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The role of multiple-scale modelling of epilepsy in seizure forecasting

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Abstract

Over the past three decades, a number of seizure prediction, or forecasting, methods have been developed. Although major achievements were accomplished regarding the statistical evaluation of proposed algorithms, it is recognized that further progress is still necessary for clinical application in patients. The lack of physiological motivation can partly explain this limitation. Therefore, a natural question is raised: can computational models of epilepsy be used to improve these methods? Here we review the literature on the multiple-scale neural modelling of epilepsy and the use of such models to infer physiological changes underlying epilepsy and epileptic seizures. We argue how these methods can be applied to advance the state-of-the-art in seizure forecasting.

Keywords

neural modelling; epilepsy; multiple-scales; seizure prediction; seizure forecasting; inference

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Introduction

Epilepsy refers to a set of neurological disorders characterized by recurring seizures. It is a debilitating disease affecting millions of people worldwide. The multiplicity of causes and types of epilepsy makes this disease very complex. This is particularly true in drug-resistant patients for whom it is problematic to i) establish an accurate diagnosis (in terms of localization of epileptic zones in the brain) and to ii) indicate efficient treatments aimed at suppressing seizures.

The majority of existing methods for seizure prediction and forecasting (Carney et al., 2011; Lehnertz et al., 2013) do not take an individual's physiology and anatomy into account. Rather, they focus on generic signal processing, data mining and pattern recognition approaches, which to date have shown some promise (Cook et al., 2013) but there is still significant room for improvement (Mormann et al., 2007; Elger & Mormann, 2013). This review proposes that a more physiologically motivated approach to seizure forecasting can potentially yield improvements. Indeed, "model-based" approaches can potentially account for an individual's (patho)physiology and anatomy and thus include prior information that is not present in purely "data-driven" approaches.

Computational models of epilepsy have been developed at multiple scales in order to describe and predict anatomical and physiological changes underlying epilepsy and epileptic seizures. The models have been developed to describe neural data at the electrophysiological measurement levels of single-unit microelectrode, local field potential (LFP), intracranial electroencephalography (iEEG), and scalp electroencephalography (EEG) recordings. Moreover, these computational models are generally defined by their states and parameters. The states are time varying quantities (i.e. variables) that typically describe the membrane potentials of individual neurons or averaged populations of neurons, and usually represent the fast dynamics of the relevant neural system. On the other hand, parameters are usually defined to be the synaptic strengths, neural time-constants, and other possibilities of either single neurons or averaged populations of neurons. In the simplest case, parameters are considered constant; otherwise, they are considered to represent the slowly-varying dynamics of the system. When parameters are time varying, an 'augmented state' vector may be constructed that consists of the original states describing the fast dynamics and the parameters describing the slow dynamics.

Various methods have been used to estimate or infer changes in states and parameters of computational models of epilepsy from limited electrophysiological measurements. Estimates of the states and parameters of neural models can be used to track in real-time the brain state, i.e. ictal or inter-ictal, because different regions in state and parameter space correspond to different types of brain behavior. Therefore, it is possible to infer changes in an epileptic patient's brain by monitoring the iEEG or EEG over the long-term and by using this signal to estimate physiological changes via neural-model-based state and parameter estimation techniques (Freestone et al., 2013). By tracking changes in an epileptic patient's brain state both detection and forecasting of epileptic seizures can potentially be achieved. Figure 1 schematizes this concept.

This review is broken into the following sections. Section 2 summarizes the work on the computational modelling of epilepsy at the scale of single neurons and networks of neurons. Section 3 summarizes work on the computational modelling of epilepsy at the scale of populations of neurons using either neural mass or neural field models. Section 4 summarizes the techniques that have been applied to infer the states and parameters of computational models of epilepsy from limited electrophysiological measurements. Section 5 summarizes the seizure prediction literature and argues for a computational model-based seizure forecasting approach. Section 6 concludes with a summary of the pros and cons of model-based seizure forecasting.

Neural modelling of epilepsy at the single neuron and neural network level

Various “microscopic” models based on a detailed description of neurons and networks at sub-cellular and cellular levels have been used to model epilepsy and epileptic seizures (Soltesz & Staley (2011) provide a comprehensive overview). Many of these models focus on electrical or electrochemical properties of neurons and typically rely on integrate-and-fire or Hodgkin-Huxley formulations of the neuron dynamics. Moreover, these models have been used to describe seizure initiation, propagation and termination (Traub & Wong, 1983; Menendez de la Prida et al., 2006; Rothkegel et al., 2011; Hall & Kuhlmann, 2013), both for neocortical and hippocampal neurons. In brief, in such single- or multi-compartmental models, the ionic channels are governed by differential equations describing their properties (voltage-gated, ligand-gated, or second messenger-activated properties) as ionic conductances across the cell membrane. Within these equations these ionic conductances drive changes in the membrane potentials of individual neurons in order to generate various neuronal behaviours such as action potentials. At the network level, excitatory and inhibitory neurons are connected together to study epileptic network behaviours such as seizures, which are typically believed to arise through an alteration of the balance of excitation and inhibition. To model epilepsy and seizures it is also sometimes important to model changes in intra- and extracellular ionic concentrations and their effects on reversal potentials (Ullah & Schiff, 2009; 2010).

Based on simulations, processes at the membrane level could be identified and hypothesized as responsible for the generation of intrinsic epileptiform bursts in single cells. In a more recent study of the hyperexcitability mechanisms in neural networks (Demont-Guignard et al., 2012), authors have shown that the synchronization among firing patterns (synchronized versus weakly synchronized) of pyramidal cells can explain the switch between epileptic spikes and high-frequency oscillations (fast ripples, 200-600 Hz), as observed in LFPs in patients or in animal models of focal epilepsy.

More recently, metabolic aspects have been included in these models. With advances in oxygen sensing technology (Ingram et al 2013), there has been a discovery that oxygen serves as an experimental bifurcation parameter for seizure activity (Ingram et al 2014). Seizures are supported within a relatively narrow band of oxygen concentrations. A computational embodiment of the dynamical effect of oxygen demonstrated the importance of the effect of neural activity on local tissue oxygen availability, the interaction with the

dependency of ion pump activity on oxygen, and the consequent emergence of instability that supports seizures (Wei et al 2014a).

Most recently, by combining this oxygen dependency with fundamental principles of conservation of energy, charge, and particles, it was demonstrated, through an extension of the classical Hodgkin-Huxley model, that there is a dynamical unification of spikes, seizures, and spreading depression along the continuum of repertoires of the neural membrane of an individual neuron in the extracellular space (Wei et al 2014b). These different dynamical behaviours were found to emerge in different regions of the joint space of oxygen and K^+ levels. This unified set of dynamics is a major advance in our understanding of seizure dynamics as it provides a universal framework to understand and describe how seizures, and also spreading depression, can arise from various factors such as hypoxia, hypoglycemia, neural injury, high concentrations of K^+ , or Na^+/K^+ pump dysfunction.

In terms of seizure prediction, such models of neuronal stability open the possibility of broadening our understanding of how gradual changes in the metabolic environment surrounding the neuron, and slow replenishment of transmembrane gradients through ion pump activity, may prepare the route for seizure onset in circumstances where measurement of spiking activity would be uninformative. It also offers novel approaches to model based control, introducing the concept of trajectory control within the phase plane of seizures, spiking, and spreading depression, the concept of energy optimization of a control device, and importantly, the ability to model the energy burden placed upon stimulated neurons themselves (Wei et al 2014b). Exploring the consequences of such unification models within networks of neurons in seizures and spreading depression are the subject of ongoing efforts.

Neural modelling of epilepsy at the mesoscopic scale

Recently, we have witnessed a considerable increase of interest in another type of modelling approach referred to as either the “neural mass” or the “neural field” approach. Conversely to “microscopic” models based on a detailed description of neurons and networks at sub-cellular and cellular levels (see previous section), mesoscopic models are intended to represent the temporal only (neural mass) or the spatio-temporal (neural field) dynamics of the activity arising from (possibly coupled) neuronal populations without explicit representation of single cells. Note that neural field models can be viewed as a generalization of neural mass models, where the state of represented neural populations is a function of both time and position on the brain cortical surface (Friston, 2008).

The basic principles of these models (based on synaptic interactions among sub-populations of excitatory and inhibitory neurons) were first established in the 70s (Wilson & Cowan, 1972; 1973) and their ability to produce dynamics similar to those observed in actual LFPs was then demonstrated for the olfactory system (Freeman, 1973) and for the cerebral cortex (Lopes da Silva et al., 1974). Interestingly, in the field of epilepsy, these models did not receive much attention from the 1980s to the 2000s, although some pioneering studies showed they can bring novel insights into stability properties of neural systems when they switch, for instance, from background activity to epileptic spikes (Zetterberg, 1978).

As briefly reviewed below, over the past fifteen years, both neural mass and neural field models led to significant advances in modelling bifurcations in epileptic systems (Touboul et al., 2011), typically the transition from interictal to ictal activity in focal (partial epilepsies) and generalized (absence epilepsies) seizures (Lopes da Silva et al., 2003). More recently, insights were also gained into the response of neuronal systems to electrical neurostimulation.

Starting from aforementioned works, Wendling and co-workers developed a mesoscopic model of hippocampus activity (Wendling et al., 2003; 2005) for partial temporal lobe epilepsy (TLE). Starting from the circuitry of the CA1 subfield, it includes sub-populations of pyramidal cells and of interneurons targeting GABAergic receptors located either in the dendritic or the somatic region of pyramidal cells. The model was shown to faithfully reproduce iEEGs recorded in patients with TLE during the transition to seizure. Transitions of dynamics on the route to seizures could be explained by a gradual decrease of dendritic inhibition. In addition, fast oscillations (beta, low gamma frequency) observed at seizure onset could be related, in the model, to GABA_A, fast inhibitory post-synaptic potentials (PSPs), which were experimentally evidenced a few years later (Gnatkovsky et al., 2008). An extension to high-frequency oscillations (HFOs) at the onset of neocortical partial seizures (also known as brain chirps, Schiff et al., 2000) was proposed later on by Molaee-Ardekani et al. (2010). For absence seizures, a neural mass model of the thalamocortical network was elaborated by Suffczynski et al. (2004). In line with other published models (Roberts & Robinson, 2008; Crunelli et al., 2011), this model includes subpopulations of thalamocortical relay cells, of reticular nucleus cells, of cortical pyramidal cells and of cortical interneurons interconnected via glutamatergic, GABAergic, and cholinergic synapses. The model was used to analyze the transitions from background to synchronous rhythmic discharges of spike-waves. Interestingly, in this model, the occurrence of seizures is explained by the bistability property of the thalamocortical loop subjected to a noise input (Marten et al., 2009a; 2009b). A strong model prediction is that absence seizures are inherently unpredictable.

Recently, mesoscopic models were also used to analyze neurostimulation effects in the epileptic tissue. Goodfellow et al. (2012) investigated the propagation of travelling waves and complex transient dynamics in response to local perturbations in a spatial extension of the neural mass model (neural field) and hypothesized that sustained rhythmic responses to stimulation result from altered excitation in regions with diminished inhibitory efficiency. Stimulation effects were also reproduced in the aforementioned hippocampus model (Wendling et al., 2005). Authors investigated how changes in model parameters controlling neuronal excitability reflect in a pulse-stimulation based quantity, referred to as the “phase clustering index” (PCI). Simulations allowed them to explain why – and how – the PCI evolves with respect to impending seizures (Suffczynski et al., 2008).

As described in this section, simplified models can capture salient features of epilepsy and point towards parameters that are most likely responsible for the appearance of paroxysmal activity. Some of these parameter changes can be turned into experimentally testable predictions and, ultimately, into validated mechanisms. In addition, the models that have been described at multiple scales can be ‘effectively’ inverted such that the parameters of

the models can be estimated using limited electrophysiological recordings. This in turn could be used for deeper understanding of physiology or, potentially, seizure forecasting.

Model-based inference of physiological changes underlying epilepsy

Methods for estimation of states and parameters from limited measurements often operate either by a sample-by-sample or window-by-window based approach. Moreover, if the computational complexity of the method is low it can be used for real time ‘online’ processing; otherwise, if computational complexity is high but the method is still effective, then analysis needs to be performed ‘offline’.

Methods that give sample-by-sample estimates include stochastic filtering techniques from signal processing theory, such as variants of Kalman filters or particle filters (Simon, 2006), and deterministic observer techniques from control theory (Besançon, 2007). These methods read in the electrophysiological measurement and update the state and parameter estimates one sample at a time. In addition, they are often computationally efficient. Window-by-window based approaches read in segments of the measurement and typically provide an estimate of the parameters for each segment based on, for example, the power-spectrum of the signal over the segment. Window-by-window based approaches typically involve genetic algorithms (Gen & Cheng, 2000) or other forms of parameter estimation (Aster et al., 2013). Some of these approaches can be computationally intense and difficult to run in real time. Depending on various factors, such as model accuracy, sample-by-sample approaches cannot always estimate parameters immediately and often some time is needed for the parameter estimates to converge. Given that many parameters in the models of interest represent slowly varying physiological variables, the finite convergence times of sample-by-sample approaches are not likely to be problematic. The differences between sample-by-sample and window-by-window approaches are not cut and dried. For example, Kalman filter sample-by-sample estimates within a window of data can be averaged producing a window-by-window method. A comprehensive review of control methods applied to neuroscience can be found in Schiff (2012).

At the scale of networks of neurons, Ullah and Schiff (2009; 2010) used a model-based predictor-controller framework from modern control theory, incorporating the unscented Kalman filter, to estimate the dynamics of small neuronal networks using a single intracellular electrode recording. Specifically, noisy membrane potential measurements from individual hippocampal neurons were used to reconstruct the dynamics of networks of these cells, their extracellular microenvironment, and the activities of different neuronal types during seizures. This work gives insights into the physiological changes underlying seizure-like behavior observed in the neuronal network activity of animal models of epilepsy. For example, it can help to explain the roles that excitation, inhibition, or sodium and potassium conductances/reversal potentials can play during seizure initiation, propagation, and termination.

At the larger mesoscale of populations of neurons, unscented Kalman filtering techniques have also been successfully used to track states and parameters of neural mass models such as the Jansen-Rit (1995) model. Freestone et al. (2013) have demonstrated that parameters

such as excitatory and inhibitory post-synaptic potential amplitudes and time-constants of neural populations can be estimated and tracked in the lead up to a seizure recorded with a single iEEG electrode. While seizure prediction was not the focus of this work, the inhibitory time constant showed a transition about 40 seconds before the onset of the seizure indicating the potential of this approach for seizure forecasting. Frogerais et al. (2007) also demonstrated the feasibility of a similar approach using sequential Monte Carlo nonlinear filtering. Other work by Freestone et al. (2011) and Aram et al. (2013) demonstrated techniques for determining connectivity parameters for neural field models that can also be used to monitor brain changes.

Deterministic observer approaches have also been developed to track states and/or parameters of neural mass models (Chong et al., 2011a; 2011b; 2012a; 2012b; Postoyan et al., 2012; Freestone et al., 2013). Observer-based approaches are more model-specific, and convergence proofs are easier to obtain than for stochastic filtering approaches; however, further work needs to be done to ensure parameter estimation is robust to input and to measurement uncertainties that occur in the practical scenario (Freestone et al., 2013).

Using genetic algorithms, the parameters of the Wendling neural mass model have been estimated directly from iEEG recordings (Wendling et al., 2002; 2002; 2005), and a multi-scale modelling analysis has also been performed (Wendling et al., 2012). These works have demonstrated that different parameter sub-spaces of the Wendling model characterize well the behavior of the iEEG and EEG during resting periods, interictal spikes, and partial seizures common to focal epilepsies. In turn, this feature can be used to estimate parameters and track brain states of epileptic individuals using genetic algorithms, or other similar but more computationally efficient approaches.

As an alternative to the above parameter estimation methods, work has also been done to fit models to data by considering data segment features (i.e. the number of spikes, their ordering and position in phase, or pseudo-stationary dominant oscillations) for spike-and-wave seizures common to generalized epilepsies (Nevado-Holgado et al., 2012) and focal seizures (Blenkinsop et al., 2012).

The various approaches of parameter estimation/inference that are described here hold significant promise for more physiologically motivated seizure prediction or forecasting methods that are constrained by physiologically-plausible computational models of electrophysiological signals.

Seizure prediction and model-based forecasting

The ability to forecast seizures, or at least to estimate their likelihood, provides the opportunity to greatly improve the quality of life of epilepsy patients. The unpredictability of seizures is the most important cause of both morbidity and mortality. If a seizure can be reliably anticipated several minutes before its onset, it would provide an opportunity for the patient to seek protection and minimize the risk of injury. Alternatively, it could provide a time window during which a therapeutic intervention, such as administration of electrical stimulation or anti-epileptic drugs, could be implemented to eliminate the seizure or reduce its severity. The development of algorithms that estimate seizure likelihood could also be

used to assist the titration of anticonvulsant drugs, since currently the only way to determine whether a dose is insufficient is the seizure occurrence rate.

Early examples of seizure prediction methods were based on linear analyses of iEEG/EEG recordings, including time-series and spectral analyses (Viglione & Walsh, 1975; D'Alessandro et al., 2005), autoregressive modelling (Rogowski et al., 1981), and expert systems that examined particular features extracted from the iEEG/EEG signals (Lange et al., 1983; Osorio et al., 1998). The focus of these approaches is to determine a set of features that can be used to separate normal brain activity from 'abnormal' activity that exists in some time window immediately prior to patients' seizures. This is based on the premise that features indicative of an impending seizure can be detected before the actual onset of the seizure. This method was further developed with the introduction of nonlinear time series analysis approaches (Babloyantz and Destexhe, 1986; Pijn et al., 1991; Pritchard and Duke, 1995; Iasemidis and Sackellares, 1996; Lehnertz and Elger, 1998; Aschenbrenner-Scheibe et al., 2003) as well as the use of Lyapunov exponents (Iasemidis et al., 1990; Moser et al., 1999) and similarity index (Le Van Quyen et al., 1999; Navarro et al., 2002) to measure the complexity of the recorded iEEG signal, with the implication that measured complexity decreases in the pre-seizure period.

Based on the observations that epileptic seizures manifest as hypersynchronous neural activity (Lange et al., 1983), the next developments in seizure prediction used measures of synchrony (Litt and Lehnertz, 2002; Chávez et al., 2003; Lehnertz et al., 2003; Mormann et al., 2003; Mormann et al., 2005; Jouny et al., 2005; Schelter et al., 2006; Winterhalder et al., 2006; Osterhage et al., 2007; Mirowski et al., 2009). These algorithms were based on the premise that changes in synchrony in iEEG recordings may indicate that the brain is moving towards a seizure. Kuhlmann et al. (2010) examined phase synchrony measured between every pair of electrodes of long-term continuous iEEG data in six patients, and found that specific electrode locations gave good prediction performance, compared to a random predictor, but that it was not possible to determine a relationship between the electrode locations and the seizure onset locations.

The outcomes of the studies gave high false positive rates and were highly variable across patients, generally only giving good performance for a subset of the patients. A major limitation imposed upon the seizure prediction research has been the short time over which iEEG/EEG recordings have been made, resulting in few seizures being recorded for each patient and a subsequent gross imbalance between the normal and pre-seizure periods in the data. This shortcoming was overcome in the NeuroVista Corp. (Seattle, WA, USA) funded clinical trial of a seizure advisory system (Cook et al., 2013). The system was chronically implanted in 15 patients and recordings were made over periods of up to 24 months. For each patient, a seizure advisory system was encoded using features such as Teager-Kaiser energy (Vakman, 1997) and line-length (Esteller et al., 2001). The system demonstrated the feasibility of seizure prediction. One important finding was that there was a period of around four months after implantation of the iEEG electrodes during which the recordings varied considerably making it difficult to develop the patient-specific predictors until after this time. This has important implications for assessing the impact of the results of short-term recordings on the development of prediction algorithms to date. The study also demonstrated

that i) seizure prediction tended to work best for individuals that did not have high seizure frequencies (<2 per month), and ii) patients who received the lowest durations of high seizure likelihood warnings had the most satisfaction with the device and were able to make lifestyle changes that reduced their risks. Moreover, it was found that patient seizure diary reporting did not accurately account for all clinical seizures observed in the iEEG, and this has implications for trials of new treatments that rely on patient seizure diaries to track seizure frequency.

All of the research described above has used passive iEEG recordings. However, passive iEEG only allows the observation of a very small fraction of the underlying generators of brain activity (O'Sullivan-Greene et al., 2011). Thus, recent research has applied an active approach for measuring seizure likelihood (Richardson et al 2003; Kalitzin et al., 2005; Suffczynski et al. 2008; Freestone et al., 2011), a method of “probing” the brain with electrical stimulation and recording the brain’s response to this using iEEG. This approach attempts to estimate the excitability of the brain, based on the premise that when the brain is in a more excitable state it is more likely to have a seizure. This premise is supported by transcranial magnetic stimulation (TMS) studies (Badawy et al., 2009; Richardson and Lopes da Silva, 2011; Badawy et al., 2012), electrical probing in canines (Freestone et al., 2013) and modelling (Suffczynski et al. 2008). The probing method enables the signal-to-noise ratio to be improved through averaging responses to multiple stimuli and enables direct measurements of the brain’s response to perturbations about its current state.

All seizure prediction algorithms described so far have been based upon features of the iEEG/EEG recordings. However, a model of epilepsy such as mesial TLE is that changes in the neural physiology causes changes in excitability and thus seizure likelihood (Lopes da Silva et al., 2003). Model-based seizure prediction or forecasting approaches provide the opportunity to estimate relevant physiological parameters by fitting the models to the iEEG/EEG recordings. This offers the possibility that the parameters may be tracked in a way that enables the susceptibility to seizures to be estimated and, possibly, a way to intervene in a closed-loop fashion to steer the brain away from the seizure state, such as by electrical stimulation and/or local drug delivery.

As described in the previous section, different models and methods have been used to estimate model parameters in order to infer physiological changes underlying epilepsy, however, only one study has directly considered seizure forecasting. Aarabi and He (2014) recently developed the first neural mass model-based seizure prediction system. They fit the model developed by Moran et al. (2007), which is an enhanced version of the Jansen and Rit (1995) model, to recordings from 21 patients with hippocampal and neocortical focal epilepsies. The method showed sufficiently good performance to indicate that the model-based approach warrants further investigation.

Conclusion

Given that only limited numbers of neurophysiological measurements can be made as a result of both biophysical and computational analysis constraints, it is clear that computational modelling methods are needed to fill in the missing unmeasured variables

needed to infer more or less gradual changes occurring in the epileptic brain during interictal, pre-ictal, and ictal periods. As has been argued here, the physiologically relevant information that these methods can provide holds considerable promise for the development of future seizure prediction or forecasting methods.

While it is clear that there are benefits of model-based seizure forecasting, improvements are still needed with regard to the biological accuracy of the models and the robustness and computational efficiency of the estimation methods, as well as a deeper understanding of which physiological variables can be inferred/observed and controlled (O'Sullivan-Greene et al., 2009a; 2009b; 2014; Whalen et al., 2013). There are also trade-offs between model accuracy and computational efficiency, with more accurate models generally requiring more computation. A likely solution will involve models with only a few parameters; however, these parameters will be critical in describing the key physiological changes of interest. Across-scale approaches can be used to establish relevant links between well-defined and well-grounded parameters of 'microscopic' models and more abstract lumped parameters of 'meso-/macroscopic' models.

It is anticipated that model-based approaches will not only be useful for seizure forecasting, but also for model-based seizure control, where different electrical stimulation and drug-delivery strategies can be simulated to determine the most effective control strategy using the model. This will also lead to model-based, closed-loop seizure control where model-based seizure forecasting and control strategies can be combined into an implantable device using control theoretic tools for improved treatment of epileptic patients.

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Glossary

LFP	local field potential
EEG	electroencephalography
iEEG	intracranial electroencephalography
K⁺	potassium ion
Na⁺	sodium ion
GABA	gamma-aminobutyric acid
CA1	hippocampus, Cornu Ammonis area 1
PSP	post-synaptic potential
TLE	temporal lobe epilepsy

HFOs	high frequency oscillations
PCI	phase clustering index

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Figure 1.

Schematic of model-based seizure forecasting. Exogenous and endogenous inputs drive multi-scale activity in epileptic neuronal networks and brain regions. This activity can be measured at multiple scales using whole cell, micro, iEEG or EEG electrodes. These measurements feed into parameter estimation algorithms to ‘effectively’ invert micro- and/or meso-scale models of epileptic neuronal networks or brain regions. These parameter estimates tell us about underlying physiological changes that cannot be measured. Whole cell measurements of cell membrane potentials at the microscale allow inference of ionic concentration changes underlying seizure-like activity in animal cortical slice tissue. Extracellular microelectrodes have the potential to enable inference of spiking activity in unmeasured neurons (i.e. that are distant from recording electrodes) in practical *in vivo* situations. At the mesoscale, iEEG and potentially EEG enable inference of changes in physiological parameters at the population level, such as changes in the balance between excitation and inhibition (reflected in estimated population averaged post-synaptic amplitudes) in the lead up to seizures. These estimates of physiological change can then be used to drive seizure forecasting algorithms that can give a warning to a patient or activate an implantable seizure control device. The neuron histology image, human brain sketch, intra-cellular recording time series, and iEEG recording time series have been adapted with permissions from Figure 1C in Ziburkus et al. (2006), the Creative Commons Attribution Licence figures from Unrestricted Stock, Figure 4A in Ullah and Schiff (2010), and Figure 5a in Freestone et al. (2013), respectively.