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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 model have been developped [28, 6, 15, 33, 35, 34, 49, 81, 14, 75, 21, 84], giving important mechanistic explanations on seizures generation and dynamics at celular 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 thalomo-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 thalomo-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, 24]. 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 makers 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 uses 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 pharmacoresistant 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 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 presonalized 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 astocytes 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.

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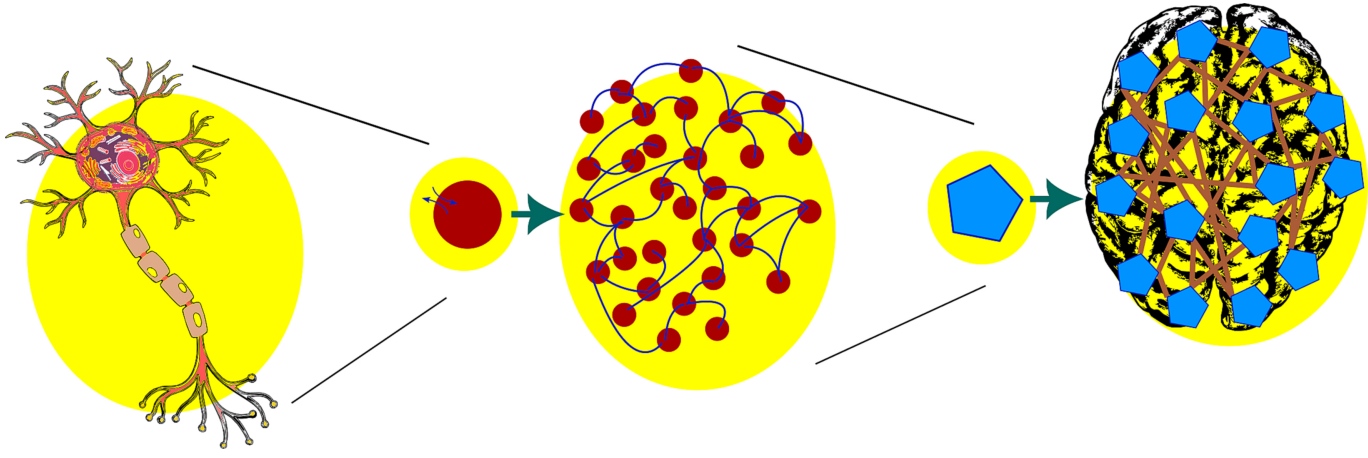

Figure 1

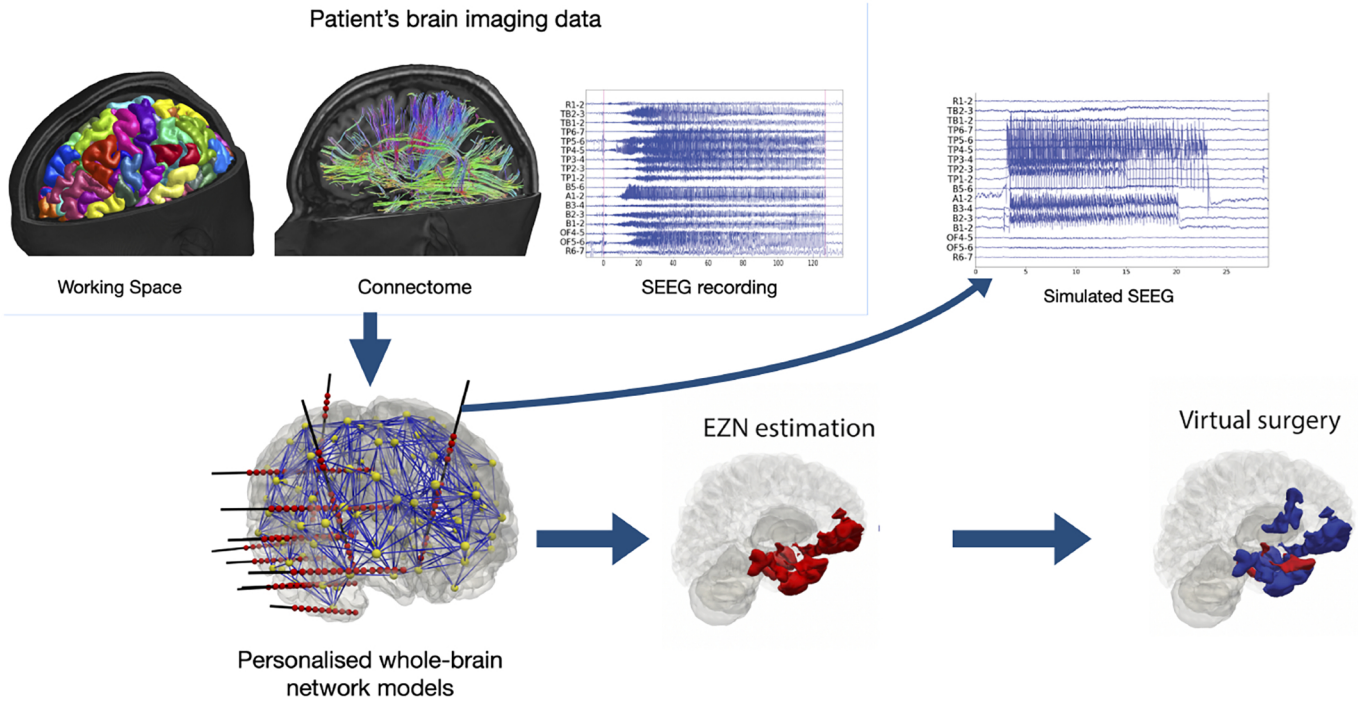
Patient's brain imaging data
Working Space
Connectome
SEEG recording
Simulated SEEG
Personalised whole-brain network models
EZN estimation
Virtual surgery

Figure 2

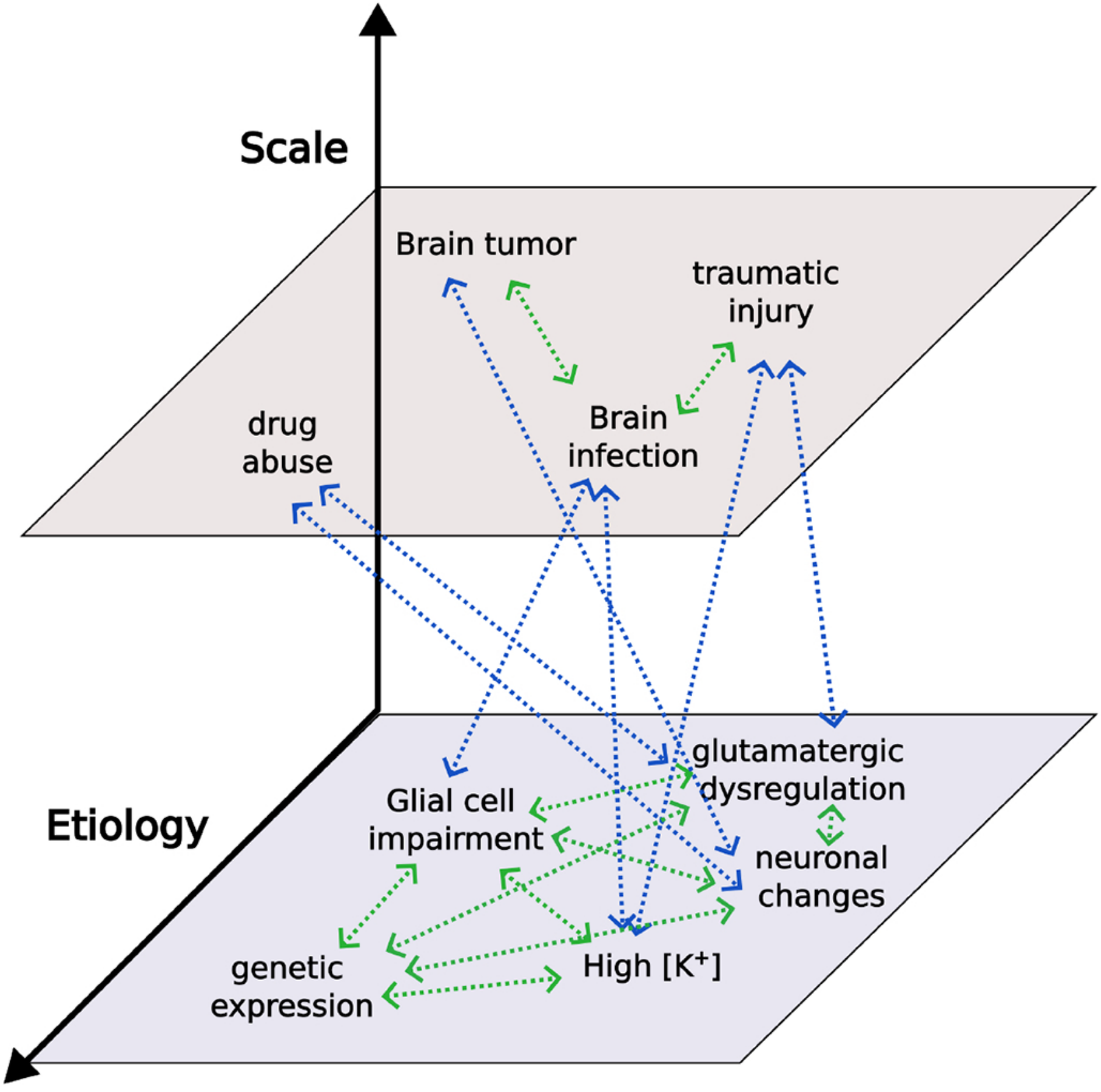
Scale
Brain tumor
traumatic injury
drug abuse
Brain infection
glutamatergic dysregulation
Glial cell impairment
neuronal changes
Etiology
genetic expression
High [K+]

Figure 3