Neurocomputational models in the study of epileptic phenomena.

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Epilepsy is a complex dynamical disease characterized by recurring seizures. Although we know that seizures are related to abnormal excessive firing and synchronization of neurons in brain networks, the cause or causes of many forms of epilepsy are still unknown.

The need to better understand basic mechanisms that lead to epileptogenesis and ictogenesis has led to the development of a variety of reliable recording techniques of brain activity. Electrophysiology still occupies an important place since it allows the activity of neurons or networks of neurons to be recorded with high time resolution. Functional imaging is also a rapidly developing field which now provides a way to acquire high-resolution spatial maps of epileptic activity. In addition to new experimental techniques, both in animal (*in vivo* and *in vitro*) and in human, in recent years novel theoretical approaches have enriched this research field since it is becoming clear that in order to integrate the plethora of experimental data available it is necessary to develop computer models with the purpose of better understanding the dynamics of neuronal networks leading to epilepsy. Although these models are used to investigate epileptic phenomena at different levels of complexity (from cellular to network levels) within specific situations, they share the common feature of providing insight into

mechanisms involved in the generation of epileptic activity either at a microscopic (subcellular to cellular) or a macroscopic (multicellular to system) level.

Many experimental models were developed in the past decades, much before computer models. *In vitro* models include brain-slice preparations as well as whole-structure (mainly the hippocampus and associated structures) or whole-brain preparations. The experimental situation allows exposition of neuronal tissue to drugs capable of provoking convulsions that act specifically on a precise target, and recording of epileptiform activity such as spikes, transient bursts or seizures. *In vitro* models have been widely used in cellular neurophysiology and allowed to identify some key features of epileptogenic circuits such as the existence of recurrent excitatory connections between pyramidal cells. In parallel herewith several *in vivo* models have been developed. A question that is often raised - and not yet solved – is whether animal epilepsies resemble human epilepsies in meaningful ways? Apart from the difficulty related to homology, most people agree on the fact that experimental models have helped a lot in our understanding of the mechanisms leading to epileptic activity. Models of chronic focal epilepsy include electrical kindling or the application of toxic compounds, such as tetanus toxin, kainate, pilocarpine, that may lead to recurrent seizures usually after a latent period of several weeks. In several of these cases an initial status epilepticus is induced. These experimental models allow developmental aspects of epileptogenesis to be studied even if clinical relevance is mainly related to the issue of seizures induced by abnormal already established changes of local brain tissue.

Computational neuroscience is an interdisciplinary field of research connected to neuroscience, applied mathematics, physics and computer sciences. This discipline discusses neurophysiogically or neurobiologically relevant mathematical models and simulation

methods that contribute to our understanding of neural mechanisms. It is a rapidly growing field, mainly because of the necessity of integrating structural, functional and dynamic approaches to study the brain. This issue of the Journal of Clinical Neurophysiology focus on computational models developed in the field of epilepsy. These models are complementary to aforementioned experimental models. They can be viewed as a way to integrate new and detailed knowledge coming from neurobiological research to explain experimental findings and to generate experimentally testable hypotheses about possible mechanisms lying at the sub-cellular, neuronal or population level depending on the scale of representation and on the nature of the experimental data under study. By formalizing and relating information across multiple levels of analysis, computational models have this unique integrative property of establishing links between successive levels of reduction. For instance, from the modeling of a network of interconnected detailed 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 (using multi-unit or field potential electrodes).

For the study of epileptic phenomena, two complementary approaches were developed over the past decades.

In the first one, referred to as "detailed", single neurons are accurately modeled regarding their structural components (dendrites, soma, axon) and functional properties (voltage-dependent channels with kinetics derived from experimental voltage-clamp studies). Neuronal networks are then built from the interconnection of a relatively large number (i.e. several thousands) of principal neurons and different types of interneurons with appropriate synaptic interactions. In these networks, the summated post-synaptic potentials of pyramidal cell

membranes that correspond to the field activity, can be studied as a function of various parameters such as the types of neurons introduced in the network, network size, connectivity patterns, and conduction delays. According to this approach that was extensively developed by Traub and collaborators since the early 80's, both spatial and temporal properties of the activity in the simulated patch of neuronal tissue are represented. Insights about tissue excitability, role of interneurons, factors leading to hypersynchronization have been put in evidence and confronted to real observations. For instance, combined experimental and theoretical work showed that some features are necessary for an epileptic discharge to occur: the population of neurons must be large enough and, inside this population, excitatory pyramidal neurons must be connected in a synaptic network in which the synapses need to have a sufficiently high probability of driving their targets above threshold. The use of such models has explained some basic mechanisms by which synchronized activity emerges. In particular, these models are able to generate activity patterns, in realistic networks, that closely mimic epileptic activity recorded *in vitro* as well as different types of electroencephalographic (EEG) activity seen in patients.

According to the second approach, referred to as "macroscopic" or "lumped", a higher level of organization, i.e. the neuronal population level, is considered. It starts from the fact that neurons form populations and that the EEG is a reflection of ensemble dynamics rising from macroscopic statistical interactions between interconnected neuronal sub-populations (pyramidal cells and interneurons). This approach was initially proposed by Wilson and Cowan and by Freeman and co-workers who made substantial progress in the understanding of perceptual processing in the olfactory system. Their studies, spanning the three last decades, are based on experimental data and on computational models in which the dynamics of each neuronal subset are simply represented by a 2nd order ordinary differential equation

having a static nonlinearity identified as a asymmetric sigmoid curve. In this way a model of olfactory area able to produce EEG signals that approximate experimentally recorded EEGs quite accurately was developed. Similar ideas developed at the same time by Lopes da Silva and collaborators led to the development of a lumped-parameter population model able to explain the alpha rhythm of the EEG and more recently to the development of a model of the thalamocortical loop providing useful insights into the interpretation of mechanisms involved in absence epilepsy.

As is clear from these brief sections, basic mechanisms of epileptic activity are an active area of research in which computational models play a major integrative role. More recent in the advances also demonstrate that computational neuroscience is becoming an accepted tool in the neurosciences with possible clinical applications. The intent of this special issue on "Neurocomputational models in the study of epileptic phenomena" is precisely to demonstrate that computational model-based methods constitute a way to bridge the gap between basic neuroscience research and clinical research in epilepsy at both microscopic and macroscopic levels. The five studies reported in this issue give a good overview of the use of physiologically-relevant models (following either the first or the second approach described in the above section) with respect to the interpretation of clinical data recorded in patients with epilepsy (partial or absence) or in patients presenting seizures under anesthesia or in the analysis of these data in the context of seizure prediction.

Suffczynski and colleagues (Amsterdam, The Netherlands and Warsaw, Poland) investigate the mechanisms of transition between normal EEG activity (i.e. non-epileptiform) and epileptiform paroxysmal activity using a computational model of thalamocortical circuits based on relevant patho(physiological) data. They compare model predictions with experimental results from different types of epilepsy, including patients with absence seizures.

Their approach allows them to derive hypotheses about physiological mechanisms of ictal transitions. They also reach conclusions about the predictability of absence seizures and open perspectives about the use of electrical stimulations to abort paroxysmal oscillations.

Liley and Bojak (Hawthorn, Australia) present recent approaches to theoretically describing the electroencephalographic effects of proconvulsant volatile general anesthetic agents. Using biologically plausible computational and mathematical models, they managed to simulate realistic EEG signals in response to specific and quantifiable physiological changes related to different anesthetic agents. This original study deals with the crucial issue of mechanisms involved in ictogenesis and provides valuable insights into the physiological workings of seizure initiation.

Chernihovskyi and colleagues (Cuernavaca, Mexico and Bonn, Germany) describe a very original approach which complements the topics of the four other contributions. Indeed, while the four other articles mainly present computational models aimed at interpreting mechanisms involved in the generation of real interictal/ictal observations (either at a microscopic or a macroscopic level), this one uses biologically inspired models to process EEG signals. Authors elaborated a nonlinear, excitable, spatially extended medium composed of coupled model neurons in which EEG recordings are applied as local perturbations that induce transient changes in the dynamics of the perturbed system. Implemented in Cellular Neural Networks (CNN), excitable media are then used to approximate the degree of synchronization in EEG recordings. This approach provides a new direction in signal processing techniques and could help to progress on difficult questions such as the prediction of epileptic seizures.

Traub and colleagues (Brooklyn, Philadelphia, USA and Leeds, U.K.) contributed to this special issue by presenting the benefit of combining experimental with modeling studies (microscopic approach) to progress in the understanding of cellular and network mechanisms of epileptogenesis in vitro and in vivo. Based on their pioneered and recent works, they review some of the means by which cellular intrinsic properties, synaptic interactions, and electrical coupling via gap junctions contribute to the anomalous population activities characteristic of seizures. Their detailed models permit to make precise hypotheses about the neurobiological substrate of certain types of oscillations (observed at the electrophysiological level) that often precede the onset of seizures (very fast oscillations, > 80 Hz). This combined experimental/model approach leads to new clinical perspectives like the development of compounds that would specifically block putative axonal gap junctions which are showed to be critical for epileptogenesis.

Finally, the fifth article by Wendling and collaborators (Rennes, Marseille, France) describes a model-based approach used to study some pathophysiological mechanisms in human partial epilepsy. In this approach, electrophysiological patterns (intracerebral EEG) recorded from the hippocampus in patients with mesial temporal lobe epilepsy are related to mechanisms involved in the transition to seizure through a macroscopic physiologically-relevant model of EEG activity. Model parameters (related to synaptic interactions between subsets of neurons and interneurons represented in the model) are automatically identified using a procedure that minimizes a distance between real and simulated signals. Analysis of identified parameters suggest that the transition from interictal to ictal activity can not be simply explained by an increase in excitation and a decrease in inhibition but rather by time-varying ensemble interactions between pyramidal cells and local interneurons projecting to either their dendritic or perisomatic region (with slow and fast $GABA_A$ kinetics). Such approaches open new

perspectives for interpretation of epileptic signals recorded in patients with drug-resistant epilepsy.