Neurobiology of Disease 130 (2019) 104488

Contents lists available at ScienceDirect

Neurobiology of Disease

journal homepage: www.elsevier.com/locate/ynbdi

Review

Epilepsy as a manifestation of a multistate network of oscillatory systems

Stiliyan Kalitzin[a], George Petkov[a], Piotr Suffczynski[b], Vasily Grigorovsky[c], Berj L. Bardakjian[c], Fernando Lopes da Silva[d,1], Peter L. Carlen[c,e,*]

[a] Stichting Epilepsie Instellingen Nederland (SEIN) Heemstede and Zwolle, The Netherlands
[b] Department of Biomedical Physics, Institute of Experimental Physics, University of Warsaw, 5 Pasteur St, Warsaw 02-093, Poland
[c] Institute of Biomaterials and Biomedical Engineering, University of Toronto, Toronto M5S 3G9, Canada
[d] Center of Neurosciences, Swammerdam Institute of Life Sciences, University of Amsterdam, P.O. Box 94215 1090, GE, The Netherlands
[e] Krembil Research Institute, UHN, and Depts. of Medicine (Neurology), Physiology & IBBME, University of Toronto, Canada

ARTICLE INFO

Keywords:
Coupled oscillators
Epilepsy
Multi-state system
Neuroglia network
Post-ictal generalized EEG suppression

ABSTRACT

The human brain, largely accepted as the most complex biological system known, is still far from being understood in its parts or as a whole. More specifically, biological mechanisms of epileptic states and state transitions are not well understood. Here, we explore the concept of the epilepsy as a manifestation of a multistate network composed of coupled oscillatory units. We also propose that functional coupling between neuroglial elements is a dynamic process, characterized by temporal changes both at short and long time scales. We review various experimental and modelling data suggesting that epilepsy is a pathological manifestation of such a multistate network – both when viewed as a coupled oscillatory network, and as a system of multistate stable state attractors. Based on a coupled oscillators model, we propose a significant role for glial cells in modulating hyperexcitability of the neuroglial networks of the brain. Also, using these concepts, we explain a number of observable phenomena such as propagation patterns of bursts within a seizure in the isolated intact hippocampus in vitro, postictal generalized suppression in human encephalographic seizure data, and changes in seizure susceptibility in epileptic patients. Based on our conceptual model we propose potential clinical applications to estimate brain closeness to ictal transition by means of active perturbations and passive measures during ongoing activity.

1. Introduction

Despite the significant progress in exploring the human brain during the last few decades, our knowledge about the brain's performance remains far from comprehensive. It is unclear, for example, how the brain achieves its remarkable performance and efficiency, what basic brain states and state transitions underlie these phenomena, and what is the best way to identify those states and relate them to cognitive functions. In extreme cases, far outside the normal brain functioning, brain networks can get entrained into large scale synchronized rhythmic activity known as epileptic seizures. Whether such a state is a product of perturbed brain dynamics, what causes this state's initiation, existence and termination, and whether networks involved in this rhythmic activity can be de-synchronized early on, comprise an active field of current epilepsy research.

This review examines the concept that the brain operates as a system of coupled oscillatory units, and that epilepsy is a particular pathological manifestation of this system. Although the concept of interacting multistate units is surely a simplification of the full biological reality behind the brain operation, computational models provide the opportunity to better understand and explore the emergent behaviours that arise from these oscillatory systems, generating hypotheses which can be tested with clinical data. But even at the abstract, analytical level of description, systems of coupled oscillatory units cannot provide in general the explanation of the existence of different dynamic modes, such as “normal” and ictal – epileptic seizure, and the phenomena of autonomous transitions between these modes. Therefore a second essential concept, that of a multistate dynamic system, has been introduced in order to account for the above clinical and biological processes.

While multistate systems are the building blocks of practically all modern digital devices, there is still the tendency to consider biological systems as single-state units. However, under the right conditions – such as electrolyte or metabolic changes, focal stimulation, hormonal

* Corresponding author at: Krembil Research Institute, 60 Leonard Ave., 7KDT402, Toronto, Ontario M5T0S8, Canada.
E-mail address: peter.carlen@uhnresearch.ca (P.L. Carlen).
[1] Deceased.

https://doi.org/10.1016/j.nbd.2019.104488
Received 12 February 2019; Received in revised form 3 June 2019; Accepted 4 June 2019
Available online 07 June 2019
0969-9961/

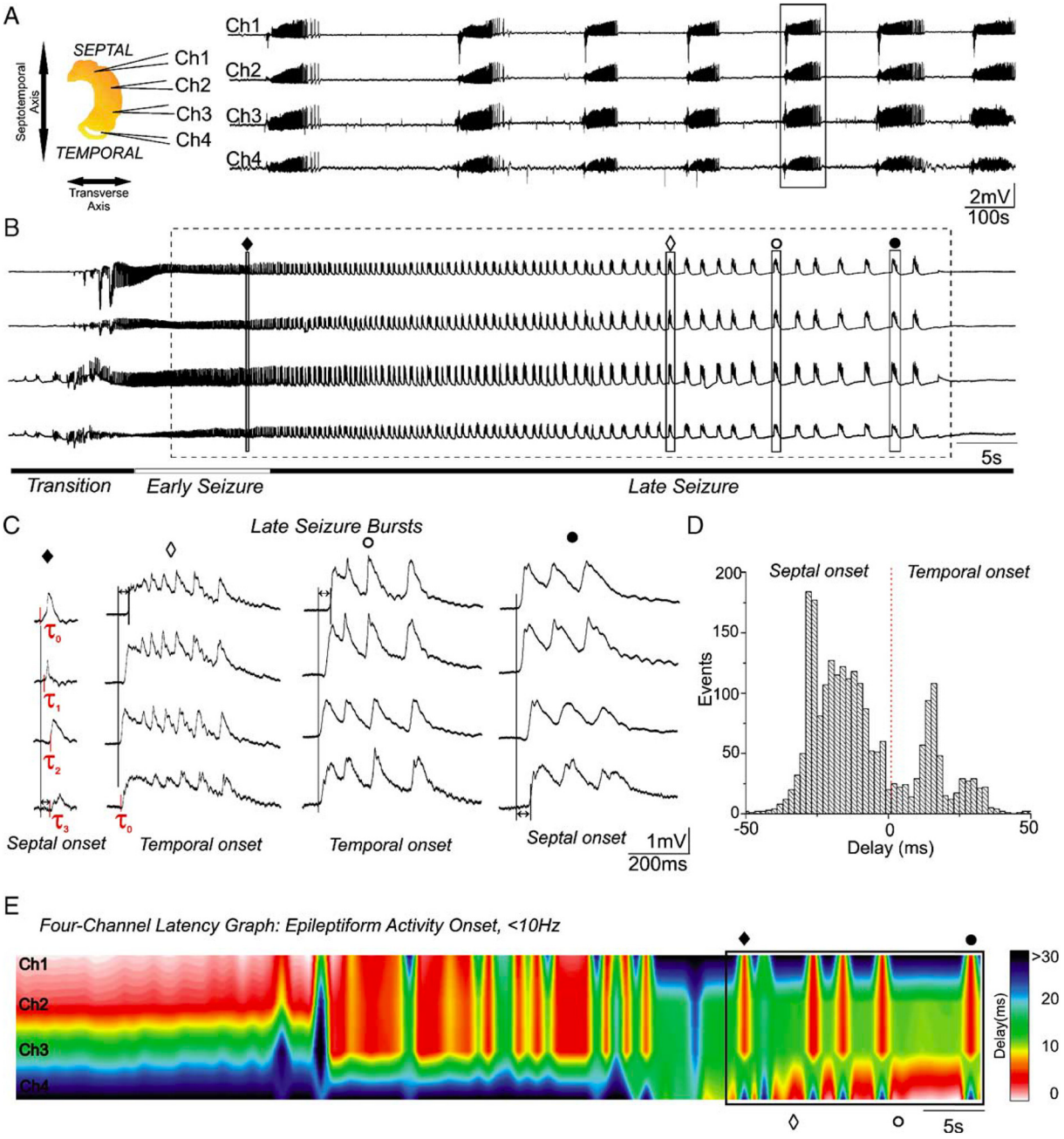

Fig. 1. Multisite field recordings illustrate bidirectionality. (A) Four field electrodes in the CA1 subfield (Ch1– Ch4) placed along the septotemporal axis of the hippocampus (left inset-arrows denote direction of two axes) record recurrent, spontaneous seizures from the intact hippocampus. (B) A single seizure (expanded from panel A), recorded from all four electrodes, shows the three characteristic phases of seizure. The transition phase is characterized by a temporal site onset during which there is a lack of evident coupling with the other recording sites, and later during the seizure (early, late phases), epileptiform activity displays bidirectionality and becomes functionally coupled across all four channels. (C) Bidirectionality of single intraseizure bursts (expanded from panel B) shows both septal (▲,●) and temporal (◊, ○) onsets. Vertical lines illustrate beginning of events as represented by their relative times of onset (τ_0, τ_1, τ_2, τ_3), and the vertical line from the earliest onset of the burst shows the difference in times between the septal and temporal events. (D) Histogram of the event delays between the two outermost electrodes (Ch1– Ch4) reveals that most epileptic activity in the analysis window is of septal origin, while the average delay between these two channels is irrespective of the site of onset. (E) Latency graph (from dashed box in panel B) plotting the differences in the relative times of the epileptiform activity across the four channels shows alternating bidirectional activity (boxed region). Bidirectional events (from panel B– ▲,●, ◊, ○) superimposed on the latency graph, illustrating timing of events. From Derchansky et al., 2006, with permission.

abnormalities, genetic predisposition, drugs, flashing lights, and many others – virtually any brain can be pushed into a state of an epileptic seizure. This suggests that the brain operates in a multistate paradigm, and in this review, we will show that the existence of multiple states on an individual unit or network scale can account for events like seizure onset, seizure termination and post-ictal suppression. The very fact that epileptic activity can spread from an epileptic zone into adjacent presumably "normal" brain tissue supports the concept that the brain circuitry, particularly in susceptible regions such as the hippocampus, entorhinal cortex, and neocortex, is capable of epileptic activity under the appropriate conditions.

In the following paragraph 1 we first introduce the abstract model of the brain as a system of coupled oscillators. The next paragraph 2 relates the concept to the phenomena of epileptic seizures and possible

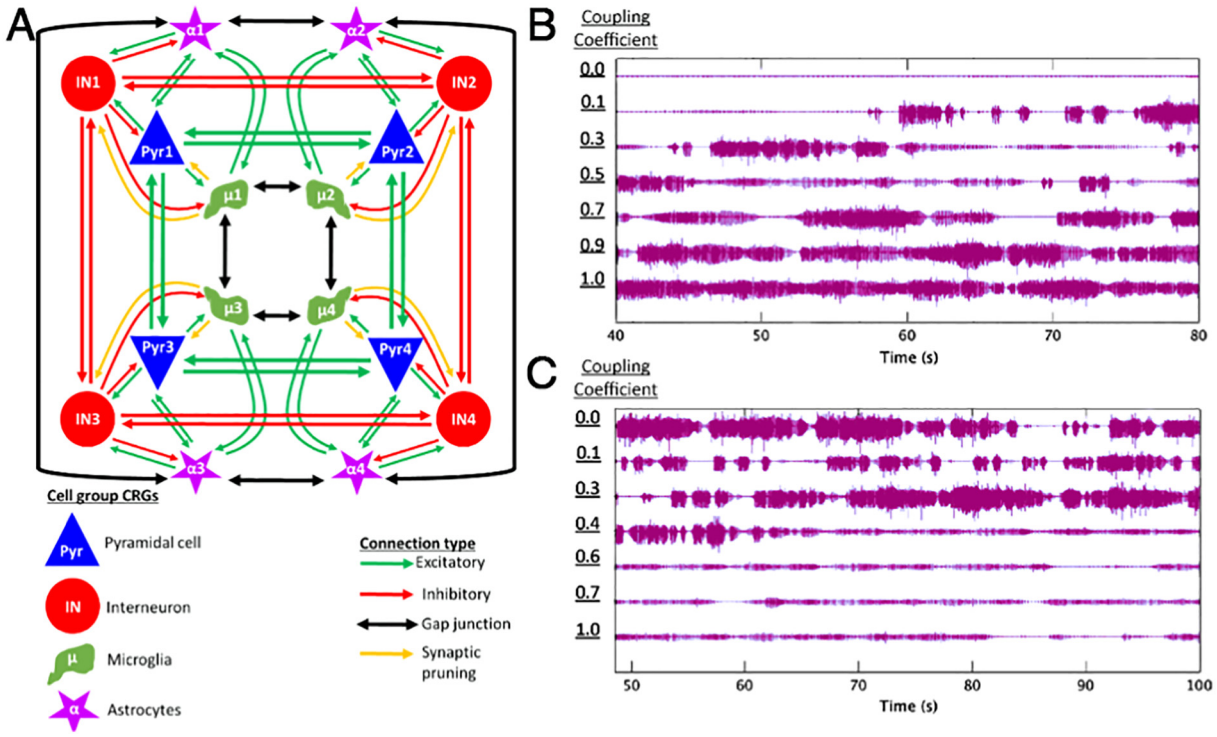

Fig. 2. Coupled oscillators model of neuroglial networks. A) Schematic of the model from Farah et al. (2018) with four subunits of four coupled CRGs each. Within each subunit, there are excitatory connections from the pyramidal populations and the astrocytes to all other CRGs, and inhibitory connections from the interneurons to all other CRGs. The microglial CRGs have an inhibitory "pruning" role on the neuronal synapses, but an excitatory effect on the astrocytes. Between subunits, the pyramidal populations are connected by excitatory connections, the interneurons by inhibitory connections, and the microglia and astrocytes by gap junctions. B) Effects of astrocyte-to-neuron coupling on network local field potential (LFP). C) Effects of microglia-to-neuron coupling on network LFP.

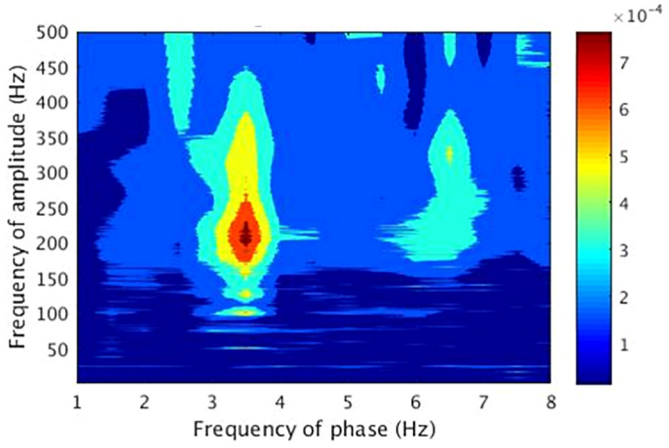

Fig. 3. Delta-HFO cross-frequency coupling (CFC) observed in a typical hyperexcitable state. Figure adapted from Farah et al. (2018), and the results are consistent with other modelling and experimental findings.

underlying biological mechanisms. Paragraph 3 introduces the second important model concept, that of multistate dynamic systems that addresses the emergent phenomena of the autonomous initiation and termination of the seizure state, as well as the existence of the post-ictal state from a common point of view – that of a multistate network of coupled oscillatory systems.

2. The brain: an oscillatory system

Oscillations are a hallmark of brain activity. Rhythmic activity in the brain can be seen in the sleep-wake cycle, hormonal states, various chemical brain constituents, and, of course, its electrical activity (Buzsáki, 2006). The gold standard for assessing this activity is using the electroencephalogram (EEG), which measures the electrical fluctuations of the brain with frequencies ranging from < 1 Hz to several kHz. In various brain network models, these oscillations appear to be coupled both in time and in space. For example, Contreras et al. (1996) showed that in barbiturate-anesthetized cats, the corticothalamic projections determined a global coherence of thalamic spindle oscillations measured in the local field potentials measured from several electrodes located in the thalamus unilaterally. When the connections between the overlying cerebral cortex and the underlying thalamus were completely disrupted by ipsilateral decortication, the synchronized spindle activity found between all recording sites within the thalamus disappeared, and instead spindle patterns were evident with much diminished spatiotemporal coherence; i.e. local spindles measured from the local field potential of each thalamic electrode persisted but were not synchronized with spindles occurring in adjacent electrodes. Furthermore, dual intracellular recordings from nearby neurons also demonstrated that in the decorticate state, there was little local thalamic synchrony. In another study, this time by Fernandes de Lima et al. (Fernandes de Lima et al., 1990), a tetanus applied unilaterally to the dorsal CA3 field resulted in bilaterally synchronous afterdischarges with zero time delay, which the authors suggested may explain why two homologous and symmetrical areas may oscillate as one single system of two strongly coupled non-linear oscillators.

3. Seizure activity and coupled oscillations

In the context of epilepsy, Derchansky et al. (2006) showed that in the intact isolated mouse hippocampus, after the seizure activity spread across the hippocampus from either low magnesium or focal stimulation from one or other end of the longitudinal intact hippocampal preparation, the bursts within a seizure became bidirectional, with different propagation patterns at different frequencies (e.g. Fig. 1;

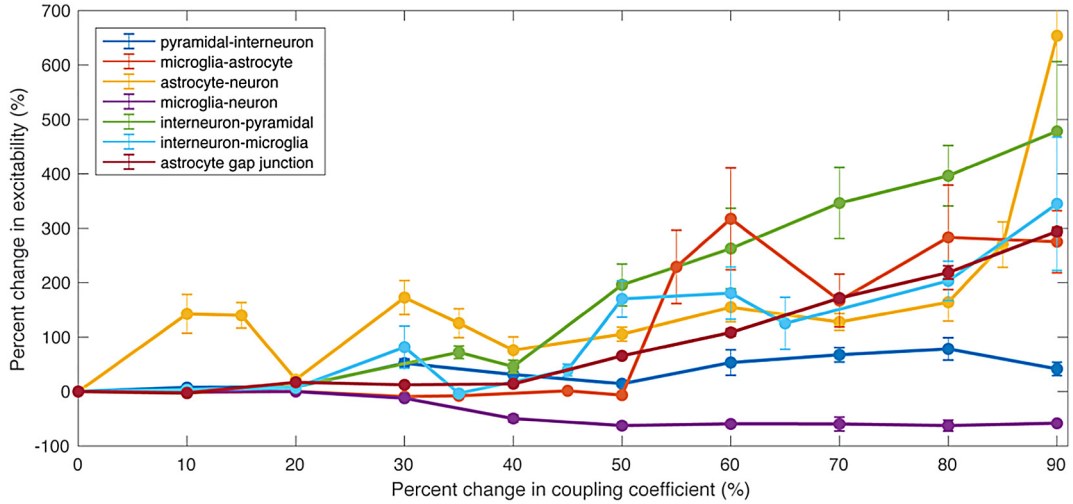

Fig. 4. The effects of connectivity on network excitability. The percent change in excitability is computed as the coupling coefficient is varied between a pair of cells.

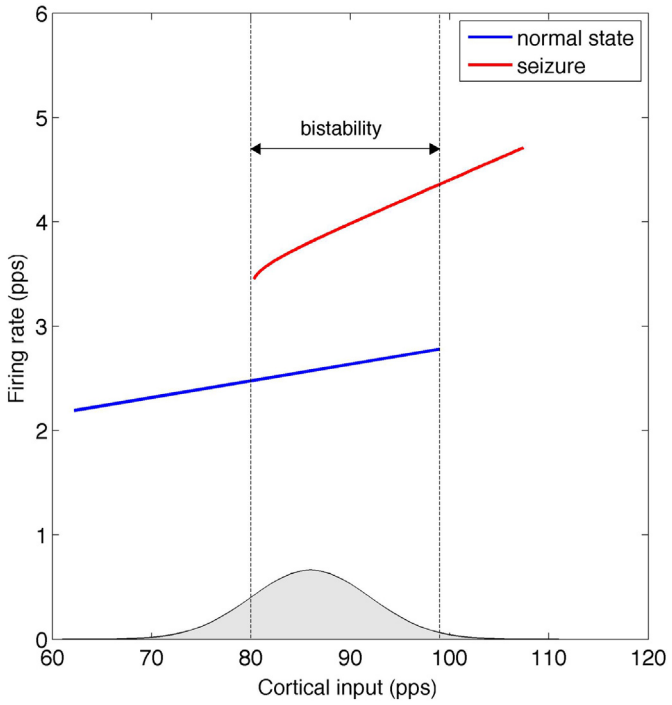

Fig. 5. Bifurcation diagram of the thalamocortical network model (from Suffczynski et al., 2004). The diagram shows the values of the maximal firing rate of the cortical pyramidal cell population in pulses per second (pps) on the y-axis as a function of input to pyramidal cells along x-axis. The diagram features two stable states - fixed point (blue) corresponding to normal activity state and limit cycle (red) corresponding to seizure activity. For a range of input values, between two vertical broken lines, the system is bistable with coexistence of two stable states. Stochastic fluctuations in the input parameter (bottom of the figure, grey) may trigger spontaneous transitions between these two states. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Derchansky et al., 2006)). In the low magnesium model, when the intact hippocampus was separated along the septotemporal axis, independent bidirectional activity was observed in the two halves. These activities are compatible with the behaviour of coupled neuronal network oscillators.

Duckrow and Spencer (1992), analyzed intracranial recordings from hippocampal depth electrodes implanted in epilepsy patients being evaluated for possible resective surgery, measuring regional coherence and the transfer of ictal activity. They concluded that “the process of neuronal entrainment during seizure onset involves a transient interaction between brain regions, but the maintenance of this interaction is not required for sustained seizure activity”. Again, these findings are compatible with the concept of seizures being the manifestation of a multistate network of oscillatory systems, which show various degrees of coupling and uncoupling.

during the seizure evolution (discussed by (Jiruska et al., 2013)).

3.1. *Glial cells modulate hyperexcitability in a coupled oscillator model of epilepsy*

One benefit of using a coupled oscillator approach to model epilepsy is that it can successfully model intermittent phenomena in the epileptic brain networks (Zalay and Bardakjian, 2009)). Unlike the traditional multistate bistable attractor approach, intermittency represents ictal events that are embedded in the interictal attractor and thus don't require system noise for state transition. One model that utilizes this approach has been used to investigate different pathways leading to hyperexcitability and suggested an important role for astrocytes and microglia in the generation of spontaneous epileptiform discharges (SEDs) (Farah et al., 2018). The model was based on coupled Cognitive Rhythm Generators (CRGs). The CRG is an oscillator ring device that transforms a given input via a non-linear mapping of instantaneous phase and amplitude values (Farah et al., 2018). This oscillator ring device may be a *clock* with an omnipresent rhythm, or a *labile clock*, where the oscillator is only active when the input is above a set threshold. The former is more appropriate for cells that exhibit constant rhythmicity, whereas the latter better describes populations that require excitation from other cells to generate an observable voltage membrane rhythm. These CRGs have been used to model various physiological phenomena, such as phase preference, and phase precession (Zalay and Bardakjian, 2009), and to model hippocampal neurons to generate spontaneous electrical discharges (SEDs) similar to SEDs observed in experimental models of epilepsy (Zalay et al., 2010).

More recently, a neuroglial network model based on CRGs has been used to investigate various pathways leading to hyperexcitability, and suggested an important role for astrocytes and microglia in the generation of SEDs (Farah et al., 2018). The model, shown in Fig. 2A, contained 16 CRGs organized into four subunits with excitatory pyramidal cells, inhibitory interneurons, microglia, and astrocytes. Pyramidal cell CRGs exhibited continuous rhythmicity with intrinsic frequencies in the theta range (McNaughton et al., 1983) while interneurons had bursting labile-clock behavior with frequencies spanning the ripple HFO range (80–250 Hz) (Sik et al., 1995). Similarly,

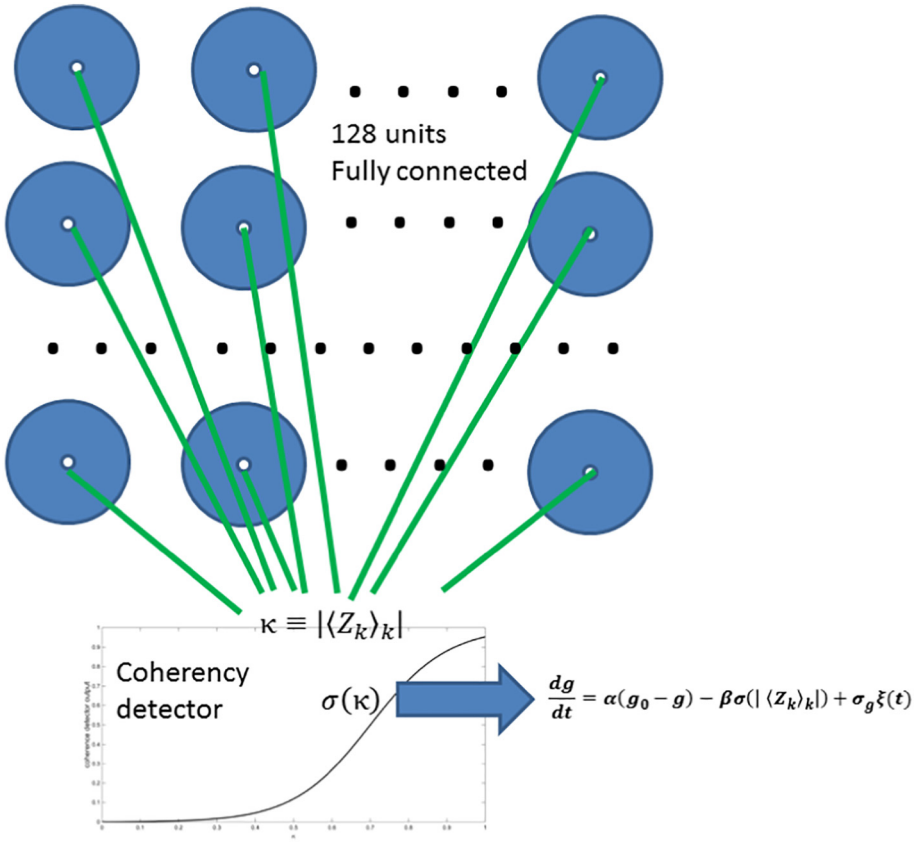

Fig. 6. Schematic representation of the model neuronal network. The model consists of 128 fully interconnected units, representing neuronal lumps including pyramidal neurons and interneurons. Any two units are equally interconnected. The collective output of all units is filtered through a sigmoid function or coherency detector (input-output function in inset). The horizontal axis represents the collective output of the model, the vertical axis is the detector response. The output of the coherency detector is a sigmoid function σ(k) of the average of all complex unit amplitudes illustrated in the inserted axis at the bottom of the frame, and is used as input for the dynamics of the connectivity parameter *g*, which is common for all units.

microglial CRGs were modelled as a clock ring device with low-delta frequencies (0.2–0.5 Hz) (Wake et al., 2009), while astrocytes were based on the labile clock with intrinsic frequencies in the 1–4 Hz range (Amzica and Steriade, 2000).

The model specifically focused on micro- and astroglial effects since recent experimental evidence revealed that glial cells are involved in modulating hyperexcitability. Astrocytes have been shown to have the ability to modulate the excitability of nearby neuronal synapses (Perea et al., 2009), and astrocytic dysfunction is associated with neurophysiological disorders such as epilepsy (Seifert et al., 2010). Meanwhile, microglial cells regulate synaptic transmission by decreasing excitatory postsynaptic potentials currents via pruning of the synapses (Seifert et al., 2010). In fact, earlier modelling work highlighted the importance of glial potassium modulation in hyperexcitability and linked glial factors as the biophysical basis for biomarkers for epilepsy (Grigorovsky and Bardakjian, 2018a). Neuroglial coupling and its effects on hyperexcitability can be seen in Figs. 2B and 2C. Qualitatively, the increase in neuron-astrocyte coupling (Fig. 2B) led to the higher incidence of SEDs, which is consistent with studies that indicate that astrocyte release of certain substances can predispose tissue to seizures (Carmignoto and Haydon, 2012; Fellin et al., 2004). In contrast, the magnitude of neuron-microglia coupling (Fig. 2C) was inversely related to the level of system hyperexcitability, with fewer SEDs of shorter duration appearing as the microglia-neuron coupling increased. This is also consistent with experimental findings that microglia are known to make contact with hyperactive neurons to reduce EPSC frequency and to downregulate their activity (Li et al., 2012; Ji et al., 2013), and that blocking certain functions of microglia have been shown to be related to the occurrence of seizures (Eyo et al., 2014; Derecki et al., 2012).

Recently a hybrid model that utilized microglial CRGs alongside the micro-scale model further qualitatively differentiated the effects of glial cells and found that microglial pruning significantly increased the time between SEDs (Grigorovsky and Bardakjian, 2018b). The model from Fig. 2A also showed delta-HFO cross-frequency coupling in the LFP when the network hyperexcitability was high (Fig. 3), which is consistent with both other modelling studies (Grigorovsky et al., 2018a,b) and experimental findings (Guirgis et al., 2015).

In order to quantitatively assess the effects of connectivity between each of the different CRGs on network excitability, the energy of the system was approximated with the excitability function (Farah et al., 2018). The slope of the linear fit of the percent change in measured excitability was used as the coefficient of impact (COI) of each connection on hyperexcitability. In most cases, strengthening the excitatory connections had the effect of increasing the hyperexcitability of the system (Fig. 4) – the excitatory connection with the greatest impact was from pyramidal cells to interneurons (COI: 5.79), and without interneuronal activity the system was not able to transition into a high-excitability state. This is consistent with the classical view of epilepsy as being caused by a disruption in the balance between excitation and inhibition in neurons (Dudek, 2009).

Other high coefficient of impact excitatory connections were microglia to astrocyte (COI: 3.95), and astrocyte to neurons (COI: 3.51). These effects are supported by the fact that under pathological conditions, microglia can release ATP that binds to astrocytes and causes an increase in excitatory transmission via a metabotropic glutamate receptor dependent mechanism (Pascual et al., 2012).

Meanwhile, increasing inhibitory connections resulted in decrease of system excitability, such as microglia-neuron (COI: −0.82), and interneuron-pyramidal cell (COI: −0.62). Interestingly, strengthening the interneuron-microglia connection resulted in increased excitability (COI: 3.50), which is supported by findings that GABAergic (inhibitory) neurotransmission can downregulate microglial dynamic behavior (Fontainhas et al., 2011). The model showed that astrocytic gap junctions also play a role in regulating system hyperexcitability (COI: 3.22), which is consistent with human patients' data, where there was an up-regulation of glial gap junctional mRNA and protein (Mylvaganam et al., 2014).

Overall, the oscillator-based model of coupled CRGs with different

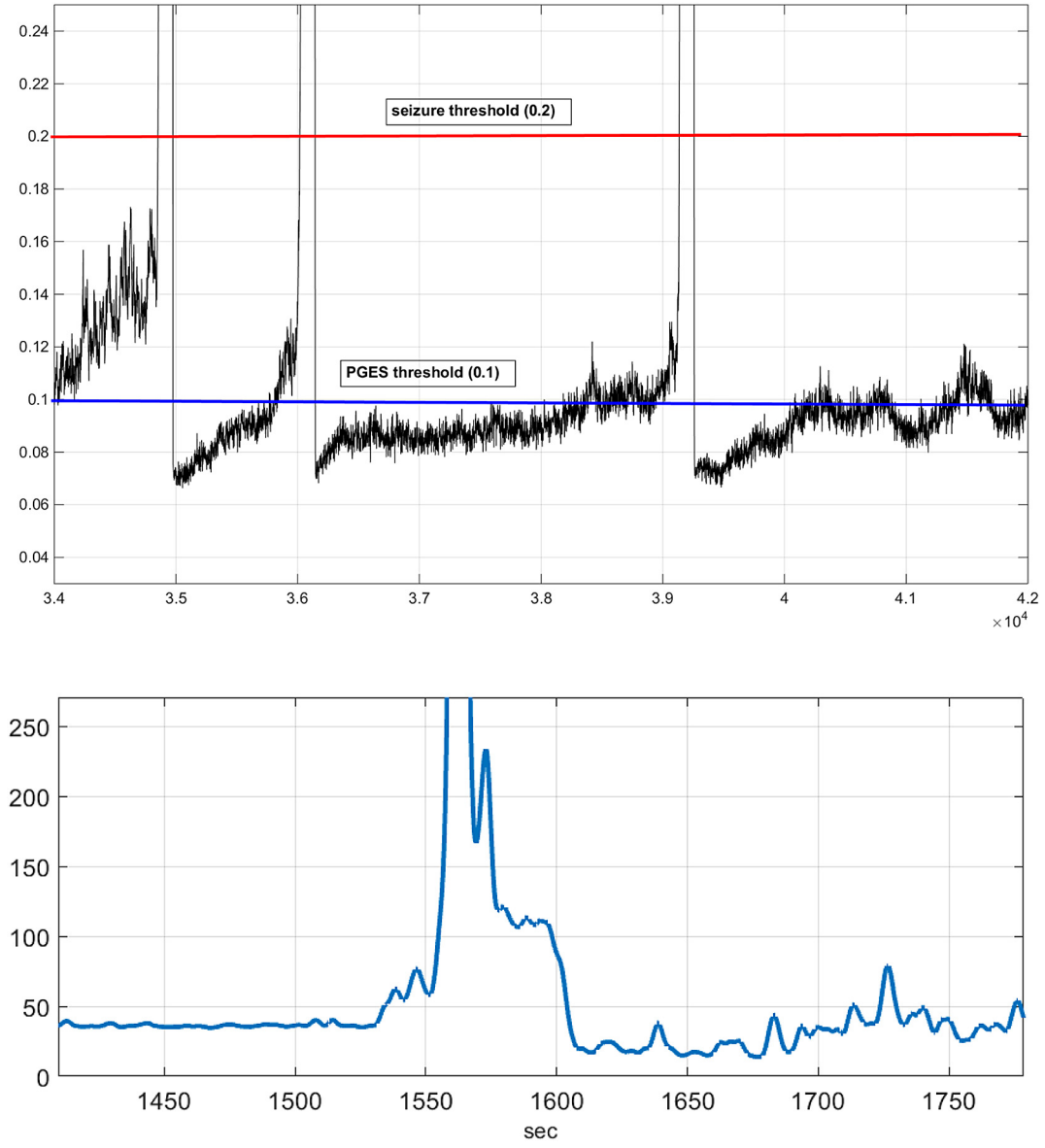

Fig. 7. Comparison between the model output (upper frame) and data from tonic-clonic seizure followed by a post-ictal generalized suppression (lower frame). On both plots the horizontal axis depicts simulation steps or samples converted to time, the vertical axis represents the energy (the envelope of the Hilbert transformed trace) of the averaged signal from correspondingly all model units or all EEG contacts. Both in simulated or clinically recorded data, the transitions from normal to ictal state is preceded by a build-up, or recruitment phase. Accordingly, in both examples the post-ictal state has a clearly lower energy than the inter-ictal, normal state.

intrinsic frequencies was able to generate emergent phenomena of both frequency coupling, and variable network hyperexcitability dependent on coupling coefficients that mimicked some of the phenomena observed in the animal and human experiments, as well as other more detailed computational models. Such approach of using coupled oscillators was recently combined with a neural field model to account for the diversity of seizure termination and propagation in a model of human epilepsy (Proix et al., 2018).

4. Multistate models of neural dynamics can *Re*-create epileptic states

In addition to coupled oscillator based models featuring intermittent dynamics, another way to represent brain activity is as multiple sustained stable states – or attractors – that co-exist for the same values of model parameters. This can be thought of as different energetic levels equivalent to different oscillatory states. These states demonstrate bistability, wherein the identified state based on initial conditions can transform autonomously, via spontaneous activity (noise leading to stochastic initiation) within the system itself or from a specific external input. These self-sustained dynamical brain states demonstrate multiple distinct synchronization states, and also desynchronization states such as the “silent period” at the end of a seizure – postictal generalized EEG suppression (PGES).

An example of a bistable network model is the thalamocortical model described in Suffczynski et al. (2004). In that study, a neural mass model consisted of four populations – thalamocortical relay cells (TC), thalamic reticular cells (RE), cortical pyramidal cells (PY) and cortical interneurons (IN). In cortical populations, the input-output relationship was described by a static nonlinear sigmoidal transformation between the mean membrane potential of a population and the firing rate of that population. In thalamic populations, the input-output transformation accounted for burst firing of thalamic cells during synchronized thalamocortical oscillations. The model dynamics was

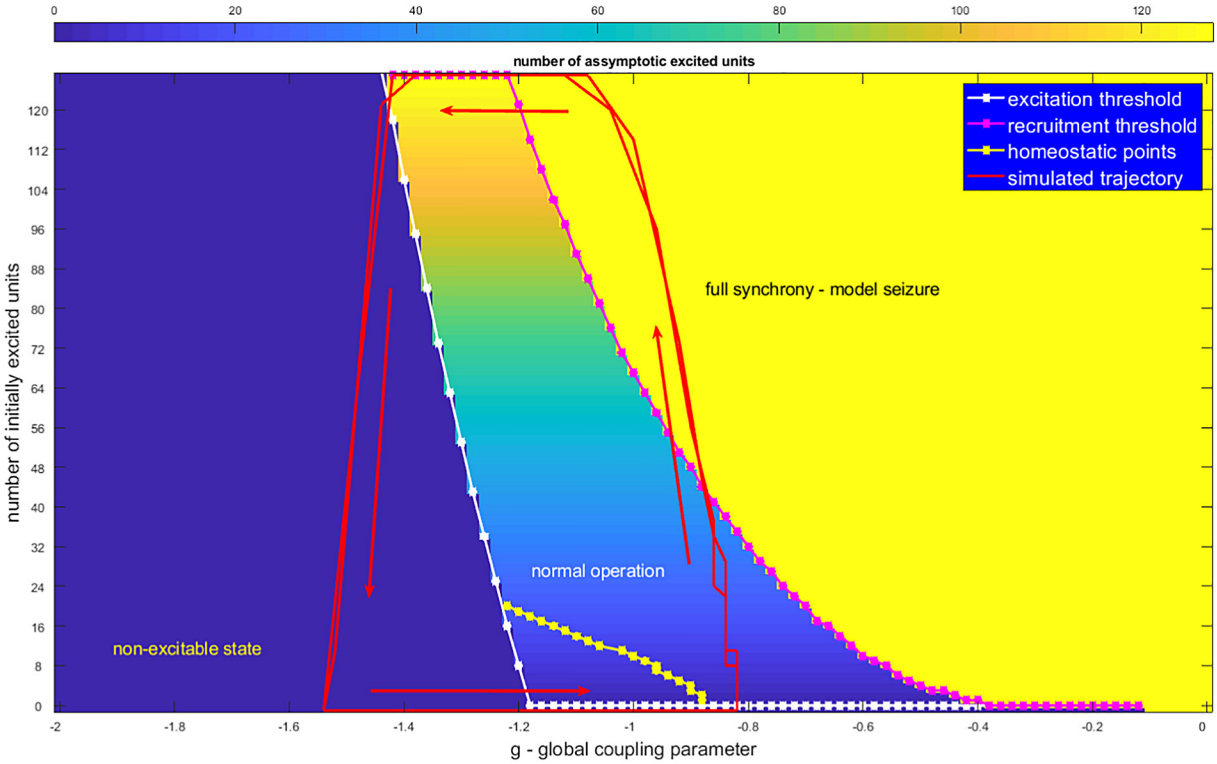

Fig. 8. Output from the computational model schematically presented on Fig. 7. Results from simulations of the system. The system output is generated for 129 values of the connectivity parameter g, ranging from 0 to 128 on the horizontal axis, and for 0 to 128 initially excited units, indicated on the vertical axes. The background colour represented on the horizontal calibration colour bar at the top is the number of excited units that remain self-sustained according to the dynamics of the coupled system of oscillators. All simulations were first done without noisy input and without changes of the connectivity parameter g. The blue region corresponds to a non-excitable state ("postictal"); yellow to a limit cycle state (total synchronization or "seizure"); and the gradually colored state in the middle, to "normal functioning", where the system sustains its initial state. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

summarized by a bifurcation diagram (Fig. 5), which shows the values of the maximal firing rate of the cortical pyramidal cell population as a function of bifurcation parameter being external input to that population.

The diagram shows that for a range of external input values the model was in a bistable regime where normal activity state coexists with seizure state. The transitions between the states may be triggered by noisy fluctuations of the model parameters including fluctuations in the external input, shown at the bottom of the figure. The consequence of stochastic transitions was the exponential distribution of seizure durations and inter-seizure intervals. This prediction was partly confirmed in experimental data (Suffczynski et al., 2006), but as discussed later, the probability of transition from seizure back to normal state may increase with the time spent in the seizure state. Accordingly, the model was extended to account for this observation (Koppert et al., 2011). Another prediction from the model was that a well-timed pulse might terminate seizures generated in the thalamocortical network. This prediction was confirmed to some extent in idiopathic human absence seizures (Rajna and Lona, 1989; Conte et al., 2007), and in generalized tonic-clonic seizures in animal models (Osorio and Frei, 2009; Berenyi et al., 2012). In the next step, the thalamocortical lumped model was simplified into a bistable lump of two interconnected cortical populations and was spatially extended to model several interacting lumps.

4.1. Seizure dynamics: onset, evolution and termination

In order to investigate whether the multistate bistable attractor approach can capture seizure dynamics, a distributed system of bistable neuronal units based on an analytical, non-linear complex model was used (Izhikevich, 2001; Kalitzin et al., 2011). This model, depending on the parameters, could feature steady state dynamics, limit cycle dynamics or both. In the last case, the model can be referred to as a bistable unit. Depending on the initial conditions, the bistable unit can either be in its steady state point or in a limit cycle. When a number of units are coupled, a system of multiple states can be created (Koppert et al., 2014). Remarkably, such system can occupy a variety of different oscillatory excited states while transitions between them can be induced by external perturbations only (Kalitzin et al., 2014).

Recent computational work has shown that the addition of a global reaction term to the dynamics of the multistate system, prevents oversynchronized activity and reveals several phenomena which can be described by the model (Bauer et al., 2017). In general, it is useful to fit state duration distributions to a gamma distribution, an extension of exponential distribution. If transitions from one state to another are caused by external stochastic perturbations, the distribution of times spent in one particular state will follow a special case of gamma distribution with the shape parameter of less than one. While such behaviour fits well the distribution of seizure-free epochs (Suffczynski et al., 2006), the distribution of seizure durations follows gamma distribution with shape parameter of above one and deviates significantly from such pure stochastic dynamics indicating that a competitive deterministic dynamic process is active in the seizure termination process (Koppert et al., 2013). A distributed model built from bistable complex units (Fig. 6) can realistically mimic the seizure onset, evolution and termination processes (Bauer et al., 2017) as illustrated in Fig. 7. Note that we have represented on the figure the total system activity by averaging all signals and then calculating the signal envelope as the magnitude of the Hilbert transform. This way we take into account also the synchronization between the individual signals. If instead we would have

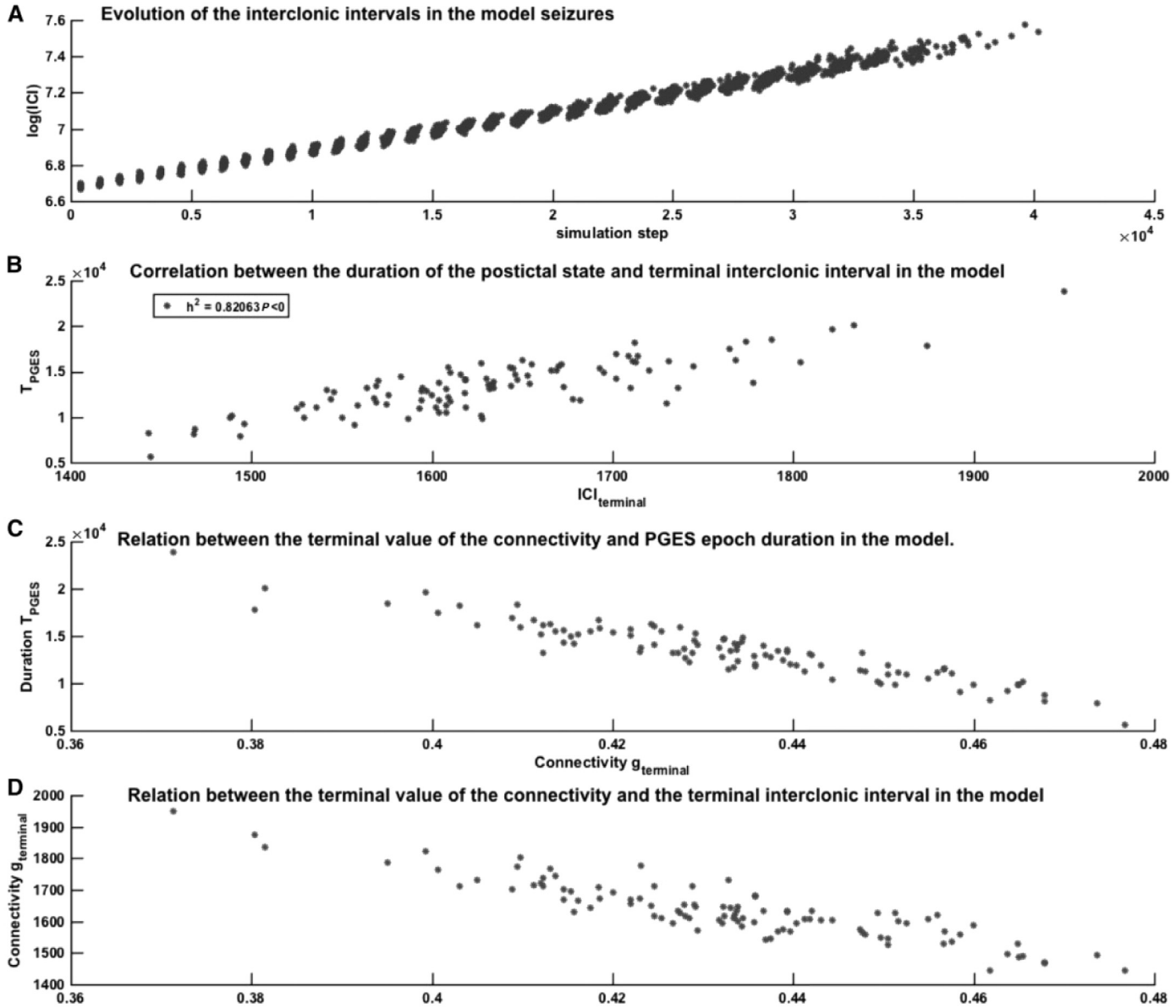

Fig. 9. Relation between the interclonic interval, connectivity and PGES in the model. A: Scatter plot showing the relation between the interclonic interval (ICI, vertical axis, logarithmic scale) determined by the strength of the connectivity parameter g during simulated seizures and the time elapsed since the beginning of the simulated seizure (horizontal axis, in simulation steps). The different data points at each time point represent different simulations. The figure shows that the interclonic interval is relatively constant at the start of the model seizure, but varies at the end of the seizure. B. The relation between the model terminal interclonic interval ($ICI_{Terminal}$, horizontal axis) value and the duration of the PGES state in the model (vertical axis). The non-linear correlation coefficient h^2 shows that the terminal interclonic interval value explains 82% of the variability of the PGES duration. C: Scatter plot showing the relation between the durations of the simulated PGES states (vertical axis, in simulation steps) and the value of the connectivity parameter g at the end of the preceding seizure (horizontal axis, dimensionless units). D: the relationship between the terminal value of the connectivity parameter g and the terminal interclonic interval in the model.

calculated first the individual signal envelopes and then averaging them, the quantity would not be sensitive to the system synchronization.

Fig. 8 shows that the inclusion of reaction term has led to a continuously degenerated state (the yellow line) where the system can freely move. If, however, an external or internal perturbation pushes the system into the yellow area, the system gets trapped into a fully synchronized behaviour, representing, in the model, the clinical seizure. The reaction dynamics then will counteract the excessive synchrony of the whole system and bring it back to the state of normal operation. Before this happens, however, a transient period of reduced activity and synchrony will take place. The latter is the model representation of post-ictal generalized suppression (PGES).

The model results showed emergent properties that could be helpful for predicting events of PGES or even possibly assessing the risk of SUDEP. More specifically, the model generated the hypothesis that the exponential evolution of a specific observable during the seizure, for example the inter-clonic interval in case of convulsive seizures, can have strong association with the duration of PGES as seen in Fig. 9. Alternative model including slow variables has been studied by other researchers (Jirsa et al., 2014) predicting that interclonic intervals increase in a logarithmic fashion rather than an exponential as it is in our model.

4.2. Multistate model biomarkers of epilepsy – state retention close to the transition point

Even at the single-unit level, the bistable model was capable of

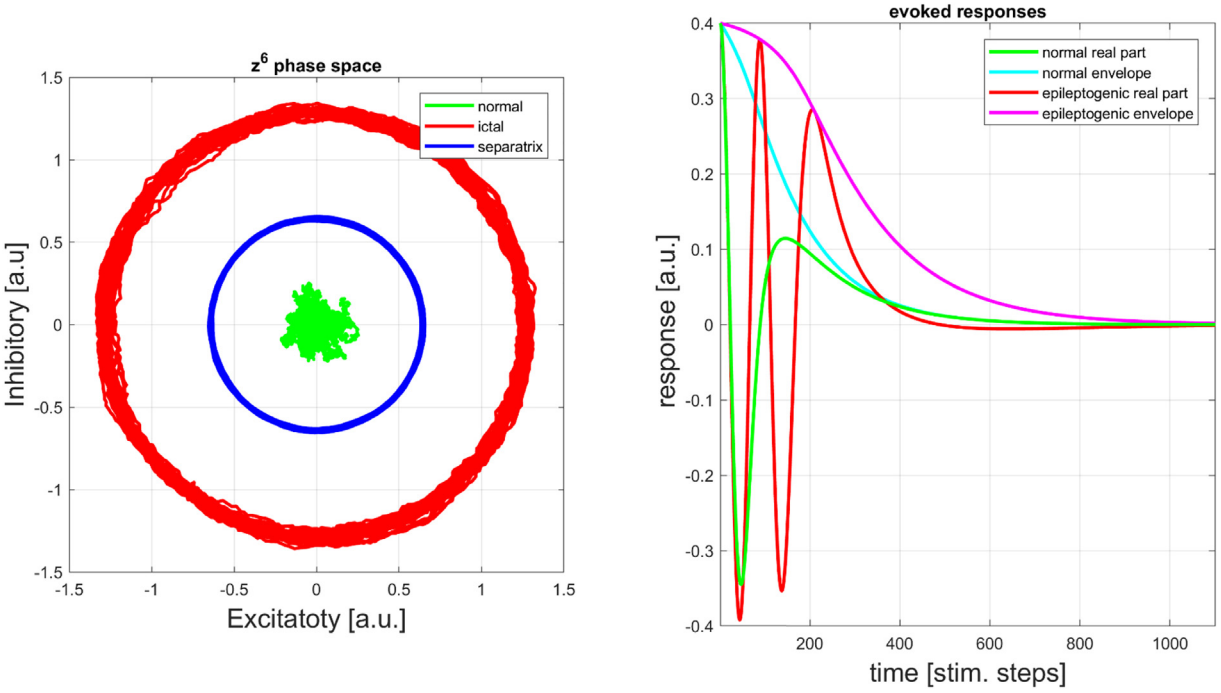

Fig. 10. Ictal transition; steady-state and the oscillatory limit cycle (the model seizure). Left frame: an example of complex phase space of the z^6 model dynamics. The two axes represent the real and imaginary components of the model variable and can be interpreted as excitatory and inhibitory activity in arbitrary units. The central cloud (in green) is the area occupied by the point-attractor and represents the normal state of the system. The red circular area is the limit-cycle attractor and corresponds to a model seizure. The blue circle in-between is the separatrix, the unstable area that separates the two states. Right frame: Response of the system with two different parameter settings to an external stimulus. The green line is the real component and the cyan line the magnitude of the response of a single unit with parameter $c = -0.8$. The red and the purple lines are the real components and the magnitude of the response of a single unit characterized by parameter $c = -0.6$. The stimulus is the same single pulse at $t = 0$ for both units. It is visible that the envelope (magnitude) of the unit response with higher epileptic potential decays slower in time. Also, the epileptogenic unit shows prolonged transient oscillatory behavior. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

generating potentially useful hypotheses for assessing the closeness to ictal transition (Petkov et al., 2018). If the system is perturbed, the closer it comes to the region dividing the "normal" steady state from the oscillatory limit cycle (the model seizure), the longer is the time for responses, or the time needed to return to the background state as shown in Fig. 10. In essence, this effect is caused by the fact that the separatrix is a manifold corresponding to unstable asymptotic state, in this case a limit cycle, and therefore the forces shifting the system out of it are infinitesimal in a close vicinity. This feature was exploited to develop a biomarker that can be used, in conjunction, for example with transcranial magnetic stimulation (TMS), for diagnostic and therapeutic prognosis protocols.

Based on that observation, a potential biomarker of "separatrix proximity" or shortly "separatricity" has been proposed for the closeness to ictal transition (Petkov et al., 2018). In this study, separatrix proximity was defined as a measure of the relative rate of increase of the ratio between the area under the response curve and the response amplitude. Fig. 11, upper frame, shows the results from applying this method to subjects with different neurological conditions. It is clear that the biomarker separates patients with pharmacologically untreated ("drug naïve") juvenile myoclonic epilepsy (JME) from healthy controls, medicated JME (all responders) and people with migraine. This test confirmed the model-derived hypothesis that active epilepsy is related to how close of the neuronal system is to the limit cycle oscillatory state. The lower frame on Fig. 11 demonstrates the effect of medication on one patient where there is a gradual decrease of the separatrix proximity, indicating the favourable effect of the drug.

4.3. Resting state global functional connectivity

Active probing of the system, or evoking a seizure-like event, can be advantageous because it provides reproducibility of the results and is to high degree independent from the background activity and additional external influences. However, it requires a dedicated stimulation protocol, which limits the possibility to validate various analytical techniques retrospectively as is the case with using on-going Resting State (*RS*) EEG. A way to overcome that is to derive a biomarker relying only on spontaneous epileptic events.

One of the ongoing research topics is to predict or to measure the likelihood of seizure (ictogenicity) by studying structural brain networks. The underlying hypothesis here is that the structural connectivity of the brain may be responsible for its pathological dynamics. In clinical practice, the in-vivo structural connectivity of the brain is largely unobservable and unknown. A large multitude of factors may influence the epileptic state, which can be of structural or functional nature or are state-dependent properties of the system.

A feasible approach, therefore, is to examine the statistical interrelationship between electroencephalogram (EEG) time series recorded at different locations in the brain, thus defining a functional rather than a structural network. In contrast to the unobservable structural connectivity of the brain, the functional connectivity can be inferred from easily accessible resting state (RS) scalp EEG data through a variety of synchrony models (Kim et al., 2017; Bialonski and Lehnertz, 2013). The rationale behind the use of functional rather than structural networks to explain pathological brain dynamics is that functional networks are determined by the structural architecture of the brain but also carry information from the state-dependent dynamics of brain activity (Honey et al., 2009).

In line with this concept, many studies have put the synchronization models for reconstruction of the functional connectivity of the brain along with the network measures for its quantification at the centre of their methodology (Rubinov and Sporns, 2010; Joyce et al., 2010; Liu

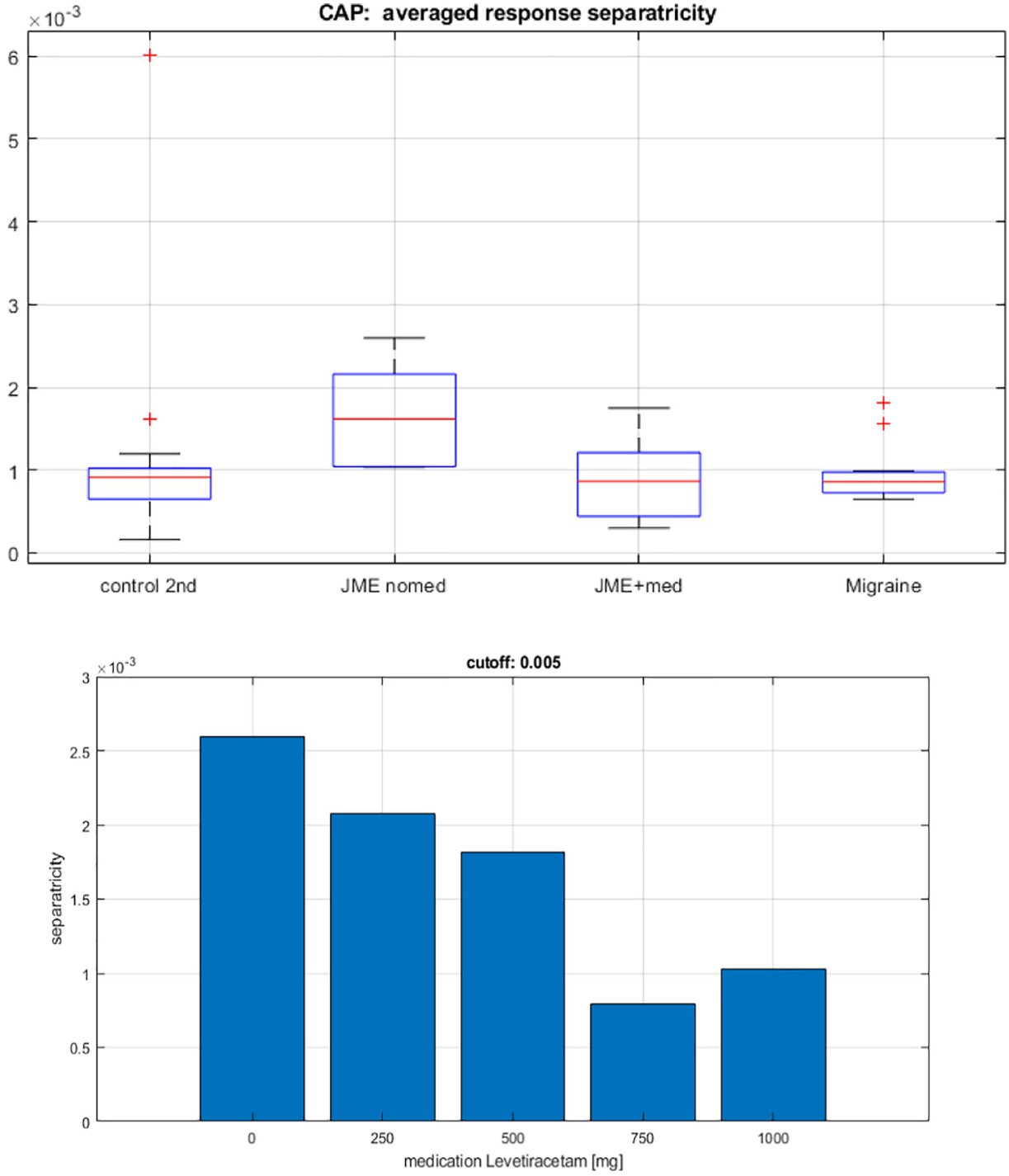

Fig. 11. Clinical application of the separatrix proximity Top frame shows the boxplots (red lines the median, boxes extend for 25–75 percentiles and the red crosses indicate outliers) of the biomarker, averaged over all 64 electrodes (10/10 montage common average reference) recorded from TMS with various groups of subjects as indicated on the horizontal axis. Bottom frame shows the evolution of the biomarker for one particular JME patient under different daily medication levels as indicated on the horizontal axis. "JME nomed" – juvenile myoclonic epilepsy, on no medications; JME + med – juvenile myoclonic epilepsy on medication. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2017). As a result a lot of useful biomarkers have been discovered, but no common solution has been found yet due to the unpredictability of combinations of network measures and synchrony models (Chowdhury et al., 2014; Stam et al., 2007). A natural way to limit this diversity is by employing mathematical models discussed above.

The models at macroscopic scale use the average response of a mass of neurons (brain regions) represented by differential equations, interconnected into a network. Such models study brain network's dynamics capturing the transitions between low amplitude "background" Steady State (*SS*) and a high amplitude "seizure" state Limit Cycle (*LC*) (Suffczynski et al., 2004; Jirsa et al., 2014; Junges et al., 2019). Some studies show high level of predictive power for model-based simulation outcomes, where the neuronal masses are connected via surrogate networks that retain specific topological or metric properties of the functional networks inferred from real *EEG* data (Petkov et al., 2014;

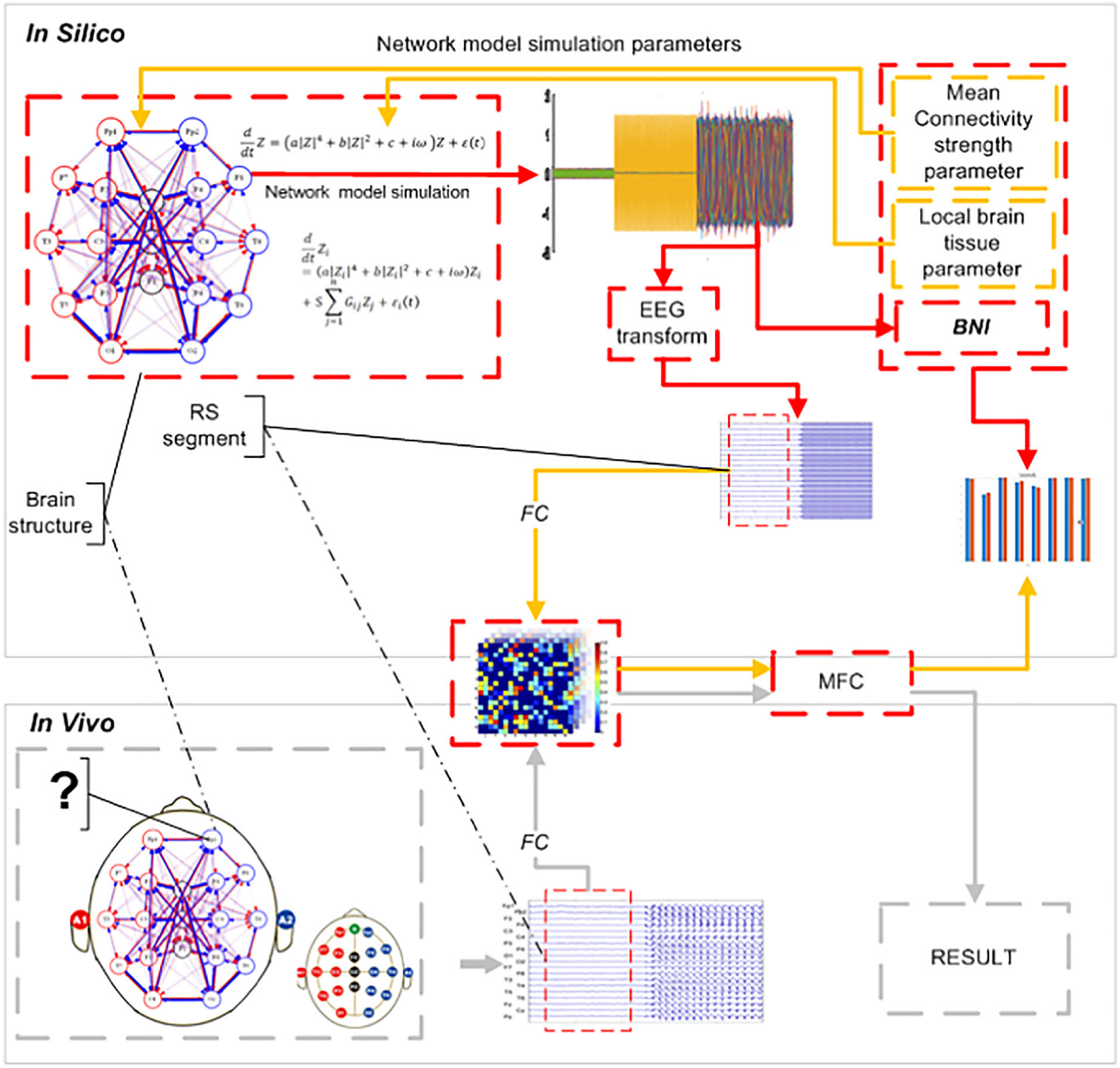

Fig. 12. Methodological framework for resting state global functional connectivity. The figure contains two panels. The upper panel "in silico" shows three computational flows using arrows in red and yellow. The middle (red arrows) flow corresponds to the modelling part: the left red rectangle shows the modelling settings, followed by the simulation resultant traces, brain network ictogenicity (BNI) calculation, and the simulation of EEG measurements. The upper yellow flow shows the application of the hypotheses checking parameters to the modelling settings. The lowest yellow flow shows the reconstruction of functional networks using resting state (RS) segment only, the computation of mean functional connectivity (MFC), and the obtained correlation levels with modelling parameters and BNI. The lower panel shows "in vivo" application of the modelling outcomes. From left to right (grey arrows): from the unknown brain structure; EEG RS segment selection; functional connectivity (FC) reconstruction and MFC calculation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Tetzlaff et al., 2015). Following the encouraging results the research attention was devoted to replacing the structural by the functional connectivity, establishing strong functional-structural mapping (Chu et al., 2015; Finger et al., 2016; Khalsa et al., 2014; Meier et al., 2016). However, the latest reported level of explanation of the variation of functional by the structural connectivity is < 55% (Moon et al., 2017). It has been shown (for different models performing bifurcation based transition between *SS* and *LC*) that the structural network "shapes" the model-based dynamics, and that the prediction quality of the outcomes for anatomical brain dynamics depends on the model's selection (Moon et al., 2017).

Instead of reconstructing structural from functional brain connectivity, a different methodological approach was recently used in (Helling et al., 2019) to find an observable quantity, i.e. a biomarker that reflects the likelihood of seizure transition. The leading hypothesis is that RS-EEG functional connectivity explains, at least partially, the ictogenicity of the brain. To test the hypothesis, the authors determine the level of association between the ictogenicity of the brain and the average connectivity of the reconstructed functional networks from RS-EEG. Under the assumption that both the brain network properties and local tissue properties may influence the effective connectivity strength of the functional networks inferred from the resting state EEG measurements. An overview of the used methodological framework is presented in Fig. 12.

Here the brain structure is modelled as a random $N = 128$-node's graph with a connectivity matrix $G = \{G_{ij}\}$, i.e. the in-silico model of the brain structure consists of 128 connected "single brain units". Single unit brain dynamics are modelled using a bistable mathematical model known as the Z^6 model (Kalitzin et al., 2010), with simulation parameters (a, b, ω) allowing bistability. To account for the fact that in in-

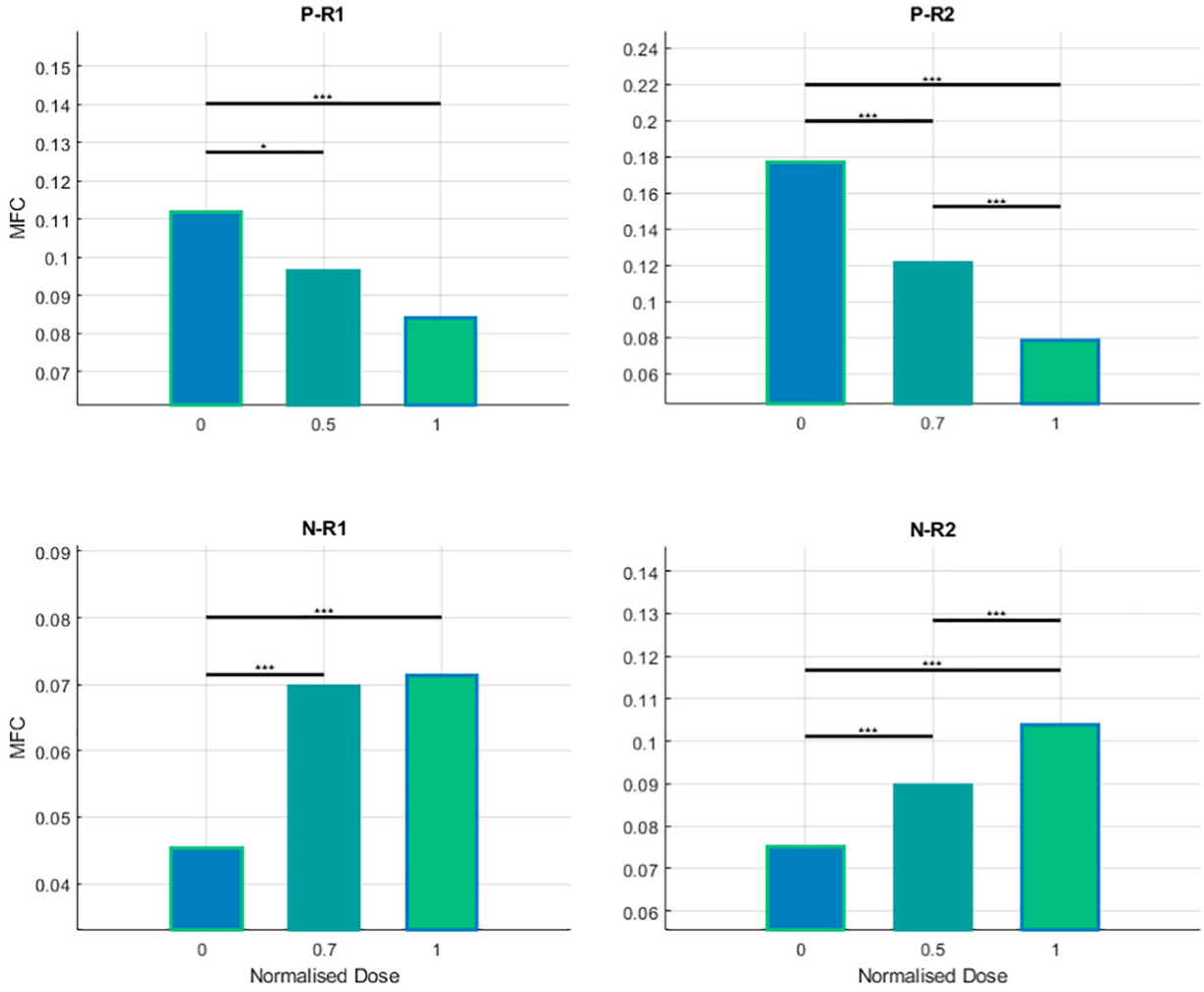

Fig. 13. In vivo results for positive and negative responders. The plots show results of the positive and negative responders' dataset. The upper panels present the MFC data for the positive responders, while the bottom panels present the data for the negative responders. Each panel shows the quantification of the level of significance of statistics of patient's MFC day values by performing Mann-Whitney multiple comparative tests between the days based on the ANOVA test statistics, Bonferroni corrected for group comparison. Colored bars show the average value of MFC. The level of statistical significance of the differences between each couple of bars (within a panel) is presented through a black line over the bars couple, marked with one, two or three stars, corresponding to *p*-values accordingly of ($p < .05$), ($p < .01$), and ($p < .001$).

vivo measurements the number of *EEG* electrodes is much lower than the number of brain units or sources, it is assumed that each electrode represents a linear combination of the simulated nodes. Accordingly, a random (8×128) matrix T is prepared, which transfers the 128 "brain signals" into eight linear combinations, representing the signals obtained from the *EEG* channels. Using the overall connectivity strength as a control parameter the authors investigated the relation between the epileptic properties of the system measured by Brain Network Ictogenicity (*BNI*) (Petkov et al., 2014), i.e. the relative amount of time that the system spent in oscillatory state and the observable overall functional connectivity measured as Mean Functional Connectivity (*MFC)*. The last is derived from the total association between all the pairs of simulated EEG traces.

When the concept of a passive signal biomarker was investigated using computational model simulations, there was a strong association between the likelihood of a seizure or ictogenicity of the system (*BNI*) and the mean functional connectivity (*MFC*) tested with different numbers of EEG electrodes. This association is largely invariant on the network topology and the mixing coefficients defining the model EEG traces. This gave credence to the biomarker based on functional connectivity as an indicator for the effectiveness of the anti-epileptic medication.

To confirm this biomarker and its usefulness in vivo, preliminary clinical testing is performed on EEG recordings from thirteen patients undergoing routine long-term monitoring diagnostics including drug dose changes. The functional connectivity is reconstructed and the MFC is calculated. The aim is to asses to what extend MFC is a strictly monotonically decreasing function of drug dose positive effect. The dataset contains two positive responders, two negative responders, and nine partial responders. The results of the dataset with two positive and two negative responders are presented in Fig. 13.

The positive responders to therapy (more than a 50% reduction in seizure frequency) showed a reduction in MFC with the increase in medication dose. The negative responders have an adverse reaction with an increase in their seizure frequency compared to baseline and showed an increase in MFC with the increase in dose. The rest of the group showed non-monotonic changes in MFC with the increase in medication dose.

5. Conclusion

Neuroscience has achieved remarkable progress in collecting data and facts about the functioning of human and animal brain, especially due to novel experimental techniques. But these advancements are, in

our view, in contrast with the lack of leading principles or theory that can put the accumulated knowledge into a comprehensive framework. In our review we attempt to demonstrate that finding the right balance between an empirical jungle of facts and over-simplified mathematical concepts is the right way to attack the challenge. We show that simple analytical models can still elicit rich properties such as phase-magnitude correlations, multiple stable states and transition dynamics, that quite realistically mirror the generic features of biological reality. But models are not just explanatory tools, they can be instruments for generating hypothesis about paroxysmal states such as epilepsy and eventually provide diagnostic and therapeutic value. Think of the periodic table of chemical elements as an historic example. It not only made a system of the existing known elements at that time, it also predicted the existence and even the properties of elements to be discovered. Or the general theory of relativity that predicted the shift of the perihelion of the planet Mercury and the existence of black holes and gravitational waves. Of course, we are not at this stage in neuroscience, perhaps not by a large distance, but still we believe that our models of multi-stable neuronal assemblies can explain and predict phenomena such as epileptic seizures, pre-ictal recruitment and post-ictal suppression that have been observed in clinical practice. We may also claim that several diagnostic approaches, currently being under validation trials, have been inspired by model concepts. Models of neural systems can be the test-benches for novel clinical concepts, but they can also be the inception substance generating new paradigms.

More specifically, in this review, we examine a particular state of brain functioning – epilepsy – as a manifestation of multistate network of coupled oscillatory systems. We show that, (a) this concept is apparent in in vitro and in vivo experimental studies, (b) simple analytical models based on multistate bistable attractor units can still elicit rich properties such as seizure-like states and transition dynamics that realistically represent features and biomarkers found in epileptic brains, and (c) models of coupled oscillator units could account for phenomena that bistable “simple” attractor models struggle with, such as the concept of intermittency associated with a “complex” attractor and cross frequency coupling between the phase of a low frequency rhythm modulating the amplitude of a high frequency rhythm as manifest in the scalp and intracranial EEG recordings from epileptic patients. We also show that models of multi-stable neuronal assemblies not only replicate the particular epileptic features, but also can explain and predict phenomena such as epileptic seizures, pre-ictal recruitment and post-ictal suppression that have been observed in clinical practice. These findings suggest that most probably, the electrical rhythms of the brain are associated with a complicated system of multi-stable “complex” attractors, where each attractor is associated with a group of coupled oscillators representing an assembly of neuroglial networks. Computer modelling is increasingly being used in epilepsy research (reviewed in Lytton (2008), Stefanescu et al. (2012)). While in some models the transitions between normal and epileptic states are induced by parameter change (Traub and Wong, 1982; Destexhe, 1998; Wendling et al., 2005), spontaneous, emergent ictal transitions has been also suggested by other computational models having complex multi-stable dynamics. In idiopathic generalized epilepsy seizures often start and terminate through a sudden transition between small amplitude normal activity and large-amplitude pathological oscillations. Apart from our work described above, a number of computational models associated these transitions with bistable dynamics in the underlying network (Ohayon et al., 2007; Marten et al., 2009; Goodfellow et al., 2011; Milton et al., 2017). Neurocomputational models have also been used to explain certain features observed in electrographic signals in focal epilepsy patients. Bistable orgin of transitions to tonic clonic seizures seizures was suggested by the model of Breakspear et al. (2006). Using interconnected neuronal populations Wang et al. (2017) showed that two focal seizure onset pattern might depend on the dynamical properties of the network surrounding the seizure focus. Low voltage activity onset pattern was observed in monostable networks while while bistable surround led to seizure-like activity with high-amplitude onset pattern. Similar considerations were presented by Kim et al., who proposed that spread of secondarily generalized seizures was associated with multistable bifurcation structure of the model (Kim et al., 2009). Similar to how the periodic table predicted the existence of elements yet to be discovered, or the general relativity explained the perihelion of Mercury, the goal of models we have reviewed is eventually to develop diagnostic and therapeutic approaches inspired by empirical experimental and clinical data coupled with model-derived concepts.

Funding

This work was supported by the CIHR, NSERC, and the Ontario Brain Institute.

References

Amzica, F., Steriade, M., 2000. Neuronal and glial membrane potentials during sleep and paroxysmal oscillations in the neocortex. J. Neurosci. 20, 6648–6665.

Bauer, P.R., Thijs, R.D., Lamberts, R.J., Velis, D.N., Visser, G.H., Tolner, E.A., Sander, J.W., Lopes da Silva, F.H., Kalitzin, S.N., 2017. Dynamics of convulsive seizure termination and postictal generalized EEG suppression. Brain, aww322. https://doi.org/10.1093/brain/aww322.

Berenyi, A., Belluscio, M., Mao, D., Buzsaki, G., 2012. Closed-loop control of epilepsy by transcranial electrical stimulation. Science (80-.), vol. 337, 735–737. https://doi.org/10.1126/science.1223154.

Bialonski, S., Lehnertz, K., 2013. Assortative mixing in functional brain networks during epileptic seizures. Chaos 23, 033139. https://doi.org/10.1063/1.4821915.

Breakspear, M., Roberts, J.A., Terry, J.R., et al., 2006. A unifying explanation of primary generalized seizures through nonlinear brain modeling and bifurcation analysis. Cereb. Cortex 16, 1296–1313. https://doi.org/10.1093/cercor/bhj072.

Buzsáki, G., 2006. Rhythms of the Brain. Oxford University Press, New York, NY, US.

Carmignoto, G., Haydon, P.G., 2012. Astrocyte calcium signaling and epilepsy. Glia 60, 1227–1233. https://doi.org/10.1002/glia.22318.

Chowdhury, F.A., Woldman, W., FitzGerald, T.H.B., Elwes, R.D.C., Nashef, L., Terry, J.R., Richardson, M.P., 2014. Revealing a brain network endophenotype in families with idiopathic generalised epilepsy. PLoS One 9, e110136. https://doi.org/10.1371/journal.pone.0110136.

Chu, C.J., Tanaka, N., Diaz, J., Edlow, B.L., Wu, O., Hämäläinen, M., Stufflebeam, S., Cash, S.S., Kramer, M.A., 2015. EEG functional connectivity is partially predicted by underlying white matter connectivity. Neuroimage 108, 23–33. https://doi.org/10.1016/j.neuroimage.2014.12.033.

Conte, A., Gilio, F., Iacovelli, E., Bettolo, C.M., Di Bonaventura, C., Frasca, V., Carbone, A., Prencipe, M., Berardelli, A., Inghilleri, M., 2007. Effects of repetitive transcranial magnetic stimulation on spike-and-wave discharges. Neurosci. Res. 57, 140–142. https://doi.org/10.1016/j.neures.2006.09.015.

Contreras, D., Destexhe, A., Sejnowski, T.J., Steriade, M., 1996. Control of spatiotemporal coherence of a thalamic oscillation by corticothalamic feedback. Science 274, 771–774.

Derchansky, M., Rokni, D., Rick, J.T.T., Wennberg, R., Bardakjian, B.L.L., Zhang, L., Yarom, Y., Carlen, P.L.L., 2006. Bidirectional multisite seizure propagation in the intact isolated hippocampus: the multifocality of the seizure “focus”. Neurobiol. Dis. 23, 312–328. https://doi.org/10.1016/j.nbd.2006.03.014.

Derecki, N.C., Cronk, J.C., Lu, Z., Xu, E., Abbott, S.B.G., Guyenet, P.G., Kipnis, J., 2012. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. Nature 484, 105–109. https://doi.org/10.1038/nature10907.

Destexhe, A., 1998. Spike-and-wave oscillations based on the properties of GABA(B) receptors. J. Neurosci. 18, 9099–9111.

Duckrow, R.B., Spencer, S.S., 1992. Regional coherence and the transfer of ictal activity during seizure onset in the medial temporal lobe. Electroencephalogr. Clin. Neurophysiol. 82, 415–422.

Dudek, F.E., 2009. Epileptogenesis: a new twist on the balance of excitation and inhibition. Epilepsy Curr. 9, 174–176. https://doi.org/10.1111/j.1535-7511.2009.01334.x.

Eyo, U.B., Peng, J., Swiatkowski, P., Mukherjee, A., Bispo, A., Wu, L.-J., 2014. Neuronal hyperactivity recruits microglial processes via neuronal NMDA receptors and microglial P2Y12 receptors after status epilepticus. J. Neurosci. 34, 10528–10540. https://doi.org/10.1523/JNEUROSCI.0416-14.2014.

Farah, F.H., Grigorovsky, V., Bardakjian, B.L., 2018. Coupled oscillators model of hyperexcitable neuroglial networks. Int. J. Neural Syst., 1850041. https://doi.org/10.1142/S0129065718500417.

Fellin, T., Pascual, O., Gobbo, S., Pozzan, T., Haydon, P.G., Carmignoto, G., 2004. Neuronal synchrony mediated by astrocytic glutamate through activation of extrasynaptic NMDA receptors. Neuron 43, 729–743. https://doi.org/10.1016/j.neuron.2004.08.011.

Fernandes de Lima, V.M., Pijn, J.P., Nunes Filipe, C., Lopes de Silva, F., 1990. The role of hippocampal commissures in the interhemispheric transfer of epileptiform afterdischarges in the rat: a study using linear and non-linear regression analysis. Electroencephalogr. Clin. Neurophysiol. 76 (6), 520–539.

Finger, H., Bönstrup, M., Cheng, B., Messé, A., Hilgetag, C., Thomalla, G., Gerloff, C.,

König, P., 2016. Modeling of large-scale functional brain networks based on structural connectivity from DTI: comparison with EEG derived phase coupling networks and evaluation of alternative methods along the modeling path. PLoS Comput. Biol. 12, e1005025. https://doi.org/10.1371/journal.pcbi.1005025.
Fontainhas, A.M., Wang, M., Liang, K.J., Chen, S., Mettu, P., Damani, M., Fariss, R.N., Li, W., Wong, W.T., 2011. Microglial morphology and dynamic behavior is regulated by ionotropic glutamatergic and GABAergic neurotransmission. PLoS One 6, e15973. https://doi.org/10.1371/journal.pone.0015973.
Goodfellow, M., Schindler, K., Baier, G., 2011. Intermittent spike–wave dynamics in a heterogeneous, spatially extended neural mass model. NeuroImage 55, 920–932. https://doi.org/10.1016/j.neuroimage.2010.12.074.
Grigorovsky, V., Bardakjian, B.L., 2018a. Neuro-glial network model of postictal generalized EEG suppression (PGES). In: Conf. Proc. ... Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. IEEE Eng. Med. Biol. Soc. Annu. Conf. pp. 2044–2047. https://doi.org/10.1109/EMBC.2018.8512661.
Grigorovsky, V., Bardakjian, B.L., 2018b. Low-to-high cross-frequency coupling in the electrical rhythms as biomarker for hyperexcitable neuroglial networks of the brain. IEEE Trans. Biomed. Eng. 65, 1504–1515. https://doi.org/10.1109/TBME.2017.2757878.
Guirgis, M., Chinvarun, Y., Del Campo, M., Carlen, P.L., Bardakjian, B.L., 2015. Defining regions of interest using cross-frequency coupling in extratemporal lobe epilepsy patients. J. Neural Eng. 12. https://doi.org/10.1088/1741-2560/12/2/026011.
Helling, Robert, Petkov, George, Kalitzin, Stiliyan, 2019. Expert System for Pharmacological Epilepsy Treatment Forecast and Optimal Medication Dose Prescription. ACMhttps://doi.org/10.1145/3309772.3309775.
Honey, C.J., Sporns, O., Cammoun, L., Gigandet, X., Thiran, J.P., Meuli, R., Hagmann, P., 2009. Predicting human resting-state functional connectivity from structural connectivity. Proc. Natl. Acad. Sci. 106, 2035–2040. https://doi.org/10.1073/pnas.0811168106.
Izhikevich, E.M., 2001. Synchronization of elliptic bursters. SIAM Rev. 43, 315–344.
Ji, K., Akgul, G., Wollmuth, L.P., Tsirka, S.E., 2013. Microglia actively regulate the number of functional synapses. PLoS One 8, e56293. https://doi.org/10.1371/journal.pone.0056293.
Jirsa, V.K., Stacey, W.C., Quilichini, P.P., Ivanov, A.I., Bernard, C., 2014. On the nature of seizure dynamics. Brain 137, 2210–2230. https://doi.org/10.1093/brain/awu133.
Jiruska, P., de Curtis, M., Jefferys, J.G.R., Schevon, C.A., Schiff, S.J., Schindler, K., 2013. Synchronization and desynchronization in epilepsy: controversies and hypotheses. J. Physiol. 591, 787–797. https://doi.org/10.1113/jphysiol.2012.239590.
Joyce, K.E., Laurienti, P.J., Burdette, J.H., Hayasaka, S., 2010. A new measure of centrality for brain networks. PLoS One 5, e12200. https://doi.org/10.1371/journal.pone.0012200.
Junges, L., Lopes, M.A., Terry, J.R., Goodfellow, M., 2019. The role that choice of model plays in predictions for epilepsy surgery. Sci. Rep. 9, 7351. https://doi.org/10.1038/s41598-019-43871-7.
Kalitzin, S.N., Velis, D.N., Lopes da Silva, F.H., 2010. Stimulation-based anticipation and control of state transitions in the epileptic brain. Epilepsy Behav. 17, 310–323. https://doi.org/10.1016/j.yebeh.2009.12.023.
Kalitzin, S., Koppert, M., Petkov, G., Velis, D., da Silva, F.L., 2011. Computational model prospective on the observation of proictal states in epileptic neuronal systems. Epilepsy Behav. 22, S102–S109. https://doi.org/10.1016/j.yebeh.2011.08.017.
Kalitzin, S., Koppert, M., Petkov, G., Lopes da Silva, F.H., 2014. Multiple oscillatory states in models of collective neuronal dynamics. Int. J. Neural Syst. 24, 1450020. https://doi.org/10.1142/S0129065714500208.
Khalsa, S., Mayhew, S.D., Chechlacz, M., Bagary, M., Bagshaw, A.P., 2014. The structural and functional connectivity of the posterior cingulate cortex: comparison between deterministic and probabilistic tractography for the investigation of structure-function relationships. Neuroimage 102, 118–127. https://doi.org/10.1016/j.neuroimage.2013.12.022.
Kim, J.W., Roberts, J.A., Robinson, P.A., 2009. Dynamics of epileptic seizures: evolution, spreading, and suppression. J. Theor. Biol. 257, 527–532. https://doi.org/10.1016/j.jtbi.2008.12.009.
Kim, M., Kim, S., Mashour, G.A., Lee, U., 2017. Relationship of topology, multiscale phase synchronization, and state transitions in human brain networks. Front. Comput. Neurosci. 11, 55. https://doi.org/10.3389/fncom.2017.00055.
Koppert, M.M.J., Kalitzin, S., Lopes da Silva, F.H., Viergever, M.A., 2011. Plasticity-modulated seizure dynamics for seizure termination in realistic neuronal models. J. Neural Eng. 8, 046027. https://doi.org/10.1088/1741-2560/8/4/046027.
Koppert, M., Kalitzin, S., Velis, D., DA Silva, F.L., Viergever, M.A., 2013. Reactive control of epileptiform discharges in realistic computational neuronal models with bistability. Int. J. Neural Syst. 23, 1250032. https://doi.org/10.1142/S0129065712500323.
Koppert, M., Kalitzin, S., Velis, D., Lopes Da Silva, F., Viergever, M.A., 2014. Dynamics of collective multi-stability in models of multi-unit neuronal systems. Int. J. Neural Syst. 24, 1430004. https://doi.org/10.1142/S0129065714300046.
Li, Y., Du, X.-F., Liu, C.-S., Wen, Z.-L., Du, J.-L., 2012. Reciprocal regulation between resting microglial dynamics and neuronal activity in vivo. Dev. Cell 23, 1189–1202. https://doi.org/10.1016/j.devcel.2012.10.027.
Liu, J., Li, M., Pan, Y., Lan, W., Zheng, R., Wu, F.X., Wang, J., 2017. Complex brain network analysis and its applications to brain disorders: a survey. Complexity 2017, 1–27. https://doi.org/10.1155/2017/8362741.
Lytton, W.W., 2008. Computer modelling of epilepsy. Nat. Rev. Neurosci. 9, 626–637. https://doi.org/10.1038/nrn2416.
Marten, F., Rodrigues, S., Suffczynski, P., et al., 2009. Derivation and analysis of an ordinary differential equation mean-field model for studying clinically recorded epilepsy dynamics. Phys. Rev. E 79. https://doi.org/10.1103/PhysRevE.79.021911.
McNaughton, B.L., Barnes, C.A., O'Keefe, J., 1983. The contributions of position, direction, and velocity to single unit activity in the hippocampus of freely-moving rats. Exp. Brain Res. 52, 41–49.
Meier, J., Tewarie, P., Hillebrand, A., Douw, L., Van Dijk, B.W., Stufflebeam, S.M., Van Mieghem, P., 2016. A mapping between structural and functional brain networks. Brain Connect. 6. https://doi.org/10.1089/brain.2015.0408.
Milton, J., Wu, J., Campbell, S.A., Bélair, L., 2017. Outgrowing neurological diseases: microcircuits, conduction delay and dynamics diseases. In: Erdi, P., Bhattacharya, S., Cochran, A. (Eds.), Computational Neurology - Computational Psychiatry: Why and How? Springer, New York, pp. 11–47.
Moon, J.Y., Kim, J., Ko, T.W., Kim, M., Iturria-Medina, Y., Choi, J.H., Lee, J., Mashour, G.A., Lee, U.C., 2017. Structure shapes dynamics and directionality in diverse brain networks: mathematical principles and empirical confirmation in three species. Sci. Rep. 7, 46606. https://doi.org/10.1038/srep46606.
Mylvaganam, S., Ramani, M., Krawczyk, M., Carlen, P.L., 2014. Roles of gap junctions, connexins, and pannexins in epilepsy. Front. Physiol.(5 May). https://doi.org/10.3389/fphys.2014.00172.
Ohayon, E.L., Kwan, H.C., Burnham, W.M., Suffczynski, P., Lopes da Silva, F.H., Kalitzin, S., 2007. Adaptable intermittency and autonomous transitions in epilepsy and cognition. In: ICCN 2007 Proceedings, Advances in Cognitive Neurodynamics. Springer, pp. 485–490 2007. ISBN 978-1-4020-8386-0.
Osorio, I., Frei, M.G., 2009. Seizure abatement with single dc pulses: is phase resetting at play? Int. J. Neural Syst. 19, 149–156. https://doi.org/10.1142/S0129065709001926.
Pascual, O., Ben Achour, S., Rostaing, P., Triller, A., Bessis, A., 2012. Microglia activation triggers astrocyte-mediated modulation of excitatory neurotransmission. Proc. Natl. Acad. Sci. U. S. A. 109, E197–E205. https://doi.org/10.1073/pnas.1111098109.
Perea, G., Navarrete, M., Araque, A., 2009. Tripartite synapses: astrocytes process and control synaptic information. Trends Neurosci. 32, 421–431. https://doi.org/10.1016/j.tins.2009.05.001.
Petkov, G., Goodfellow, M., Richardson, M.P., Terry, J.R., 2014. A critical role for network structure in seizure onset: a computational modeling approach. Front. Neurol. 5, 261. https://doi.org/10.3389/fneur.2014.00261.
Petkov, G., Kalitzin, S., Demuru, M., Widman, G., Suffczynski, P., Lopes da Silva, F.H., 2018. Computational model exploration of stimulation based paradigm for detection of epileptic systems. Front. Artif. Intell. Appl. 310, 324–335. https://doi.org/10.3233/978-1-61499-929-4-324.
Proix, T., Jirsa, V.K., Bartolomei, F., Guye, M., Truccolo, W., 2018. Predicting the spatiotemporal diversity of seizure propagation and termination in human focal epilepsy. Nat. Commun. 9, 1–15.
Rajna, P., Lona, C., 1989. Sensory stimulation for inhibition of epileptic seizures. Epilepsia 30, 168–174.
Rubinov, M., Sporns, O., 2010. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 52, 1059–1069. https://doi.org/10.1016/j.neuroimage.2009.10.003.
Seifert, G., Carmignoto, G., Steinhäuser, C., 2010. Astrocyte dysfunction in epilepsy. Brain Res. Rev. 63, 212–221. https://doi.org/10.1016/j.brainresrev.2009.10.004.
Sik, A., Penttonen, M., Ylinen, A., Buzsáki, G., 1995. Hippocampal CA1 interneurons: an in vivo intracellular labeling study. J. Neurosci. 15, 6651–6665.
Stam, C.J., Nolte, G., Daffertshofer, A., 2007. Phase lag index: assessment of functional connectivity from multi channel EEG and MEG with diminished bias from common sources. Hum. Brain Mapp. 28, 1178–1193. https://doi.org/10.1002/hbm.20346.
Stefanescu, R.A., Shivakeshavan, R.G., Talathi, S.S., 2012. Computational models of epilepsy. Seizure 21, 748–759. https://doi.org/10.1016/j.seizure.2012.08.012.
Suffczynski, P., Kalitzin, S., Lopes Da Silva, F.H., 2004. Dynamics of non-convulsive epileptic phenomena modeled by a bistable neuronal network. Neuroscience 126, 467–484. https://doi.org/10.1016/j.neuroscience.2004.03.014.
Suffczynski, P., Lopes da Silva, F.H., Parra, J., Velis, D.N., Bouwman, B.M., van Rijn, C.M., van Hese, P., Boon, P., Khosravani, H., Derchansky, M., Carlen, P., Kalitzin, S., 2006. Dynamics of epileptic phenomena determined from statistics of Ictal transitions. IEEE Trans. Biomed. Eng. 53, 524–532. https://doi.org/10.1109/TBME.2005.869800.
Tetzlaff, R., Elger, C.E., Lehnertz, K., 2015. Recent advances in predicting and preventing epileptic seizures. Q. Rev. Biol. 90, 241.
Traub, R., Wong, R., 1982. Cellular mechanism of neuronal synchronization in epilepsy. Science 216, 745–747. https://doi.org/10.1126/science.7079735.
Wake, H., Moorhouse, A.J., Jinno, S., Kohsaka, S., Nabekura, J., 2009. Resting microglia directly monitor the functional state of synapses in vivo and determine the fate of ischemic terminals. J. Neurosci. 29, 3974–3980. https://doi.org/10.1523/JNEUROSCI.4363-08.2009.
Wang, Y., Trevelyan, A.J., Valentin, A., et al., 2017. Mechanisms underlying different onset patterns of focal seizures. PLoS Comput. Biol. 13, e1005475. https://doi.org/10.1371/journal.pcbi.1005475.
Wendling, F., Hernandez, A., Bellanger, J.-J., et al., 2005. Interictal to ictal transition in human temporal lobe epilepsy: insights from a computational model of intracerebral EEG. J. Clin. Neurophysiol. 22, 343–356.
Zalay, O.C., Bardakjian, B.L., 2009. Theta phase precession and phase selectivity: a cognitive device description of neural coding. J. Neural Eng. 6, 036002. https://doi.org/10.1088/1741-2560/6/3/036002.
Zalay, O.C., Serletis, D., Carlen, P.L., Bardakjian, B.L., 2010. System characterization of neuronal excitability in the hippocampus and its relevance to observed dynamics of spontaneous seizure-like transitions. J. Neural Eng. 7. https://doi.org/10.1088/1741-2560/7/3/036002.