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PC Based Model of the Epileptic Brain

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Abstract

Epilepsy is known since ancient history and affects the lives of millions. Due to various physiological and ethical reasons, it is extremely difficult to conduct thorough examination of the human brain. As a result, even after millennia of identifying epilepsy and treating it, we know relatively little about what is causing epilepsy and what is the best way to manage it. In order to meet this challenge, we have developed an artificial neural network, one that allows us to mimic several aspects of the epileptic brain. Our model is based upon a specially designed neuron "cell", and the network is formed in a manner that offers several degrees of flexibility in its formation: Starting with the neurotransmitter and up to properties of the entire network. We compare the activity of our model to that recorded from real brains of epilepsy patients, and demonstrate resemblance in key properties of the neuronal activity. Using this artificial network offers an easier experimental platform that manifests epileptic-like behavior, which allows to investigate the underlying mechanisms causing epilepsy on one hand, and to examine potential treatments on the other hand. The model can be adopted to manifest other physiological properties that can be suitable for modeling other neurological disorders.

Keywords: Epilepsy; Epileptic brain; Medical treatment; Neurological disorders

Introduction

Epilepsy is a well-known affliction characterized by recurrent and unprovoked seizures, affecting 1-2% of the population. Epilepsy exact prevalence is difficult to quantify especially in rural populations and pediatric epilepsy [1]. Two thirds of epilepsy patients respond to medical treatment, and for those that remain, surgery is the best viable option [2,3]. Epilepsy is not a single disorder, but rather a group of neurological disorders characterized by epileptic seizures, ranging from nearly undetectable events to long periods of vigorous shaking [4].

The cause of most epilepsy cases is unknown [5]. Few cases are genetically related, and some people develop epilepsy as a result of brain injury, stroke, brain tumor, or drug abuse. Recent research also connects epilepsy with autoimmune diseases [6,7]. The diagnosis typically involves ruling out other conditions known to cause similar symptoms, such as syncope. Epilepsy is often confirmed by electroencephalography (EEG), but a normal test is not enough to rule out the disease [8-10]. Other than the actual seizure and the risks involved in it, the sudden and unpredictable nature of the seizure is one of the most disabling aspects of epilepsy. Thus, finding a method capable of predicting epileptic seizures would open new therapeutic possibilities, and this can be attempted by analyzing network activity [11-14].

The human brain is the most difficult organ in our body to experiment with, due to physiological and ethical reasons. This fact, along with the variability in epilepsy pathogenesis and the difference in epilepsy manifestation, is making clinical research very limited, which reduces the quality of care for epilepsy patients.

Most epilepsy data is obtained by EEG and electrocorticography (ECoG) [15-17]. Our previous work with this type of data has taught us that, while offering real in-vivo data, both techniques are limited in the number of channels, difficult to obtain [16,18-20], and does not allow manipulating the source of the data (the real human brain) which is required for understanding the mechanisms which result in seizures. Facing these challenges, in order to support epilepsy research, we have designed an artificial neural network that possesses key elements of the real brain, and allows hands-on experiments with various epilepsy related factors. The artificial neural network is a model that mimics the behavior of the epileptic brain. It allows changing various factors that affect the brain behavior while allowing easy access to the output of the model. By no means do the authors state that this model captures the vast complexity of the brain as a whole, yet we believe that it can shed some light in understanding the underlying mechanisms causing epilepsy, and offer accessible and safe "laboratory" for experimenting with epilepsy treatments. The same model and platform can be applicable to other neurological disorders.

Materials and Methods

EpilePC - neural network model: In order to support the work done in our lab with ECoG, EEG and Multi-Electrode Array signals, we have generated an artificial brain model called "EpilePC". This model is simple enough to be coded and run on a standard PC, yet complex enough to allow manifestation of the network properties we have investigated. EpilePC starts by using a single neuron module, many of which are integrated according to the network variables and probabilities, forming one unified network. The cells then start to act and react based on their design and network setup. Figure 1 presents an overview of the concept behind this work:

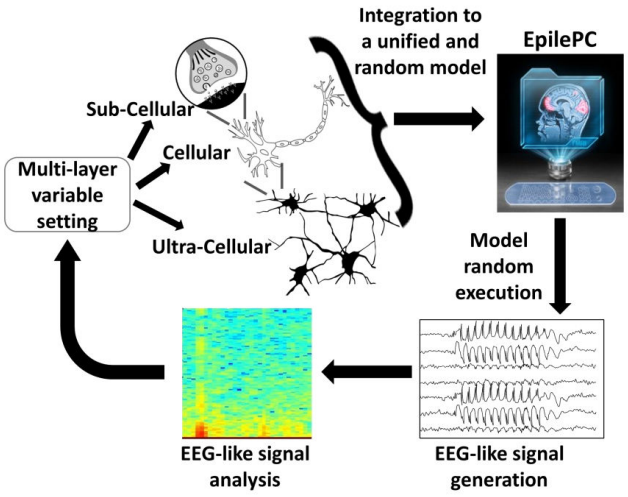

Figure 1: EpilePC model concept. We start by setting the network variables. Neuron model cells are connected according to the variables and form a random network representing the brain. The network operates and generates action potentials and EEG-like output which is analyzed into various components. We can then change the input variable and observe the effect over the output.

Neuron Model

The basic component of the network is a single neuron cell, designed based upon Morris-Lecar neuron model. The model is a two-dimensional "reduced" excitation model that allows relatively simple calculation of the membrane voltage by governing Potassium and Calcium conductance [21,22]. The computational neuronal model was designed by D. Tishler [23]. Other computational neuron modules are available as well and we have examined several, such as the thalamocortical model [24], Spiking neural P systems [25] and others. These were found to be less agile and too computational-resources consuming for our purposes. There now also exist VLSI based neuron modules that allow emulation of neural behavior, typically on a configurable circuit [26], these devices are quite difficult to master and are less convenient for integration into existing analytical tools of neuronal data.

EpilePC Network Design

Network model was designed with the following three objectives:

Scalability

There are about 10 billion neurons in the human brain with about 10^{16} connections between them [27]. At this point, there is no super-computer that can model even a fraction of this immense complexity, let alone a PC. In order to allow the user to optimally balance the computing capacity at hand with the model complexity, our network model is using a single neuron model that can be connected to any number of other neurons, and in any network morphology. We have identified key elements in the network behavior while using as little as 20 such cells, and were able to experiment with up to 500 neurons. As our key purpose was to experiment with as many different networks as possible, 100 cells were few enough to allow the creation of thousands of different networks in a relatively short time, and more than enough to represent the key properties we wanted to examine in the network. Time is another scalable factor, and each simulation can be run in order to create a couple of seconds of activity or days, again, depending on the research goals and computing capacity. There is no meaning for the real time in that aspect: we can generate the progress of an entire year's worth of data within a course of minutes (if we keep the network small enough), and it can last an entire day to run a simulation of a couple of seconds worth of data (if we take a very large network). The correlation between the real time and the simulation time is based on the time constants which are attributed to the simulation through its variables. Once a network is generated, it can be set to run for an infinite time, yet, the key characteristics of the network can be noticed even after a couple of seconds of activity. We have captured network output from the scale of milliseconds to hours, for this paper all the analysis was done based on 100 seconds worth of data per network.

Multi-level access

Since neurological disorders can originate in various levels of the brain, our model allows accessing those various levels too. It is impossible to model all the properties of a single neuron, let alone the entire brain, at the same time. However, one can pick a couple of neurophysiological properties as input variables and observe their effect over the brain activity, while keeping others unchanged. We are grouping these variables into three levels: Sub-Cellular – By that we refer to variables that are manifested within the neuron itself e.g. ion-channels, neurotransmitters etc. Cellular – properties attributed to the entire neuron, e.g. refractory period, inhibition\excitation etc. Ultra-Cellular – Network properties: How the neurons are distributed, connected and affecting each other.

Simplicity

Another consideration for making EpilePC easy to use is its interface. The network is created by applying a set of inputs, that are used in order to configure each of the network variables, in each of the layers mentioned above, and from that moment, automatic execution is creating the network and simulation.

Randomness

It is important to note that, while the inputs for forming the network are predetermined by the user, the network is randomly generated and operated. This means that each network, even if set by the same input variables, is different than any other network. For example, we can generate an almost infinite number of different networks while using the same inhibition\excitation ratio: in each network, different neurons will belong to each group and will be connected differently. At the same time, even within the same network, the activity pattern in any given time is different than any other time. This randomness has two reasons: first, our model is designed to be a statistical model. As any real brain of a real patient differs from the brain of any other patient, even if dramatically simplified, our artificial network must allow the same variation. Thus, every result reported in this work is obtained by running many iterations with many different networks. Second, there is randomness of activity within any living network, and this is also included into the model, where each action potential (AP) is triggered according to the neuron probabilistic attributes.

Network Output

Real brain electrical activity is typically presented by analog signals, which is the case for EEG and ECoG. In EpilePC, after setting the model variables and running the simulation, an analog output signal is produced for each neuron in the network. This signal is in the form of a voltage trace of the membrane potential (very much like a patch clamp). In order to analyze the average activity of the network, voltage traces of neuron clusters are averaged into channels (summed and divided by the number of neurons per channel). This step is done in order to simulate the receptive field of the EEG\ECoG electrodes. The number of grouped neurons per channel is set by the user. Any AC modeling that the user wishes to apply to the signal (e.g. electrode RCL model, noise, filtering) can be applied at this stage. Since, unlike in the case of the real brain, we know the exact voltage of each neuron, we can also sample the activity per neuron: the voltage trace of every single neuron is run through a peak detection algorithm [23] which turns it into a discrete binary signal. This output represents all the time stamps when each neuron was triggered, for each index-channel (ic). The algorithm detects all local maxima (peaks) which are above threshold, we used 20 mV for excitatory neurons, 10 mV for inhibitory neurons. After all neurons' activity traces has been turned into binary signals, we generate a raster plot with a [t, ic] matrix representing all the time stamps of each action potential in [t], for each channel in [ic]. As this kind of format is widely used, generating the output in this format allows detailed analysis with existing [t, ic] tools and algorithms. Figure 2 demonstrates the output of the artificial network. By aggregating signals from 50 neurons we generate an ECoG-like signal. In (A) the network is quieter, demonstrating relatively infrequent bursts, which are of relatively low energy, in (B) we zoom in into one of these bursts. In (C) we see a more active network, with more frequent bursts, and each with higher activity. In (D) we zoom in into one of these bursts. In (E) we see the output of the network as a raster plot, in alignment to the ECoG-like signal that is plotted in (B) above. This figure presents our control over the neural network characteristics on one hand, while keeping it random on the other hand.

While Figure 2 shows the network at the operating zone, Figure 3 presents the network in its two extremes.

Activity Rate – Spikes Per Seconds

Several parameters are used in order to quantify the signals obtained from EEG or ECoG signals. Practically any neuronal analysis starts by looking at the network activity as depicted by the electrodes. Therefore, the key element we chose for quantifying and comparing the neural activity is the Spike Per Seconds count (sps) and not the energy of the analog signal (which is extrapolated from the sps). Any analog signal can be generated from the sps by picking the proper RCL model of the electrodes. The opposite is not possible to do (calculating sps from the analog data) as, for example, when X neurons are firing randomly near f0 frequency, and grouped into one electrode, the result will be a similar analog signal as half the number of neurons firing in twice the frequency. Thus, unlike in the case of real EEG or ECoG signals, which are a summation aggregation of many neurons, our model offers the privilege of knowing exactly which neuron had spiked and when, so this information will be used for the model output.

Scale and Normalization

We have set a limit of over 40 sps per neuron (on average) as a saturated network. ECoG-like signals with higher sps appear very similar to real ECoG signals recorded during an epileptic seizure, and when comparing their frequency modulation to real ECoG signals, it is clear that this limit indeed corresponds to the real physiological values [28-30]. For the sake of simplicity, all outputs were normalized to an Activity scale between 0 and 1, where 0 represents a totally inactive network, and 1 represents a seizure.

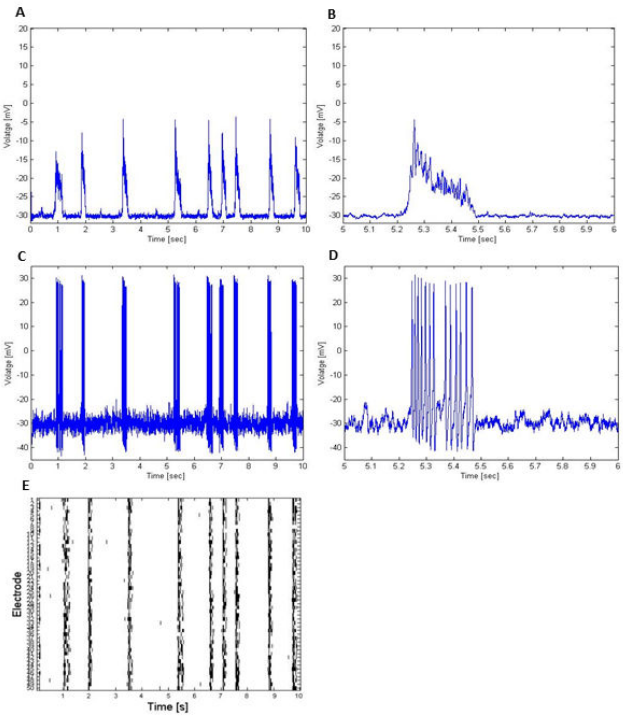

Figure 2: Simulation output example. (A) Voltage trace of an average of 50 neurons during a 10 seconds timeframe. (B) Zooming in for one burst during a 1 second timeframe. (C) Voltage trace of a single neuron during a 10 second timeframe in a more active period. (D) Single neuron zoom-in for one burst during a 1 second timeframe. (E) Raster plot of the frame used for generating the ECoG-like signal in (C).

Multi-level Variables Inputs

One of the guiding principles in designing EpilePC was to allow access to the various layers in the neuronal activity. In order to demonstrate and experiment with this approach, we have chosen three variables to investigate, one for the sub-cellular, one for the cellular, and one for the ultra-cellular levels. All the variables chosen are ones that are known to be related to neurological disorders in general and epilepsy in particular, and the values examined were according to their actual physiological values. As mentioned above, there are several potential pathogens of epilepsy, so we can try and model their impact on the network. We choose one pathogen for each level.

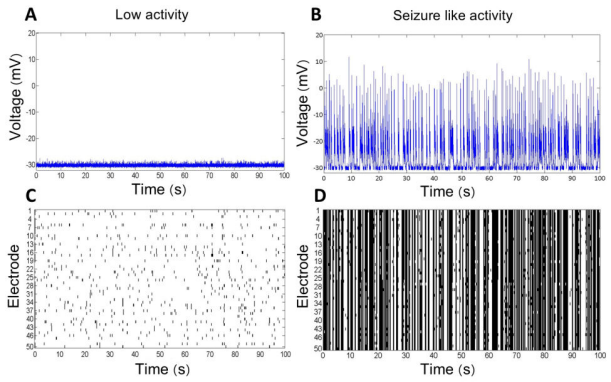

Figure 3: Analog *vs.* binary display: Raster plot (bottom) and ECoG-like signal (above) in two extreme cases: Low activity (left column) and Seizure like activity (right column).

Sub-Cellular level - TauRec (τ_{rec})

In the sub-cellular level one example for epilepsy factor is gamma-aminobutyric acid (GABA) which holds a key importance in neuronal activity. GAT-1, encoded by SLC6A1, is one of the major GABA transporters in the brain and is responsible for re-uptake of GABA from the synapse. SLC6A1 mutation is found in patients with epilepsy demonstrating spontaneous spike-wave discharges [31]. In order to model the transporter reuptake, we use τ_{rec}. Synaptic resources have three states: active (y), inactive (z) and recovered (x).τ_{rec} represents the time constant of resource recovery, the transfer of resources from the inactive state to the recovered state, τ_d represents the time constant of decay of active resources, the transfer of resources from the active state into the inactive state. Both τ_{rec} and τ_d are constant. t_{AP} represents the time of arrival of the last AP to the pre-synaptic terminal. μ represents the amount of resources which are activated when an AP arrives to the synapse from the source neuron, the fraction transferred from the recovered state to the active state when an AP arrives [32,33]. The transfer of resources between the states is governed by the following equations, the connections are and presented in Figure 4. These equations were included into the neuron cell module affecting the sps.

$$\dot{x} = \frac{z \bullet (-\tan(1.2z - 1.2))}{\tau_{rec}} - ux\delta(t - t_{AP}) \qquad (1)$$

$$\dot{y} = -\frac{y}{\tau_d} + ux\delta(t - t_{AP}) \qquad (2)$$

$$\dot{z} = \frac{y}{\tau_d} - \frac{z \bullet (-\tan(1.2z - 1.2))}{\tau_{rec}} \qquad (3)$$

$$x + y + z = 1 \qquad (4)$$

Cellular Level - Excitatory\Inhibitory Synapses

The ratio between inhibitory and excitatory synapses is another known factor of epilepsy, as evident from reduction of inhibitory synapses [34], identification of decrease of inhibitory GABAergic nerve terminals at epilepsy foci [35], the impact of sodium channels in inhibitory interneurons which causes seizures [36] and more. Neuronal synapses can be either excitatory or inhibitory, respectively increasing or decreasing the likelihood of the post-synaptic neuron to trigger an AP. While we can control the nature of each separate synapse in the neuron model, for the sake of simplicity, we have grouped all the synapses in each neuron to the same type so, instead of an inhibitory synapse, we look at inhibitory neuron where all of its synapses are inhibitory. The inhibition of the formed network is defined as ratio between inhibitory and excitatory synapses (connections) in the network [37,38]. Thus, in our case, setting Inhibition to 25% means that 25% of the connections are inhibitory.

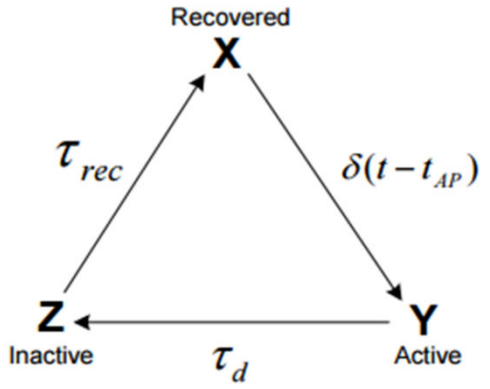

Figure 4: Synaptic resources time constants.

Ultra–cellular Level – Connectivity

Finally, network connectivity has perhaps the biggest impact of all, with large-scale network connectivity resulting with seizures and even cognitive dysfunction [39]. This is why surgery has high chances for preventing seizures from happening, along with many other indications obtained by both medical experience and research [40-42]. Connectivity is represented by a matrix that attributes the strength of the connections between all the permutations of neurons in the network. This matrix can be used in order to isolate one section from the rest, to generate hubs, and control the linkage level in the network in general. Global network connectivity is defined as the total number of connections in the network divided by the number of potential connections [27,37,43]. Connectivity of 25%, for example, means that each neuron is fed (on average) by 25% of the neurons via synapses.

Setting the Operating Point

As we are experimenting with three input variables, each one with a large range of values that can be assigned to it, it was important to set the operating point. We have been using physiological values reported in the literature as a starting point and examined the network around it. Operating point value for TauRec (100) was taken from the original Tsodyks-Uziel-Markram (TUM) model [22]. In the neocortex, which is the target of our model, there are about 10 billon neurons [27]. It has been reported in literature that each neuron in the neocortex is connected to 5000 to 200000 neurons [44]. Bernhard Hellwig reports that in one cubic millimeter there are about 75000 neurons [33]. Hellwig also reports that every neuron is connected on average to about 7000 other neurons [33,37] and that the probability to be connected to neuron distant more than 0.5 mm is very low (i.e. most connections arrive from near neurons – within radius of about 0.5 mm). This means an average network connectivity ratio of about

~10%, and up to 80% for the closest four neighbors. We have set connectivity operating point to 25%, somewhat above the average since we wanted to generate a relatively connected network, and inspected the network relative to this point. In the neocortex, inhibition level is typically around 20% [27,38,45] so this was the operating point chosen for the inhibition level.

For validation purposes, we have been keeping two variables fixed at the operating point, which is the physiological norm, changed the third variable, and observed the network behavior. In all three cases, the third variable converged near to its own reported norm value, which increases our confidence in the artificial network and increases its usability for representing real brain characteristics. We have used Matlab 2014b (by Mathworks), EpilePC is free for use, in order to obtain the code, please contact the authors.

Human ECoG Data

The ECoG recordings that were used as our reference were approved by the University of Michigan IRBMED. The data was provided by Prof. O. Sagher from the University of Michigan. The data provided to the authors was fully anonymized. Subjects signed a written consent for participation in the trial. The data provided includes multi-channel recording of several patients during seizures and between them, and we were thus able to analyze the data while knowing when seizures took place.

Results

We start by presenting the network ECoG-like output as compared with real ECoG signals. Having presented the similarity between the two, we will then demonstrate the observability our model offers by measuring the network activity as a factor of the three input variables described above (sub-cellular, cellular, ultra-cellular). We start by one-dimensional analysis, namely, we change one input variable and present the network output dependency. Then we present a two-dimensional representation of the network, and then a three-dimensional one.

Artificial to Real Analog Signal Comparison

We start our comparison by a visual inspection of some examples. Figure 5 shows two such comparisons. In each electrogram, the top five channels are real (derived from the real ECoG data), and the bottom five ones are simulated. Clearly, the human derived data is "richer" in its patterns and shapes. One has to keep in mind that even when using ECoG, the results are more distorted then our data, each electrode records a much larger and deeper area, the electrical environment is noisier etc. Nevertheless, what we are after is a dramatic increase in the activity rate, which the model can produce. As no two patients are alike, so does the simulation varies between one iteration and the other, depending on the input variables and probabilities. Besides the visual comparison that is presented in this paper, a detailed statistical comparison was conducted, comparing several key quantitative parameters between EpilePC and real human data. This detailed report can be obtained by contacting the authors.

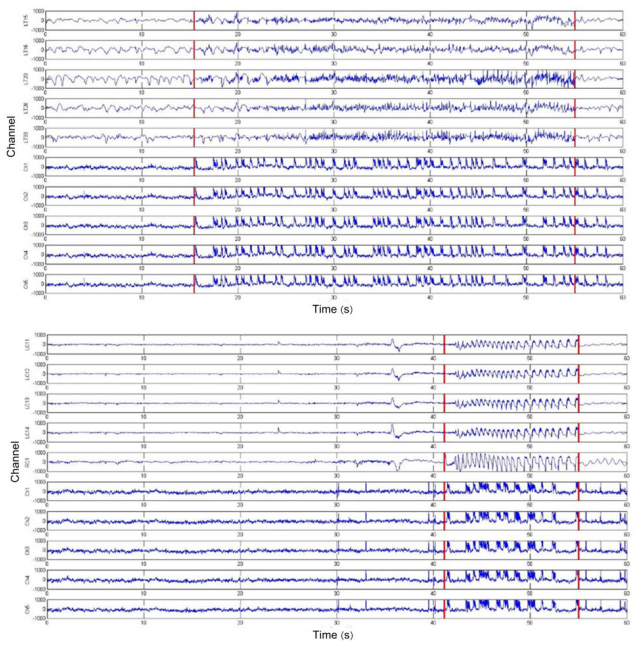

Figure 5: Real brain to EpilePC output comparison. Two example comparisons for two patients (patients A and C in our database). The top five channels are real ones, the lower five channels are simulated. Red markers indicate epileptic seizure.

Artificial to Real Signal Frequency Comparison

Another comparison is done in the frequency domain. Brain regions that demonstrate high frequency oscillations, higher than 10Hz and especially in the range of 60-100Hz are correlated with epileptogenic foci [29,30]. We compare the spectrograms of real ECoG signals to those generated by our model. The patterns observed are similar to what is reported in literature [30,46], in the "bands" it displays during the seizure as presented in Figure 6.

Changing EpilePC Input Variables

We start by examining the effect of changing our three input variables, over the network output. Figure 7 shows how changing τ_{rec} is affecting the network activity. As expected, when τ_{rec} is getting larger (as we view the subplots from top to bottom), activity is decreasing. When τ_{rec} = 70 ms (top) we get a very high firing rate of 1677 sps in this example, a firing rate that drops to 140 sps when τ_{rec} = 140 ms (bottom).

Figure 8 presents the effect of changing the inhibition to excitation ratio. As expected, increasing the portion of the inhibitory neurons (top to bottom) decreases the activity.

Finally, in Figure 9 we examine the activity level while changing connectivity ratio. We see that increasing connectivity is increasing activity.

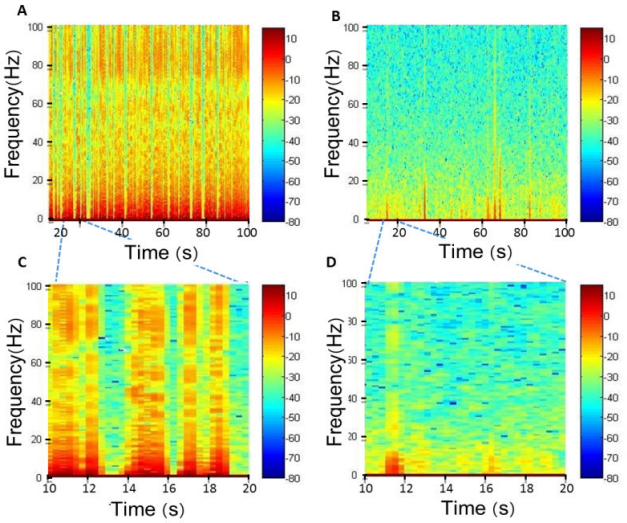

Figure 6: Example of ECoG-like spectrogram of 100 seconds a seizure (A) and between seizures (B), and zoom in of 10 seconds window in (C) and (D) respectively.

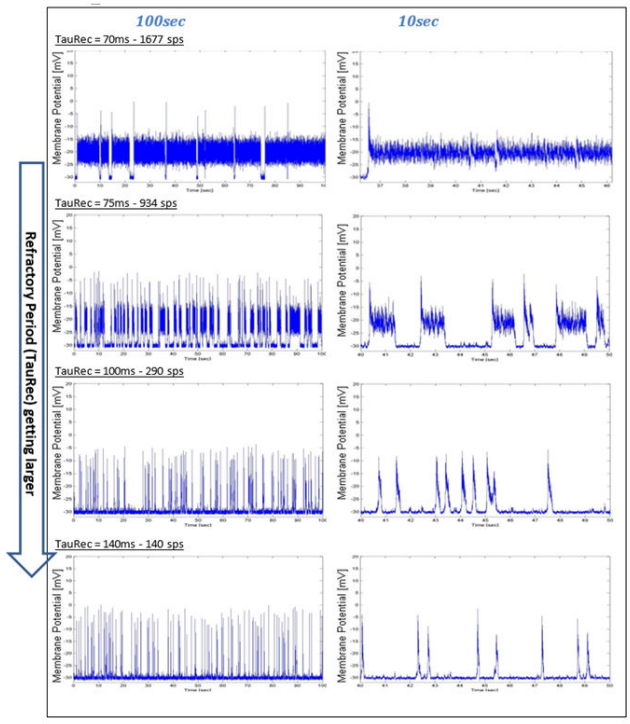

Figure 7: Activity over time for different levels of refractory period (τ_{rec}). On the left, 100s view, on the right we zoom into 10s view. When τ_{rec} is getting larger, (as we move downwards with the subplots) activity decreases.

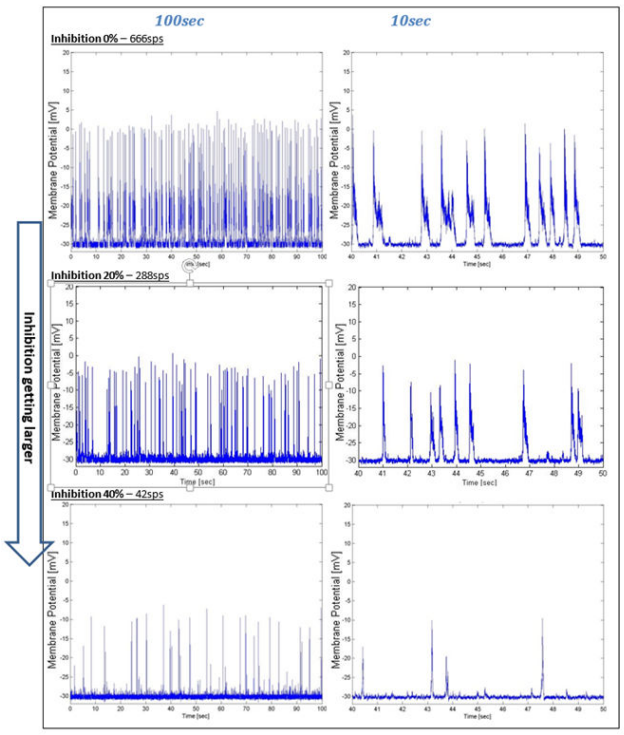

Figure 8: Activity over time for different levels of inhibition. On the left, 100s view, on the right we zoom into 10s view. Top: Inhibition=0%, middle, 20%, bottom, 40%. As expected, when inhibition is getting larger, activity decreases.

One-dimensional Analysis

In Figures 7-9 we give an example for the effect of changing each input variable (τ_{rec}, Inhibition\Excitation ratio and Network Connectivity) over the network activity (by sps). These examples were generated by one network in a specific timeframe, in order to present the analog output signal. We now look on a broader view of each of these input variables. In the following charts, each marker represents the average activity of twenty randomly generated networks. All the networks (in all three charts) are normalized to the same scale. As we change one input variable, we hold the remaining two at their operation point. Standard deviation across samples in all cases was smaller than 0.073 so it was omitted for clarity. Figure 10 examines the effect of τ_{rec}, in Figures 11 and 12 we repeat the same process for Inhibition ratio and Connectivity.

Two-dimensional Analysis

Figures 10-12 show how changing each input variable, statistically affects the network activity. However, the brain is not a one-dimensional but a multidimensional system, with the accumulative effect of many variables determining its overall behavior. It is therefore important to observe the behavior of our model in more than one dimension. In Figure 13 we demonstrate the network activity as a factor of two variables, while the third is kept in the operating point. Here too, every pixel is generated by running 20 random networks and averaging their activity.

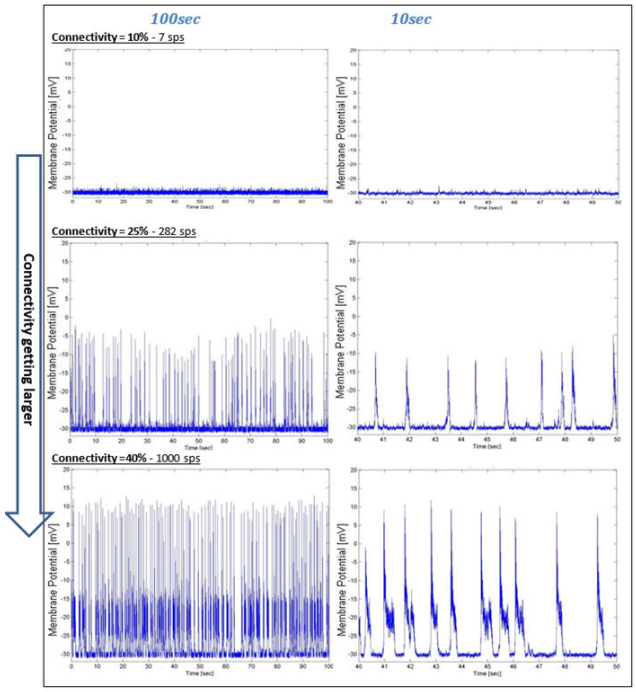

Figure 9: Activity over time for different levels of connectivity: On the left, 100s view, on the right we zoom into 10s view. Top: Connectivity = 0%, middle, 25%, bottom, 40%. When connectivity is getting larger, activity increases.

In these charts, the "deep blue water" regions represent very low neural activity. The "hot" zone represents epileptic behavior. We can see that the neural model operating point (values that were chosen according to the real physiological ones) sets the network to operate in the "shallow water" zone. These are the regions where the combination of variables allows the network to operate in high enough activity, allow even some increase, while still keep sufficient margin from the epileptic zone.

Three-dimensional analysis

We now present the three-dimensional space. Looking at Figure 14 we can see sphere layers of the network: on the outside envelope, there is the "deep blue" area of no activity at all, the core of the sphere is the "hot spot" where ultra-activity takes place. In between we see the transition sphere, which we expect normal brain activity to take place.

Discussion

EpilePC is a software based brain model that can run on any PC, and generate normal and pathological brain patterns. In particular, EpilePC can generate artificial neural networks patterns which resemble the epileptic brain. While other brain models exist, using software or hardware emulation, these solutions usually require expensive devices and heavy computation capabilities.

EpilePC allows modifications of various network variables which affect different levels of the network activity, from the neurotransmitter up to the entire network, and observe the overall manifestation of these modifications. The behavior of the network can be examined and quantified in a much higher resolution and accuracy than what can be achieved by real EEG\ECoG recording. By no means do the authors claim that EpilePC provides a complete representation of the human brain, yet it allows modifying key elements in the brain-model structure, express key features in the brain behavior, and doing so in an easy to access and harmless manner. We have used the overall network activity (as manifested by sps), generated a scale of activity ranging from zero activity to epileptic seizure, and found the model operation point to be in acceptance with what is known from physiological observations. We then shifted from this point and demonstrated how the network activity alters in response. EpilePC is also useful in the sense that it allows getting large statistics promptly, and thus to examine seizure likelihood as a rate for the "epilepticity" of each condition. Clearly, the threshold of a seizure in the model may differ from that of a real patient, namely, the conditions and level of activity beyond which a real seizure occurs. Nevertheless, there are many differences between the seizure patterns of one patient to another as well – EpilePC allows us to objectively compare all the networks generated, according to the same scale, and it is this relative comparison that allows measuring the impact of each change. We have demonstrated that we can add and control different network variables, and examine their independent and combined effect.

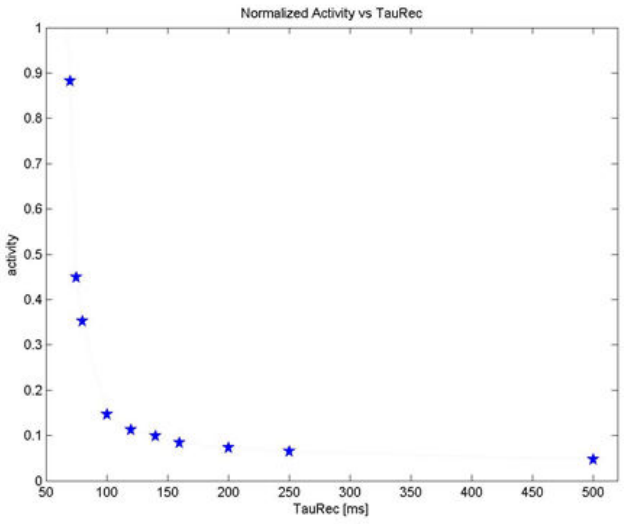

Figure 10: Activity as function of TauRec (all other parameters are kept at operating point): Each point is a result of 20 iterations of 100s each. Activity scale is between 0 (no activity) and 1 (constant seizures). Activity "knee" is occurring around TauRec = 100ms. As expected, when increasing TauRec, (moving right from the knee) activity decays since the recovery period is prolonged. When TauRec is decreasing (moving left from the knee), recovery time is getting shorter and neurons can spike too frequently, network activity dramatically increases towards being an entirely epileptic behavior.

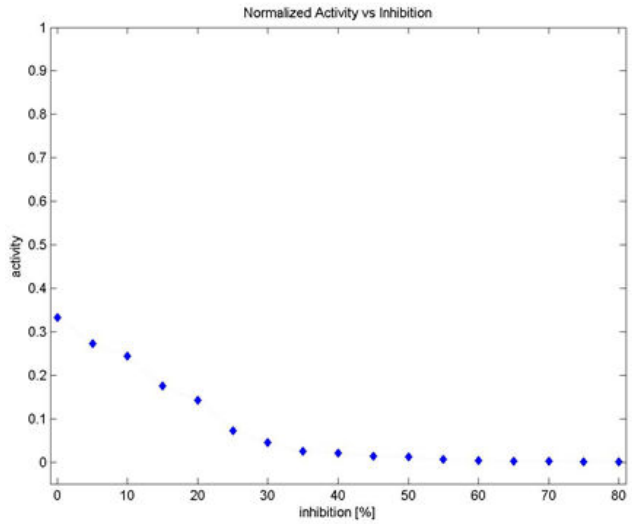

Figure 11: Activity as function of Inhibition ratio (all other parameters are kept at operating point): Each point is a result of 20 iterations of 100s each. When Inhibition ratio is getting lower we see that the networks demonstrate a higher activity as expected, but even when there is no inhibition at all, the networks do no go entirely out of control. When excitation-inhibition is about two to one (inhibition = 33%) we see that the network is almost entirely inactive. Inhibition "knee" is at about 25%.

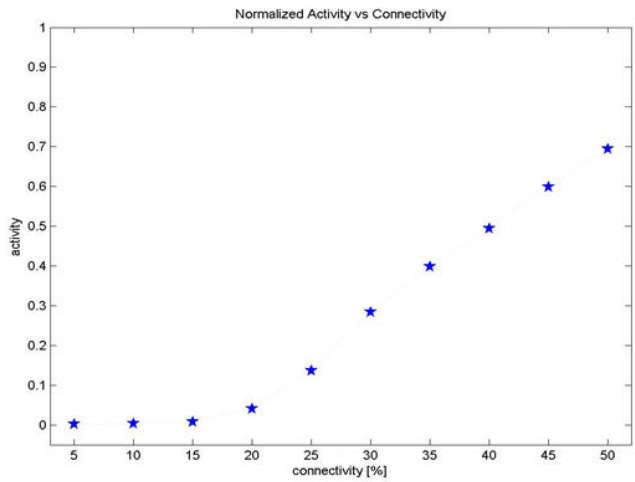

Figure 12: Activity as function of Connectivity (all other parameters are kept at operating point): Each point is a result of 20 iterations of 100s each. As expected, as connectivity is getting higher we see the networks increase their activity towards the seizure level. The "knee" of connectivity is around 25%.

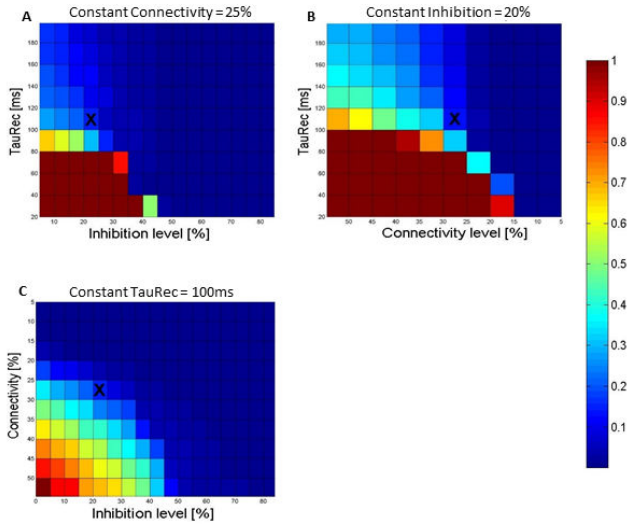

Figure 13: Network activity as a factor of two input variables: The higher the value is (red color), the networks are becoming more epileptic. A) Keeping Connectivity to a constant value and alternating TauRec and Inhibition. B) Keeping Inhibition to a constant value and alternating TauRec and Connectivity. C) Keeping TauRec to a constant value and alternating Inhibition and Connectivity. In each case, X marks the operating point.

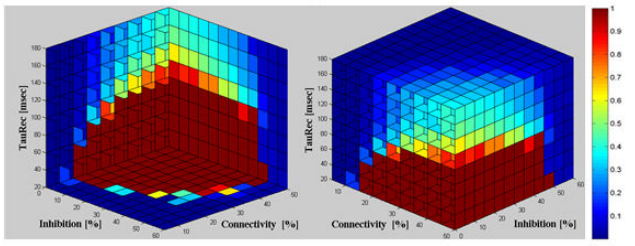

Figure 14: Network activity as a factor of three input variables. The higher the value is (red color), the more epileptic the network is. The two charts represent the same three-dimensional space from two angles to better present the sphere like nature of this space.

Conclusion

While being much simpler than the real brain, EpilePC can still be used for "experimenting" with the brain. The behavior of the artificial properties we have explored, converge with known physiological records. Using EpilePC, the multidimensional nature of epilepsy is presented in a clear and visual manner. EpilePC suggests that it is not necessarily a single factor that is the sole factor of epilepsy, but rather the combination of several factors that can cause the network to be more likely to demonstrate seizures. This concept suggests that proper treatment is more likely to be obtained by addressing various aspects of the brain rather than one. For a patient who can be located on the three-dimensional space, one can determine a multidimensional treatment for that patient, which will "push" the patient out of the "hot zone" in the shortest path. This might have a lesser impact on the

patient's normal life. For example, a combination of the right drugs that will have some effect on inhibition and some effect on neurotransmitter uptake can have the same reduction in seizure likelihood, as a major shift on the connectivity dimension – obtained by brain surgery.

Using EpilePC we can also examine the effect of different treatments on the network, as long as we can attribute a mathematical description for that property or treatment, and apply them into the network. For example, a brain surgery, where a certain part of the brain is disconnected from its surrounding, would be manifested as zero values in the connection matrix around the chosen area.

EpilePC can be useful for examining other brain properties and different neurological conditions. EpilePC was already used to simulate Ataxia-Telangiectasia (AT), a rare, neurodegenerative, autosomal recessive disease. In the case of AT, EpilePC was used to simulate the cortical plasticity, estimate the time constant of the DNA damage response, and was correlated to data obtained from AT mutagenic mice. The authors believe that EpilePC can be of service to expedite and simplify the work of other brain scientists, offering an accessible toolbox for validating their hypothesis prior to engaging with the real brain. While we have demonstrated that the model parameters converge to the real physiological ones (which were already known), we suggest that EpilePC can be used for extrapolating unknown physiological properties by tuning the model's parameters until the overall activity resembles the real one.

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