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From phenomenological to biophysical models of seizures

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Abstract

Epilepsy is a complex disease that requires various approaches for its study. In this short review, we discuss the contribution of theoretical and computational models. The review presents theoretical frameworks that underlie the understanding of certain seizure properties and their classification based on their dynamical properties at the onset and offset of seizures. Dynamical system tools are valuable resources in the study of seizures. By analyzing the complex, dynamic behavior of seizures, these tools can provide insights into seizure mechanisms and offer a framework for their classification. Additionally, computational models have high potential for clinical applications, as they can be used to develop more accurate diagnostic and personalized medicine tools. We discuss various modeling approaches that span different scales and levels, while also questioning the neurocentric view, and emphasize the importance of considering glial cells. Finally, we explore the epistemic value provided by this type of approach.

1 Introduction

Any brain in most species, from flies to humans, can generate a seizure, for example, after an electroconvulsive shock (see [44]). In a given brain, many different mechanisms can be used to trigger a seizure, suggesting that many different paths can be taken to reach seizure onset [44]. In addition, the existence of at least 16 types of dynamotypes (dynamic signatures of seizures) in patients [44, 79] further increases the number of possible seizure mechanisms. Importantly, individuals with epilepsy display different types of dynamotypes [79], characterized by the type of bifurcation at the onset and the offset of the ictal event. One bifurcation can be generated by several underlying mechanisms, and on the contrary several bifurcations can be generated by one mechanism. This classification is thus based on observable dynamical features instead of specific identified underlying mechanisms. A given animal may display different dynamotypes [12]. Experimental research in epilepsy is based on the unstated assumption that one mechanism may be at play for a given type of epilepsy. Detailed molecular and physiological studies revealed a plethora of modifications in brain regions in epilepsy as compared to control [13]. Which of these modifications are relevant to a given seizure type [44, 79] at a given time during the night and day cycle [4] is unknown. To add to the difficulty, the said differences may correspond to homeostatic alterations, i.e. the circuits underwent extensive modifications, which allow them to perform the same functions as before. This is known as degeneracy, the fact that different parameter configurations can produce the same output [58]. If degeneracy is a universal principle that applies to all living organisms in physiological conditions, it likely also applies to pathological activities. Said differently, there may be multiple ways (parameter configurations in the network) to produce a given type of seizure. These properties of degeneracy exist in multiscale systems [42]. In such a context, a computational approach can be helpful, as it allows for testing different possible

mechanisms *in silico*. The validity of a model depends on the associated objective and scientific question, thus only reproducing the apparent behaviours of experimental observations (e.g. interictal spikes and seizures) may not be informative. How a seizure is defined in the model and which aspects of the model are relevant and useful for the study of epilepsy are the key questions. It depends on the research objective in using models, and the level of description of the phenomenon being considered [19]. One important goal is to make predictions that can be tested experimentally. Predictions are particularly interesting when they point at mechanisms that were not expected/considered *ab initio*. Depending on their size and level of biophysical details, a more or less full parameter exploration can be done in models. For example, a parameter exploration can lead to predictions regarding which parameter values best explain the occurrence of a given type of seizure. We present here the different types of models, from single cells to networks, which can be used to make predictions regarding seizure mechanisms. It is important to stress that most models developed so far are neurocentric. We will also highlight some current efforts to incorporate glial cells. Finally, we discuss the complexity and the epistemic value of computational models of seizures.

2 Modeling seizures dynamics

Models of seizures try to reproduce electrophysiological activities, which can be recorded in nervous tissues. Different recording techniques providing different types of information are available at different scales of analysis. The patch-clamp technique allows observing the evolution of the membrane potential and the activity of channels. Extracellular electrodes can collect the local-field potential (LFP) at the micro/macro-circuit level. Large-scale non-invasive techniques such as electroencephalography (EEG) provide access to a more mesoscopic scale. Such readouts

of brain activity can be generated by models, which are usually based on differential equations, which capture the evolution of electrophysiological signals in time. They constitute dynamical systems.

A dynamical system is a mathematical model that describes the evolution of a system over time. The most common type of dynamical system used in computational neuroscience is the ordinary differential equation (ODE) system, which describes the time evolution of a system based on its current state. These equations take the form of $\frac{dx}{dt} = f(x)$, where x is the state of the system and $f(x)$ is a function that describes the rate of change of x . Another common type of dynamical system is the partial differential equation (PDE) system, which describes the time evolution of a system based on both its current state and the spatial distribution of the system. These equations take the form of $\frac{\partial u}{\partial t} = f(u, x, y, z, t)$, where u is the state of the system, x, y, z are the spatial coordinates, t is the time, and $f(u, x, y, z, t)$ is a function that describes the rate of change of u .

These systems are based on the principles of nonlinear dynamics. In contrast to linear systems, which can be easily solved and have predictable behavior, non-linear systems can exhibit a wide range of complex and sometimes chaotic behaviors.

A non-linear system is defined as a system in which the relationship between the inputs and outputs is not proportional. This means that small changes in the input can result in large changes in the output, and that the system can exhibit multiple dynamics or multiple outcomes for the same input. These behaviors are observed in a complex system such as the brain. A simulation is a trajectory in the phase space constituted by the variables of the system. Different types of attractors may (co)exist in this space, and change depending on the value of the parameters. A bifurcation corresponds to the appearance or disappearance of stable and unstable fixed points, limit cycles, or

strange attractors in the phase space. This change can be described as a divergence in the phase space of the system, meaning that two different types of behavior can coexist for different parameter values. In the study of epilepsy healthy and ictal states can be described as two attractors. Different mechanisms can lead to the transition from one attractor to the other, such as external perturbations or the presence of a slow variable driving the transition. These dynamical aspects can be captured and studied by phenomenological models.

3 Role of phenomenological models

Phenomenological models of seizure dynamics aim to understand basic rules of seizure genesis and propagation by studying the observed patterns and behaviors of seizures rather than focusing on the specific biophysical processes that lead to them. Said differently, a phenomenological model only describes the observed phenomenon, but it does not directly inform upon the underlying biological mechanisms. However, when phenomenological models can extract basic rules in terms of dynamics of the system under study, these rules can be used to constrain the behavior of detailed biophysical models. The Epileptor [44, 79] is a phenomenological model that reduces the number of variables and parameters to enable an exhaustive study of the dynamics of seizures. This model reproduces the most common electrophysiological signature of seizures found in patients and experimental models, including status epilepticus and depolarization block. Sixteen possible types of seizure dynamics, called dynamotypes, can be identified [79], each of which differs in terms of the transition between the healthy state and the seizure state. This corresponds to the types of bifurcation at the onset and the offset of the seizure, which can be displayed on a map of brain dynamics. This approach not only leads to a taxonomy of clinically observed seizures but also offers a theoretical framework to explain the coexistence of healthy and

pathological regimes and how to understand the map of brain dynamics. Moreover, it does provide a theoretical framework and predictions in terms of dynamics to build more detailed biophysical models. However, it does not inform on the biophysical mechanisms underlying seizure dynamics. Other approaches using dynamical system theory, succeeded in capturing the phenomenon of seizure observed in large-scale recording such as electroencephalography [59, 5, 87]. Thanks to such approaches central aspects of the dynamics of seizure, such as time scale separation can be understood [5, 44]. Indeed, slower variables enable the transition from healthy to pathological states, at the onset of the seizure exhibited by the fast variable capturing the strong oscillation visible in electrophysiological recording. Phenomenological models can be particularly useful when studying seizures at the whole brain scale [95].

4 Biophysical models

Biophysical models cannot cover all scales, from molecules to the entire brain. They are usually constrained to a specific scale [17, 54] and have a specific level of description [19]. For a given scale, different models can have different levels of description, from the most phenomenological to the most biophysically detailed. A biophysical model of electrophysiological seizures is a mathematical representation of the electrical activity of neurons during a seizure. These models are based on the physiological properties of neurons, such as membrane potentials, ion channels, and synaptic connections, and their interactions. The most common, and historical approaches for the description of neuron membrane excitability are based on equivalent electrical circuit [51, 40], or direct properties of permeability of the membrane [56].

Based on these approaches, it is possible to detail some aspects of the neuron, such as its morphology, using multiple compartments, each with specific electrical properties according to its

location along the somato-dendritic axis. These models can be used to simulate the behavior of individual neurons and small networks of neurons. However, such models may become very complex, with a large number of equations, and so many parameters rendering a full exploration of the parameter space impractical. In this case, it becomes difficult to make predictions, as the latter will depend upon a specific choice of parameter values. The choice of parameters for a model can be directly linked to the degeneracy observed in biological tissues, which have the dual role of processing information and maintaining homeostatic conditions. Assessment of degeneracy as a framework for achieving the joint goals of encoding and homeostasis without interference is crucial. It is hypothesized that the complexity of biological systems, including interactions among multiple parameters across various levels of analysis, may offer multiple routes towards accomplishing these joint objectives [71].

Many biophysically detailed models have been developed [28, 6, 15, 33, 35, 34, 49, 81, 14, 75, 21, 84], giving important mechanistic explanations on seizures generation and dynamics at cellular level. Considering ionic mechanisms influencing excitability and leading to seizure-like events at cells levels have been included into computational models [3, 14, 31]. Such works give important insight into biophysical interactions related to seizure generation and evolution. However, it remains complex to be studied in terms of dynamical systems point of view as it has numerous variables. Thus in that direction, it is interesting to bridge phenomenological and biophysical point-neuron models. In the case of point neurons, the neuron's morphology is not considered. Yet, point neuron models can include numerous variables influencing membrane excitability, such as ionic regulation [2, 18, 9], oxygen [98], sodium-potassium pump [50], neuron-glia coupling [63]. Such models can be reduced to a minimal number of dimensions to make a dynamical analysis and build the correspondence with the theoretical framework of

phenomenological models [18, 9].

To model a larger scale, it is necessary to use spiking network models, which represent large populations of neurons and their interactions [74, 16, 14, 75, 20, 84, 97]. Some of these models can be constrained by dynamical properties [62]. Other models make use of the different biophysical properties described for different brain regions, such as the thalamo-cortical loop or the hippocampus [21, 22, 89, 14, 80]. Such models are useful to understand the onset [97] and the propagation of seizures in populations of cells [100, 74, 16]. Spiking network models form the basis for building population models [99, 7]; a useful tool to study seizure network properties [73].

Once the model is developed, it can be used to simulate seizures under different conditions and test hypotheses, for example to identify potential therapeutic targets [74, 16].

The parameters of the models should be adjusted and refined as new experimental data is obtained, particularly when the predictions are not validated, or the modelling approach. However, sometimes the modeling approach and the ingredients incorporated into the model must be reconsidered. Therefore, it is sometimes difficult to determine whether the difference with the data comes from a problem of parameter choice or from the nature of the model itself. This is especially difficult to distinguish when the model is complex, with numerous dimensions. Indeed, attempting to model large networks of cells implies dealing with a very high dimensional space (determined by the number of differential equations and their parameters). In that case, it is not easy to study the structure underlying the dynamics (phase space) and, if relevant, to perform a bifurcation analysis. To apprehend such large-scale systems, it is first necessary to define the read-out - which measurement - that will be used to assess the activity of the model. Typical measures include the population firing rate and statistics of membrane potentials (mean and standard deviation). These measurements can become the variable of the model at a larger scale. To decrease the complexity

of these networks, a solution consists in modeling directly the firing rate or the mean membrane potential. This approach used in large-scale models is discussed in the next section. It follows the idea of reduction of the microscopic complexity while going from lower scales to the whole brain (see figure 1).

Figure 1: Cartoon of bottom-up approach in building model of electrophysiological activities. The complexity of single neuron cells can be reduced to minimal models to capture membrane excitability. These models can be used as a building block to constitute networks. The complexity of network dynamics can be reduced by capturing some aspects with mean-field approaches. To build a whole-brain model, mean-field models are connected, each representing a large group of cells of a region of the brain.

5 Large-scale models

Mean-Field models are used to study the collective activity of a large number of neurons by averaging their activity, such as the mean membrane potential or firing rate. These models can be derived from single-neuron models or based on the assumption that a single neuron can represent the mean activity of a population of neurons.

Wilson and Cowan's historical model has been used to study focal epilepsy and the path toward depolarization block at the population level [60]. Subsequent developments [61, 8, 1], allowed refining the specific properties of the populations considered, including ion concentration dynamics [1].

Mean-Field models simplify the analysis, reducing the number of variables and allowing for a bifurcation analysis and comparison with phenomenological models. However, this

simplification also results in the loss of information regarding certain internal dynamics and collective effects, which may be acceptable for characterizing seizures [41, 1]. The temporal dissection of seizures, including transitions to and from the ictal state, is also possible through the variation of parameters or slow variables [44, 1]. A variable operating at a slow time scale may be required to enable the transition between healthy and ictal states. At a lower scale, this slow variable may represent homeostatic responses or emerging properties of the network. The results of this scale of analysis are relevant to human EEG recordings, allowing the study of interactions between regions, such as thalamo-cortical interactions [59], and network properties [87].

These models can be connected to create a large scale network that can account for whole-brain dynamics [32]. Whole-brain models have direct clinical application, mainly concerning the identification of the epileptogenic zone of pharmacoresistant patient that undergoes resection surgery [47, 83, 45, 55, 95, 23]. Different approaches exist in this direction, with different type of data from the patient and different dynamical model. Thus, efficient method have been developed using ECoG data, with bistable dynamical model [83]. This study develops patient-specific dynamical network models of epileptogenic cortex using a bi-stable switch. By conducting simulations with this model, the study identifies nodes with short transition times as highly epileptogenic, which can be surgically resected to reduce the overall likelihood of a seizure. In this retrospective study, the proposed computational approach accurately predicts surgical outcomes (81.3% on 16 patients) and suggests alternative resection sites in patients with unsuccessful outcomes. Another work developed a model-based framework to study the ictogenic brain networks [36], finding that conventional markers do not always predict the best resection strategy. By analyzing ECoG recordings from epilepsy surgery patients [36], and then sEEG data in a second study [52], they validated their framework data and observed that it can predict better

surgical strategies and provide quantitative prognoses for patients.

Other methods use intracranial EEG, and personalized workspace and structural connectivity. In particular, the virtual epileptic patient (VEP) is a workflow to use personalized whole brain network modelling and machine learning methods for the diagnosis and treatment of epilepsy [45, 55, 95, 43]. VEP uses both personalized anatomical data to define the working space and patient's connectome, and functional data to further refine the parameters of the models ((see figure 2) for VEP workflow). Its first use is in the presurgical evaluation of drug-resistant epilepsy by identifying the regions most likely to generate seizures. A study was conducted to assess the performance of VEP in estimating the epileptogenic zone and predicting surgical outcomes. The study involved retrospectively in a cohort of 53 patients with pharmaco-resistant epilepsy, and by comparing the regions identified as epileptogenic networks by VEP to the ones defined by clinical analysis. VEP reproduced the clinically defined epileptogenic regions with a precision of 0.6, where the physical distance between epileptogenic regions identified by VEP and the clinically defined ones was small. Compared with the resected brain regions of 25 patients who underwent surgery, VEP showed lower false discovery rates in seizure-free patients (mean, 0.028) than in non-seizure-free patients (mean, 0.407) [95]. VEP is now being evaluated in an ongoing clinical trial (call EPINOV) with an expected 356 prospective patients with epilepsy [55, 95, 43]. They also have developed the concept of degeneracy for uncertainty quantification and subsequent proper use in the clinical context using four types of patients [95]. This framework has also been further applied to study the dynamics of status epilepticus, and in particular how the propagation depends on the structural connectivity and the global state of the network [26]. Such approach use The Virtual Brain (TVB) simulator, populated with phenomenological models of regional excitability [44].

Figure 2: The VEP workflow. A virtual epileptic patient is to build a personalized whole brain network model (in the middle, bottom left) from the patient's data (top). T1-weighted MRI was done to obtain brain geometry data and to define distinct brain regions according to the VEP atlas [94](top left). Tractography was done to estimate the length and density of white matter fibres from diffusion-weighted MRI (top middle), which establishes the connectome (blue lines in the personalized model) that specifies the connection strength. Intracranial recordings during seizure activity were used to further refine the parameters of the personalized models, including epileptogenic zone approximation. The personalized brain model can be used to simulate the consequences of different epileptogenic zone hypotheses (red areas show epileptogenic zone regions) and corresponding SEEG recordings, and these simulated data can subsequently be used to predict brain activity and behaviour under various conditions. Different virtual surgical strategies can be tested in the personalized model to achieve the best outcome.

Brain dynamics are mostly linked to the electrophysiological activity of neurons. However, it is important to note that neurons are not the only contributors to brain activity.

6 Beyond neurocentrism

The neuron dogma is the fundamental concept in neuroscience that states that the brain is composed of individual cells called neurons and that these neurons are the basic functional unit of the brain. Neurons are connected to one another through specialized structures called synapses, where information is transmitted from one neuron to another. This principle of communication through synapses is considered as the fundamental mechanism of neural computation and information processing in the brain. If the neuron doctrine has been a powerful framework to

accumulate knowledge about brain structure-function relationships, it provides a very reductionist view of the brain. Although we all know that glial cells are integral to brain function, they are barely integrated into conceptual frameworks to understand how the brain works.

Since glial cells seem to play a significant role in seizures, they should be integrated in our search for mechanisms [10, 92]. Oligodendrocytes, which form and maintain the myelin sheath can also modulate seizure activity by regulating the conduction of electrical signals along axons [48]. Microglia, the immune cells of the brain, play a role in the inflammatory response and are involved in seizures by modulating the activity of neurons and astrocytes [39]. Astrocytes are involved in the regulation of neurotransmitters and the maintenance of the extracellular environment. They modulate the initiation and propagation of seizures [92]. Astrocytes are integral of the "tripartite synapse" that includes the pre-synaptic terminal, the post-synaptic site and fine astrocytic processes. Recent studies have shown that seizures may be linked to a dysfunction at the level of the tripartite synapse, leading to abnormal communication between neurons and glial cells [77]. Astrocytes also play a crucial role in mediating communication between capillaries and neurons, regulating blood flow and thus the delivery of important compounds to the parenchyma.

This strategic placement of astrocytes, and the fact that they can be coupled to each other over large distances, make them ideally poised to regulate network excitability. This regulation can be achieved by directly modulating the availability of metabolites and neurotransmitters, as well as maintaining water and ion homeostasis, in particular potassium. Dysregulation of one or more astrocytic pathways has been shown to trigger or exacerbate epileptogenesis [93].

Several computational models have included some functional aspects of astrocytes in an indirect manner (i.e. without modeling directly astrocytes themselves). For example, to understand

the contribution of astrocytes to the high extracellular potassium (K^+) epilepsy hypothesis, many models including the possibility to buffer extracellular K^+ have been developed to simulate such type of astrocyte-dependent mechanism [85] [18]. These models depict the relationship between K^+ concentration dynamics and the occurrence of seizures [11], [65] as well as spreading depression [46].

Most of these models focus on describing the phenomena at the cellular scale (single cell, circuit of a few cells), with varying levels of biophysical plausibility. This can range from multi-compartmental electrodiffusive models [38] to point models that possess an adequate level of biophysical details (i.e. numbers of variables) for bifurcation analysis [63]. However, epilepsy is predominantly a network-level disease. To understand the impact of astrocytic buffering failure on the generation of seizures, models such as [90], [65] simulate the resulting positive feedback loop in neuron-astrocyte interactions at the network scale. More recently this effect was captured by a neural mass model in a whole-brain simulation [1], a first attempt to include such biophysical mechanisms in whole-brain simulations. Some effort are going in this direction considering the role of astrocytes at the mesoscopic level [88].

Astrocytes control the dynamics of extracellular glutamate and GABA whether it is through neurotransmitter recycling or via calcium-mediated glutamate release [67]. In addition, experimental data suggests that the astrocytic syncytium can modulate the bursting activity of neural networks [64]. Together these observations lead to the development of various neuron-glia network models of epilepsy. Focusing on abnormal astrocyte feedback action to neuronal networks that could disrupt the excitation inhibition balance due to gliosis [101] or highly active gap junction coupling [92], these models interrogate the role of glial dysfunctions in shaping the dynamics of bursting neuronal networks. In one such model, adding a syncytium (network of glial

cells) to a previously developed neural network model capable of capturing transitions to high amplitude oscillations upon reduced GABAergic inhibition, enabled the transition towards generalized seizure like dynamics [76].

Utilizing a Data-driven approach Grigorovsky et. al [37] introduced a hybrid neuroglial network in which the glia was represented as an oscillator. This network model could reproduce features of an important EEG-based pathological biomarker that matched well with that of the epileptic patients' data. Along with the same etiology, at the mesoscopic scale, Garnier et al.[30] introduced a neural mass model together with astrocytic compartments to study the contribution of astrocytic glutamate/GABA uptake to neuronal excitability, applying bifurcation theory.

This non-exhaustive list shows that integrating astrocytes in models allows for producing activities that pure neuronal models fail to produce. The complexity of the model increases, but so does its relevance.

Quantifying energy expenditure in the brain before, during, and after seizures is also integral to the questions we should ask of the system. Although the debate regarding the mismatch between blood flow and oxygen consumption during neural activation is not settled [96], it is worth noting that efforts to better understand this issue by incorporating astrocytes in the neurovascular system have led to two main theories on how astrocytes contribute to metabolic support (ANLS and GSG hypothesis)[68], [78]. The astrocyte-neuron lactate shuttle (ANLS) hypothesis states that astrocytic glutamate uptake invokes the higher rate of the anaerobic metabolic pathway in astrocytes that leads to the production of lactate as a major source of oxidative fuel for neurons during high energy demands of glutamatergic neurotransmission [68]. However, this theory has proved to be controversial as it fails to provide a correct glucose–lactate stoichiometry ratio and justify the mismatch of the cerebral metabolic rate (CMR) of glucose and

oxygen and contradicts with *in vitro* and *in vivo* observations of many labs.[23]

A more recent theory based on observations of Dinuzzo et al. [25] proposed that glycogenolysis inhibits glucose utilization in astrocytes thereby sparing glucose for neurons upon their activation. The transport of glucose across the blood-brain barrier may pose a limitation during activation, potentially hindering the brain's energy supply. In order to sustain the necessary energy demands, neuronal glucose metabolism may rely on glycogenolysis to replace glucose consumed by astrocytes. This hypothesis is known as Glucose Sparing by Glycogenolysis (GSG) [78] and can be indirectly corroborated by a few studies. [69] [29].

A recent study by Dienel et al. [24] supports the latter theory and suggests a potential new role for glycogen in epilepsy. More work needs to be devoted to these important questions.

Finally, glial cells play a crucial role in seizures by modulating the activity of neurons, maintaining the extracellular environment, and coordinating the activity of neurons. Further research, developing the computational modelling [57], are needed to understand the mechanisms of glial cells in seizures fully, and complete the full picture with robust models. But at present, it is already clear that glial cells are important targets for the development of new treatments for seizures. The development of new treatment is of course linked to the etiology of the seizures.

The etiology of seizures is complex and can be classified into several categories [82], including genetic [86], structural [27], metabolic [72], and acquired causes [53]. Seizures are emergent properties, in fact, a readout, of what is happening in brain circuits, which have been reorganized by brain insults. Following the principle of degeneracy, different insults may result in similar seizure mechanisms, and, conversely, different mechanisms may be at play for seizures caused by a given insult. More research is needed to study the complex interaction that may exist at a given scale and between scales (see figure 3), in particular when it is becoming clear that all the

above-mentioned parameters may contribute to seizure mechanisms. It is essential to consider multifactorial aspects when building computational models. These aspects are discussed in the next section.

Figure 3: Etiology of seizures can be understood as several underlying causes interacting at the same scale in addition to the relationships between scales and this complexity must therefore be considered so as not to be reduced to a single mechanism at a given scale.

7 Complexity and epistemic values

A complex system is defined as a system composed of many interacting components that exhibit emergent behaviour. In biology, complex systems are found at multiple levels, from the molecular and cellular levels to the ecosystem level. Typically the brain is a complex system. The brain includes a complex network of cells and structures that can control and coordinate most body functions. The complexity of the nervous tissue arises from the diverse range of cell types, the intricate patterns of connections between cells, and the dynamic nature of neural activities. To apprehend such a complex system, many different models can be built, as described in the preceding sections. One way of evaluating these models is to consider their epistemic values. Epistemic value refers to the value of knowledge or information in terms of its ability to increase understanding or improve decision-making. In other words, it is the value or worth of knowledge or information from an epistemological perspective.

In general, in science, the epistemic value of a piece of information is often determined by its ability to advance understanding or solve a problem. For example, in the field of medicine, the epistemic value of a new drug or treatment is determined by its ability to improve patient

outcomes. In order to determine the epistemic value of models, we should first evaluate their function, in other words, why do we build models? Research in epistemology has detailed 21 different specific functions of models [91] that can be organised into 5 main functions: facilitate sensitive apprehension, facilitate intelligible formulation, facilitate theorizing, facilitate the co-construction of knowledge, facilitate decision and action.

In order to determine the epistemic value of a model, one can evaluate it based on factors such as its reliability, validity, and usefulness. Reliability refers to the consistency and reproducibility of the information, while validity refers to the accuracy and truthfulness of the information. Usefulness refers to the extent to which the information can be applied to solve a problem or advance understanding.

It is important to note that the epistemic value of a piece of information can change over time as new information or advances in understanding are made. Therefore, it is important to continuously evaluate and re-evaluate the epistemic value of existing knowledge. Additionally, the epistemic value of information can vary depending on the context and the intended use. For example, the same piece of information may be perceived as having a different epistemic value for a researcher in one field than for a researcher in another field. This appears particularly when objects and scale of studies with associated concepts of references are very different. Thus, the elements considered as knowledge are not evaluated in the same way according to the discipline and the theoretical framework of attachment.

As described above, models may tend to be reduced to the core elements underlying the dynamics of pathological events such as seizures. While reductionism in brain activity models can provide valuable insights into the behaviour of specific components of the brain, and useful clinical application as describe previously, it is important to note that this approach can also have

limitations. For example, by focusing only on specific components or regions, one may overlook the important interactions and influences that occur between different parts of the brain. Additionally, the complexity of the brain makes it difficult to fully understand the behaviour of the whole system by studying only its individual components.

Therefore, it is important to consider the limitations of reductionism in brain activity models and to integrate multiple levels of analysis, including molecular, cellular, systems, and behavioural levels, in order to gain a more complete understanding of brain function. Additionally, the use of multiple types of models, such as experimental, theoretical and computational, can provide a more complete understanding of brain activities, and in particular pathological ones, such as seizures.

It is therefore interesting to complete the picture by having different models at different scales (from the subcellular level to whole brain networks) and different levels of description [19]. For this, it is also interesting to extend by systematically considering other cells (glial cells, erythrocytes etc) [14, 75], but also other mechanisms of interaction (ephaptic, ionic electro-diffusion, etc..) [14, 70]. And finally, it would be interesting to develop models whose purpose is not solely focused on the modulation of neuronal excitability. In other words, considering that excitability is just one aspect among many characteristics that nervous tissues have and not focusing only on how a given mechanism modulates neuronal excitability.

Living organisms are complex systems, from the molecular and cellular level to the individual. Understanding the complexity of biological systems is crucial for understanding the functioning of living organisms and their interactions with their environment. This applies even more in the healthy and pathological distinction and particularly in the case of diseases like epilepsy with potential multiple underlying causes.

8 Conclusion

It is important to note that the complexity of the brain and of seizures, as well as the lack of complete understanding of the underlying mechanisms, make it challenging to develop accurate general computational models. However, by integrating experimental data and by using advanced computational techniques, the models can be refined and improved. Additionally, the use of multiple types of models can provide a more complete understanding of seizures and can guide the development of new treatments. Finally, although we tried to insist on the necessity to go beyond a neurocentric approach, we focused on the brain, with the unstated assumption that it is enough to understand the brain to understand seizures. The brain is just one organ among many that make a body. Our organs interact in a complex manner. How much seizure mechanisms depend on these interactions remains an open field.

References

- [1] Abhirup Bandyopadhyay, Giovanni Rabuffo, Carmela Calabrese, Kashyap Gudibanda, Damien Depannemaecker, Anton Ivanov, Christophe Bernard, Viktor K. Jirsa, and Spase Petkoski. Mean-field approximation of network of biophysical neurons driven by conductance-based ion exchange. November 2021.
- [2] Ernest Barreto and John R. Cressman. Ion concentration dynamics as a mechanism for neuronal bursting. *Journal of Biological Physics*, 37(3):351–373, January 2011.
- [3] M. Bazhenov, I. Timofeev, M. Steriade, and T. J. Sejnowski. Potassium model for slow (2–3 Hz) in vivo neocortical paroxysmal oscillations. *Journal of Neurophysiology*, 92(2):1116–1132, August 2004.
- [4] Christophe Bernard. Circadian/multidimensional molecular oscillations and rhythmicity of epilepsy (MORE). *Epilepsia*, 62(S1), October 2020.
- [5] Alex Blenkinsop, Antonio Valentin, Mark P. Richardson, and John R. Terry. The dynamic evolution of focal-onset epilepsies - combining theoretical and clinical observations. *European Journal of Neuroscience*, 36(2):2188–2200, July 2012.
- [6] Anatoly Buchin, Anton Chizhov, Gilles Huberfeld, Richard Miles, and Boris S. Gutkin. Reduced efficacy of the KCC2 cotransporter promotes epileptic oscillations in a subiculum network model. *The Journal of Neuroscience*, 36(46):11619–11633, November 2016.
- [7] Anatoly Buchin, Cliff C. Kerr, Gilles Huberfeld, Richard Miles, and Boris Gutkin. Adaptation and inhibition control pathological synchronization in a model of focal epileptic seizure. *eNeuro*, 5(5):ENEURO.0019–18.2018, September 2018.
- [8] M. Carlu, O. Chehab, L. Dalla Porta, D. Depannemaecker, C. Héricé, M. Jedynek, E. Köksal Ersöz, P. Muratore, S. Souihel, C. Capone, Y. Zerlaut, A. Destexhe, and M. di

- Volo. A mean-field approach to the dynamics of networks of complex neurons, from nonlinear integrate-and-fire to hodgkin–huxley models. *Journal of Neurophysiology*, 123(3):1042–1051, March 2020.
- [9] Anton V. Chizhov, Artyom V. Zefirov, Dmitry V. Amakhin, Elena Yu. Smirnova, and Aleksey V. Zaitsev. Minimal model of interictal and ictal discharges “epileptor-2”. *PLOS Computational Biology*, 14(5):e1006186, May 2018.
- [10] Douglas A Coulter and Christian Steinhäuser. Role of astrocytes in epilepsy. *Cold Spring Harb. Perspect. Med.*, 5(3):a022434, March 2015.
- [11] John R. Cressman, Ghanim Ullah, Jokubas Ziburkus, Steven J. Schiff, and Ernest Barreto. The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: I. single neuron dynamics. *Journal of Computational Neuroscience*, 26(2):159–170, January 2009.
- [12] Dakota N Crisp, Warwick Cheung, Stephen V Gliske, Alan Lai, Dean R Freestone, David B Grayden, Mark J Cook, and William C Stacey. Quantifying epileptogenesis in rats with spontaneous and responsive brain state dynamics. *Brain Communications*, 2(1), January 2020.
- [13] Vincenzo Crunelli, Nathalie Leresche, and David W Cope. GABAA receptor function in typical absence seizures. In *Jasper’s Basic Mechanisms of the Epilepsies*, pages 228–241. Oxford University Press, July 2012.
- [14] Antônio-Carlos G. de Almeida, Antônio M. Rodrigues, Fúlvio A. Scorza, Esper A. Cavalheiro, Hewerson Z. Teixeira, Mário A. Duarte, Gilcélio A. Silveira, and Emerson Z. Arruda. Mechanistic hypotheses for nonsynaptic epileptiform activity induction and its transition from the interictal to ictal state-computational simulation. *Epilepsia*,

- 49(11):1908–1924, November 2008.
- [15] S. Demont-Guignard, P. Benquet, U. Gerber, and F. Wendling. Analysis of intracerebral EEG recordings of epileptic spikes: Insights from a neural network model. *IEEE Transactions on Biomedical Engineering*, 56(12):2782–2795, December 2009.
- [16] Damien Depannemaecker, Mallory Carlu, Jules Bouté, and Alain Destexhe. A model for the propagation of seizure activity in normal brain tissue. *eneuro*, 9(6):ENEURO.0234–21.2022, November 2022.
- [17] Damien Depannemaecker, Alain Destexhe, Viktor Jirsa, and Christophe Bernard. Modeling seizures: From single neurons to networks. *Seizure*, 90:4–8, August 2021.
- [18] Damien Depannemaecker, Anton Ivanov, Davian Lillo, Len Spek, Christophe Bernard, and Viktor Jirsa. A unified physiological framework of transitions between seizures, sustained ictal activity and depolarization block at the single neuron level. *Journal of Computational Neuroscience*, 50(1):33–49, January 2022.
- [19] Damien Depannemaecker, José Pic-Lopez, and Christophe Gauld. Does deep learning have epileptic seizures? on the modeling of the brain. *Cognitive Computation*, February 2023.
- [20] Damien Depannemaecker, Luiz Eduardo Canton Santos, Antônio Márcio Rodrigues, Carla Alessandra Scorza, Fulvio Alexandre Scorza, and Antônio-Carlos Guimarães de Almeida. Realistic spiking neural network: Non-synaptic mechanisms improve convergence in cell assembly. *Neural Networks*, 122:420–433, February 2020.
- [21] Alain Destexhe. Spike-and-wave oscillations based on the properties of GABA_{sub}/subreceptors. *The Journal of Neuroscience*, 18(21):9099–9111, November 1998.
- [22] Alain Destexhe. Can GABA_{sub}/subconductances explain the fast oscillation frequency of

- absence seizures in rodents? *European Journal of Neuroscience*, 11(6):2175–2181, June 1999.
- [23] Gerald A. Dienel. Brain glucose metabolism: Integration of energetics with function. *Physiological Reviews*, 99(1):949–1045, January 2019.
- [24] Gerald A. Dienel, Lisa Gillinder, Aileen McGonigal, and Karin Borges. Potential new roles for glycogen in epilepsy. *Epilepsia*, 64(1):29–53, November 2022.
- [25] Mauro DiNuzzo, Silvia Mangia, Bruno Maraviglia, and Federico Giove. The role of astrocytic glycogen in supporting the energetics of neuronal activity. *Neurochemical Research*, 37(11):2432–2438, May 2012.
- [26] Borana Dollomaja, Julia Makhlova, Huifang Wang, Fabrice Bartolomei, Viktor Jirsa, and Christophe Bernard. Personalized whole brain modeling of status epilepticus. *Epilepsy & Behavior*, 142:109175, may 2023.
- [27] Alan B. Ettinger. Structural causes of epilepsy: Tumors, cysts, stroke, and vascular malformations. *Neurologic Clinics*, 12(1):41–56, February 1994.
- [28] Gerson Florence, Markus A. Dahlem, Antônio-Carlos G. Almeida, José W.M. Bassani, and Jürgen Kurths. The role of extracellular potassium dynamics in the different stages of ictal bursting and spreading depression: A computational study. *Journal of Theoretical Biology*, 258(2):219–228, May 2009.
- [29] A E Fray, R J Forsyth, M G Boutelle, and M Fillenz. The mechanisms controlling physiologically stimulated changes in rat brain glucose and lactate: a microdialysis study. *The Journal of Physiology*, 496(1):49–57, October 1996.
- [30] Aurélie Garnier, Alexandre Vidal, and Habib Benali. A theoretical study on the role of astrocytic activity in neuronal hyperexcitability by a novel neuron-glia mass model. *The*

- Journal of Mathematical Neuroscience*, 6(1), December 2016.
- [31] Damiano Gentiletti, Marco de Curtis, Vadym Gnatkovsky, and Piotr Suffczynski. Focal seizures are organized by feedback between neural activity and ion concentration changes. *eLife*, 11, August 2022.
- [32] Jennifer S. Goldman, Lionel Kusch, Bahar Hazal Yalcinkaya, Damien Depannemaecker, Trang-Anh E. Nghiem, Viktor Jirsa, and Alain Destexhe. Brain-scale emergence of slow-wave synchrony and highly responsive asynchronous states based on biologically realistic population models simulated in the virtual brain. *bioRxiv*, 2020.
- [33] Oscar C. González, Giri P. Krishnan, Sylvain Chauvette, Igor Timofeev, Terrence Sejnowski, and Maxim Bazhenov. Modeling of age-dependent epileptogenesis by differential homeostatic synaptic scaling. *The Journal of Neuroscience*, 35(39):13448–13462, September 2015.
- [34] Oscar C. González, Giri P. Krishnan, Igor Timofeev, and Maxim Bazhenov. Ionic and synaptic mechanisms of seizure generation and epileptogenesis. *Neurobiology of Disease*, 130:104485, October 2019.
- [35] Oscar C. González, Zahra Shiri, Giri P. Krishnan, Timothy L. Myers, Sylvain Williams, Massimo Avoli, and Maxim Bazhenov. Role of KCC2-dependent potassium efflux in 4-aminopyridine-induced epileptiform synchronization. *Neurobiology of Disease*, 109:137–147, January 2018.
- [36] M. Goodfellow, C. Rummel, E. Abela, M. P. Richardson, K. Schindler, and J. R. Terry. Estimation of brain network ictogenicity predicts outcome from epilepsy surgery. *Scientific Reports*, 6(1), July 2016.
- [37] Vasily Grigorovsky, Vanessa L. Breton, and Berj L. Bardakjian. Glial modulation of

- electrical rhythms in a neuroglial network model of epilepsy. *IEEE Transactions on Biomedical Engineering*, 68(7):2076–2087, July 2021.
- [38] Geir Haldnes, Ivar Østby, Klas H. Pettersen, Stig W. Omholt, and Gaute T. Einevoll. Electrodiffusive model for astrocytic and neuronal ion concentration dynamics. *PLoS Computational Biology*, 9(12):e1003386, December 2013.
- [39] Toshimitsu Hiragi, Yuji Ikegaya, and Ryuta Koyama. Microglia after seizures and in epilepsy. *Cells*, 7(4):26, March 2018.
- [40] A. L. Hodgkin and A. F. Huxley. A quantitative description of membrane current and its application to conduction and excitation in nerve. *The Journal of Physiology*, 117(4):500–544, August 1952.
- [41] Kenza El Houssaini, Anton I. Ivanov, Christophe Bernard, and Viktor K. Jirsa. Seizures, refractory status epilepticus, and depolarization block as endogenous brain activities. *Physical Review E*, 91(1), January 2015.
- [42] Viktor Jirsa and Hiba Shehatah. Entropy, free energy, symmetry and dynamics in the brain. *Journal of Physics: Complexity*, 3(1):015007, February 2022.
- [43] Viktor Jirsa, Huifang Wang, Paul Triebkorn, Meysam Hashemi, Jayant Jha, Jorge Gonzalez-Martinez, Maxime Guye, Julia Makhalova, and Fabrice Bartolomei. Personalised virtual brain models in epilepsy. *The Lancet Neurology*, 3 2023.
- [44] Viktor K Jirsa, William C Stacey, Pascale P Quilichini, Anton I Ivanov, and Christophe Bernard. On the nature of seizure dynamics. *Brain : a journal of neurology*, 137(Pt 8):2210–30, 8 2014.
- [45] V.K. Jirsa, T. Proix, D. Perdikis, M.M. Woodman, H. Wang, J. Gonzalez-Martinez, C. Bernard, C. Bénar, M. Guye, P. Chauvel, and F. Bartolomei. The virtual epileptic patient:

- Individualized whole-brain models of epilepsy spread. *NeuroImage*, 145:377–388, January 2017.
- [46] H. Kager, W. J. Wadman, and G. G. Somjen. Conditions for the triggering of spreading depression studied with computer simulations. *Journal of Neurophysiology*, 88(5):2700–2712, November 2002.
- [47] Stiliyan N. Kalitzin, Demetrios N. Velis, and Fernando H. Lopes da Silva. Stimulation-based anticipation and control of state transitions in the epileptic brain. *Epilepsy & Behavior*, 17(3):310–323, March 2010.
- [48] Juliet K. Knowles, Haojun Xu, Caroline Soane, Ankita Batra, Tristan Saucedo, Eleanor Frost, Lydia T. Tam, Danielle Fraga, Lijun Ni, Katlin Villar, Sydney Talmi, John R. Huguenard, and Michelle Monje. Maladaptive myelination promotes generalized epilepsy progression. *Nature Neuroscience*, 25(5):596–606, May 2022.
- [49] Giri P. Krishnan, Gregory Filatov, Andrey Shilnikov, and Maxim Bazhenov. Electrogenic properties of the Na^+/K^+ ATPase control transitions between normal and pathological brain states. *Journal of Neurophysiology*, 113(9):3356–3374, May 2015.
- [50] Giri P. Krishnan, Gregory Filatov, Andrey Shilnikov, and Maxim Bazhenov. Electrogenic properties of the Na^+/K^+ ATPase control transitions between normal and pathological brain states. *Journal of Neurophysiology*, 113(9):3356–3374, May 2015.
- [51] L. Lapicque and M. Lapicque. Recherches quantitatives sur l’excitation électrique des nerfs traitée comme une polarisation. *Journal de Physiologie et Pathologie General*, 9:620–635, 1907.
- [52] Marinho A. Lopes, Mark P. Richardson, Eugenio Abela, Christian Rummel, Kaspar Schindler, Marc Goodfellow, and John R. Terry. An optimal strategy for epilepsy surgery:

- Disruption of the rich-club? *PLOS Computational Biology*, 13(8):e1005637, August 2017.
- [53] Wolfgang Löscher. The holy grail of epilepsy prevention: Preclinical approaches to antiepileptogenic treatments. *Neuropharmacology*, 167:107605, May 2020.
- [54] William W. Lytton. Computer modelling of epilepsy. *Nature Reviews Neuroscience*, 9(8):626–637, July 2008.
- [55] Julia Makhlova, Samuel Medina Villalon, Huifang Wang, Bernard Giusiano, Marmaduke Woodman, Christian Bénar, Maxime Guye, Viktor Jirsa, and Fabrice Bartolomei. Virtual epileptic patient brain modeling: Relationships with seizure onset and surgical outcome. *Epilepsia*, 63(8):1942–1955, June 2022.
- [56] Jaakko Malmivuo and Robert Plonsey. *Bioelectromagnetism. 3. Subthreshold Membrane Phenomena*, pages 44–65. 01 1995.
- [57] Tiina Manninen, Jugoslava Aćimović Riikka Havela, Heidi Teppola, and Marja-Leena Linne. Challenges in reproducibility, replicability, and comparability of computational models and tools for neuronal and glial networks, cells, and subcellular structures. *Frontiers in Neuroinformatics*, 12, May 2018.
- [58] Eve Marder and Adam L Taylor. Multiple models to capture the variability in biological neurons and networks. *Nature Neuroscience*, 14(2):133–138, January 2011.
- [59] Frank Marten, Serafim Rodrigues, Piotr Suffczynski, Mark P. Richardson, and John R. Terry. Derivation and analysis of an ordinary differential equation mean-field model for studying clinically recorded epilepsy dynamics. *Physical Review E*, 79(2), February 2009.
- [60] Hil G. E. Meijer, Tahra L. Eissa, Bert Kiewiet, Jeremy F. Neuman, Catherine A. Schevon, Ronald G. Emerson, Robert R. Goodman, Guy M. McKhann, Charles J. Marcuccilli, Andrew K. Tryba, Jack D. Cowan, Stephan A. van Gils, and Wim van Drongelen.

- Modeling focal epileptic activity in the Wilson–Cowan model with depolarization block. *The Journal of Mathematical Neuroscience (JMN)*, 5(1), March 2015.
- [61] Ernest Montbrió, Diego Pazó, and Alex Roxin. Macroscopic description for networks of spiking neurons. *Phys. Rev. X*, 5:021028, Jun 2015.
- [62] Sebastien Naze, Christophe Bernard, and Viktor Jirsa. Computational modeling of seizure dynamics using coupled neuronal networks: Factors shaping epileptiform activity. *PLOS Computational Biology*, 11(5):e1004209, May 2015.
- [63] Leiv Øyehaug, Ivar Østby, Catherine M. Lloyd, Stig W. Omholt, and Gaute T. Einevoll. Dependence of spontaneous neuronal firing and depolarisation block on astroglial membrane transport mechanisms. *Journal of Computational Neuroscience*, 32(1):147–165, June 2011.
- [64] Tanja Paavilainen, Anssi Pelkonen, Meri E.-L. Mäkinen, Marja Peltola, Heini Huhtala, Dmitriy Fayuk, and Susanna Naitilahti. Effect of prolonged differentiation on functional maturation of human pluripotent stem cell-derived neuronal cultures. *Stem Cell Research*, 27:151–161, March 2018.
- [65] Eun-Hyoung Park and Dominique M. Durand. Role of potassium lateral diffusion in non-synaptic epilepsy: A computational study. *Journal of Theoretical Biology*, 238(3):666–682, February 2006.
- [66] Eun-Hyoung Park, Zhouyan Feng, and Dominique M. Durand. Diffusive coupling and network periodicity: A computational study. *Biophysical Journal*, 95(3):1126–1137, August 2008.
- [67] Vladimir Parpura and Philip G. Haydon. Physiological astrocytic calcium levels stimulate glutamate release to modulate adjacent neurons. *Proceedings of the National Academy of*

- Sciences*, 97(15):8629–8634, July 2000.
- [68] L Pellerin and P J Magistretti. Glutamate uptake into astrocytes stimulates aerobic glycolysis: a mechanism coupling neuronal activity to glucose utilization. *Proceedings of the National Academy of Sciences*, 91(22):10625–10629, October 1994.
- [69] Mateja Prebil, Nina Vardjan, Jørgen Jensen, Robert Zorec, and Marko Kreft. Dynamic monitoring of cytosolic glucose in single astrocytes. *Glia*, 59(6):903–913, March 2011.
- [70] Chen Qiu, Rajat S. Shivacharan, Mingming Zhang, and Dominique M. Durand. Can neural activity propagate by endogenous electrical field? *The Journal of Neuroscience*, 35(48):15800–15811, December 2015.
- [71] Rahul K. Rathour and Rishikesh Narayanan. Degeneracy in hippocampal physiology and plasticity. *Hippocampus*, 29(10):980–1072, July 2019.
- [72] Jong M. Rho and Detlev Boison. The metabolic basis of epilepsy. *Nature Reviews Neurology*, 18(6):333–347, March 2022.
- [73] Scott Rich, Homeira Moradi Chameh, Jeremie Lefebvre, and Taufik A. Valiante. Loss of neuronal heterogeneity in epileptogenic human tissue impairs network resilience to sudden changes in synchrony. *Cell Reports*, 39(8):110863, May 2022.
- [74] Scott Rich, Axel Chutt, Frances K. Skinner, Taufik A. Valiante, and Jérémie Lefebvre. Neurostimulation stabilizes spiking neural networks by disrupting seizure-like oscillatory transitions. *Scientific Reports*, 10(1), September 2020.
- [75] Antônio Márcio Rodrigues, Luiz Eduardo Canton Santos, Luciene Covolan, Clement Hamani, and Antônio-Carlos Guimarães de Almeida. pH during non-synaptic epileptiform activity-computational simulations. *Phys. Biol.*, 12(5):056007, September 2015.
- [76] Richard E. Rosch and Chris G. Dulla. A tale of two networks—glial contributions to

- generalized seizures. *Epilepsy Currents*, 20(2):108–110, February 2020.
- [77] Richard E. Rosch and Éric Samarut. Epileptic seizures: Glia–neuron interactions for better or for worse. *Current Biology*, 29(23):R1248–R1251, 2019.
- [78] Douglas L Rothman, Gerald A Dienel, Kevin L Behar, Fahmeed Hyder, Mauro DiNuzzo, Federico Giove, and Silvia Mangia. Glucose sparing by glycogenolysis (GSG) determines the relationship between brain metabolism and neurotransmission. *Journal of Cerebral Blood Flow & Metabolism*, 42(5):844–860, January 2022.
- [79] Maria Luisa Saggio, Dakota Crisp, Jared M Scott, Philippa Karoly, Levin Kuhlmann, Mitsuyoshi Nakatani, Tomohiko Murai, Matthias Dümpelmann, Andreas Schulze-Bonhage, Akio Ikeda, Mark Cook, Stephen V Gliske, Jack Lin, Christophe Bernard, Viktor Jirsa, and William C Stacey. A taxonomy of seizure dynamotypes. *Elife*, 9, July 2020.
- [80] Vijayalakshmi Santhakumar, Ildiko Aradi, and Ivan Soltesz. Role of mossy fiber sprouting and mossy cell loss in hyperexcitability: A network model of the dentate gyrus incorporating cell types and axonal topography. *Journal of Neurophysiology*, 93(1):437–453, January 2005.
- [81] Calvin J. Schneider, Marianne Bezaire, and Ivan Soltesz. Toward a full-scale computational model of the rat dentate gyrus. *Frontiers in Neural Circuits*, 6, 2012.
- [82] Simon D. Shorvon. The etiologic classification of epilepsy. *Epilepsia*, 52(6):1052–1057, March 2011.
- [83] Nishant Sinha, Justin Dauwels, Marcus Kaiser, Sydney S. Cash, M. Brandon Westover, Yujiang Wang, and Peter N. Taylor. Predicting neurosurgical outcomes in focal epilepsy patients using computational modelling. *Brain*, 140(2):319–332, December 2016.

- [84] Ivan Soltesz and Kevin Staley, editors. *Computational Neuroscience in Epilepsy*. Academic Press, San Diego, CA, February 2008.
- [85] G. G. Somjen, H. Kager, and W. J. Wadman. Computer simulations of neuron-glia interactions mediated by ion flux. *Journal of Computational Neuroscience*, 25(2):349–365, February 2008.
- [86] Ortrud K. Steinlein. Genetic mechanisms that underlie epilepsy. *Nature Reviews Neuroscience*, 5(5):400–408, May 2004.
- [87] John R. Terry, Oscar Benjamin, and Mark P. Richardson. Seizure generation: The role of nodes and networks. *Epilepsia*, 53(9):e166–e169, June 2012.
- [88] Federico Tesler, Marja-Leena Linne, and Alain Destexhe. A key role of astrocytic calcium dynamics to link neuronal activity with the Ca^{2+} signal. April 2021.
- [89] Roger D. Traub and Andrea Bibbig. A model of high-frequency ripples in the hippocampus based on synaptic coupling plus axon–axon gap junctions between pyramidal neurons. *The Journal of Neuroscience*, 20(6):2086–2093, March 2000.
- [90] Ghanim Ullah, John R. Cressman Jr., Ernest Barreto, and Steven J. Schiff. The influence of sodium and potassium dynamics on excitability, seizures, and the stability of persistent states: II. network and glial dynamics. *Journal of Computational Neuroscience*, 26(2):171–183, December 2008.
- [91] Franck Varenne. *From models to simulations*. Routledge, Abingdon, Oxon New York, NY, 2019.
- [92] Carmen Diaz Verdugo, Sverre Myren-Svelstad, Ecem Aydin, Evelien Van Hoeymissen, Celine Deneubourg, Silke Vanderhaeghe, Julie Vancraeynest, Robbrecht Pelgrims, Mehmet Ilyas Cosacak, Akira Muto, Caghan Kizil, Koichi Kawakami, Nathalie

- Jurisch-Yaksi, and Emre Yaksi. Glia-neuron interactions underlie state transitions to generalized seizures. *Nature Communications*, 10(1), August 2019.
- [93] Quirijn P. Verhoog, Linda Holtman, Eleonora Aronica, and Erwin A. van Vliet. Astrocytes as guardians of neuronal excitability: Mechanisms underlying epileptogenesis. *Frontiers in Neurology*, 11, November 2020.
- [94] Huifang E. Wang, Julia Scholly, Paul Triebkorn, Viktor Sip, Samuel Medina Villalon, Marmaduke M. Woodman, Arnaud Le Troter, Maxime Guye, Fabrice Bartolomei, and Viktor Jirsa. VEP atlas: An anatomic and functional human brain atlas dedicated to epilepsy patients. *Journal of Neuroscience Methods*, 348:108983, January 2021.
- [95] Huifang E. Wang, Marmaduke Woodman, Paul Triebkorn, Jean-Didier Lemarechal, Jayant Jha, Borana Dollomaja, Anirudh Nilalini Vattikonda, Viktor Sip, Samuel Medina Villalon, Meysam Hashemi, Maxime Guye, Julia Makhalova, Fabrice Bartolomei, and Viktor Jirsa. Delineating epileptogenic networks using brain imaging data and personalized modeling in drug resistant epilepsy. *Science Translational Medicine*, 15(680), January 2023.
- [96] Rubin Wang, Ichiro Honda, and Zhikang Zhang. A new work mechanism on neuronal activity. *International Journal of Neural Systems*, 25(03):1450037, April 2015.
- [97] Yujiang Wang, Andrew J Trevelyan, Antonio Valentin, Gonzalo Alarcon, Peter N Taylor, and Marcus Kaiser. Mechanisms underlying different onset patterns of focal seizures. *PLOS Computational Biology*, 13(5):e1005475, May 2017.
- [98] Y. Wei, G. Ullah, and S. J. Schiff. Unification of neuronal spikes, seizures, and spreading depression. *Journal of Neuroscience*, 34(35):11733–11743, August 2014.
- [99] F. Wendling, F. Bartolomei, J. J. Bellanger, and P. Chauvel. Epileptic fast activity can be

explained by a model of impaired GABAergic dendritic inhibition. *European Journal of Neuroscience*, 15(9):1499–1508, May 2002.

- [100] Jyun you Liou, Elliot H Smith, Lisa M Bateman, Samuel L Bruce, Guy M McKhann, Robert R Goodman, Ronald G Emerson, Catherine A Schevon, and LF Abbott. A model for focal seizure onset, propagation, evolution, and progression. *eLife*, 9, March 2020.
- [101] Yangyang Yu, Zhixuan Yuan, Yongchen Fan, Jiajia Li, and Ying Wu. Dynamic transitions in neuronal network firing sustained by abnormal astrocyte feedback. *Neural Plasticity*, 2020:1–13, November 2020.

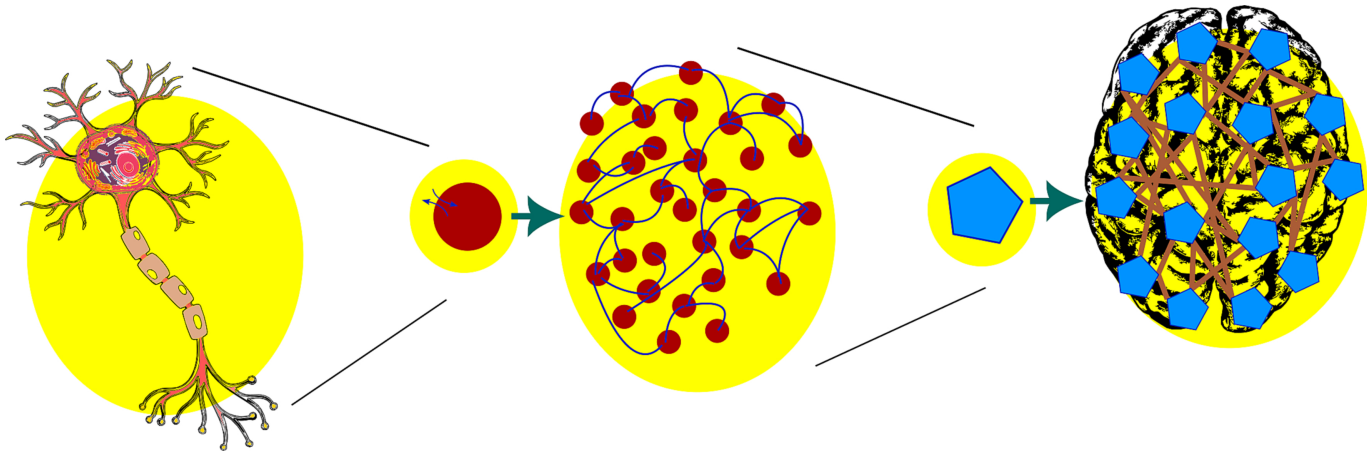
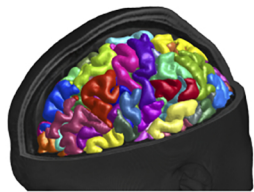
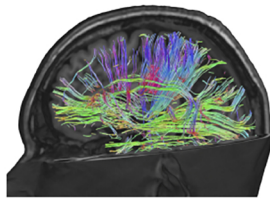


Figure 1

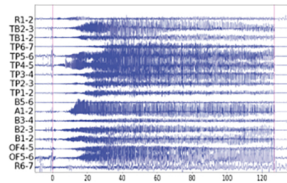
Patient's brain imaging data



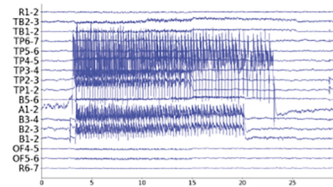
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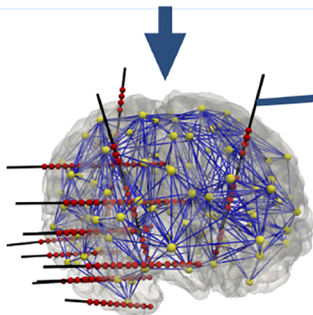
Connectome



SEEG recording

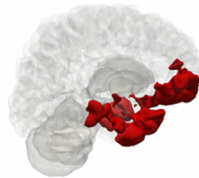


Simulated SEEG



Personalised whole-brain
network models

EZN estimation



Virtual surgery

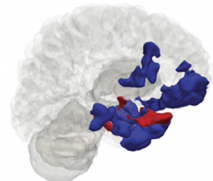


Figure 2

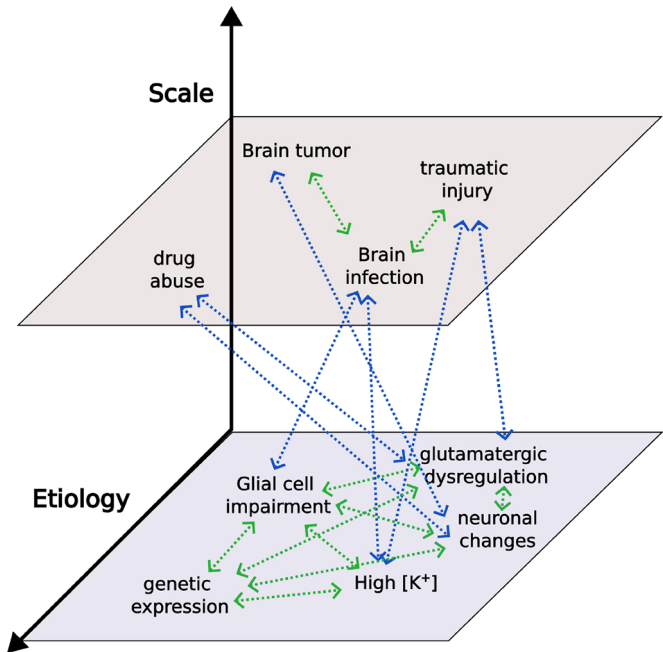


Figure 3