulations using small networks of neurons, we can identify the "healthy" state because it shows bursts of activity of all sizes. That is, we see many small bursts, fewer medium bursts, and a small number of large bursts. Since there is no characteristic burst size, this distribution is called "scale-free".

In contrast, if the sodium ion gates become sticky, each neuron is now slightly hyperexcitable, leading to all-or-nothing synchronization in which many neurons fire in unison, as in an epileptic seizure. The effect of a tiny change therefore cascades until the network is pushed "over the cliff" into pathological synchronization.

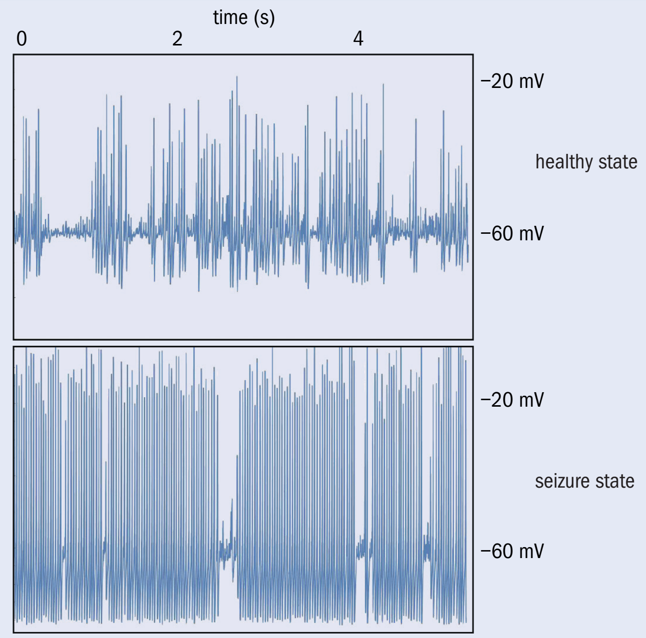
2 Communication network

Louis Nemzer



Simulation of a small network of neurons, with the nodes that are "firing" highlighted.

3 Simulating seizures



Comparing the "healthy" and "seizure" states of the simulated network. The healthy state shows bursts of various sizes, while the seizure state is usually locked into a repeating, synchronized pattern.

Our computer simulations help us understand the hallmarks of the seizure state. But predicting if a seizure is likely to start within the next 15 minutes is a much bigger task. It's the difference between trying to tell if it's raining right now (which you can do by just sticking your hand outside) and predicting whether it'll rain tomorrow (better call in your best team of meteorologists).

For this task, we need actual patient data. Monitoring the activity of the brain is conventionally done via an electroencephalogram (EEG), in which electrodes are placed directly on to a patient's scalp to detect the brain's electrical signals. However, EEG data are imperfect because high-frequency signals cannot penetrate the skull, and there may be spurious blips from eyeblinks and other muscle movements. A more accurate method is electrocorticography (ECoG), which uses an electrode grid surgically implanted inside the cranium, just on top of the brain. Obviously, this technique involves a very invasive operation and is not something patients undergo lightly. Only people with severe seizures that continue to occur even after repeated attempts at treatment will elect to have the electrodes implanted.

But even after scouring ECoG data for identifiable signs that indicate when a seizure is about to start, nothing stands out. What's the point of generating high-quality data if you don't even know what patterns to look for? This is where machine learning, the burgeoning new field of computer science, can help.

The *je ne sais quoi* of Jane

You may not realize it, but machine learning is already hard at work in your daily life, tagging people in photos on Facebook, recommending your next movie on Netflix, and alerting your bank to questionable transactions (see "A learning revolution", March pp45–48).

To understand the power of machine learning, you first need to think about how conventional programming takes advantage of what computers are very good at: namely, following the rules. Computers, after all, can run through a flowchart much faster than any human. However, there are some tasks that we mortals are still better at, like identifying your friend Jane. Think how long it would take to list the "rules" for telling a picture of Jane apart from anyone else, especially if you include photos with different lighting conditions and angles.

In fact, it might seem hopeless to try and train a computer using a set of rigid rules. But this is where machine learning comes in. Instead of attempting to programme the computer manually, we train it with many labelled examples. We can take a hard drive full of snaps and tell the algorithm, "this is Jane" or "this is not Jane". Over time, the computer learns, via reinforcement, the features that distinguish Jane from everyone else.

So to classify the risk of seizures, our group in Florida is adapting machine-learning algorithms that are already used in medicine to diagnose radiology images. We are currently training the machine-learning models – and the simulations we created before are helping by generating simulated data that the algorithms can learn from. Next, as long as we have enough labelled ECoG data from patients, we hope to be able to build a highly accurate warning program even if we do not know which features in the signal the algorithm is using. While this "black-box" approach may seem disconcerting at first, the primary test will be the usefulness, if not the explainability, of the resulting system.

Sounding out the focus

Some epilepsy patients who do not find relief using medications are candidates for more invasive treatments, including surgery to remove the seizure focus. However, while operations can often be effective, there is a big risk that they could damage normal brain structures. One promising new method involves using targeted ultrasonic waves to eliminate the seizure focus, without having to open the skull at all – just as sound waves can be focused on a kidney stone inside a patient to destroy it non-invasively. An early test of this technology was led by Vibhor Krishna, a surgeon at Ohio State University in the US. His patient was awake inside a magnetic resonance imaging (MRI) machine, when focused ultrasound waves were used to safely ablate the seizure focus while minimizing side effects. According to the Focused Ultrasound Foundation – which is dedicated to the development and application of focused-ultrasound technologies in medicine – the process minimizes damage to healthy brain by eliminating the need for incisions, holes in the skull, or electrodes in the brain.

Ultimately, we hope to use the algorithm to develop an accurate, straightforward smartphone app that would use data transmitted from wireless scalp electrodes to provide real-time information about seizure risk to patients and healthcare providers – just as people with diabetes can now receive automated alerts from a blood-sugar monitor. This information would allow patients to take medication or at least get to a safe space. Some people could even have an electric shock administered to avert the seizure entirely.

Detect and treat

If a seizure has been predicted to be imminent – or has already begun – ideally you want to be able to prevent it escalating. One possible method is to directly administer drugs to the seizure focus inside the brain – an approach that may work even for patients who do not usually respond to oral medications.

George Malliaras and colleagues at the University of Cambridge in the UK have even been able to fabricate such a method. Their hybrid device can be implanted into the brain, and not only detects when a seizure is starting, but also automatically delivers GABA – a neural inhibitor – to quickly calm it (*Science Advances* **4** eaau1291). Improvements in this kind of "on-demand" drug release complement seizure prediction methods, since knowing when a seizure is coming is much more valuable if there are effective, rapid means for preventing it entirely, especially if the warning comes just seconds before the seizure is about to start.

Humanity has been dealing with epilepsy for millennia, and its effects on patients range from mildly inconvenient to devastating. However, modern physics is providing new optimism that real improvements in quality of life are possible. People who do not receive relief with drugs or surgery may still be able to lead normal lives by monitoring their condition as a manageable chronic disorder. My hope is that an increased understanding of the physics of the brain will have a real positive impact on people's lives.