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Special Report

Computational models of epileptic activity: a bridge between observation and pathophysiological interpretation

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Abstract

Epilepsy is a neurological disorder characterized by the recurrence of seizures. It affects 50 million people worldwide. Although a considerable number of new anti-epileptic drugs with reduced side-effects and toxicity have been introduced since the 1950s, 30% of patients remain pharmacoresistant. Although epilepsy research is making progress, advances in understanding the drug resistance have been hampered by the complexity of the underlying neuronal systems responsible for epileptic activity. In such systems where short- or long-term plasticity plays a role, pathophysiological alterations may take place at sub-cellular (membrane ion channels, neurotransmitter receptors), cellular (neurons), tissular (networks of neurons) and regional (networks of networks of neurons) scales. In such a context, the demand for integrative approaches is high and neurocomputational models become recognized tools for tackling the complexity of epileptic phenomena. The purpose of this report is to provide an overview on computational modeling as a way of structuring and interpreting multi-modal data recorded from the epileptic brain. Some examples are briefly described. They illustrate how computational models closely related with either experimental or clinical data can markedly advance our understanding of essential issues in epilepsy like the transition from background to seizure activity. A commentary is also made on the potential use of such models in the study of therapeutic strategies like rational drug design or electrical stimulations.

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Epilepsies as diseases of complex dynamical system*s*

Epilepsy is a neurological disease that directly affects 50 million people worldwide [1]. It is characterized by the recurrence of seizures that markedly deteriorate the patient's quality of life. There exist many possible causes for the occurrence of seizures in the mammalian brain. In fact, any disturbance of the normal neuronal activity due to illness, brain damage or abnormal brain development can provoke seizures and subsequently lead to chronic epilepsy. It is noteworthy to mention that the term "epilepsy" refers to a wide variety of neurological syndromes and disorders. Indeed, epilepsy is polymorphic and characterized by a large variability of clinical manifestations as symptoms strongly depend on the localization of the neuronal systems responsible for the initiation of seizures as well as on the brain structures that are affected during seizure spread.

Although the first reports about epilepsy and seizures are several thousand years old, most of our knowledge about this pathology in particular, and about the many ways the central nervous system can be perturbed in general, comes from researches performed during the last century. Basic and clinical research has advanced our understanding of the pathophysiology of epilepsy. Many experimental models have been elaborated (figure 1, left). These include acute dissociated cultures of cerebral tissue [2], brain slices developed by biochemists in the 1930s [3], whole-brain preparations first introduced in the 1980s [4] and living animals in which the kindling model makes use of electrical or convulsant stimulation to induce seizures. In these "in vivo" models, chronic focal epilepsy can also be obtained, usually after a latent period of several weeks, by application of toxic compounds (such as kainate or pilocarpine) [5]. Considerable technical progress has also been accomplished since the first galvanometric recordings of the cortical activity in animals performed by Caton in the 1870s. Electrophysiological recording techniques considerably improved allowing for

acquisition of functional data from microscopic (subcellular to cellular) to macroscopic (multicellular to system) level. New techniques were also developed like microscopic imaging (two-photon imaging used in conjunction with voltage-sensitive dyes, for instance) [6] which now gives access to network activity with appropriate time *and* spatial resolution.

However, a commonly accepted statement of fact is that only few advances in epilepsy research have led to novel and effective therapeutic solutions. Indeed, although a considerable number of new anti-epileptic drugs with reduced side-effects and toxicity have been introduced since the discovery of carbamazepine and valproate in the 1950s and the 1960s, 30% of patients are still pharmacoresistant [7]. In patients with drug-resistant focal seizures, epilepsy surgery remains the only option to significantly reduce the frequency of seizures [8].

The progress in understanding the drug resistance in epilepsy has been hampered by the complexity of the underlying neuronal systems and processes.

First, we are facing mechanisms, most often *nonlinear*, taking place at sub-cellular (membrane ion channels, neurotransmitter receptors), cellular (neurons), tissular (networks of neurons) and regional (networks of networks) scales within systems where *short-* or *long-term plasticity* also plays a crucial role. Second, the data recorded from such systems can only *partially* capture the underlying mechanisms. For instance, biophysical arguments indicate that the local field potentials recorded from a cortical tissue mainly reflect the post-synaptic activity generated at the level of the main pyramidal cells and not the whole neuronal activity generated by all cells of the network [9]. Third, we must deal with the *incompleteness* of the observations, in *time* and in *space* and, in the clinical case, make a decision based upon these sparse observations. Indeed, epilepsy is a *progressive disease* but in most of the cases, data are recorded over a *limited time window*. Epilepsy generally involves quite extended and distributed areas but in most of the cases, a *spatial undersampling* of data cannot be avoided

due to the difficulty of exploring simultaneously all parts of the brain. Finally, complexity is also rising from the fact that epileptic phenomena *emerge* at *different temporal scales*: the duration of epileptic spikes is typically around a few hundred of milliseconds whereas seizures can last from a few seconds up to several minutes. The frequency (a few/day up to a few/month) of seizures which can strongly differ from one patient to another also indicates that upper-level *regulatory mechanisms* play a role. All these arguments demonstrate that epilepsy is a physiopathological condition resulting from multiple causes and leading to the alteration of some parameters in complex dynamical systems, probably at multiple levels. In such a context where the demand for integrative approaches is high, neurocomputational models become recognized tools for tackling the complexity of epileptic phenomena [10].

Computational modeling as a way of structuring and interpreting multi-modal epileptic data

Computational neuroscience is an interdisciplinary research field at the crossroads of neurosciences, physics, applied mathematics, and computer sciences. This discipline discusses neurophysiogically-, neurobiologically-, and/or biophysically-relevant mathematical models and simulation methods that contribute to our understanding of the brain function, from neuronal mechanisms to behavior. Although the use of mathematical descriptions to study and explain observable facts has long been developed in many scientific domains, neurocomputational modeling is a relatively young but rapidly growing field, mainly because of the necessity - and the opportunity - of integrating structural, functional and dynamical properties of neural systems into "coherent and interpretable views".

Computational models are now considered as an efficient way of structuring new and detailed knowledge coming from neurobiological research in order to interpret experimental

findings and, in some cases, to generate hypotheses that can further be tested experimentally. A recognized virtue of computational models is also their unique ability to formalize and relate variables across multiple levels of analysis offering the possibility of establishing links between successive levels of reduction. For instance, from the modeling of networks of interconnected neurons and interneurons, computational models can help to simultaneously study mechanisms lying at the cell level and at the network level and to simulate corresponding activities that can be experimentally recorded (intracellular or multi-unit activity versus local field potentials).

In the field of epilepsy, pioneer works started in the 1970s and two complementary approaches developed over the past decades (figure 1, right).

The first one is known as the *microscopic* or *detailed approach* (figure 2, upper left box) because it relies on an accurate modeling of neuronal cells in both their structure (dendrites, soma, axon) and their function which strongly depends on the passive and active properties of their membrane (neurons are excitable cells). The development of this approach was boosted by single-cell recordings and was considerably reinforced at theoretical level by adapted versions of the equations proposed by Hodgkin and Huxley [11] who were the first to explain the voltage-dependence of ion channels using a biomathematical model. Nowadays, a considerable number of neuron models is available [12]. Most of them are based on a multi-compartmental structure. The most sophisticated versions may include hundreds of compartments and account for the main transmembrane currents as well as for the 3D geometry of actual dendritic trees. Models of principal neurons and interneurons can also be interconnected via appropriate links (either synaptic or non-synaptic) in order to obtain network models in which the population activity can be studied as a function of various

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parameters such as the types of neurons introduced in the network, the network size, the connectivity patterns, and the conduction delays, among others. This approach was extensively developed by Traub and collaborators [13] in the 1980s and led to innovative hypotheses about tissue excitability, role of interneurons and factors leading to hypersynchronization. For instance, combined experimental and theoretical work allowed the authors to find some necessary conditions for an epileptic discharge to occur: i) the population of neurons must be large enough, ii) inside this population, excitatory pyramidal neurons must be connected in a synaptic network, and iii) within this network, the synapses need to have a sufficiently high probability of driving their targets above threshold. Detailed models have explained some basic mechanisms by which synchronized "seizure-like" activity emerges [14]. In particular, realistic network models are able to generate activity patterns that closely mimic the epileptic activity recorded in vitro. Some paroxysmal events like very fast oscillations [15] observed in intracerebral electroencephalographic (EEG) signals at the onset of human partial seizures were also reproduced in detailed models and were explained by the crucial role of gap junctions between axons. Similar comments can be made about the insights brought by detailed models in the pathogenesis of absence epilepsy that revealed the key role the threshold activation of $GABA_B$ receptors in the characteristic transition from background to 3 Hz spike-and-wave activity [16]. Computational models of neuron networks were also used to study the transitions from clonic to tonic activity [17], which are often observed in epilepsy. Although implemented networks were of moderate size (1000 to 3000 neurons), they disclosed the presence of epileptiform behavior either consisting of repetitive high-amplitude population events ("clonic-like") or consisting of a latch-up near maximal activity ("tonic-like"). Paradoxically, neuronal excitability was not always a sufficient condition for appearance of epileptiform activity. As an interesting finding, it was even found to produce antiepileptic effects, depending on the adjustment of other parameters.

The second approach is often referred to as the *macroscopic* or *lumped* approach (figure 2, upper left box). As above, the same level of organization in the nervous system, i.e. the neuronal population level, is considered but in an aggregated manner. The physiological relevance of this model stems from the fact that neurons in a given brain area are organized as populations, themselves composed of interconnected sub-populations (for instance, pyramidal cells and interneurons in the cortex). Moreover, it is assumed that local field potentials induced at the level of a nearby electrode is the reflection of ensemble dynamics rising from macroscopic statistical interactions (mainly synaptic) between neuronal sub-populations. Pioneer works on models of localized populations of neurons started in the early 1970's with Wilson and Cowan [18] who established the theoretical bases starting from a crucial assumption, considered, at that time, as an axiom: all neural processes depend upon the interaction of excitatory and inhibitory cells. Following the same approach, Freeman and colleagues [19] developed a comprehensive model of the olfactory system able to produce EEG signals that approximate experimentally recorded EEGs quite accurately. Similar ideas developed at the same time by Lopes da Silva and collaborators [20] led to the development of a lumped-parameter population model able to explain the alpha rhythm of the EEG. Paradoxically, macroscopic models did not receive much attention from the 1980s to the 2000s especially in the field of epilepsy.

However, the recent past years have witnessed a considerable increase of interest for such approaches, probably because epilepsy is a disease which often involves relatively extended areas or systems that can hardly be represented at cellular level, given the still limited power of computers for simulating large scale neuronal networks with explicit representation of all neurons. Indeed, using macroscopic modeling, some advances were recently made about one essential and still poorly understood aspect of human epilepsy: the

transition from interictal to ictal activity. Starting from the aforementioned works, Suffczynski and co-authors [21] elaborated a computational model of the thalamo-cortical network which includes sub-populations of thalamocortical relay cells, of reticular nucleus cells, of cortical pyramidal cells and of cortical interneurons. The main ascending specific afferents and projections to a localized region of the cortex and to the reticular nucleus are also represented in the model. Synaptic interactions involve glutamatergic, GABAergic and cholinergic mechanisms. The model is used to analyze the transitions from normal to synchronous epileptic activity (rhythmic discharge of spike-waves). It shows that the random nature of the occurrence of absence seizures and the interval between these events can be explained by the bistability property of the thalamocortical loop model submitted to a noise input. A conclusion is that absence seizures could be unpredictable. Transition to partial seizures in temporal lobe epilepsy was also studied in a macroscopic model of the hippocampus activity by our team [22,23]. The model starts from the circuitry of the CA1 subfield and includes sub-populations of main pyramidal cells and of interneurons targeting GABAergic receptors located either in the dendritic or the somatic region of pyramidal cells. We found that the model is able to faithfully reproduce intracerebral EEGs recorded in patients during the transition from interictal to ictal activity with, in particular, an accurate simulation of the fast rhythmic activity observed at seizure onset. We also made use of this model to predict the time evolution of excitation- and inhibition-related parameters leading to the occurrence of interictal epileptic spikes and then to seizures. This work also demonstrates that simplified macroscopic models can capture salient features of epilepsy and point towards parameters that are most likely responsible for the appearance of paroxysmal activity.

To conclude with this brief literature review, it is noteworthy to mention that readers may refer to the book entitled "Computational Neuroscience In Epilepsy" [24] for a recent and quite comprehensive state-of-the-art in this domain. Through the thirty-three chapters of

this book, multiple facets of computation modeling are dealt with such as the mechanisms leading to synchronization, the influence of topology [25] and stability parameters in network models [26], the effect of homeostasis [27] or the dynamics of seizures [28,29], among others. Some practical aspects for building and running models, like simulation environments and software, are also presented. Regarding this last point, a number of software packages developed over the two past decades are now available making the implementation tasks much easier for the modeler. Among these packages, "Neuron" and "Genesis" have reached a maturity level that permits the simulation of biologically-inspired neurons and networks with high degree of realism. More recent software like "neuroConstruct" focus on specific aspects related to the modeling of 3D networks. One should also notice that some initiatives like the "SenseLab Project" promote the diffusion and the sharing of models among the neuroscientific community by providing an accessible location for storing and efficiently retrieving computational neuroscience models in open databases (in particular "NeuronDB" and "ModelDB").

Expert Commentary

Computational neurosciences have considerably evolved over the past twenty years and modeling is becoming an accepted tool in epilepsy research. The examples briefly described in the above section demonstrate that computational models closely related with either experimental or clinical data can markedly advance our understanding of how hyperexcitability develops in a neuronal tissue, how hypersynchronization between neurons arises and leads to paroxysmal activity or how and why seizures start, spread and stop within a restricted or more extended part of the brain.

I think that the integrative virtue of models is now recognized: we are entering a new and exciting era where computational modeling serves as a "forum" inside which people with

different and complementary background in mathematics, engineering, computer sciences, neurobiology, neurophsysiology, epileptology can exchange and contribute together to the development of formal descriptions of epileptic mechanisms, whatever the level ranging from receptor subunits to large scale networks. This trend in epilepsy research is parallel to a more general evolution in life sciences where a rise of computational biology [30] is observed due, in part, to recent progress in bio-informatics as well as to persistent advances in the computation power and the memory capacity of computers.

In this favorable context, a natural question is raised: can we take advantage of the tremendous potential of computational models either in computer-aided drug design or in the elaboration of therapeutic procedures based on stimulation?

To me, the answer to this question is definitely positive. As mentioned earlier, the need to discover new anti-epileptic drugs persists as an ongoing priority in epilepsy research. One the one hand, the past decade has seen the emergence of innovative approaches in cheminformatics aimed at making the design of drugs more rational. For instance, structural biochemistry methods can now provide accurate descriptions of the 3D shape of a receptor protein allowing for the "virtual" study of drug molecules for which the binding with this receptor will be facilitated (receptor-based versus ligand-based drug design). On the other hand, it is obvious that computational models in epilepsy allow for bridging between highly-complex mechanisms involved into neuronal activity and possibly altered local or global brain oscillations. Therefore, my impression is that the connection between computer-aided drug design and computational modeling is now feasible by integrating/improving the molecular level in developed models. Such an extension will allow for direct study of the effects of neuropharmacological agents "*in silico*", and particularly their aptitude to reduce the frequency of epileptic events as reflected in simulated electrophysiological recordings.

On the front of electrical or magnetic neurostimualtions and potential therapeutic effects in epilepsy, I can sense that a more rational approach to the definition of stimulation parameters can also benefit from advances in computational modeling [31,32]. Indeed, as many developed models behave as nonlinear dynamical systems, they offer the unique opportunity to address the stimulation issue from a mathematical perspective using tools coming from nonlinear control theory. The validation of theoretical findings in experimental in-vivo models would bring some answers to an essential question that is likely to impact on the current management of the disease: "how, where and when to stimulate in order to optimize anti-convulsing effects".

Five-year view

In the next five years, we can expect that computational neurosciences will continue to develop and epilepsy research will benefit from new advances. At cellular level, the fidelity of proposed models will be improved. They will incorporate more and more details of actual neurons (ions channels, receptors). At network level, large scale neural systems integrating a high number biologically-inspired neurons will be simulated (see, for instance, the project called "Blue Brain" [33] aimed at reproducing a neocortical column composed of accurately modeled pyramidal cells interconnected through 30 million synapses with precise 3D locations). I expect that network models will not only include neuronal cells but also astrocytes as their role is still a matter of debate in the field of epilepsy. Processes like those involved in neuroinflammation or ischemia and leading, in some cases, to epileptic activity might also be represented and studied into models.

At population level, more macroscopic models will develop in order to study and explain how the epileptic activity starts and spreads over extended brain regions. For instance, in temporal lobe epilepsy, modeling the entire closed-loop system formed by the hippocampus and the

entorhinal cortex [34] will bring some clues about the respective role of these two limbic structures in the initiation of seizures. In parallel, as multiple scales of description will be considered in modeling studies of epileptic phenomena, efforts will certainly be made to develop or adapt some methodologies allowing for bridging between microscopic and macroscopic levels. For instance, parameter aggregation methods could be considered to establish relationships between parameters lying at cellular level in detailed models and parameters lying at population level in lumped models. My impression is also that computational modeling will integrate more information coming from biophysics in order to solve forward problems more accurately and therefore to better reproduce and interpret real observations. Along the same line, I think that optimization advanced methods for model parameter identification will start to be used in computational models for epilepsy. As illustrated in figure 2 on electrophysiological recordings from human hippocampus, the key issue is to derive model parameter values directly from real data and to study the evolution of these parameters in time in order to gain insights into transitions between normal and epileptic activity. Finally, I am convinced that computational models must be developed in close relationship with experimental models, whatever the considered level [35]. This marriage is not easy but is necessary. We should not forget that a model is always an oversimplification of the real and complex object under study. Model validation is a difficult issue [36] in which the modeling level is crucial. There is an inherent compromise between building more and more detailed models versus being able to compute them in short time and using them in practical situations [37]. Validation difficulties increase with the level of detail as emergent phenomena may occur and degrade the confidence we may have about their correctness, even when these phenomena exactly correspond to what should occur. Successful models gain power and acceptance by retaining their validity upon new experimental observations.

Combined theoretical/experimental approaches provide an ideal framework to elaborate robust models that can further be used for clinical applications in epileptology.

Key issues

1. Epilepsy is a neurological disorder characterized by the recurrence of seizures and affecting 50 million people worldwide.

2. A considerable number of new anti-epileptic drugs with reduced side-effects and toxicity have been introduced since the 1950s. However 30% of patients remain pharmacoresistant.

3. Although epilepsy research is making progress, advances in understanding the drug resistance have been hampered by the complexity of the underlying neuronal systems responsible for epileptic activity.

4. Epilepsy is a physiopathological condition resulting from multiple causes and leading to the alteration of some parameters in complex dynamical systems, probably at multiple levels.

5. In epilepsy research, the demand for integrative approaches is high. Computational modeling provides an efficient way of structuring detailed knowledge and multi-modal data coming from research in neurobiology and neurophysiology. It serves as a "forum" for exchanges between people with different and complementary background in mathematics, engineering, computer sciences, neurobiology, neurophsysiology and epileptology.

6. Two complementary modeling approaches developed over the past decades: the detailed approach (cellular level) and lumped approach (neuronal population level).

7. At both levels of description, existing models have shown relevant to capture salient features of epilepsy and to reveal parameters that are most likely responsible for the appearance of paroxysmal activity.

8. The tremendous potential of computational models can be used either in computer-aided drug design or in the elaboration of therapeutic procedures based on neurostimulations.

9. Model validation is a difficult issue. Successful models gain power and acceptance by retaining their validity upon new experimental observations. Combined theoretical/ experimental approaches provide an ideal framework to elaborate robust computational models that can further be used for data interpretation in epilepsy.

10. Computational models closely related with either experimental or clinical data could markedly advance our understanding of how hyperexcitability develops, how hypersynchronization leads to paroxysmal activity or how and why seizures start, spread and stop within a restricted or more extended part of the brain.

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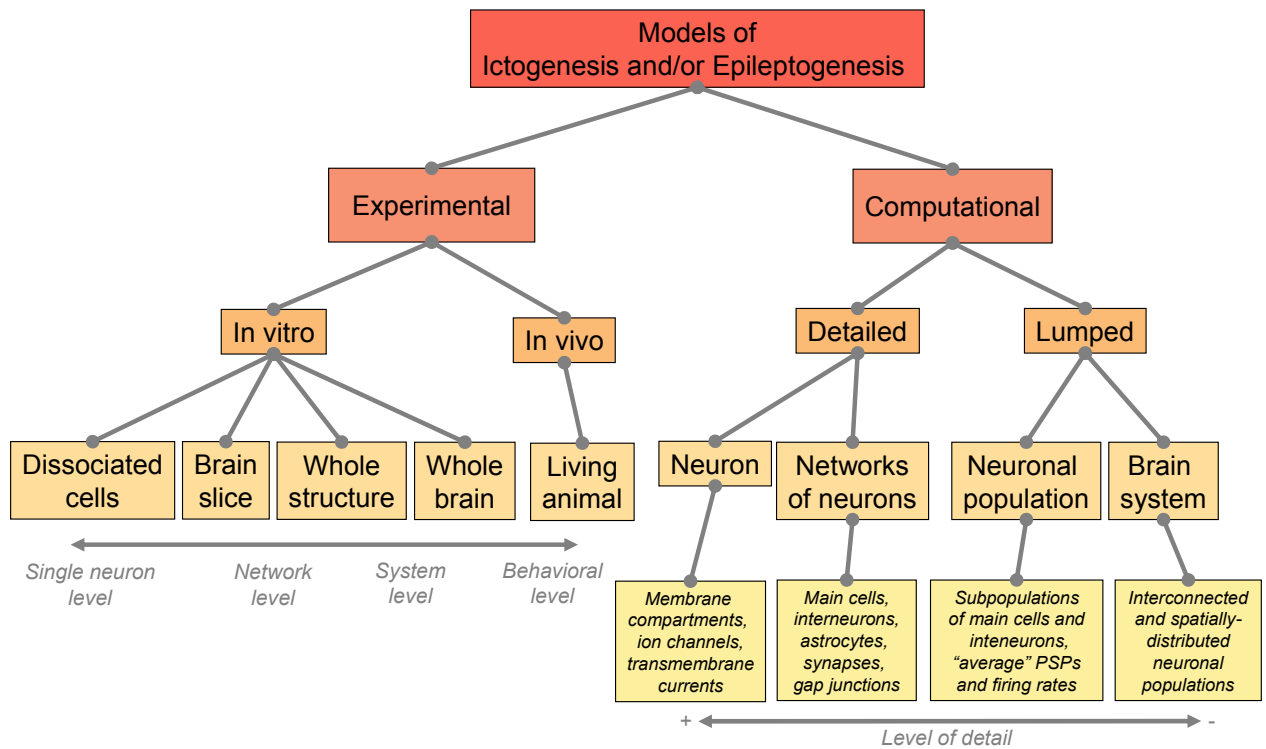
Figure 1: a taxonomy of models used in the study of ictogenesis and/or epileptogenesis mechanisms
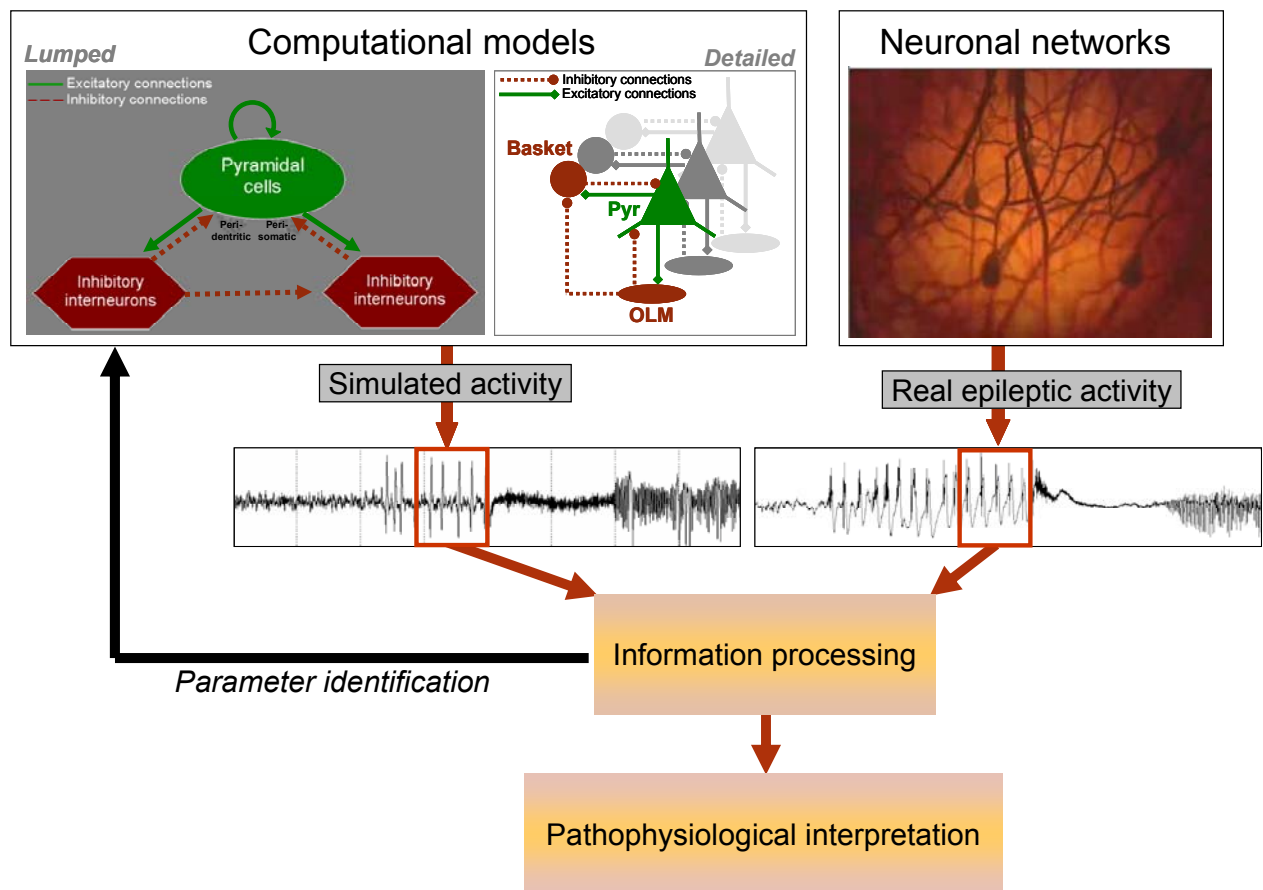
Figure 2: a future perspective is to identify excitability-related model parameters directly from real data. Computational models can be developed according to either a lumped (based on the representation of neuronal sub-populations and interactions) or a detailed (based on the explicit representation of cells and interconnections) approach. Simulated activity (for instance, the local field potentials) can be quantitatively compared to real activity using information processing techniques (for instance, signal analysis if electrophysiological data are to be compared). This quantitative analysis allows for identifying the parameters settings for which models best reproduce real data. Performing this identification over a sliding window would lead to follow, in time, the evolution of model parameters. It would provide insights into pathophysiological transitions between normal and epileptic activity as parameters in biologically-inspired models have a physiological meaning. Model diagram in upper left box and the simulated activity were respectively adapted from [23] and [38].