Master Thesis

Writing Assignment

Epilepsy at different scales: considerations for the medical application of dynamical models

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Abstract

Epilepsy is a complex and poorly understood disease characterized by a susceptibility to recurrent seizures. One in three patients does not respond to available anti-seizure drugs, raising the need for alternative treatments. Epileptic seizures result from changes in electrical patterns of activity on the scale of large neuronal networks. The underlying mechanisms that lead to these changes can be multifactorial and patient-specific, and may range from synaptic protein dysfunction to changes in the connectivity patterns of the network. Furthermore, the changes in electrical activity observed during seizures resemble dynamic phase transitions, making dynamical modeling a natural choice for the study of epilepsy. However, although epilepsy has been a subject of computational modeling for years, little progress has been made in identifying clinically relevant parameters. Seizure prediction algorithms and intervention strategies that are employed on a systemic level to interrupt seizures have had mixed results, partly because of the lack of understanding of the underlying mechanisms of action. Because of the nature of seizure prediction and prevention methods, which measure from and act upon large networks of neurons, a systems-level understanding of epilepsy based on dynamical models could be very beneficial in improving their effectiveness. Large-scale brain networks are also being integrated into dynamical models, following recent findings on the role of distributed newtork metrics in epileptogenesis. Nevertheless, such models still face a problem of scaling and have not yet produced clinically relevant results. The future of dynamical modeling in epilepsy treatment seems to lie in patient-specific models.

Layman's Summary

Epilepsy is a neurological disease characterized by recurrent seizures. Seizures are temporary changes in the patient's behavior lasting seconds to minutes, and can include spasms, loss-of-consciousness and other effects such as visual hallucinations. Through a method called Electroencephalography (EEG), it has been observed that seizures also coincide with changes in the electrical activity of neuronal networks in the brain. During seizures, large groups of connected neurons fire synchronously and in an abnormal manner, causing the signal detected by EEG to increase in strength and to change shape. These large-scale changes in how neuronal networks behave are thought to cause the symptoms experienced by patients during seizures, but we still don't understand what triggers the change in electrical activity. Identifying the triggers of epileptic seizures is an important step, because it will lead to the development of treatments, or at least of interventions that can help prevent seizures or stop them when they occur.

The most common treatment for epilepsy is using anti-seizure drugs (ASDs), which are meant to prevent seizures from happening in epilepsy patients. ASDs only work for around 60% of patients, so researchers are looking for alternative approaches to treat the remaining 30%. A lot of attention has gone into the development of seizure prediction algorithms, which can predict an oncoming seizures based on continuous EEG measurements and warn the patient before they occur. Seizure intervention, where the nervous system is stimulated to stop seizures before or once they occur, has also been used as a treatment strategy. While these methods are effective in some patients, their success rate is too low to make them a viable alternative to ASDs. The mechanisms by which these treatments work is not clear, and neither is the reason that they work in some patients and not in others.

Computational models can help improve the effectiveness of epilepsy treatments. Virtual "model brains" are easy to experiment with, so one can simulate an epileptic brain, apply a given treatment, and see how effective the treatment is in predicting or preventing the "virtual" seizures. One can then fine-tune the treatment to improve its effectiveness in the simulation, and hopefully to also improve effectiveness if the fine-tuned treatment is used in a real patient. Computational modeling can also be used to better understand what makes a brain epileptic. For example, there is evidence that the network properties of a brain (the structure, number and strength of connections between neurons) can make it more vulnerable to seizures. By changing these network properties in a virtual brain, one can see what network structures make it more likely to produce seizures in the simulation.

The evidence so far shows that the cause of epileptic seizures can be multifactorial and patient-specific, ranging from genetic mutations causing protein dysfunction to altered network structure due to brain injuries. The approach to developing treatments should therefore be personalized, using a combination of the aforementioned computational modeling approaches to find the causes of epilepsy in each patient and to optimize the treatment to the patient's needs.

1 Introduction

Epilepsy is a neurological disease characterized by a chronic disposition to generate recurrent seizures [1, 2] It is one of the most common neurological disorders, affects all age groups, and is highly debilitating for those who suffer from it [1]. Around two thirds of epileptics are successfully treated with anti-seizure drugs (ASDs), but for the rest, available treatments like resection surgery and brain stimulation therapies remain largely ineffective [1, 2]. This is due to a limited understanding, firstly, of how the brain can produce seizures, and secondly, of what all the factors are that make a person chronically susceptible to seizures.

There are many types of epilepsy, and the clinical symptoms of seizures can vary substantially depending on the type. Patients can experience a range of physiological symptoms including involuntary muscle contraction (myoclonic seizure), muscle relaxation (atonic seizure), visual phenomena and loss-of-consciousness [2]. The clinical symptoms are a result of excessive abnormal or hypersynchronous firing of neurons in the brain [1, 3], an electrical signature which is often detected using Electroencephalography (EEG). EEG shows that the electrical patterns associated with seizures initiate in one or several anatomical networks (groups of interconnected neurons in an area occupying around 0,01% of the brain, around 10^8 neurons [4]). These networks may be located in a single brain hemisphere (focal onset seizures) and or in both hemispheres (generalized onset seizures) [1, 2]. Focal onset seizures sometimes spread (seizure generalization), taking over both brain hemispheres. The location of seizure-generating networks depends on the type of epilepsy. In temporal lobe epilepsy, for example, seizure generation may involve subregions of the temporal lobe like the amygdala or hippocampus.

The underlying cause of seizure initiation in neuronal networks has long been suspected to be excessive synaptic excitation compared to inhibition [5, 2]. However, as apparent by the fact that the >20 available ASDs (all of which target excitatory or inhibitory molecular mechanisms) fail to treat a large portion of patients, this understanding is incomplete. Epilepsy is a complex disease; It can be caused by a large number of factors (i.e. brain injuries, strokes, genetic mutations, autoimmune or infectious diseases [2, 5, 1]) which result in dysfunction at different levels of brain activity, from ion channel function to circuit level connectivity. Over 500 genes have been associated with epilepsy, yet we still don't understand how the various possible causes can lead to similar behaviors at the level of networks or the whole brain [5, 1]. Ultimately, epilepsy is defined by the collective patterns of activity in large networks of neurons instead of that of individual cells. Our incomplete understanding of the disease is therefore related to a limited understanding of brain network function in general [6].

There is a lack of experimental techniques with sufficient spatiotemporal resolution to study mesoscale network behavior in the human brain. Animal and *in vitro* seizure models are very useful in the study of seizure dynamics, but the evidence so far suggests that they are not sufficient to reproduce the whole range of etiologies of epilepsy in humans, and they have not led to the development of effective treatments for drug-resistant epilepsies [7]. We therefore need computational models that can integrate data from connectomics, EEG, functional magnetic resonance imaging (fMRI) and other experimental techniques [6]. Some theoretical models of diseases like parkinson's, alzheimer, schizophrenia and depression employ dynamical systems analysis, explaining changes in behavior in terms of network phase transitions, or changes in network behavior [8, 9]. Epilepsy is particularly interesting from a dynamical systems perspective because of the measurably distinct dynamical states associated with it (changes in a patient's behavior that overlap with changes in the EEG signal), and because of the transitions between these states which are reminiscent of bifurcations. This makes epilepsy a frequent focus of theoretical and computational modeling.

Dynamical models approach the problem of epilepsy in various ways; some just try to reproduce the phenomenology of epilepsy and the transitions between states as seen in electrographic data, while others include biological or structural detail about the involved networks. Still, there are several factors that have prevented these models producing medically applicable insights. Computational models need to predict epileptiform activity, but this activity varies significantly between patients [10]. Furthermore, epileptiform activity is defined by observations made using EEG, whose measurements are a convoluted and noisy projection of electrical activity in large neuronal networks (on the order of 10^4 to 10^7 neurons per electrode [11]). Mapping EEG measurements to their source is a challenge of its own (the "inverse problem" of EEG [11]). The other problem is the limited understanding of what the control parameters underlying the transitions to a seizure are. In many models, control parameters are not clearly defined or are speculated to be a combination of several factors [12, 13]. Identification of control parameters that can be manipulated in a clinical setting is crucial to generate treatments from theoretical models. Eventually, properties of brain networks, such as their connectivity, organization and plasticity, may also become feasible treatment targets [13].

In this review we will present the dynamical systems view of epilepsy and present some representative computational models developed to study epilepsy. We will then discuss current and potential applications of the dynamical models in the medical field for the development or improvement of interventions for intractable epilepsy.

2 Is there a common footprint of epileptic seizures?

The wide range of clinical symptoms in which epileptic seizures manifest themeselves are accompanied by changes in the electical activity in one or more regions of the brain [3]. Seizures also follow patient-specific biological cycles; The risk of a patient experiencing a seizure is modulated by multiple cycles operating at different timescales ranging from ultradien to circannual [14]. Seizures are rythmic discharges lasting at least 10 seconds (typically lasting between 30 seconds and 2 minutes), and can be identified using Electroencephalography (EEG) or related methods like intracranial EEG (iEEG), chronic EEG (cEEG) and Magnetoencephalography (MEG). In EEG, electrodes are placed on a patient's scalp to measure the electrical activity of clusters of neurons (10^4-10^7 neurons per electrode) at multiple locations in the cerebral cortex (Fig. 1A). More specifically, EEG measures the voltage fluctuations generated by ionic currents within cortical neurons [11]. Besides being an important diagnostic tool for epilepsy, EEG has revealed that the footprint of epilepsy is not limited to periods of seizures (*ictal* periods), but also persists through seizure-free (*interictal*) periods, with dynamic changes detectable seconds to hours before the onset of a seizure (*post-ictal* period) and up to 24 hours after seizure offset (Fig. 1B). The abnormal activity detected in epileptic patients during all of these periods is referred to collectively as epileptiform activity; In the context of EEG, this is activity that deviates from the baseline cortical rhythms. Depending on the area of the cortex and the cognitive state of the subject (e.g. awake, sleeping), this baseline oscillatory activity typically ranges between the *theta* (4-7 Hz), *alpha* (8-13 Hz), and *beta* bands (13-30 Hz) [15]. Because of the variety of epileptiform and non-epileptiform activity detectable by EEG, visual inspection of EEG recordings by an expert remains the golden standard for the distinction between the baseline and epileptiform activity [16].

EEG seizure patterns vary significantly in morphology and frequency, and they change in amplitude, frequency and shape during the course of the seizure [10]. Regardless of their variety, most of these patterns are marked by an increase in the density of high frequency oscillations (HFO's, >200 Hz) not seen in healthy subjects [17]. During interictal periods, high amplitude discharges can often be detected (<400 ms). These transient events are called interictal epileptiform discharges (IEDs) and their most common form consists of a sharp spike that may be followed by waves (high or low frequency) [10]. At the cellular level, IEDs are a result of a paroxysmal depolarizing shift (PDS), an abnormal reaction to depolarization in neurons. In a PDS, depolarization of a neuron triggers a series of action potentials followed by a plateau of continued depolarization, as opposed to a single action potential followed by repolarization [18]. When PDSs synchronize over a large collection of cortical neurons, they are detected in EEG as an

IED.

In the seconds to hours before seizure onset (pre-ictal stage), EEG patterns undergo spatiotemporal changes [19]. Some studies report an increase in the the frequency and amplitude of IED-like spikes, and have termed these spikes pre-ictal discharges (PIDs) [20]. However, pre-ictal markers may be patient specific, and they are typically not distinguishable through visual inspection of EEG alone [19]. Post-ictal patterns, on the other hand, are easier to spot. In the hours to days after a seizure, patients can experience symptoms which are associated with dysfunction in cognitive processes, like memory and speech disturbances, confusion, decreased alertness or even delirium and visual or auditory hallucinations [21]. Along with these clinical symptoms, EEG recordings of a majority of patients show a set of characteristic changes known as post-ictal suppression or slowing, lasting up to 24 hours after the seizure. Post-ictal slowing involves a slowing down of brain rhythms and a reduction in their amplitude (<10mV). Initially, cortical activity slows to <4 Hz (delta slowing) and the frequency increases to the theta band (4-7 Hz) before returning to the baseline background activity [21]. The mechanism behind postictal slowing is unknown [21],

The literature outlining characteristics of each phase of epilepsy typically relies on visual markers spotted in EEG recordings. EEG has been very instrumental in understanding electrical patterns of epileptiform activity, but it tells us very little about about spatial patterns in epileptic networks other than the fact that they involve large scale synchronization of neuronal activity. For this purpose, animal and *in vitro* models in combination with methods like calcium imaging are useful. Another downside of EEG is its low signal to noise ratio, which limits the range of epileptiform patterns that can be observed. On scalp EEG, the seizure becomes detectable only after a large brain volume of 6-8 cm^3 has synchronized, meaning that the initial focal onset of seizures, as well as pre-ictal markers, are difficult to spot [10]. Nevertheless, the large number of studies analysing EEG, iEEG and MEG data have revealed some commonnalities characteristic of epileptiform activity. HFOs and IEDs are typical of epilepsy patients, and rare among the general population [17, 22]. Post-ictal slowing is also characteristic of a majority of patients [21]. The cyclical nature of epilepsy points to the possibility of slow changing variables being involved in triggering seizure onset and offset [14], but the specificity of these cycles to patients also means that the mechanism by which cycles trigger seizures may not be universal.

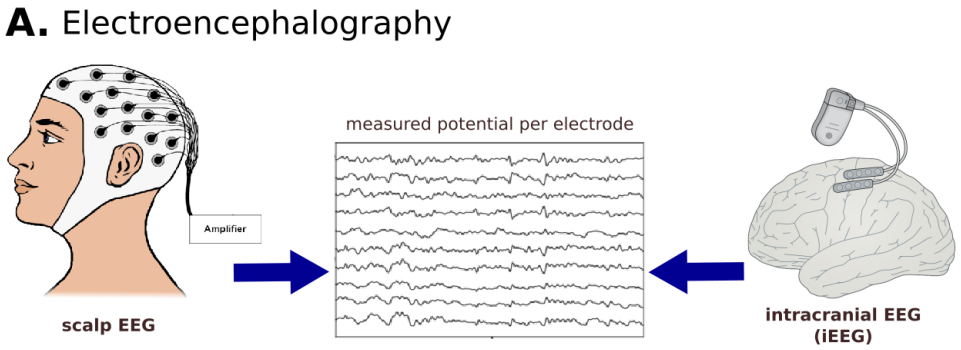

Figure 1: (**A**) EEG measures fluctuations in the local field potential at different sections of the cortex. In scalp EEG, electrodes are placed at many locations on the subject's scalp. In iEEG, the electrodes are surgically placed under the scalp, offering better sensitivity and access to deeper brain regions. (adapted from [23, 14]). (**B**) Multi-electrode iEEG recording of epileptiform activity including an IED and the onset of a seizure. (adapted from [14]). (**C**) IEDs recorded by EEG are a result of synchronized PDSs in large networks of neurons(adapted from [24, 25])

3 Epileptic transitions, networks and criticality

The changes in electrical activity observed in epilepsy are reminiscent of the change of state observed in a variety of equilibrium and nonequilibrium systems. Dynamical changes of state or phase in networks of interacting elements can be influenced by the global and local network properties, and are often described in terms of dynamical systems theory. In this section we will introduce aspects of dynamical systems and network theory that are relevant to epilepsy research and to the models described in later sections.

3.1 Dynamical systems

Dynamical systems may exhibit multiple **phases or dynamical states**. In a phase, which exists within a certain parameter range, the system has specific properties. For example, water can be in a liquid, solid (ice) and gaseous (water vapor) phase. A **phase transition** refers to the switch of the system from one state to the other (e.g. the evaporation or freezing of water). The phase is described by the **order parameter**, whose value changes when the system transitions from one phase to another and indicates which phase the system is in. A **control parameter** is the parameter by which the system's phase is manipulated. In the case of of water evaporating, the density of the system is an order parameter and the temperature is a control parameter. In a different example from population dynamics, a fish farm may have a healthy population as long as the harversting rate remains under a certain threshold. If it crosses that threshold, the population abruptly dies off. In this system, the harvesting rate is a control parameter and the population density an order parameter.

A system can be described by a set of differential equations of the following form:

$$\frac{\mathrm{d}x}{\mathrm{dt}} = f(k, x) \tag{1}$$

Here, x is a system variable (or set of variables) that include order parameters and k is the control parameter (or the set of control parameters). For a nonlinear $f(k, x)$ with respect to x, there may be multiple equilibria, or more than one values of x^* at which the system is at equilibrium or steady state. A steady state is defined as

$$\frac{\mathrm{d}x}{\mathrm{dt}} = 0 \tag{2}$$

and x^* are solutions of

$$f(k, x^*) = 0 \tag{3}$$

For x^* (equilibrium or steady state values of x) x does not change with time. Some equilibria are stable, meaning that if the system is perturbed to

a value away from x^*, it will be pushed back to and converge to its original state. At unstable equilibrium, on the other hand, any perturbation will push the system further away from the equilibrium. A useful analogy for this is a ball placed on the bottom of a valley compared to one placed on top of a hill [12] (Fig. 2A). If the ball at the bottom of the valley is moved slightly from its position, it will roll back and forth and eventually stop at it's original (stable) position. This position, in the context of dynamical systems, is called an **attractor**. A ball placed on top of the hill is only at equilibrium as long as it is kept perfectly still. Any small perturbation (like the wind blowing on it) will cause it to roll away from it's position towards a stable equilibrium.

The existence and value of stable equilibria also depends on the control parameter k. For example, the stable state of water depends on the temperature. At room temperature, water is stable in a liquid state. If the temperature is slowly reduced, it will maintain it's stable liquid state. However, once the temperature is below 0 °C, the water will switch to a solid phase. The stable equilibria of system variables determining the water's phase will have switched, making the solid phase stable. Many systems for which $f(k, x^*)$ is nonlinear in x can exhibit multistability (multible equilibrium solutions), and they may have multiple stable equilibria for the same value of a control parameter. The change in the number and nature of equilibrium solutions of a system as k is changed is called a **bifurcation** (Fig. 2B). This phenomenon happens close to the critical value of k and can be interpreted as a phase transition of the system brought about by changes in the control parameter. Here, the system can show complex behaviour, being very sensitive to external stimuli and noise and switching back and forth from the different equilibrium states. Such behavior can be seen as large fluctuations in x on several length scales (**avalanches**) and slow recovery to equilibrium (**critical slowing down**). This type of behavior is particularly interesting to neuroscientists that may wish to interpret the electrical activity in the brain as the variable x in a dynamical systems model. In such a model, $f(k, x)$ describes a neuronal network of the brain that operates close to a critical point. It is thought that many mental illnesses, including epilepsy, are a result susceptibility of the brain towards sub- or supercritical regimes, away from criticality [8]. The question which naturally arises when considering this hypothesis is what factors determine whether the brain operates at a critical state (i.e. what are the control parameters). We discuss the simplest model of network criticality below, after introducing some aspects of network theory.

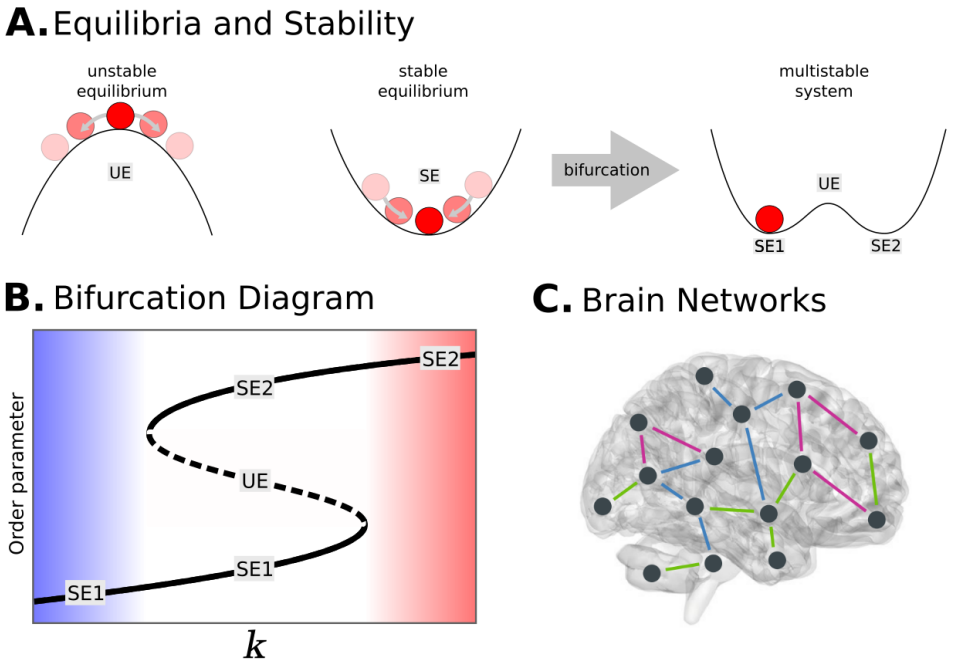

Figure 2: **A-B.** Dynamical Systems **A.** The ball analogy: A ball placed on top of a hill is at an unstable equilibrium (UE), because a small perturbation will cause it to roll off. A ball in a valley is at a stable equilibrium (SE), as a it will return to its original position following a small perturbation. At a bifurcation, multiple stable equilibria can exist. The two stable equilibria in this example (valleys SE1 and SE2) are separated by an unstable equilibrium (hill UE) **B.** A bifurcation diagram shows how the stability landscape changes as a function of a control parameter k. Solid lines indicate stable equilibria as a function of k, and the dotted line indicates an unstable equilibrium. At low k, one stable solution exists (SE1), As k increases, the system reaches a bifurcation, where multiple stable equilibria exists (SE1 and SE2) and the system can transition between them. If k is increased further, only one stable equilibrium remains (SE2). The order parameter indicates which state the system is in. In the ball analogy (A), the order parameter could be the position of the ball on the horizontal axis. **C-D.** Brain networks and graph theory (adapted from [26]). **C.** Brain networks can be expressed in terms of graphs with nodes (neurons, small networks or large brain regions) connected through edges. Edges can represent the structural (physical, white matter) or functional (effective, dynamic, electrical) connectivity between nodes. **D.** Examples of common network structures from graph theory. Different structures give the system different properties.

3.2 Brain networks and graph theory

Brain networks can be represented by graphs, which are composed of nodes and edges (Fig. 2C). Nodes represent neural elements which can be single neurons, populations of neurons or whole brain regions. Edges, which carry weight and direction, describe the connectivity between nodes in one of two ways, either structurally or functionally [26]. In **structural networks**, edges represent the physical wiring connecting nodes (e.g. synaptic connections between neurons or white matter tracts connecting distant brain regions). *In vivo*, structural networks can be constructed using methods such as computerized axial tomography (CAT) or diffusion tensor imaging (DTI) [26]. In **functional networks**, edges describe the correlation between the activity in different nodes, and they may represent excitatory or inhibitory interactions. Functional networks are constructed using methods that can record brain activity at multiple nodes simultaneously, such as EEG or functional magnetic resonance imaging (fMRI) for large-scale brain networks. To generate a functional connectivity map, a time series recording from each node (each electrode in the case of EEG and each voxel in the case of fMRI) is correlated with the time series of each other node. The level of correlation (or anti-correlation) of the timeseries determines the strength of connections in the network.

Network analysis relies heavily on graph theory. Graph theory can be used to characterize network structure using specific measures that describe connectivity and patterns such as the average number of links connected to a node, the clustering of nodes, or the existence of modularity and hubs [26, 27] (See Fig. 2D for examples). Dynamic processes on networks may involve the study of how node properties, given the edge structure (node connectivity), change with time and/or how the connectivity (edge weights and directions) change with time. Both types of processes are relevant to neuroscience. The dynamics can be modeled by deterministic differential equations, or stochastic differential equations. In this review we concentrate on the former [27].

3.3 Criticality and network structure

The simplest model that can be used to describe how network properties relate to criticality is a stochastic network model by Muñoz [28](Fig. 3). Each node i is in a state s_i which can be either active ($s_i = 1$) or inactive ($s_i = 0$). After every timestep, the state of each node is updated. An active node has a probability μ of being deactivated (This is set to 1), and an inactive node has a probability λ of being activated by an active connected node. λ and μ represent critical parameters. If a mean-field deterministic equation is constructed for the activity density of the system $\rho(t)$ where $\rho = \sum_{i=1}^{N} s_i/N$ at any given time t, a bifurcation appears at $\lambda = \lambda_c = \mu$ (rate of deactivation

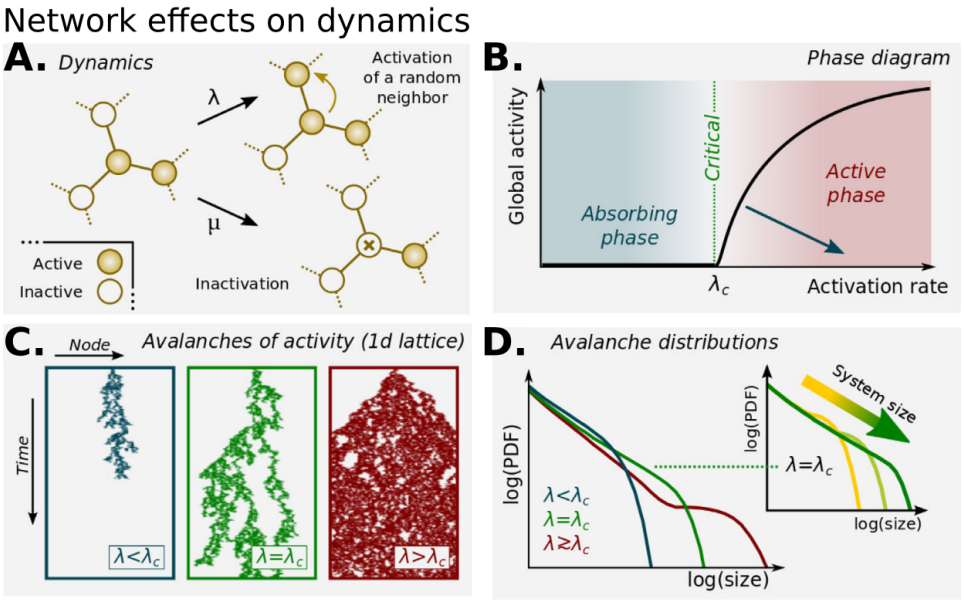

Figure 3: How network properties can influence dynamics, illustrated through a simple model (adapted from [28]). **A.** A node in the network can be activated by another node with probability λ. An active can switch of with probability μ. **B.** The reaction of the network to a set of intial conditions depends on the ratio of λ and μ and on the number of connections per node. A critical transition occurs at λ_c. **C.** In the subcritical domain ($\lambda < \lambda_c$), activity dies off. In the supercritical domain ($\lambda > \lambda_c$), it is amplified. At λ_c, Avalanches of activity on multiple scales are observed. **D.** The decay of activity during avalanches follows a power law.

equals rate of activation). At the subcritical regime ($\lambda < \lambda_c$), ρ decays exponentially to 0. In the supercritical regime ($\lambda > \lambda_c$), ρ reaches a steady state value which is a function of λ. At the critical value of λ_c, the decay of $\rho(t)$ follows a power law ($\rho(t) \sim t^{-1}$). The factor λ can be interpreted as the excitability of the network. Since the probability of activating a node depends on the number of connected active nodes, it follows that a larger average number of connections (synapses in a neuronal network) will produce supercritical behavior for the same λ_c. Similarly, for the same connectivity, higher excitability will produce supercritical behavior. This model is not specific to neuronal networks, but it indicates that besides a higher excitability, higher structural connectivity can make the network dynamics supercritical.

4 The dynamical systems view of epilepsy

In the dynamical systems view of epilepsy, the brain exhibits multistability and the ictal (seizure) state represents an attractor seperate from that of baseline neural activity. While a healthy brain never transitions to the ictal state under physiological conditions, an epileptic brain is more susceptible to transition. A minimal dynamical model of epilepsy must satisfy the following conditions [6]. Firstly, it must be able to explain the existence of normal (baseline) and seizure states, i.e. to predict different dynamical states. Secondly, it must replicate certain specific features of epileptiform activity that are invariant or common across patients and models. These may include the high frequency oscillations and spikes discussed in section 2. The last requirement is that the model should replicate seizure onset and offset i.e. the transition to and from seizure states. In this section we will discuss several approaches to dynamical modeling of epilepsy, how they differ and what each of them can teach us about the disease.

4.1 Dynamical models of epilepsy

The different types of models used to study epilepsy describe brain activity at different scales [24, 29]. **Detailed network models** are the most biologically accurate. They include detailed compartmentalized models of different types of neurons, which incorporate both the morphological and electrical properties of single neurons and the synaptic connections between neurons. These are usually based on the Hodgkin-Huxley formalism and can be used to study factors that cause epilepsy at the molecular level, such as dysfunction in ion-channel conductivity. Due to their complexity, however, detailed network models are difficult to scale up to large networks of neurons.

On the other end of biological detail, **generic phenomenological models** attempt to describe the main features of a system's behavior using only the minimum necessary number of variables. A prominent example of a phenomenological model in epilepsy research is the "Epileptor", a five-dimensional dynamic model developed by Jirsa et al [13]. The Epileptor aims to describe the invariant features of seizures. The features considered are fast discharges, IEDs, and a direct current (DC) shift in the local field potential (LFP) at seizure onset which reverses at seizure offset. These features were identified in iEEG data and direct current recordings from animal models. The resulting model consists of a set of five coupled differential equations. Fast discharges and IEDs are modeled as coupled oscillators, each represented by two state variables. A slower variable z acts a a control variable, guiding the system between seizures and through the seizure time course (Fig. 4A). z was not associated with a specific process, but hypothesized to be a combination of a large number of extracellular pro-

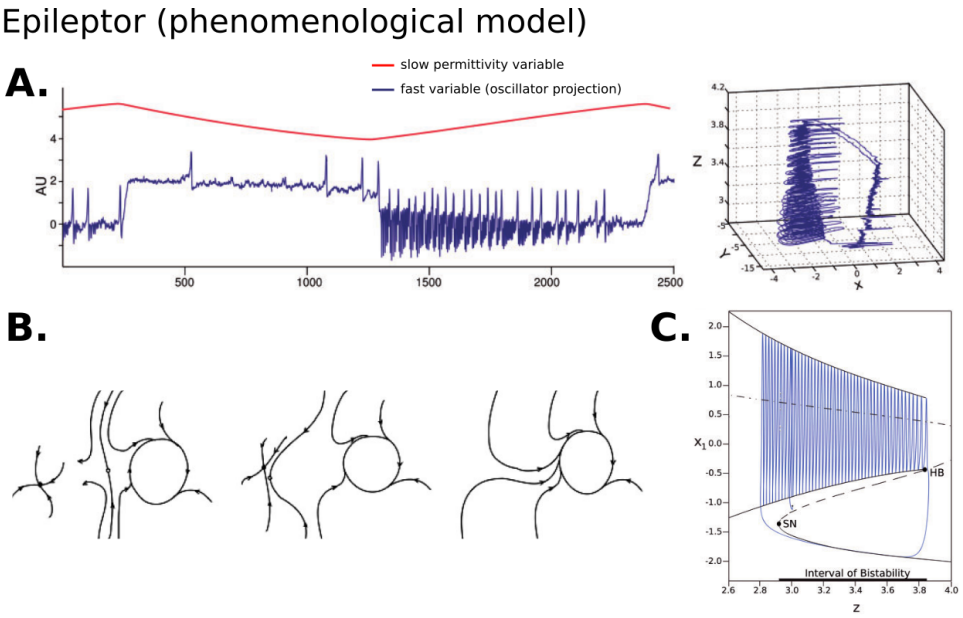

Figure 4: The Epileptor (adapted from [13]). **A.** Simulated seizure. *Left*: time-plot. Seizure onset, time course and offset are controlled by the slow state variable z varying in time (red). *Right*: the seizure trajectory projected in 3D space as a function of fast variables x and y, and slow variable z. **B.** Simplified caricature of the flows of two fast variables in state space at seizure onset. *From left to right*: As z decreases, the interictal state loses its stability and the system transitions to the ictal state (seizure). The reverse situation happens at seizure offset. **C.** Bifurcation diagram of the Epileptor. The system displays bistability between the left saddle-node bifurcation point (SN) and the homoclinic bifurcation point (HB).

cesses that occur on a slow time scale and influence the likelihood of seizure occurrence. The evolution of z through the course of seizure onset and offset significantly overlapped with that of extracellular parameters measured during seizures in experimental models, such as the levels of K^+, oxygen and ATP consumption. Slowly evolving extracellular parameters like these may be control parameters that cause epileptogenic networks to cross the threshold of seizure generation. Generic phenomenological models like the Epileptor cannot tell us what exact properties of a neuronal network make it epileptogenic, but they show us how such a network can produce seizure-like phenomena in a time-dependent manner.

Neural mass models (NMMs) can be placed between generic phenomenological and detailed network models in terms of biological detail, and they are used to model the combined dynamics of larger neuronal networks. NMMs do not include cellular detail and instead model sub-populations of neurons using variables like the average firing rate, average post-synaptic potential (inhibitory or excitatory), and coupling constants representing the number

and strength of synaptic connections. An early example of a widely used NMM on which later models are based is the one by Wilson and Cowan [30]. The basic model includes two neuronal populations, one excitatory and one inhibitory, with synaptic connections between them and to themselves (Fig. 5A). The model consists of two coupled differential equations:

$$\tau_e \frac{\mathrm{d}E}{\mathrm{d}t} = (1 - r_e E) S_e\{c_1 E - c_2 I + P\} - E \tag{4}$$

and

$$\tau_i \frac{\mathrm{d}I}{\mathrm{d}t} = (1 - r_i I) S_i\{c_3 E - c_4 I + Q\} - I \tag{5}$$

where $E(t)$ and $I(t)$ represent the proportion of excitatory and inhibitory cells firing per unit time at the instant t, respectively. Each population receives external input P and Q in addition to the input it receives from the other population and from itself. A sigmoid function $S\{...\}$ transforms the the total input (given as a membrane potential) to a spiking rate. Furthermore, since active or refractory neurons do not respond to stimulation, the converted input is multiplied by the fraction of available neurons. This fraction is calculated as $1 - r_e E$, where r_e is a scaling factor that estimates the fraction of active plus refractory neurons from the fraction of active neurons. Active neurons eventually return to a level of baseline activity, so a decay factor proportional to the amount of activity in each population is also added. Lastly, the rates of change of E and I are multiplied by a time constant τ. c_1 and c_4 represent the strength of self-excitation and self-inhibition of the neuronal populations respectively, and c_2 and c_3 represent the strength of the synaptic interactions between the populations.

The simple Wilson and Cowan model presented above shows the most basic configuration of interacting excitatory and inhibitory populations. The same idea can be applied to model specialized neuronal circuit architectures, like the cortical networks involved in seizure generation. One of these models is the hippocampal/neocortical NMM originally developed by Lopes da Silva et al. to explain the presence of alpha oscillations in EEG [31]. This model consists of a population of pyramidal cells (PY) and three populations of interneurons; one excitatory (EX), and two inhibitory (Fig. 5B,C). Of the inhibitory interneuron populations, one represents neurons that project their synapses on the dendrites of pyramidal cells (slow synaptic kinetics, SIN) and one represents somatic-projecting interneurons (fast synaptic kinetics, FIN) (Fig. 5C). In the Lopes da Silva model, the presynaptic pulse density from each interneuron population is converted into a post-synaptic potential through a respective impulse response function $h_e(t) = A\,a\,te^{-at}$, $h_i(t) = B\,b\,te^{-bt}$ or $h_g(t) = G\,g\,te^{-gt}$ (excitatory, slow inhibitory and fast inhibitory populations, respectively). Here, A, B and G are the synaptic gains of

each population and $1/a$, $1/b$ and $1/g$ are the respective time constants. The difference between fast and slow inhibitory interneurons is reflected in the time delays; $1/g$ is 10 times lower than $1/b$. The excitation of each interneuron population by pyramidal cells and the additional inhibition of the FIN population by the SIN population all assume slow synaptic kinetics ($h(t) = h_e(t)$ and $h_i(t)$ respectively, see Fig. 5D).

Wendling et al used the aforementioned model to see if the same networks can generate epileptiform activity [22]. By altering A, B and G (simulating an amplification or depression of synaptic responses) they were able to generate 2 types of activity that closely matched interictal EEG activity, as well as 4 patterns of activity which matched activity observed during seizures (Fig. 5D). They also demonstrated that the transition from the ictal to the interictal state, as well as the time course of some recorded seizures during which multiple types of activity where produced, could be replicated in the model by gradually dampening dentritic inhibition (lowering B). These results again point to the balance of excitation and inhibition (and more specifically the strength of GABAergic dendritic inhibition), as being a control parameter during the course of a seizure, guiding the network dynamics through the different observed behaviors. The reduction of dendritic inhibition could be caused by selective loss of inhibitory interneuron connections [22], but, given that the change in synaptic gain occurs in the timescale of a single seizure, it is more likely that inhibition is somehow modulated without immediate loss of synaptic connectivity (e.g. by an extracellular process).

Large-scale dynamical network models (LNMs) consider interactions between distinct brain regions based on brain network data; either structural (e.g. DTI) or functional (e.g, EEG, MEG, fMRI)[26] (Fig. 4C). LNMs may consist of very few nodes (4-30) representing large functionally interconnected regions (i.e. regions whose activity is measured with a single EEG electrode) [34]. They may also be larger (i.e 100 nodes), including structural information about large-scale connectivity [35, 36]. The dynamics of each node is governed by an underlying model, which may be a network (i.e. Wilson-Cowan) or more abstract dynamical model. LNMs have gained a lot of attention recently, partially due to advances in the field of connectomics which allow us to characterize brain network properties in humans. The aim of LNMs is to incorporate the network structure of the whole brain into the dynamical model [35].

There is evidence that even focal epilepsies do not originate from a single onset zone, but from a distributed large-scale network [37], and that epileptiform activity may be a characteristic behavior of specific network structures. This view of epilepsy emerged with the development of Stereoelectroencephalography (SEEG), a more invasive form of EEG where mul-

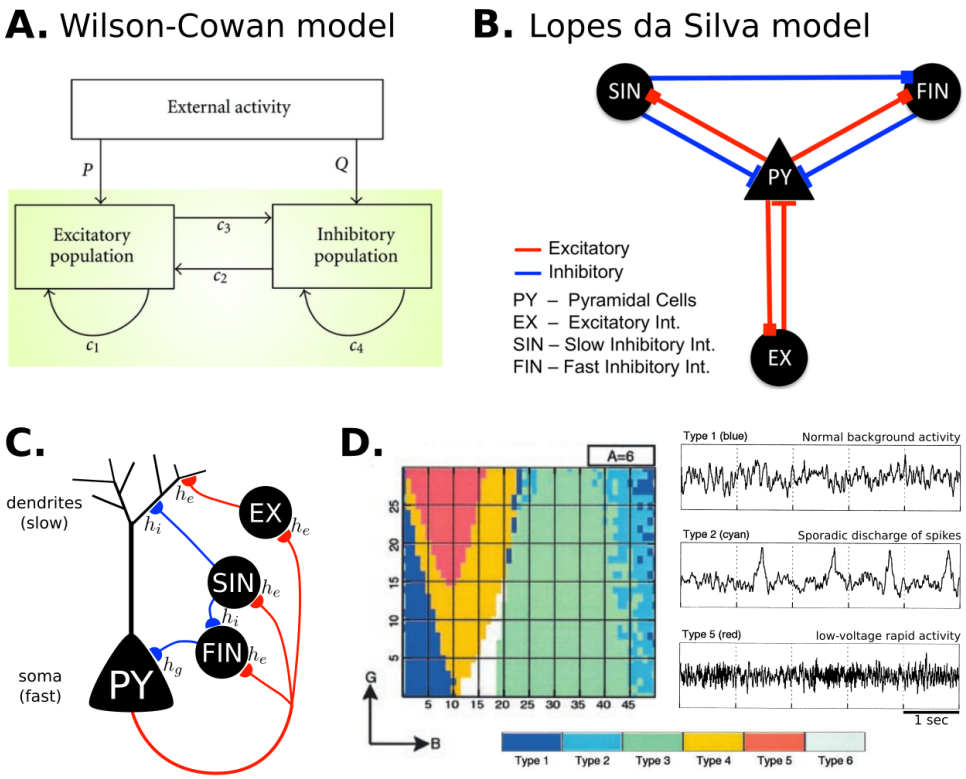

Figure 5: Neural mass models **A.** The Wilson-Cowan model (eq. 4 and 5) (adapted from [32]). **B-D.** The Lopes da Silva model, which implements a more complex mechanism to model synapses. **B.** Schematic representation of the populations and their interactions (adapted from [33]). **C.** The model incorporates two inhibitory interneuron populations, representing dendrite projecting (SIN) and somatic-projecting (FIN) interneurons. The FIN population has faster synaptic kinetics than SIN. **D.** *left*: One slice of the 3D parameter space of varying synaptic gains (A,B and G) in the Wendling model. The colors represent different dynamic states of the model, where the simulated activity resembles healthy or epileptic brain acticity. *right*: Three of the simulated dynamic states. (adapted from [22])

tiple depth electrodes are implanted into a patient's brain tissue. SEEG allows for simultaneous recording of cortical and previously-inaccesible subcortical brain regions with higher spatiotemporal resolution. SEEG revealed that epileptic discharges often initiated simultaneously in multiple anatomically connected foci and led to the conclusion that previously labeled focal epilepsies were non-focal [38]. It also increased interest in the role of network properties in "focal" epilepsies.

Small-world networks are a common network structure in the brain, characterized by both high clustering and short path lengths, and allowing for both isolation of specialized brain structures and efficient communiacation between distant structures [39]. Netoff et al. [40] investigated the role of network metrics (overall connectivity, clustering and synaptic strength) in determining the behavior of small world networks consisting of 3000-24000 neurons with 30-90 synapses each. Single neurons were modeled using various formalisms (Poisson, integrate-and-fire, and stochastic Hodgkin-Huxley). The authors found that the model networks were more likely to generate IEDs as the clustering decreased (modelled by increasing the proportion of long-range connections). Furthermore, higher overall connectivity (i.e. number of edges) led to seizure-like behavior, and removal of nodes followed by compensatory increase in the strength of the remaining connections led to an increase of both IEDs and seizure-like behavior. The study's results were independent of the single-cell modeling formalism, suggesting that the network properties determined the observed behavior and not the details of the individual neurons [40]. This study concentrated on local network properties involving single neurons, but other studies looking at the structure of larger networks, specifically at the functional connectome of large-scale patient networks, have suggested that large-scale epileptic networks are more segregated, with higher local connectivity but decreased long-range connectivity [41, 42]

In addition to deriving general network properties that may lead to epileptiform activity, LNMs can be used to examine the behavior of patient-specific networks. It has become possible to construct dynamical models using patient-specific structural and functional networks [36], and this concept is beginning to be applied in epilepsy research. For example, Gerster et al. [35] used MRI, DTI and diffusion weighted imaging (DWI) data to reconstruct patient-specific connectomes in a structural network consisting of 90 cortical and sub-cortical brain regions. For this they used 20 healthy subjects and 15 patients with drug-resistant focal epilepsy. They then analyzed various network metrics, constructed a multi-population NMM for each of the connectomes, and investigated their dynamical properties. They found that, during seizures, the speed of recruitment of different regions decreased with the length of the shortest path between the epiloptogenic and recruited zones. They also found that brain areas that were more strongly connected

were more likely to transition to a seizure-like state.

4.2 Criticality and epilepsy

A number of theoretical and experimental studies suggest that a healthy brain operates near a critical point (near a bifurcation), and that this behavior is beneficial for brain functions such as optimal information propagation and processing [43]. In this view, a healthy cortex displays near-critical dynamics, operating between premature termination (subcritical domain) and explosive amplification of neuronal activity (supercritical domain)[16, 8]. This theory derives from observations of scale-free (power-law) behavior in avalanches (spontaneous activity among clusters of interacting neurons) and long correlation times of neuronal activity. Furthermore, there is evidence that this scale-free behavior can be disturbed by manipulating the balance of excitatory and inhibitory activity. Applied to epilepsy, this theory suggests that epileptic neuronal networks shift away from criticality towards a supercritical, excitation-dominated state. Arviv et. al. [16] tested this hypothesis in patients with refractory epilepsy. Using MEG, they measured brain activity during interictal periods in the epileptic patients and compared it to healthy subjects. They found higher values of the connectivity in epileptic patients and a deviation from a power-law in avalanche sizes (towards larger avalanches), suggesting a shift towards supercriticality.

The case for the "critical brain" is compelling, but there is currently no consensus about whether the brain operates at a critical point, and if epilepsy represents a deviation from criticality or a complete phase transition. A study by Maturana et al [44] provided evidence for phase transitions when they analysed long-term iEEG data from focal epilepsy patients. The study found that, in anticipation of a seizure, there was an increase in the autocorrelation and variance of iEEG measurements. These results are consistent with critical slowing down, a phenomenon that is typical of phase transitions in many dynamical systems (see section 3). Maturana's results do not necessarily contradict the critical brain hypothesis, as it is possible for a phase transition to occur from a near-critical (e.g. slightly subcritical) point towards supercriticality. However, another recent study found no evidence of a shift away from criticality or a phase transition before seizures [45], leaving the brain criticality hypothesis and it's role in epilepsy up for debate.

5 Clinical applications of epilepsy as a dynamic disease

The first course of action in treating epilepsy today is through anti-seizure drugs (ASDs), which can have side-effects, affect long term development in children [46], and are only effective in around 60% of patients. For the remaining patients, treatment options are very limited. From prognosis to treatment, new methods are necessary. Here we will focus on current and prospective medical interventions that are based on a dynamical systems approach to epilepsy, or that have the potential to be improved if principles of dynamical systems theory are applied.

5.1 Seizure prediction

Seizure prediction is based on the idea that patients can be warned about an oncoming seizure or a high risk of seizures using a system that continuously measures electrical activity in the brain [47] (e.g. through iEEG, Fig. 6). Seizure prediction has been attempted multiple times since the 1970s, and most implementations to date have used a data-analytic or artificial intelligence (AI) approach that looks for pre-ictal markers in the EEG signal (e.g. wavelet entropy and energy [19] and critical slowing down [44]) without relating these to an underlying dynamical model. Numerous seizure prediction algorithms have been proposed based on the observation of such markers. However, the seizure prediction field has a history of mixed or unreplicable results and no biomarkers have been been proposed that can predict seizures reliably and in all patients [48]. This is likely due to the complexity of epilepsy and to the myriad of factors that may influence the EEG signal. In principle, seizure prediction does not require a dynamical model, but the mixed success of current prediction implementations suggest that a model-based approach would be beneficial. A model would help patient-specific[49] and epilepsy-specific calibration, and it would enable the discrimination of the different factors influencing the EEG signal.

5.2 Seizure intervention strategies

Given that seizure prediction is feasible, the next step would be to develop strategies to intervene and prevent seizure generalization or even seizure onset (Fig. 6, see dotted arrows). Currently used and suggested seizure intervention strategies act on a systemic level by directly influencing parameters like the local field potential or temperature at the focal onset zone. Mesoscale and large-scale dynamical models can therefore be useful for understanding the mechanism of action of these interventions and improving their effectiveness. Dynamical models will require more detail than models used for seizure detecton, at least with regard to simulating the targeted

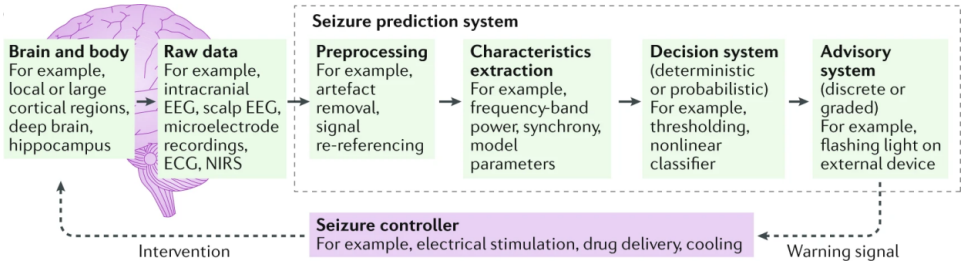

Figure 6: Seizure prediction and intervention (adapted from [47]). To predict seizures, the brain is continuously monitored through electrical or other biosensors. This data is processed and analysed for pre-ictal markers. Based on this analysis, the risk of a seizure is assessed and the user is notified accordingly. Optionally. the system's output can be fed-back into a controller which stimulates the brain locally to reduce the risk of seizure (dotted arrows). If a dynamic model of the epiletogenic system is available, a closed-loop feedback controller can be developed to automatically adjust control parameters and prevent seizures entirely.

mechanisms, whether those are synaptic inhibition or network connectivity.

There are several ways to stop and prevent seizures. One way is by delivering powerful short-acting ASDs locally to the region of epileptic focus [50]. So far, this method has only been demonstrated in animal models for interruption of seizures after onset (using seizure detection instead of prediction). However, the ability to deliver drugs locally, based on an accurate assessment of the seizure risk, could allow for the use of more powerful doses of these drugs only when they are necessary. This would make ASDs more effective while preventing the side effects of chronic use.

5.2.1 Rapid cooling

Local rapid cooling, where a small implanted device is used to the cool down the seizure onset zone down to temperatures between 15°C and 25°C, is another potential method for seizure prevention. Experiments *in vitro* have shown that rapid cooling reduces the frequency and magnitude of ictal discharges. When rapid cooling was attempted *in vivo* in an animal model however, only the magnitude of discharges was reduced [33]. A study by Soriano et al. [33] used computational modeling in an attempt to understand the mechanism underlying focal cooling, and the discrepancy between the *in vitro* and *in vivo* results. Based on evidence that rapid cooling supressed seizures through a synaptic mechanism, they introduced temperature-dependence in the cortical NMM by Wendling et al. [22] (see section 4.1 for Wendling model). The model was able to reproduce the *in vivo* effect of cooling on epileptic discharges, and involved two temperature-dependent mechanisms: a synaptic mechanism that resulted in a reduction of discharge frequency, and an excitability mechanism that compensated

for the reduction in frequency and led to suppression in the magnitude of discharges.

5.2.2 Electrical stimulation

Electrical brain stimulation has gained a lot attention in the past 25 years as a possible epilepsy treatment. There are many variations, such as Vagus Nerve Stimulation (VNS), Responsive Neurostimulation (RNS), and Deep Brain Stimulation (DBS). The aim is to either interrupt seizures at onset or to reduce the frequency and severity of seizures in the long-term. Unfortunately, while these treatments do help some patients, the nonresponder rates are high [51] and the implantation procedure is invasive, making brain stimulation therapies an unattractive option for many. There is extensive medical literature outlining the efficacy of these treatments for different categories of patients [51, 52], but the literature attempting to explain their mechanism of action is lacking. Electrical stimulation therapies are prime candidates for integration into existing dynamical models, since they act on a system-wide level [12, 26]. In fact, there is increasing interest in the implementation of control systems theory in brain stimulation systems, in the form of closed-loop controllers [53, 54].

Closed-loop feedback control systems are ubiquitous in engineering applications, one example being thermostats. Their basic form consists of an input, a controller and an output. The controller is tuned to a desired reference value. It continuously receives input from the system (e.g. the local field potential at the seizure onset zone measured by iEEG) and compares it to the reference (local field potential at baseline neural activity). It then generates an output that stabilizes the system according to the reference (e.g. by electrical stimulation). There is an extended history of applications of controllers in various dynamical systems, and control theory has shown to be effective when applied to theoretical network models simulating epileptic seizures [53, 54]. However the success of control-theory methods in actual epileptic neuronal networks has not been proven.

6 Discussion

A big challenge in the modeling of epilepsy is the large variation in the morphology, frequency and dynamics of seizures. This makes the task of identifying common features in epileptiform activity difficult. Still, interictal epileptiform discharges (IEDs), high frequency oscillations and post-ictal slowing [10] are very common in epileptic patients and uncommon in the general population. IEDs and high frequency oscillations have been the focus of most dynamical modeling studies to date.

In terms of modeling approaches, the challenge is to find a balance between the ability to replicate the collective behavior characterizing epilepsy on the meso- and macroscale, and the usefulness of the model in medical applications (linking behavior to specific control parameters). From this perspective, the most mature models are generic phenomenological models (e.g. Jirsa et al. [13]), and mesoscale NMMs (e.g. Wendling et al. [22]) that are motivated by the known connectivity patterns between excitatory and inhibitory neural masses. Network analysis and graph theory are also beginning to contribute to our understanding of epileptogenic networks at the meso and macroscales. These methods reveal how network properties, like increased local but decreased long-range connectivity, may also change the dynamic behavior of large-scale neuronal networks, making them more prone to seizures [40, 41, 42]. The implication of these findings on network properties is that an important difference between many epileptic brains and their non-epileptic counterparts may lie in the structure of their networks and the strength and number of synapses. A genetic mutation causing dysfunction in GABAergic inhibition, or disruption of connectivity patterns after a brain injury, can make a network epileptogenic. This may lead to compensatory strengthening of other synapses, exacerbating the problem [22, 40]. Changes in network structure and in number of synapses, however, happen on a much slower timescale that the onset and offset of seizures [39]. A change in connectivity may therefore be a factor that brings networks close to the threshold of seizure generation, but not the control parameter that triggers them on the timescale of single seizures.

Dynamical modeling has so far not uncovered what control parameters trigger seizure onset and offset, but, through experimental findings and dynamical models, we do have some clues about their nature. Seizures are likely to be triggered by fluctuating extracellular parameters (e.g. K^+, oxygen, ATP, glucose and neurotransmitter concentrations, as sugested by Jirsa et al. [13]). These change on a faster timescale than cell death, synapse formation and synaptic plasticity, but on a slower timescale than electrophysiological variables. This set of parameters is largely patient-specific or epilepsy type-specific, and it is influenced further by patient-specific biological cycles [14, 44].

The complexity of epileptogenic mechanisms and difficulty in diagnosing them has shifted the focus of much of the epilepsy research towards seizure-prediction, which does not require a complete understanding of the underlying mechanisms. Seizure prediction algorithms currently use a data-analytic or AI approach based on pre-ictal EEG markers, and have so far produced mixed or inconsistent results. This may be due to limitations of EEG sensitivity, but it may also be a limitation of the approach itself. EEG signals and multifactorial, and the black-box methods used in prediction may fail to discriminate between all factors that contribute to an EEG measurement. In contrast to AI, dynamical model-based prediction methods are more connected to underlying mechanisms. These models include a few parameters whose values are fitted by EEG signals. The quality of a set of minimal control parameters in a calibrated model is judged by the model's predictive power. Even if the minimal control-parameter set may be somewhat abstract, the parameters do have meanings in the context of the underlying dynamical model. Further, starting from minimal dynamical model that can predict seizures, a more detailed model can be derived for which the control parameters are less abstract and more connected to specific anatomical features or neural processes.

Such detail is required to allow for interventions like seizure prevention or supression, where control parameters have to be more clearly defined. Nevertheless, for these interventions, EEG may not be the best reference signal. Many extracellular parameters which do not have a electophysiological signature (e.g. oxygen and glucose levels, the variable release of neurotransmitters following biological cycles) may be a more direct measure of factors that increase the risk of seizures [13]. With more detailed dynamical models (whose control parameters can be associated with physiological processes) the use of sensors specific to the control parameters may dramatically increase the prediction effectiveness provided that the parameter values are patient-specific. Furthermore, if meso-scale interventions for seizure prediction and control can be succesful, dynamical modeling studies of the interventions, like the one on local cooling by Soriano et al [33], can be very helpful. Such models allow for virtual experiments to test these interventions on patient-derived networks, and to propose strategies to improve them.

Many of the currently proposed strategies for seizure prediction and interventions do not consider the growing theory of "epileptogenic networks". This theory suggests that focal epilepsies originate from distributed large-scale networks rather that from a single meso-scale focus, as previously thought. The idea of epileptogenic networks is relatively new and, as suggested by debates during the 2019 ICTALS conference [55], poorly defined, highly debated, and not yet fully integrated with existing ideas about focal epilepsies. Current studies focus on the implication of epileptogenic networks on epilepsy surgery, where the supposed seizure onset zone is re-

sected [35]. This procedure is often unsuccessful, an outcome that has been attributed to the existence of large-scale epileptogenic networks [35], and which also implies that localized seizure prediction and control will never be widely succesful if it does not consider the patient's network structure. If epileptogenic networks are indeed distributed over the whole brain, it will be necessary for dynamical models to incorporate the structural and functional connectome, and possibly to model whole-brain dynamics on multiple scales. Studies in this direction are already underway (Gerster et al.[35]), but compared to NMMs of smaller networks, this approach is not as mature and employs significant simplifications. In the study of Gerster et al., for example, only the structural connectome is considered, and the strengths of synaptic connections do not have an experimental basis. There are methods that combine structural with functional data to generate more realistic, patient-specific, large-scale dynamical network models [36]. These have not yet been applied to epilepsy research, and large-scale epilepsy models have not yet been able to propose practical solutions to the epileptogenic network problem.

For a long time, epilepsy had been considered to be a disease caused solely by excessive synaptic excitation compared to inhibition. All available anti-seizure drugs are based on this understanding and target related systems, like voltage-gated ionic channels or GABA receptors. Over time it has been shown that the traditional excitation/inhibition view is not sufficient to explain and treat all epilepsy cases. Treatments like resective surgery, seizure prediction systems and brain stimulation have been studied as alternatives that approach epilepsy as a network disease or from a top-down perspective. Although these methods have a decades-long history, they still suffer from low efficacy due to a limited understanding of the underlying mechanisms of action. Experimental animal and *in vitro* models cannot replicate the details of individual patient's networks, so they are not sufficient to predict how patients will respond to an intervention. Dynamical modeling, which has been used extensively in theoretical studies to uncover possible mechanisms by which neuronal networks can generate seizures states, have not been applied sufficiently in interventions like seizure prediction and prevention that currently follow a largely black-box methodology. The multifactorial and network structure-dependent nature of epilepsy means that these interventions could benefit from calibrated dynamical models. In order to make dynamical modeling applicable to medical interventions however, a shift needs to occur from abstract modeling studies towards medically-oriented models that include patient-specific structural and functional network information, as well as sufficient physiological detail and biologically relevant control parameters.

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