Focal seizures are organized by feedback between neural activity and ion concentration changes

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Abstract

Human and animal EEG data demonstrate that focal seizures start with low-voltage fast activity, evolve into rhythmic burst discharges and are followed by a period of suppressed background activity. This suggests that processes with dynamics in the range of tens of seconds govern focal seizure evolution. We investigate the processes associated with seizure dynamics by complementing the Hodgkin-Huxley mathematical model with the physical laws that dictate ion movement and maintain ionic gradients. We show that the disturbance of K^+ and Cl^- homeostasis by the fast discharge of inhibitory interneurons is sufficient to initiate seizures, which are maintained by positive feedback between ion concentration changes and neuronal activity. Gradual Na^+ accumulation increases the rate of the Na^+/K^+ -pump, creating negative feedback which slows down and terminates ictal discharges and contributes to the postictal state. Our results emphasize ionic dynamics as elementary processes behind seizure generation and indicate targets for new therapeutic strategies.

Introduction

Focal seizure patterns recorded with intracranial and intracerebral electrodes in patients submitted to presurgical evaluation often consist of distinct phases (Fraszczuk et al., 1998; Spencer et al., 1992; Velasco et al., 2000). A frequently observed onset pattern in patients with temporal lobe epilepsy (TLE) is characterized by low-voltage fast (LVF) activity in the gamma range (30–80 Hz) (Avoli et al., 2016; de Curtis & Gnatkovsky, 2009; Lagarde et al., 2019; Perucca et al., 2014). LVF seizure onset is followed by the recruitment of irregular spiking behavior which evolves into periodic burst discharges that gradually decrease in frequency and suddenly cease. Seizures are often followed by a period of reduced EEG amplitude known as postictal EEG suppression. The traditional view on epileptic seizures is that they result from an imbalance of synaptic excitation and inhibition (Bradford, 1995; Bragin et al., 2009). It is unclear how this concept may account for the electroencephalographic complexity of TLE seizures and their characteristic progression from one phase to the next. The findings of several studies have not confirmed the role of synaptic interaction in seizure generation or progression. It has been shown that blocking synaptic transmission via a low Ca^{2+} solution led to the development of synchronized seizure-like events (SLE) in hippocampal CA1 slices (Jefferys & Haas, 1982; Yaari et al., 1983) and in the intact hippocampus (Feng & Durand, 2003). Moreover, the synchronized epileptiform activity can be recorded across two hippocampal regions separated by a mechanical lesion, without the involvement of electrochemical synaptic communication (Lian et al., 2001). Finally, in photosensitive baboons, light-induced neocortical seizure discharges were accompanied by depletion of extracellular Ca^{2+} to levels incompatible with the chemical synaptic transmission (Pumain et al., 1985). Additionally, a paradoxical increase in inhibitory cell firing and a decrease in pyramidal cell activity at seizure onset was documented in *in vitro* rodent slices (Derchansky et al., 2008; Fujiwara-Tsukamoto et al., 2007; Lévesque et al., 2016; Lillis et al., 2012; Ziburkus et al., 2006), in the *in vitro* whole guinea pig brain (Gnatkovsky et al., 2008; Uva et al., 2015), and in human and animal *in vivo* recordings (Elahian et al., 2018; Grasse et al., 2013; Miri et al., 2018; Toyoda et al., 2015; Truccolo et al., 2011). The above-mentioned studies suggest that processes at the network level related to changes in synaptic gains cannot be the sole mechanisms that control seizure generation and progression, and that other factors must be involved in the process of ictogenesis.

Although several non-synaptic mechanisms have been proposed to influence abnormal synchronization (Blauwblomme et al., 2014; de Curtis et al., 2018; Jefferys et al., 2012;

Raimondo et al., 2015), the specific mechanisms responsible for seizure induction, evolution and termination remain unclear. In the present study, we investigated the possible mechanisms of the LVF seizure pattern using a realistic computational model of the hippocampal network that included activity-dependent ion concentration changes. We based our simulations on the data recorded in the *in vitro* isolated guinea pig brain preparation, which is an animal model of human temporal lobe seizures (de Curtis et al., 2006; de Curtis & Gnatkovsky, 2009). We used these experimental recordings to guide our *in silico* study due to the availability of data at the network, cellular and ionic levels. A computer model was used to demonstrate that seizures initiated via increased interneuron discharges, evolved, and terminated autonomously due to activity-dependent ion concentration shifts and homeostatic mechanisms that worked continuously to restore physiological transmembrane ion levels. Our modelling results suggest a link between the seizure termination mechanism and postictal suppression state and predict a specific scaling law of inter-bursting intervals observed at the end of seizures, which was validated experimentally.

Results

The model consisted of five cells, four pyramidal neurons (PY) and a fast-spiking inhibitory interneuron (IN), arranged as a chain structure (Fig. 1). The ionic dynamics of K^+ , Na^+ , Ca^{2+} and Cl^- were incorporated and activity-dependent changes in their concentrations were computed. Concentration changes in each extracellular or intracellular compartment were dependent on several mechanisms such as active and passive membrane currents, inhibitory synaptic GABA_A currents, Na^+/K^+ -pump, KCC2 cotransporter, glial K^+ buffer, Ca^{2+} pump and buffer, radial diffusion, longitudinal diffusion and volume changes. Additionally, we included impermeant anions (A^-) with concentration dependent volume changes and bicarbonate ions (HCO_3^-) that contributed to GABA_A currents.

Figure 1. Model diagram. The model consisted of four pyramidal cells (orange) and an interneuron (green) linked by excitatory (AMPA) and inhibitory (GABAa) synaptic connections. Each cellular compartment was surrounded by an interstitial compartment. The interstitial space was enclosed in a common bath (blue) which represented the surrounding tissue and vasculature not included in the model. The model included variable intracellular and extracellular ion concentrations computed according to ionic currents flowing across neuronal membranes, longitudinal diffusion between the dendritic and somatic compartments, radial diffusion between neighboring interstitial compartments and diffusion to/from the bath. Additionally, the model included ionic regulation mechanisms: a Na^+/K^+ -pump, a KCC2 cotransporter and K^+ buffering by astrocytes.

Three phases of an LVF onset SLE

A simulated SLE emerging from normal background activity is shown in Fig. 2. To test the hypothesis that the onset of focal seizures is associated with an increased discharge of IN (de Curtis & Avoli, 2016), we applied a depolarizing current (Fig. 2C, yellow trace) to the IN at second 60. Strong firing (initial rate of 270 Hz) of the IN (Fig. 2C) led to small amplitude fast activity in the LFP signal (Fig. 2A between the 60 and 65-second timestamps) associated with the onset of the simulated SLE. After approximately 10 seconds, the PY cells began to generate a strong tonic discharge, resulting in an irregular LFP spiking signal with increased amplitude typically associated with the SLE tonic phase (Fig. 2B; 65–80 seconds). Approximately 15–20

seconds after the onset of the SLE, the cellular firing pattern of PY cells switched from tonic to bursting discharge, leading to LFP oscillations which corresponded to the bursting phase (Fig. 2A, after 80 seconds). As the SLE progressed, the burst rate gradually decreased and ictal discharges spontaneously terminated. Postictally, the SLE was followed by a period of silence for approximately 30 seconds which was visible in the LFP signal and in the PY and IN traces (Fig. 2A–C). After the postictal depression, the background firing reappeared and gradually returned to a baseline level. The SLE discharges were accompanied by significant changes in the intracellular and extracellular ionic concentrations. At the onset of the seizure, extracellular potassium concentration ($[K^+]_o$) increased sharply in the somatic compartment, remained elevated throughout the SLE and slightly decreased toward the end of the episode (Fig. 2D). Intracellular sodium concentration ($[Na^+]_i$) steadily increased during the bursting phase in both somatic and dendritic compartments and reached a plateau around the offset of the SLE (Fig. 2E). Intracellular chloride concentration ($[Cl^-]_i$) exhibited a gradual increase from the beginning of the SLE and was highest at the end of the paroxysmal firing (Fig. 2F).

Figure 2. Model behavior during an SLE. (A) Local field potential (LFP) signal. **(B)** Pyramidal cell (PY) membrane potential. **(C)** Interneuron (IN) membrane potential. **(D)**

Extracellular potassium concentration. **(E)** Intracellular sodium concentration. **(F)** Intracellular chloride concentration. In the interictal phase (0–60 seconds), the model generated irregular background firing and the ion concentrations were at their resting values **(A–F)**. The current injected into the interneuron at second 60 (**C**, yellow) triggered fast IN spiking (**C**, black) which also manifested as low voltage fast activity in the LFP signal (**A**). Approximately 10 seconds after the initiation of the SLE, PY cells initiated tonic firing that subsequently shifted to bursting **(B)**. The behavior of the PY cells was reflected in the LFP trace which showed irregular activity and synchronized bursting (**A**). The SLE terminated at approximately second 120 and was followed by a period of reduced excitability **(A–C)**. The cellular activity was accompanied by significant ion concentration shifts. Extracellular potassium in the somatic compartment increased sharply and remained elevated throughout the SLE (**D**, dark blue). The $[K^+]_o$ increase in the dendritic compartment was slower and less pronounced (**D**, violet). The intracellular sodium increased gradually toward a plateau (**E**). The intracellular chloride accumulated steadily throughout the SLE (**F**).

A comparison of the simulation results with the available experimental data is shown in Fig. 3. In the isolated guinea pig brain, the SLE activity with an LVF onset pattern (Fig. 3A, top trace) was induced by the arterial application of bicuculine. The transition from preictal to ictal state which occurred at approximately second 10 was associated with a strong discharge of fast-spiking interneurons (Fig. 3A, third trace) and transient silencing of the PY cells (Fig. 3A, second trace). The strong preictal firing of the PY cells was artificially triggered by the injection of a steady depolarizing current via the intracellular recording electrode to analyze the intracellular firing correlates during the SLE (Gnatkovsky et al., 2008). Within a few seconds from the initiation of the sustained interneuron discharge, the principal PY cells were recruited first into tonic firing and subsequently into bursting discharges which were visible in the PY membrane potential and LFP signals. $[K^+]_o$ sharply increased at the onset of the SLE and remained elevated afterward (Fig. 3A, bottom trace). The *in silico* results (shown for comparison in the same timescale in Fig. 3B) replicated the experimental data in many respects including LFP signal characteristics, cellular firing pattern and $[K^+]_o$ time course.

Figure 3. A comparison between the experimental data and the model simulation. (A) Experimental recordings of a seizure-like event (SLE) in the *in vitro* isolated whole guinea pig brain preparation (de Curtis et al., 2006; Gnatkovsky et al., 2008; Uva et al., 2015). From top to bottom: LFP signal, intracellular recording of pyramidal cell (PY) and interneuron (IN), extracellular potassium. The onset of the SLE was associated with increased IN firing, silencing PY and low-voltage fast (LVF) activity in the LFP signal. Approximately 10 seconds after the onset of the SLE, the PY exhibited a tonic and then burst firing behavior. The extracellular potassium increased up to approximately 10 mM at the onset of the SLE and remained elevated afterward. **(B)** The activity patterns in the LFP signal, pyramidal cells, interneuron and $[K^+]_o$ were reproduced accurately by the model except for preictal firing of the PY cell seen in A, which was artificially depolarized above resting membrane potential to highlight the role of the inhibitory interneurons during the SLE (Gnatkovsky et al., 2008).

In the simulations, the excitatory and inhibitory synaptic conductances were “clamped” throughout the entire simulation period, hence, they could not contribute to the progression from one phase to another. Conversely, variations in ion concentrations were expected to affect neuronal excitability. For example, an increase in $[K^+]_o$ reduces the driving force of K^+ currents responsible for hyperpolarized resting membrane potential and spike repolarization. $[Na^+]_i$ and $[K^+]_o$ affect the rate of the Na^+/K^+ -pump that transports three Na^+ ions out of the cell for every two K^+ ions pumped into the cell, thus producing an outward current. Accumulation of $[K^+]_o$ and

$[\text{Na}^+]_i$ increases the pump rate and enhances the hyperpolarizing pump current. Hence, to determine the intrinsic mechanism that modulates excitability, we first investigated the behavior of the model in response to variations in extracellular potassium and intracellular sodium concentrations.

The effects of $[\text{K}^+]_o$ and $[\text{Na}]_i$ on the network model

Activity-dependent changes in ion concentrations are slow compared to neuronal dynamics, which are relatively fast. To analyze such a system, with slow and fast timescales, it is possible to decouple the fast variables (e.g., membrane potential) from the slow variables (e.g., ionic concentrations). Accordingly, to analyze the role of $[\text{K}^+]_o$ and $[\text{Na}^+]_i$ in shaping single-cell and network dynamics, we disabled all mechanisms controlling ionic concentrations and analyzed the behavior of the model for different values of $[\text{K}^+]_o$ and $[\text{Na}^+]_i$. The values of these variables were modified externally and treated as control parameters. In the single cell analysis, all synaptic connections were removed. In the network analysis, all synaptic connections were intact except afferent excitatory input, which was removed from PY cells to eliminate the stochastic component from the analysis; depolarizing current injection was removed from the interneuron. The behavior of a single PY cell was analyzed for different values of extracellular potassium in the dendritic ($[\text{K}^+]_{o,dend}$) and somatic compartments ($[\text{K}^+]_{o,soma}$). During the analysis, for each fixed value of $[\text{K}^+]_{o,dend}$, we performed simulations when sweeping the $[\text{K}^+]_{o,soma}$ value from 3 mM to 14 mM (in steps of 0.25 mM) in the forward and backward direction. The initial conditions for each $[\text{K}^+]_{o,soma}$ corresponded to the final states in the previous step. For each $[\text{K}^+]_{o,soma}$ step, we simulated 5 seconds of activity. After a full sweep with all $[\text{K}^+]_{o,soma}$ steps in both directions, the $[\text{K}^+]_{o,dend}$ was increased and the analysis was repeated. The analysis was performed for the $[\text{K}^+]_{o,dend}$ values in the range of 3–7 mM, in steps of 0.5 mM (or 0.25 mM if a better resolution was required). We found that the behavior of the single cell and network models was the same for increasing and decreasing steps of $[\text{K}^+]_{o,soma}$ with small domains of bistability not larger than one step (0.25 mM) between the activity phases. Analysis of the dynamics of a single isolated cell for a reference value of $[\text{Na}^+]_i$ at 10 mM can be found in Supplementary material (Fig. S1). In the network analysis, a full sweep with all $[\text{K}^+]_{o,soma}$ and $[\text{K}^+]_{o,dend}$ steps (as described above) was performed for three different values of $[\text{Na}^+]_i$, namely, 10 mM, 11 mM and 12 mM. We assumed, that $[\text{Na}^+]_i$ in the dendritic and somatic compartments were equal. In the model simulation shown in Fig. 2E, $[\text{Na}^+]_{i,dend}$ values were lower than $[\text{Na}^+]_{i,soma}$ values. Accordingly, our assumption may have led to an overestimation of $[\text{Na}^+]_{i,dend}$ and the dendritic

Na⁺/K⁺-pump current. The analysis results are shown in Fig. 4A, in which the various activity patterns, i.e., rest, tonic firing and bursting are color-coded (shown on the right). A comparison of the network activities for different values of [Na⁺]_i in the three graphs in Fig. 4A demonstrates that the main effect of an increase in [Na⁺]_i was a shrinking of the tonic and bursting domains and an expansion of the resting domain due to upregulation of the hyperpolarizing effect of increased [Na⁺]_i on the pump current.

The evolution of the SLE mediated by [K⁺]_o and [Na]_i

In the previous section, the influence of [K⁺]_o and [Na]_i on network behavior was examined without accounting for the time factor. Here, we present a fast-slow system analysis approach that considers the time evolution of ionic concentrations, as shown in Fig. 2. Hence, we assessed the dependence of the evolution of an SLE on externally manipulated changes in [K⁺]_o and [Na]_i with fixed concentrations of all other ions. To obtain improved affinity with the reference simulation (Fig. 2), the chloride concentration in the dendritic compartment of the PY cells was set to 7.5 mM, which corresponded to its peak value during the SLE (Fig. 2F). To schematically describe the extracellular potassium time course from preictal to postictal state (as shown in Fig. 2D), we identified four distinct stages (as shown in Fig. 4B top panel): I) a sharp increase in [K⁺]_{o,soma}, II) elevated [K⁺]_{o,soma}, a slow increase in [K⁺]_{o,dend}, III) elevated [K⁺]_{o,dend}, a slow decrease in [K⁺]_{o,soma}, IV) a decrease in [K⁺]_{o,soma} and [K⁺]_{o,dend} back to their resting values. Variations in potassium concentrations were accompanied by changes in [Na⁺]_i (Fig. 2E). In the preictal period and during the SLE tonic firing phase, [Na⁺]_i in the soma and dendrite was stable, while it increased during the burst firing phase and reached a plateau toward the end of the episode. In the postictal period, [Na⁺]_i in both compartments slowly returned to the initial value. The time course of [Na⁺]_i approximating intracellular somatic sodium evolution is shown in Fig. 4B (middle panel). For simplicity, we assumed that these depicted [Na⁺]_i variations were the same in the dendritic and somatic compartments. The corresponding representative PY cell activity is shown in Fig. 4B (bottom trace). To distinguish different SLE phases, the PY cell activity pattern was marked using a color-code, as in Fig. 4A. As [K⁺]_o and [Na⁺]_i followed their predefined time course, PY cells exhibited transitions from rest to tonic firing, progressed into bursting with a slowing-down pattern and eventually returned to the resting state. In the postictal period (after stage IV), the [Na⁺]_i remained elevated for approximately 40 seconds (Fig. 4B middle panel) giving rise to an enhanced hyperpolarizing Na⁺/K⁺-pump current that reduced the excitability of the network and contributed to postictal depression, as described in the last

paragraph (Fig. 7). To further observe the time evolution of the SLE in the $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ parameter space, we superimposed potassium changes on the bifurcation diagrams in Fig. 4A. The distinct stages of the potassium time course are marked by arrows. The crossing of a border by an arrow corresponds to a transition between different firing regimes. The initial increase of somatic $[K^+]_o$ (stage I) led to a transition from the resting state to tonic firing (Fig. 4A, first panel), while a subsequent increase of dendritic $[K^+]_o$ (stage II) led to a transition from tonic firing to bursting (Fig. 4A, middle panel). A subsequent decrease in somatic $[K^+]_o$ (stage III) led to the termination of the SLE, as the cell activity reentered the resting state region (Fig. 4A, last panel). After termination of the SLE, $[K^+]_{o,soma}$ and $[K^+]_{o,dend}$ returned to their resting values (stage IV in Fig. 4A, last panel).

Figure 4. A bifurcation diagram of the model. In the bifurcation analysis extracellular potassium and intracellular sodium concentrations in the PY and IN cells were control parameters. Concentrations of all other ions were fixed at their reference values (except chloride: $[Cl^-]_{i,dend} = 7.5 \text{ mM}$), all ion accumulation mechanisms were blocked and background input was removed. **(A)** Bifurcation diagrams showing the dependence of the behavior of the model on

$[K^+]_{o,dend}$ and $[K^+]_{o,soma}$ for varying values of $[Na^+]_i$. The diagram colors correspond to types of activity shown on the right: rest (yellow), tonic firing (violet) and bursting (dark blue). An increase in $[Na^+]_i$ progressively decreased the domains of tonic firing and bursting and increased the resting domain indicating a general decrease in network excitability. The black and gray arrows correspond to the evolution of $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ during different phases of the SLE, shown in part **B**. **(B)** A simulation of the model with $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ and $[Na^+]_i$ as the external control parameters, that illustrated the occurrence of transitions between different types of activity during the SLE. The top two panels show the time course of $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ and $[Na^+]_i$ and approximate their evolution during the SLE (Fig. 2). The third panel shows the resulting PY cell behavior. The parameter evolution is divided into four phases indicated by the arrows denoted as I–IV in part **A** and **B**. Phase I corresponds to a sharp increase in $[K^+]_{o,soma}$ which led to a transition from rest to tonic firing (marked as a black arrow ‘I’ in the first panel in **A**). Phase II corresponds to a slow increase in $[K^+]_{o,dend}$ which led to a transition from tonic firing to bursting (marked as a black arrow ‘II’ in the first and second panels in **A**). Phase III represents a period of increased $[Na^+]_i$ and decreasing $[K^+]_{o,soma}$ which led to the termination of the SLE (represented by a black arrow ‘III’ with its tip in the yellow domain in the third panel in **A**). Phase IV corresponds to the postictal period with elevated $[Na^+]_i$ and a return of $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ to their baseline values (marked as a black arrow ‘IV’ in the third panel in **A**).

The role of $[Cl^-]_i$

Chloride accumulation depends on Cl^- currents, but it is also affected by variations in potassium concentrations mediated via KCC2 cotransport. Hence, chloride and potassium could not be considered as independent control parameters in the fast-slow system analysis approach. Furthermore, visualization of the results with four control parameters ($[K^+]_{o,soma}$, $[K^+]_{o,dend}$, $[Na^+]_i$ and $[Cl^-]_i$) is challenging. Therefore, to evaluate the role of chloride accumulation, we compared the reference model with the model in which chloride dynamics was excluded (Fig. 5). In these simulations, afferent excitatory input was removed from the PY cells to eliminate the stochastic component from the analysis. When considering the role of chloride homeostasis mediated via KCC2, the direction of K–Cl cotransport depends on the ratio $[K^+]_i[Cl^-]_i/[K^+]_o[Cl^-]_o$ (J. A. Payne et al., 2003). If $[Cl^-]_i$ is greater than $[K^+]_o$ (disregarding the changes in $[K^+]_i$ and $[Cl^-]_o$, which are relatively small), the ratio is greater than 1 and KCC2 extrudes Cl^- and K^+ . If $[K^+]_o$ is greater than $[Cl^-]_i$, the KCC2 flow is reversed and Cl^- and K^+ ions are transported into the cell. When chloride accumulation was removed (Fig. 5A), the reversal potentials of the Cl^- and GABA_A

currents (E_{Cl} and E_{GABAa}) were fixed (blue and violet lines in Fig. 5A, second panel). Under such conditions, the firing of the interneuron (Fig. 5A, third panel) exerted a steady inhibitory influence on the PY cells. Additionally, it increased $[K^+]_o$ above fixed $[Cl^-]_i$ level (Fig. 5A, fourth panel). As a result, the KCC2 transported K^+ and Cl^- into the cells (Fig. 5A, bottom panel) and reduced the external K^+ concentration. All these effects prevented the PY cells from firing and the SLE was not manifested, as seen in the LFP signal which displayed only low amplitude fast activity (Fig. 5A, top panel) mediated by GABAa inhibitory postsynaptic currents (IPSC). Conversely, activation of the IN in the reference model, with chloride accumulation intact, led to a typical SLE (Fig. 5B, top panel). The chloride dynamics increased the excitability in three ways: i) it increased the chloride reversal potential (blue line in Fig. 5B, second panel) toward the PY membrane potential and reduced the hyperpolarizing chloride leak current; ii) it increased the GABAa reversal potential that approached the PY cell membrane potential (violet line in Fig. 5B, second panel), reducing the postsynaptic inhibitory current and iii) it contributed to $[K^+]_o$ accumulation as increased $[Cl^-]_i$ reduced the inflow of Cl^- and K^+ into the cell via KCC2 (Fig. 5B, bottom panel).

Figure 5. A comparison of the model without and with chloride accumulation. The five panels in each column show (from top to bottom): the LFP signal, the PY cell membrane potential, the IN membrane potential, the extracellular potassium concentration and intracellular chloride concentration combined with the chloride and potassium KCC2 currents in the somatic

compartments, respectively. Additionally, the equilibrium potential of chloride and GABA_A are shown in the second panel from the top. In **A** and **B**, the background input was removed to exclude the stochastic component. **(A)** When the $[Cl^-]_i$ accumulation mechanism was blocked, the chloride concentration was fixed at the reference value (fourth panel). Without chloride accumulation, the PY cell remained inhibited (second panel) by the IN discharge triggered by the current injection (yellow, third panel). Additionally, elevated $[K^+]_o$ and fixed $[Cl^-]_i$ promoted K^+ influx via KCC2 (bottom panel, red), thus lowering $[K^+]_o$ and further preventing the generation of the SLE. **(B)** With chloride accumulation, the IN discharge led to an increase in E_{Cl} and E_{GABA_A} (second panel, blue and violet) which reduced the hyperpolarizing $I_{Cl,leak}$ and I_{GABA_A} currents and enhanced excitability. The increased $[Cl^-]_i$ reduced K^+ influx via KCC2 (bottom panel, red) which led to prolonged $[K^+]_o$ accumulation (fourth panel, red). All three effects contributed to the SLE.

Model predictions

The computer model generated predictions about features that were not explicitly implemented but were consequences of the elementary neurobiological mechanisms used to create the model. These phenomena are described below. The experimental confirmation of features predicted by a model is an essential step in model validation.

The evolution of the inter-burst interval duration

It is well known that muscle jerking during the clonic phase of tonic-clonic seizure slows down before ceasing when seizure ends (Bromfield et al., 2006). Frequency slowing has also been observed in video sequences (Kalitzin et al., 2016) and electrographic counterparts of a seizure revealed by either EEG (Franaszczuk et al., 1998; Schiff et al., 2000) or EMG (Conradsen et al., 2013). In the model, a gradual increase in the interval between ictal bursts (IBI) was visible (Fig. 2A and 3B). To observe the evolution of the IBI more precisely, the background noise was removed from the simulation and was compensated with a steady depolarizing current of 6 pA injected into the somas of all PY cells to preserve the duration of the SLE. A simulated SLE trace and the detected ictal bursts (short bars) are shown in Fig. 6A (top panel). The evolution of the IBI is shown below with either a linear (Fig. 6A, middle panel) or logarithmic (Fig. 6A, bottom panel) y-axis. The IBI on the semi-log graph laid on a straight line suggesting an exponential relationship. The evolution of the IBI during an SLE in a whole-brain *in vitro* preparation (Fig. 6B) and a human TLE seizure (Fig. 6C) exhibited the same characteristics. An

exponential relationship was confirmed via the root mean square error (RMSE) calculated for linear and exponential fits. In all examples, the exponential fit had a lower RMSE.

Figure 6. The evolution of IBI in the model and experimental data. (A) In the simulation, the background input was removed and compensated with a small depolarizing current injected into the PY cells to preserve the duration of the SLE. A decreasing rate of bursting is visible in the LFP signal and in the detected bursts marked above the trace (top panel). The evolution of the IBI is shown with the y-axis on a linear scale (middle panel) and a log scale (bottom). On a linear y-axis plot, the data appear curved while on a semi-log plot they lay on a straight line, suggesting exponential scaling of the IBI with time. The red line in each plot represents the best fit for the detected IBI; linear function (middle panel) and exponential function providing a linear relationship on a semi-log plot (bottom panel). The root mean square error (RMSE) between the data points and fitted function is shown in each window. The exponential function fit yielded a smaller RMSE compared to the linear fit, providing quantitative confirmation that at the end of the simulated SLE, the IBI duration increased exponentially, rather than linearly, with time. (B) The evolution of the IBI during the SLE induced by application of bicuculline in the whole-brain *in vitro* preparation (Boido et al., 2014; Gnatkovsky et al., 2008). (C) IBI evolution during a seizure recorded with intracerebral electrodes positioned in the temporal lobe in a patient submitted to presurgical evaluation (courtesy of Laura Tassi, Epilepsy Surgery Center, Niguarda Hospital, Milano, Italy). In B and C, the detected IBI lay on a straight line on the semi-log plot

and the exponential fit resulted in a smaller RMSE compared to the linear fit, validating the model prediction of an exponential increase in the IBI at the end of a seizure. The linear fit, $IBI(t) = A + Bt$, was obtained using the *polyfit* procedure, while the exponential function, $IBI(t) = A + B \exp(Ct)$, was fitted using the *fminsearch* procedure in Matlab.

The postictal period

An additional model prediction concerned the postictal period which is characterized by reduced excitability and firing. As shown in Fig. 2A–C, after the termination of a seizure there was an approximate 30- to 50-second period during which firing was either absent or reduced with respect to the interictal period. The exact duration of the postictal period was difficult to assess, as the gap in firing after the SLE was dependent on background fluctuations. To directly investigate the network excitability, we analyzed the responsiveness of the model to external periodic stimulation (see Boido et al. (2014)). The background noise was removed and was compensated with a steady depolarizing current, as in Fig. 6. Stimulation was delivered by activating the excitatory synapses every 5 seconds at each PY soma (arrows in Fig. 7B). The amplitude of the excitatory postsynaptic current (EPSC) was set at just above the threshold for triggering the spike in the interictal period (before the timestamp at 60 seconds). The external stimulation triggered two burst responses after the SLE termination (Fig. 7, vertical broke line) and failed to trigger a suprathreshold response for approximately 40 seconds afterwards. In line with the PY response pattern, no response to the simulated stimulation was observed in the LFP signal during the postictal suppression period (Fig. 7A). The high excitability immediately after termination of the SLE (timestamps between seconds 110 and 120) was correlated with elevated $[K^+]_o$ which was present shortly after the SLE (Fig. 7C). The subsequent postictal reduction of excitability was associated with decay of $[K^+]_o$ and an increased hyperpolarizing Na^+/K^+ -pump current that decayed with a slower time constant associated with a gradual clearance of $[Na^+]_i$ by the pump (Fig. 7D).

Figure 7. An analysis of network excitability in the postictal period. In this figure, the background input was removed from the simulation and compensated with a small depolarizing current injected into the PY cells, as in Fig. 6. **(A)** The LFP signal. **(B)** The PY cell membrane potential with external periodic stimulation delivered every 5 seconds, marked by the arrows. The amplitude of the stimulation was set at just above the threshold for triggering a spike in the interictal period. **(C)** The extracellular potassium in the somatic compartment. **(D)** The net Na^+/K^+ -pump current in the somatic compartment. The vertical broken line in all panels marks the SLE offset time without periodic stimulation. Immediately after termination of the SLE, the network was still excitable due to increased $[\text{K}^+]_o$. Shortly afterward, the excitability decreased due to an increased Na^+/K^+ -pump current that outlasted the increase in $[\text{K}^+]_o$. Increased I_{pump} and decreased $[\text{K}^+]_o$ which occurred shortly after the termination of the SLE, led to a postictal period during which the network did not respond to external stimulation for approximately 40 seconds.

Discussion

The present study aimed to better define the mechanisms underlying focal seizures. The ictal pattern most frequently observed in human and experimental TLE, i.e., the LVF onset pattern, exhibits a stereotypical sequence of fast activity, irregular spiking and periodic bursting (as shown in Fig. 3A, first panel) (Avoli et al., 2016; de Curtis & Avoli, 2016; Devinsky et al., 2018; Velasco et al., 2000). We successfully reproduced this pattern in the computer model by

transiently increasing the firing of the IN. After this trigger, the simulated SLE phases evolved autonomously. Our study suggests that various seizure phases and transitions from one phase to another are mediated by feedback mechanisms between neuronal activities, ion concentration changes and ion homeostasis processes. The distinct mechanisms that shape the activities at various seizure stages are discussed below.

Seizure initiation

There is increasing evidence showing that seizures with LVF onset are initiated by discharges of fast-spiking GABAergic interneurons (de Curtis & Avoli, 2016; de Curtis & Gnatkovsky, 2009; Devinsky et al., 2018). Intracellular chloride accumulation and the elevation of $[K^+]_o$ due to interneuron activity leads to subsequent depolarization of PY cells and seizure development. Increased interneuron discharges and decreased PY activity around the time of seizure onset were first evidenced in *in vitro* and *in vivo* animal models (Gnatkovsky et al., 2008; Grasse et al., 2013; Lévesque et al., 2016; Lopantsev & Avoli, 1998; Miri et al., 2018; Toyoda et al., 2015; Ziburkus et al., 2006). A similar scenario was observed with single-unit recordings performed during intracerebral presurgical monitoring in neocortical and temporal lobe epilepsy patients (Elahian et al., 2018; Truccolo et al., 2011). The hypothesis that seizure initiation is related to an elevation in $[K^+]_o$ caused by a strong initial discharge has been tested in computational models with ion concentration changes. In these simulations, seizure-like activity has been induced by DC stimulation of the PY cells alone (Bazhenov et al., 2004; Buchin et al., 2016; Kager et al., 2002), by a brief increase in $[K^+]_o$ (Fröhlich et al., 2006), by stimulation of the IN and PY cells (Ho & Truccolo, 2016) or by varying the extracellular concentration of K^+ and O_2 . (Wei et al., 2014) The initial *in silico* tests on seizure initiation by selective involvement of fast-spiking interneurons were conducted earlier by us (Gentiletti et al., 2017) and others (González et al., 2018). We demonstrated that an increase in interneuron firing triggered a transition to a self-sustained SLE. González et al. (2018) showed that interneuron stimulation by current pulses led to the development of an SLE via a gradual increase in $[K^+]_o$ mediated by Cl^- -dependent activation of the KCC2 cotransporter. In our present model, the IN was activated by a depolarizing, decreasing current ramp of 30 seconds. Initially, the IN discharge led to the silencing of the PY cells, which was correlated with low amplitude fast activity in the LFP signal. The sustained interneuron activity caused a gradual increase in $[Cl^-]_i$ and $[K^+]_o$ in the PY cells. The increase in $[K^+]_o$ produced a positive shift in the K^+ reversal potential which led to a reduction in the K^+ leak current and membrane depolarization. The accumulation of $[Cl^-]_i$

increased the Cl^- reversal potential and decreased the driving force of the Cl^- ions, which led to a reduction in GABA_A IPSC and the Cl^- leak current. A depolarization in the E_K , E_{Cl} and E_{GABA_A} , and a weakening of the associated hyperpolarizing currents resulted in a gradual depolarization of the PY cells and sustained firing, which was correlated with the tonic SLE phase.

To address the role of potassium and chloride accumulation in seizure initiation, we considered the elevation of $[\text{K}^+]_o$ and $[\text{Cl}^-]_i$ separately. As shown in Fig. 5, a selective increase in $[\text{K}^+]_o$ with a fixed concentration of Cl^- did not trigger an SLE. The same result was observed when $[\text{Cl}^-]_i$ was increased and the concentration of $[\text{K}^+]_{o,i}$ remained fixed (not shown). This suggests that in our model, a change in the concentrations of either $[\text{K}^+]_o$ or $[\text{Cl}^-]_i$ was not sufficient to initiate an SLE and that an increase in both is necessary. These findings corroborate the results of a study by Alfonsa et al. (2015) which demonstrated that optogenetic chloride loading of PY cells did not trigger ictal events, while the addition of a subictal dose of 4-aminopyridine (4-AP) led to full ictal activity.

The observation that the development of seizures may be related to an increase in $[\text{K}^+]_o$ beyond the physiological values suggests that the modulation of $[\text{K}^+]_o$ by the use of K^+ chelators is a potential strategy for the control of seizures. Moreover, in our previous work, we demonstrated that an artificial potassium buffer, which mimicked the function of astrocytes by balancing neuronal K^+ release, could reduce neuronal excitability and prevent an SLE (Suffczynski et al., 2017).

The mechanisms of $[\text{K}^+]_o$ accumulation

A question arises: what causes $[\text{K}^+]_o$ accumulation? The buildup of Cl^- inside the PY neurons during interneuron-induced GABA release results in the activation of the KCC2 cotransporter, which extrudes Cl^- and K^+ into the extracellular space. This hypothesis is supported by *in vitro* experiments which showed that activation of GABA_A receptors led to an increase in $[\text{K}^+]_o$ and cell depolarization, which were eliminated by the KCC2 inhibitor, furosemide (Viitanen et al., 2010). The above-mentioned hypothesis is also consistent with the findings that the application of the KCC2 blockers VU0240551 and bumetanide prevented SLEs during 4-AP application in rat brain slices (Hamidi & Avoli, 2015). However, it is not clear whether the ictal activity is consistently based on K^+ efflux through KCC2. In the pilocarpine model, the enhancement of KCC2 in principal cortical neurons is associated with a reduction in seizure duration (Magloire et al., 2019). Based on these results, the authors suggested that KCC2 activity does not affect

seizure initiation, but influences seizure maintenance during a prolonged period of Cl^- accumulation. The antiepileptic role of enhanced KCC2 activity has also been suggested by Moore et al. (2018), who showed that KCC2 potentiation delayed the onset of an SLE after 4-AP application *in vitro* and reduced the severity of kainate-induced seizures *in vivo*. When considering the role of KCC2 in $[\text{K}^+]_o$ accumulation, it is necessary to note that the direction and magnitude of KCC2 transport depend on the concentration gradients of Cl^- and K^+ (Kaila et al., 2014). Under normal conditions, when $[\text{K}^+]_o$ is sufficiently controlled by homeostatic mechanisms, GABAergic activity leads to the extrusion of Cl^- and K^+ . However, an increase in $[\text{K}^+]_o$ may reverse the K^+-Cl^- cotransport, thus contributing to $[\text{K}^+]_o$ buffering rather than accumulation (Payne, 1997; Thompson & Gahwiler, 1989). The activation of IN in our model led to a rapid increase in K^+ in the narrow extracellular interstitial compartments, while intracellular Cl^- accumulation was more gradual (Fig. 2). This generated an influx of K^+ and Cl^- via KCC2 (Fig. 5B), which led to $[\text{K}^+]_o$ buffering and $[\text{Cl}^-]_i$ accumulation. The exclusion of KCC2 involvement in the increase in $[\text{K}^+]_o$ suggests that the primary mechanism of $[\text{K}^+]_o$ accumulation in our model was due to other processes, such as the outward K^+ current that repolarizes action potentials in activated IN and PY cells. This observation is consistent with *in vivo* experimental evidence that showed a significant local $[\text{K}^+]_o$ rise due to increased spiking activity following electrical stimulation of the cat cerebral cortex (Heinemann & Lux, 1975).

The tonic-to-bursting transition

Potassium ions released by interneuron discharges initially diffused to the somatic extracellular compartments of the PY cells and contributed to PY soma depolarization and tonic firing, as described above. Subsequently, K^+ diffusion from the somatic to dendritic compartments promoted regenerative dendritic spikes in PY cells (Fig. 2D). High $[\text{K}^+]_o$ in the soma and dendrites favored burst firing (Supplementary Fig. S1) through the reduction of repolarizing K^+ currents, the activation of a Na^+ persistent current, and a shift from spike after-hyperpolarization toward depolarizing after-potentials. Prolonged depolarization led to the activation of slow M-type K^+ conductance (Supplementary Fig. S2), which hyperpolarized the PY cells after a series of fast spikes. The bursting mechanism in our model originated from currents used in the original entorhinal cortex cells model (Fransen et al., 2002) and was similar to the mechanism in CA1 neurons (Golomb et al., 2006).

Seizure termination

Various mechanisms underlying seizure termination have been suggested (Lado & Moshé, 2008; Zubler et al., 2014), however, researchers have not yet reached a consensus regarding which one plays a dominant role. In our model, the SLE terminated spontaneously. Following the fast-slow analysis approach (Fröhlich et al., 2006) we created a simplified model in which $[K^+]_{o,soma}$, $[K^+]_{o,dend}$ and $[Na^+]_i$ were treated as control parameters. Hence, the influence of neuronal activity on ionic variations was removed and the dependence of network activity on K^+ and Na^+ concentrations was analyzed (Fig. 4A). When the time course of the concentration changes of these two ions were tuned to reproduce the decrease in $[K^+]_o$ and increased level of $[Na^+]_i$ observed in the late SLE phase, the ictal activity spontaneously terminated (Fig. 4B). This indicates that SLE cessation in the model can be explained by two coincident factors, namely the decrease in $[K^+]_o$ during stable levels of increased $[Na^+]_i$. An increase in $[Na^+]_i$ led to an increased hyperpolarizing Na^+/K^+ -pump current, which increased the firing threshold in the neurons. The increased pump activity also contributed to a progressive decrease in $[K^+]_o$. Potassium repolarization currents increased after each burst and eventually prevented the initiation of a new cycle of the oscillation. The idea that negative feedback between $[Na^+]_i$ accumulation and neuronal firing is responsible for seizure termination was first formulated by Jensen & Yaari (1997). Even though it has not been tested experimentally, this hypothesis is consistent with the observation that the inhibition of Na^+/K^+ -pump activity occurring during hypoxia prolongs SLE discharges in hippocampal slices with blocked synaptic transmission (Haas & Jefferys, 1984). It was also observed that a decrease in Na^+ channel conductance via the antiepileptic drug phenytoin, increased the seizure threshold but prolonged the afterdischarges and seizure durations in the rat kindling model of epilepsy (Ebert et al., 1997). In the computational model developed by the Bazhenov team (Krishnan et al., 2015; Krishnan & Bazhenov, 2011) and Chizhov et al. (2018), a progressive increase in $[Na^+]_i$ and activation of the electrogenic Na^+/K^+ -pump were identified as the primary factor of SLE termination. The seizure termination mechanism in the above-mentioned studies is similar to the mechanism observed in the present study, even though different specifications of neuronal mechanisms, network characteristics and seizure morphologies were used.

It should be also noted that activation of the Na^+/K^+ -pump by $[Na^+]_i$ is not the only proposed mechanism of seizure termination. An alternative mechanism, also linked to an increase in $[Na^+]_i$, is dependent on the Na^+ -activated K^+ channels (Igelström, 2013). Moreover,

many other mechanisms such as acidosis (Ziemann et al., 2008), the upregulation of inhibitory neurons (Wen et al., 2015), glutamate depletion (Lado & Moshé, 2008), the depolarization block of neurons mediated by K^+ release from astrocytes (Bragin et al., 1997), after-hyperpolarization due to K^+ channels (Timofeev & Steriade, 2004), postburst depression (Boido et al., 2014), increased synchrony (Schindler et al., 2007) and the release of adenosine (During & Spencer, 1992; Uva & de Curtis, 2020) have been suggested to play a role in seizure termination. The abrupt termination of a seizure across the entire brain requires long-range communication which may involve thalamocortical interactions (Aracri et al., 2018; Evangelista et al., 2015), travelling waves (Martinet et al., 2017; Proix et al., 2018) and ephaptic interactions (Jefferys, 1995; Shivacharan et al., 2019). Multiple neuromodulatory, ionic, synaptic and neuronal components likely cooperate to terminate a seizure. Further insight into these mechanisms may be obtained by their selective blockage (Uva & de Curtis, 2020), the tracking of EEG signal changes as seizure offset approaches (Boido et al., 2014; Saggio et al., 2020) and from analysis of the duration of postictal suppression (Payne et al., 2018).

Frequency Slowing

The approach of seizure termination is often (but not always) accompanied by an increase in the intervals between successive bursts that form the late seizure phase. Saggio et al. (2020) analyzed frequency slowing in human focal onset seizures and estimated that approximately 40% exhibited unequivocal discharge slowing down toward the end. Burst frequency slowing was confirmed in a study on the entorhinal cortex of the isolated brain preparation during bicuculline- and 4AP-induced SLE (Boido et al., 2014). Our model prediction of the exponential increase in the IBI toward the SLE offset (Fig. 6A) was confirmed with experimental data (Fig. 6BC). These findings are also consistent with those of Bauer et al. (2017), which demonstrated that inter-burst intervals in focal epilepsy patients were predominantly described by the exponential scaling law. Conversely, it has been suggested that depending on the bifurcation which leads to seizure termination, the burst oscillation frequency can be constant or decrease according to the logarithmic or square root relationship (Jirsa et al., 2014). The IBI scaling law depends on the slow process leading to seizure termination. In our model, termination of the seizure was related to the slow evolution of ion concentrations which led to a progressive decrease in excitability, primarily via an increased Na^+/K^+ -pump rate. The lower the excitability, the more time it took for the burst firing threshold to be reached. Hence, bursts frequency slowing in the model was causally related to variations in ion concentrations. If the time course of the ionic concentrations

were different, the evolution of the IBI would also shift. Several alternative explanations for the increasing inter-burst intervals have been proposed. Bauer et al. (2017) included a plasticity parameter that progressively decoupled spatially distributed neural mass units based on the synchrony level. This mechanism accounted for seizure termination, exponential IBI increase and the presence of a transient postictal state. In the model of Liou et al. (2020) the IBI was constant during seizure expansion and only when the spatial propagation of ictal discharge ceased, the seizure entered the pre-termination stage with a slowing-down trend. An increase in the IBI in this phase was related to the recovery of inhibition and restoration of the Cl^- concentration gradient. These studies indicate that spatial properties related to seizure propagation and synchrony are other factors that may affect the evolution of the IBI.

The postictal period

Seizures are followed by the suppression of physiological rhythms known as postictal EEG suppression (PES) that lasts for seconds or minutes (Pottkämper et al., 2020). Using the stimulation protocol, we investigated the duration of PES in the model. Our results showed that shortly after termination of the SLE, burst responses were still triggered, however, after few seconds, the excitability decreased and remained reduced for approximately 40 seconds (Fig. 7B). This postictal reduction in excitability was associated with subsequent decay of $[\text{K}^+]_o$ and an increased hyperpolarizing Na^+/K^+ -pump current, which decreased gradually due to slow clearance of $[\text{Na}^+]_i$ by the pump (Fig. 7D). The PES duration in our model is consistent with single-unit recordings in epileptic patients that are suppressed for 5 to 30 seconds after seizure termination (Truccolo et al., 2011). Our *in silico*-derived prediction that postictal ‘silence’ depends on the hyperpolarizing Na^+/K^+ -pump has been previously suggested (Fisher & Schachter, 2000) and simulated (Krishnan et al., 2015; Krishnan & Bazhenov, 2011). However, in these models, an increased Na^+/K^+ -pump rate due to elevated $[\text{Na}^+]_i$ terminated the SLE and reduced $[\text{K}^+]_o$ to below baseline level, resulting in a postictal state via a negative shift in E_K and membrane hyperpolarization. A below-reference value of $[\text{K}^+]_o$ was observed after seizure termination (Heinemann et al., 1977) and may lead to decreased excitability. In our model, the postictal state was not associated with $[\text{K}^+]_o$ undershoot, as it decayed to baseline level within a few seconds after the SLE offset (Fig. 7C). This was also observed in several previous studies (Fisher et al., 1976; Futamachi et al., 1974). The findings generated by our computational model suggest that the mechanisms of seizure termination and PES involve ion homeostatic processes

activated and sustained by the excessive seizure discharges, eventually leading to the cessation of the seizure and restoration of the normal state.

Methods

Geometry

The cell morphology was based on entorhinal cortex PY cells and an interneuron model (Fransen et al., 2002), further reduced to equivalent cylinder models. The PY consisted of two compartments: a soma with a length of 20 μm and a diameter of 15 μm , and a dendrite with a length of 450 μm and a diameter of 6.88 μm . The interneuron only had a somatic compartment with a length of 20 μm and a diameter of 15 μm . Each compartment was surrounded by its own extracellular space (ECS). The extracellular compartments were embedded in a common bathing medium which represented the surrounding neural tissue and vasculature. The size of the ECS was estimated by the extracellular volume fraction, α defined as the ratio volume of extracellular space/volume of tissue. We used $\alpha = 0.131$ which corresponded to the CA1 *st. pyramidale* and a K^+ concentration of 3.5 mM (McBain et al., 1990).

Biophysics

The active membrane currents in the PY were the fast Na^+ and K^+ currents (I_{Na} and I_{Kdr} , respectively) in both compartments and were responsible for action potential generation; a persistent Na^+ current, I_{NaP} in the soma; a high-threshold Ca^{2+} current, I_{CaL} in both compartments; a calcium-dependent after-hyperpolarization K^+ current, I_{KAHP} in both compartments; a fast calcium- and voltage-dependent K^+ current, I_{KC} in both compartments; and a noninactivating muscarinic K^+ current, I_{KM} in the soma. The IN included only the I_{Na} and I_{Kdr} currents responsible for spike generation. All the equations for the active currents were initially based on those described by Fransen et al. (2002), however, an additional modification of the parameters described below was required to account for ionic regulation mechanisms. Simulations were performed using the NEURON simulator with a fixed integration step of 0.05 ms.

Passive properties

The reversal potentials were obtained via the Nernst equation:

$$E_X = 2.3 \frac{RT}{zF} \log \left(\frac{[X]_o}{[X]_i} \right)$$

where $[X]_i$ and $[X]_o$ are intra- and extracellular concentrations, respectively, of the ions. $X = \{Na^+, K^+, Ca^{2+}, Cl^-\}$, F is the Faraday constant, R is the gas constant, z is the valence of the ions and $T = 273,16 + 32$ is the absolute temperature (Gnatkovsky et al., 2008). A leak current, I_{leak} , was present in all compartments of both cells and was a sum of the leak currents of Na^+ , K^+ and Cl^- , modelled as:

$$I_{i,leak} = g_{i,leak}(V - E_i)$$

where $g_{i,leak}$ is the leak current conductance of the ion of interest $i = \{Na^+, K^+, Cl^-\}$. The resting membrane potential was -62 mV in the pyramidal cell and -70 mV in the interneuron. The specific axial resistance in both cells was set to $R_a = 100 \text{ Ohm*cm}$ and the specific membrane capacitance was set to $C_m = 1 \mu\text{F/cm}^2$, as in Fransen et al. (2002). Based on the R_a and PY cell geometry, the somato-dendritic coupling conductance, g_c , was calculated as 1.5 mS.

Active currents

The original equations used time constant units in seconds (s) and voltage units in volts (V), with 0 V corresponding to the resting membrane potential. All equations were modified to account for the millivolt (mV) and millisecond (ms) units used in our model and the voltage was shifted by -60 mV to correspond to the membrane potential relative to the extracellular space, which was assumed to be 0 mV. Additional modifications of the parameters were required to account for the ionic regulation mechanisms that were not present in the original model. I_{NaP} : the activation gate exponent was 2 and the inactivation gate time constant, τ_h , was estimated by fitting the activation function form described by Fransen et al. (2002) to the experimental data (Magistretti & Alonso, 1999). I_{Kdr} : the steady-state activation function, n_{inf} , and the activation gate time constant, τ_n , were estimated by empirical fit to the experimental data (Sah et al., 1988). To increase the firing threshold, the activation curve was shifted toward positive potentials by 16 mV in the soma and 7 mV in the dendrites. The model generated spontaneous fast spiking otherwise. I_{KAHP} , I_{KC} : these Ca^{2+} -dependent currents were modelled according to the model described by Traub et al. (2003) and were implemented in ModelDB (<https://senselab.med.yale.edu/ModelDB/>), accession number 20756. Due to the arbitrary units for Ca^{2+} concentration in Traub's model, we modified the current formula to correspond to mM units and resting level of $[Ca^{2+}]_i$ used in our model. In pyramidal cells, the soma and dendrite

membrane potentials, V_s and V_d , respectively, were governed by the following Hodgkin-Huxley equations:

$$C \frac{dV_s}{dt} = -I_{Na,soma} - I_{NaP} - I_{Kdr,soma} - I_{CaL} - I_{KAHP} - I_{KC} - I_{KM} - I_{leak} - I_{NaKpump} - I_{Capump} - g_c(V_s - V_d) - I_{syn}$$

$$C \frac{dV_d}{dt} = -I_{Na,dend} - I_{Kdr,dend} - I_{CaL} - I_{KAHP} - I_{KC} - I_{NaKpump} - I_{CaPump} - g_c(V_d - V_s) - I_{syn}$$

Transient sodium current

$$I_{Na,soma} = g_{Na,PYsoma} m^3 h (V - E_{Na})$$

$$I_{Na,dend} = g_{Na,PYdend} m^2 h (V - E_{Na})$$

Persistent sodium current:

$$I_{NaP} = g_{NaP} m^2 h (V - E_{Na})$$

Delayed rectifier:

$$I_{Kdr,soma} = g_{Kdr,PYsoma} n^4 (V - E_K)$$

$$I_{Kdr,dend} = g_{Kdr,PYdend} n^2 (V - E_K)$$

High-threshold Ca^{2+} current:

$$I_{CaL} = g_{CaL} m^2 (V - E_{Ca})$$

Ca^{2+} -dependent K^+ (afterhyperpolarization) current:

$$I_{KAHP} = g_{KAHP} m (V - E_K)$$

Fast Ca^{2+} - and voltage-dependent K^+ current

$$I_{KC} = g_{KC} \min([Ca^{2+}]_i/250, 1) m (V - E_K)$$

Muscarinic current:

$$I_{KM} = g_{KM} m (V - E_K)$$

Equations of gating variables are given in Table 1. Conductance values are given in Table 2.

Table 1. Gating variables of the ionic currents in pyramidal cell model

Current	Kinetics/time constant (ms)	
$I_{Na,soma}$	$\alpha_m = \frac{0.8(-V - 40.8)}{\exp\left(\frac{-V - 40.8}{4}\right) - 1}$	$\beta_m = \frac{0.7(V - 15.8)}{\exp\left(\frac{V - 15.8}{5}\right) - 1}$
	$\alpha_h = 0.32 \exp\left(\frac{-V - 18}{18}\right)$	$\beta_h = \frac{10}{\exp\left(\frac{-V - 18}{5}\right) + 1}$
$I_{Na,dendrite}$	$\alpha_m = \frac{0.32(-V - 50.9)}{\exp\left(\frac{-V - 50.9}{4}\right) - 1}$	$\beta_m = \frac{0.28(V - 15.9)}{\exp\left(\frac{V - 15.9}{5}\right) - 1}$

	$\alpha_h = 0.128 \exp\left(\frac{-V-45}{18}\right)$	$\beta_h = \frac{10}{\exp\left(\frac{-V-22}{5}\right) + 1}$
I_{NaP}	$m_\infty = \frac{1}{1 + \exp\left(\frac{-48.7 - V}{4.4}\right)}$	$\tau_m = \frac{1}{\frac{0.091(V+38)}{1 - \exp\left(\frac{-V-38}{5}\right)} - \frac{0.062(V+38)}{1 - \exp\left(\frac{V+38}{5}\right)}}$
	$h_\infty = \frac{1}{1 + \exp\left(\frac{48.8 + V}{9.98}\right)}$	if $V_m \leq -60$: $\tau_m = 3700 + \frac{2000}{\frac{0.091(V+60)}{1 - \exp\left(\frac{-V-60}{5}\right)} - \frac{0.062(V+60)}{1 - \exp\left(\frac{V+60}{5}\right)}}$ if $V_m > -60$: $\tau_m = 1200 + \frac{8000}{\frac{0.091(V+74)}{1 - \exp\left(\frac{-V-74}{5}\right)} - \frac{0.062(V+74)}{1 - \exp\left(\frac{V+74}{5}\right)}}$
$I_{Kdr,soma}$	$n_\infty = \frac{1}{1 + \exp\left(\frac{-20.8 - V}{13.6}\right)}$	$\tau_m = \frac{1.6(C + \exp(\frac{V}{5}))}{D \exp(-\frac{V}{40})(C + \exp(\frac{V}{5})) + 0.016 \exp(\frac{V}{5})(64.9 + V)}$ $C = -0.00000230599$; $D = 0.0338338$
$I_{Kdr,dend}$	$n_\infty = \frac{1}{1 + \exp\left(\frac{-11.8 - V}{13.6}\right)}$	$\tau_m = \frac{1.6(C + \exp(\frac{V}{5}))}{D \exp(-\frac{V}{40})(C + \exp(\frac{V}{5})) + 0.016 \exp(\frac{V}{5})(64.9 + V)}$ $C = -0.00000230599$; $D = 0.0338338$
I_{CaL}	$\alpha_m = \frac{1.6}{1 + \exp(-0.072(V-5))}$	$\beta_m = \frac{0.02(V+8.9)}{\exp\left(\frac{V+8.9}{5}\right) - 1}$
I_{KAHP}	$\alpha_m = 2000([Ca]_i - [Ca]_{i,rest})$	$\beta_m = 0.01$
I_{KC} , if $V_m \leq -10$	$\alpha_m = \frac{\exp\left(\frac{V+50}{11} - \frac{V+53.5}{27}\right)}{18.975}$	$\beta_m = 2 \exp\left(-\frac{V+53.5}{27}\right) - \alpha_m$
I_{KC} , if $V_m > -10$	$\alpha_m = 2 \exp\left(-\frac{V+53.5}{27}\right)$	$\beta_m = 0$
I_{KM}	$m_\infty = \frac{1}{1 + \exp\left(-\frac{V+35}{5}\right)}$	$\tau_m = \frac{1000}{3.3[\exp(\frac{V+35}{40})] + [\exp(-\frac{V+35}{20})]}$

667
668 Membrane potential of the interneuron was governed by the following Hodgkin-Huxley
669 equations:

670
$$C \frac{dV}{dt} = -I_{Na} - I_{Kdr} - I_{leak} - I_{NaKpump} - I_{syn} - I_{stim}$$

671 Current equations, kinetics and time constants of these currents were the same as in pyramidal
672 cell soma. Due to lower resting membrane potential in the interneuron as compared to pyramidal
673 cell, activation curve of I_{Na} was shifted 2 mV towards more negative potential values, while
674 activation curve of I_{Kdr} was shifted 14 mV towards more negative potential values.

675 Table2. Conductances used in the model

Current conductance	Description	Values (mS/cm ²)
$g_{Na,leak,PY}$	$I_{Na,leak}$ conductance in PY soma and dendrite	$0.9 \cdot 10^{-5}$
$g_{K,leak,PY}$	$I_{K,leak}$ conductance in PY soma and dendrite	$2.2 \cdot 10^{-5}$
$g_{Cl,leak,PY}$	$I_{Cl,leak}$ conductance in PY soma and dendrite	$1 \cdot 10^{-6}$
$g_{Na,PYsoma}$	I_{Na} conductance in PY soma	0.02
$g_{Na,PYdend}$	I_{Na} conductance in PY dendrite	0.002
$g_{Kdr,PYsoma}$	I_{Kdr} conductance in PY soma	0.03
$g_{Kdr,PYdend}$	I_{Kdr} conductance in PY dendrite	0.0035
g_{NaP}	I_{NaP} conductance in PY soma	$60 \cdot 10^{-5}$
g_{CaL}	I_{CaL} conductance in PY soma and dendrite	$15 \cdot 10^{-5}$
g_{KAHP}	I_{KAHP} conductance in PY soma and dendrite	$5 \cdot 10^{-5}$
g_{KC}	I_{KC} conductance in PY soma and dendrite	$0.196 \cdot 1e3$
g_{KM}	I_{KM} conductance in PY soma	0.007
$g_{Na,leak,IN}$	$I_{Na,leak}$ conductance in IN	$0.8 \cdot 10^{-5}$
$g_{K,leak,IN}$	$I_{K,leak}$ conductance in IN	$2.2 \cdot 10^{-5}$
$g_{Cl,leak,IN}$	$I_{Cl,leak}$ conductance in IN	$5 \cdot 10^{-6}$
$g_{Na,IN}$	I_{Na} conductance in IN	0.025
$g_{Kdr,IN}$	I_{Kdr} conductance in IN	0.055

676

677

678 Ionic dynamics

679 The model included six types of ions (K^+ , Na^+ , Cl^- , Ca^{2+} , A^- and HCO_3^-) with variable intra- and
680 extracellular concentrations (except for HCO_3^-). The evolution of the ion concentrations was
681 based on the following equations:

$$682 \quad \frac{d[K^+]_i}{dt} = J_K^i + J_{K,longitudinal}^i + J_{K,KCC2}^i + J_{K,Pump}^i + J_{K,vol}^i$$

$$683 \quad \frac{d[K^+]_o}{dt} = J_K^o + J_{K,radial} + J_{K,longitudinal}^o + J_{K,bath} + J_{K,KCC2}^o + J_{K,Pump}^o + J_{glia} + J_{K,vol}^o$$

$$\begin{aligned}
 684 \quad & \frac{d[Na^+]_i}{dt} = J_{Na}^i + J_{Na,longitudinal}^i + J_{Na,Pump}^i + J_{Na,vol}^i \\
 685 \quad & \frac{d[Na^+]_o}{dt} = J_{Na}^o + J_{Na,radial} + J_{Na,longitudinal}^o + J_{Na,bath} + J_{Na,Pump}^o + J_{Na,vol}^o \\
 686 \quad & \frac{d[Cl^-]_i}{dt} = J_{Cl}^i + J_{Cl,GABAA}^i + J_{Cl,longitudinal}^i + J_{Cl,KCC2}^i + J_{Cl,vol}^i \\
 687 \quad & \frac{d[Cl^-]_o}{dt} = J_{Cl}^o + J_{Cl,GABAA}^o + J_{Cl,longitudinal}^o + J_{Cl,bath} + J_{Cl,KCC2}^o + J_{Cl,vol}^o \\
 688 \quad & \frac{d[Ca^{2+}]_{i,tot}}{dt} = J_{Ca}^i + J_{Ca,longitudinal}^i + J_{CaPump}^i + J_{Ca,vol}^i \\
 689 \quad & \frac{d[Ca^{2+}]_o}{dt} = J_{Ca}^o + J_{Ca,longitudinal}^o + J_{CaPump}^o + J_{Ca,vol}^o \\
 690 \quad & \frac{d[A^-]_i}{dt} = J_{A,vol}^i
 \end{aligned}$$

691 where $[Ca^{2+}]_{i,tot}$ is the total intracellular calcium concentration (see calcium buffer below). All
 692 fluxes (mM/ms) are specified below.

693

694 *Membrane currents*

695 The contribution of transmembrane currents to variations in intra- and extracellular ion
 696 concentrations was obtained via the following equations:

$$\begin{aligned}
 697 \quad & J_X^i = -\frac{\sum I_X S}{zFV_i} \\
 698 \quad & J_X^o = \frac{\sum I_X S}{zFV_o}
 \end{aligned}$$

699 where the sum of I_X is a net membrane current carrying ion X , S is the surface area of the
 700 compartment, z is the valence of the ions, F is the Faraday constant and V_i and V_o are the volumes
 701 of the intra- and extracellular compartments.

702

703 *Longitudinal diffusion.*

704 Longitudinal diffusion of K^+ , Na^+ , Ca^{2+} and Cl^- was implemented between the somatic and
 705 dendritic compartments in the intracellular and extracellular space of the same cell. It was
 706 described by Fick's first law:

$$707 \quad J_{X,longitudinal}^{io} = D_x \frac{([X]_{io,a} - [X]_{io})S}{LV_{io}}$$

708 where D_x is the diffusion coefficient for the ion X , $[X]_{io}$ is the ion concentration in a given intra-
 709 or extracellular compartment, $[X]_{oi,a}$ is the ion concentration in the adjacent compartment, S is

the cross-sectional area between the compartments, V_{io} is the compartment volume, L is the distance between the centers of the compartments. The diffusion coefficients were (in $\mu\text{m}^2/\text{ms}$): $D_{Na} = 1.33$, $D_K = 1.96$, $D_{Ca} = 0.6$, $D_{Cl} = 2.03$ (as in Somjen et al., 2008).

Radial diffusion.

Na^+ and K^+ ions diffused radially between adjacent extracellular compartments modeled as concentric shells around the neurons. The radial exchange of ions between adjacent shells was described by Fick's first law:

$$J_{X,radial} = D_x \frac{\sum ([X]_{o,a} - [X]_o) S}{drV}$$

where $[X]_o$ is the ion concentration in a given shell and the sum goes over all adjacent shells having concentrations $[X]_{o,a}$, V is a given shell volume, dr is the distance between the centers of the shells and S is the surface contact area between the shells calculated at 16% of the total outer shell surface. The electrostatic drift of ions was neglected as the ion movement due to the electrical potential gradient in the extracellular space was small compared to the diffusion.

Diffusion to/from the bath

Radial diffusion of K^+ , Na^+ and Cl^- between the ECS and the bath was described by Fick's first law:

$$J_{X,bath} = \frac{1}{s} D_x \frac{([X]_{bath} - [X]_o) S}{drV}$$

where D_x is the diffusion coefficient for the ion X , s is the scaling constant, S is the outer surface of the shell, $[X]_{bath}$ is the bath concentration of the ion X , $[X]_o$ is the ion concentration in a given shell, V is the shell volume, dr is the distance between the extracellular space and the bath (assumed to be half of the shell thickness). Flux J_{bath} represents various processes such as diffusion to more distant areas of the brain and cerebrospinal fluid, active transport of potassium into capillaries and potassium spatial buffering by astrocytes. The effective time constant of these joint processes is likely to be much slower than that of radial and longitudinal diffusion and is described by the scaling constant $s = 4 \times 10^4$.

The Na^+/K^+ pump

The Na^+/K^+ pump was modelled as the sodium and potassium transmembrane currents (Kager et al., 2000):

$$I_{Na,Pump} = 3I_{max}flux([Na^+]_i, [K^+]_o)$$

$$I_{K,Pump} = -2I_{max}flux([Na^+]_i, [K^+]_o)$$

$$flux([Na^+]_i, [K^+]_o) = \left(1 + \frac{Km_K}{[K^+]_o}\right)^{-2} \left(1 + \frac{Km_{Na}}{[Na^+]_o}\right)^{-3}$$

with $I_{max} = 0.008$ mA/cm², $Km_K = 2$ mM and $Km_{Na} = 10$ mM. As in the previous model, ion concentrations and membrane potentials at rest deviated slightly from the equilibrium conditions, with and without background excitatory synaptic input. This was due to the presence of the Na⁺/K⁺-pump glial buffer and ion diffusion, which cannot be balanced and induce small oscillations around the baseline values.

KCC2 cotransport

The KCC2 cotransporter currents were modelled according to Wei et al. (2014):

$$I_K = \gamma U_{KCC2} \log \left(\frac{[K^+]_i [Cl^-]_i}{[K^+]_o [Cl^-]_o} \right)$$

$$I_{Cl} = -I_K$$

with cotransporter strength, $U_{KCC2} = 0.3$ mM/s. Conversion factor $\gamma = (FV)/S$ from mM/s units to current density units mA/cm² was calculated for soma and dendrites based on the compartment surface area (S), intracellular volume (V_i) and the Faraday constant (F).

Glial uptake

Potassium uptake by the glia was modelled as a set of differential equations (Kager et al., 2000):

$$J_{glia} = -k_2[K^+]_o[B] + k_1[KB]$$

$$\frac{d[B]}{dt} = -k_2[K^+]_o[B] + k_1[KB]$$

$$\frac{d[KB]}{dt} = k_2[K^+]_o[B] - k_1[KB]$$

where $[B]$ is the free buffer, $[KB]$ is the bound buffer ($= [B]_{max} - [B]$), $B_{max} = 500$ mM. $k_1 = 0.0008$

ms⁻¹ and $k_2 = \frac{k_1}{1 + \exp\left(\frac{[K]_o - 18}{-1.25}\right)}$ are backward and forward rate constants, respectively.

The calcium pump and buffer

The calcium pump and buffer which altered the intracellular Ca²⁺ were modelled according to the model implementation of Somjen et al. (2008) in ModelDB, accession number 113446. The calcium pump which extruded Ca²⁺ from the cells was modelled as a Ca²⁺ transmembrane current:

771
$$I_{CaPump} = \frac{I_{max}}{1 + \frac{K_{pump}}{[Ca^{2+}]_i}}$$

772 with $I_{max} = 2.55 \text{ mA/cm}^2$ and $K_{pump} = 0.0069 \text{ mM}$. Intracellular Ca^{2+} was buffered by first-order
 773 chemical Ca^{2+} buffer with a total concentration of $[B]_i$ and an equilibrium constant of K_d .
 774 Calcium buffering was fast and under the assumption of equilibrium conditions, the relationship
 775 between the total and free intracellular calcium concentrations, $[Ca^{2+}]_{i,tot}$ and $[Ca^{2+}]_i$, was given
 776 by (Borgdorff, 2002, pg. 27):

777
$$[Ca^{2+}]_{i,tot} = [Ca^{2+}]_i \frac{[B]_i + K_d + [Ca^{2+}]_i}{K_d + [Ca^{2+}]_i}$$

778 where $[B]_i = 1.562 \text{ mM} \cdot (V_i^0/V_i)$, V_i is the intracellular compartment volume, V_i^0 is the
 779 intracellular compartment volume at rest and $K_d = 0.008 \text{ mM}$.

780
 781 *Volume changes*
 782 Volume changes were modelled according to Somjen et al. (2008). The rates of intra- and
 783 extracellular volume changes were proportional to the difference in osmotic pressure between
 784 the intra- and extracellular compartments and fulfilled the conservation of total volume.

785
$$\frac{dV_i}{dt} = \Delta$$

786
$$\frac{dV_o}{dt} = -\Delta$$

787 where

788
$$\Delta = \frac{c(\pi_i - \pi_o)}{\tau}$$

789
$$\pi_i = [Na^+]_i + [K^+]_i + [Cl^-]_i + [Ca^{2+}]_i + [HCO_3^-]_i + [A^-]_i$$

790
$$\pi_o = [Na^+]_o + [K^+]_o + [Cl^-]_o + [Ca^{2+}]_o + [HCO_3^-]_o + [A^-]_o$$

791 V_i and V_o are the volumes of the intra- and extracellular compartments and $\tau = 250 \text{ ms}$. The
 792 constant c is introduced for unit conversion and is equal to $1 \text{ um}^3/\text{mM}$, hence units of Δ are
 793 um^3/ms . The extracellular volume was initially 13.1% of the cellular volume and was allowed to
 794 shrink maximally down to 4%. Volume changes affected concentrations but not the total mass
 795 of each ion within a compartment. The conservation of mass required additional fluxes:

796 Intracellular

797
$$J_{X,vol}^i = -\frac{\Delta}{V_i} [X]_i$$

798 Extracellular

$$J_{X,vol}^o = \frac{\Delta}{V_o} [X]_o$$

Initial ion concentrations

The initial concentrations of $[Na^+]_i$, $[Ca^{2+}]_i$, $[Na^+]_o$, $[K^+]_o$, $[Ca^{2+}]_o$ and $[A^+]_o$ were based on Somjen et al. (2008), and the initial concentration of $[HCO_3^-]_i$ was based on Doyon et al. (2011). Chloride concentrations were set to satisfy the thermodynamic equilibrium of KCC2, i.e., $[Cl^-]_o = [K^+]_i$ and $[Cl^-]_i = [K^+]_o$ giving $E_{Cl} = E_K$. The remaining ions, i.e., $[K^+]_i$, $[A^+]_i$ and $[HCO_3^-]_o$ were solved to fulfil electroneutrality and osmotic equilibrium conditions. Hence, the initial concentrations were as follows (in mM): $[Na^+]_i = 10$, $[Na^+]_o = 140$, $[K^+]_o = 3.5$, $[Ca^{2+}]_i = 5e-5$, $[Ca^{2+}]_o = 2$, $[A^+]_o = 0$, $[HCO_3^-]_i = 15$, $[K^+]_i = 136.5$, $[A^+]_i = 128$, $[HCO_3^-]_o = 11$, $[Cl^-]_o = 3.5$ and $[Cl^-]_i = 136.5$.

Synaptic connections and model inputs

The pyramidal cells created excitatory AMPA synaptic connections with the interneuron and all other pyramidal cells. The interneuron created an inhibitory GABA_A synaptic connection with each pyramidal cell. Excitatory synapses were placed in the middle of the PY dendrite and the middle of the IN soma. Inhibitory synapses were placed in the middle of the PY soma. The time course of synaptic conductance was modelled with a built-in NEURON mechanism Exp2Syn, implementing a dual exponential function:

$$g = g_{max} \left[\exp\left(-\frac{t}{\tau_2}\right) - \exp\left(-\frac{t}{\tau_1}\right) \right]$$

where the rise and decay time constants, τ_1 and τ_2 , were 2 ms and 6 ms, respectively, for all synapses. $g_{max} = \text{weight} * \text{factor}$, where the factor was defined so that the normalized peak was 1. The weights for the synapses between the PY and from the PY to the IN were $w_{ee} = 0.0006 \mu S$ and $w_{ei} = 0.001 \mu S$, respectively. The inhibitory synaptic weight, w_{ie} , was $0.0003 \mu S$. All pyramidal cells received background input modelled as a Poisson spike train, which was different in each cell, activated an excitatory synapse at a rate of 5 Hz and had a synaptic weight $w_{input} = 0.0005 \mu S$. To initiate the SLE, a depolarizing ramp current, I_{inj} , was injected into the interneuron, with the initial amplitude of 0.8 nA linearly decreasing toward 0 over 30 seconds. The inhibitory GABA_A postsynaptic currents were carried by Cl^- and HCO_3^- ions. The receptor pore conducts Cl^- and HCO_3^- at a ratio of 4:1 (Voipio et al., 1991), hence, E_{GABA_A} was calculated as (Doyon et al., 2011):

$$E_{GABAa} = 2.3 \frac{RT}{F} \left(\frac{4[Cl^-]_i + [HCO_3^-]_i}{4[Cl^-]_o + [HCO_3^-]_o} \right)$$

HCO_3^- concentrations were assumed to be constant and equal to $[HCO_3^-]_i = 15$ mM and $[HCO_3^-]_o = 11$ mM.

Calculation of the LFP

The local field potentials were calculated based on all transmembrane currents in all cells using the following equation (Nunez & Srinivasan, 2006):

$$\phi(r, t) = \frac{1}{4\pi\sigma} \sum_{n=1}^N \frac{I_n(t)}{|r - r_n|}$$

Where I_n is a point current source at position r_n (taken as the position of a mid-point of a compartment) and r is the position of the electrode. $\sigma = 0.3$ S/m is the extracellular conductivity (Lindén et al., 2014). The electrode was located in the middle of the somatic layer of the PY and IN cells, approximately 16 μ m from the centers of the somas of two neighbouring PY cells. The currents from the interneuron were taken with a weight of 0.2 to decrease their contribution. Also, the influence of the injected current on the LFP was removed. The amplitude of the simulated LFP signal was an order of magnitude smaller than the experimental data. This was due to current point-source approximation and the small number of cells in the modeled network.

Software Accessibility

If accepted, the model will be publicly available in the ModelDB (<https://senselab.med.yale.edu/modeldb/>)

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Competing interests

The authors report no competing interests.

References

- Alfonsa, H., Merricks, E. M., Codadu, N. K., Cunningham, M. O., Deisseroth, K., Racca, C., & Trevelyan, A. J. (2015). The Contribution of Raised Intraneuronal Chloride to Epileptic Network Activity. *Journal of Neuroscience*, 35(20), 7715–7726. <https://doi.org/10.1523/JNEUROSCI.4105-14.2015>
- Aracri, P., de Curtis, M., Forcaia, G., & Uva, L. (2018). Enhanced thalamo-hippocampal synchronization during focal limbic seizures. *Epilepsia*, 59(9), 1774–1784. <https://doi.org/10.1111/epi.14521>
- Avoli, M., De Curtis, M., Gnatkovsky, V., Gotman, J., Köhling, R., Lévesque, M., Manseau, F., Shiri, Z., & Williams, S. (2016). Specific imbalance of excitatory/inhibitory signaling establishes seizure onset pattern in temporal lobe epilepsy. *Journal of Neurophysiology*, 115(6), 3229–3237. <https://doi.org/10.1152/jn.01128.2015>
- 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*, 140(3), 655–668. <https://doi.org/10.1093/brain/aww322>
- Bazhenov, M., Timofeev, I., Steriade, M., & Sejnowski, T. J. (2004). Potassium model for slow (2–3 Hz) in vivo neocortical paroxysmal oscillations. *Journal of Neurophysiology*, 92(2), 1116–1132. <https://doi.org/10.1152/jn.00529.2003>
- Blauwblomme, T., Jiruska, P., & Huberfeld, G. (2014). Mechanisms of ictogenesis. In *International Review of Neurobiology* (Vol. 114, pp. 155–185). Academic Press Inc. <https://doi.org/10.1016/B978-0-12-418693-4.00007-8>
- Boido, D., Gnatkovsky, V., Uva, L., Francione, S., & De Curtis, M. (2014). Simultaneous enhancement of excitation and postburst inhibition at the end of focal seizures. *Annals of Neurology*, 76(6), 826–836. <https://doi.org/10.1002/ana.24193>
- Borgdorff, J. A. (2002). *Calcium dynamics in hippocampal neurones* [University of Amsterdam]. <https://hdl.handle.net/11245/1.201021>

- 885 Bradford, H. F. (1995). Glutamate, GABA and epilepsy. *Progress in Neurobiology*, 47(6),
886 477–511. [https://doi.org/10.1016/0301-0082\(95\)00030-5](https://doi.org/10.1016/0301-0082(95)00030-5)
- 887 Bragin, A., Azizyan, A., Almajano, J., & Engel, J. (2009). The Cause of the Imbalance in the
888 Neuronal Network Leading to Seizure Activity Can Be Predicted by the Electrographic
889 Pattern of the Seizure Onset. *Journal of Neuroscience*, 29(11), 3660–3671.
890 <https://doi.org/10.1523/JNEUROSCI.5309-08.2009>
- 891 Bragin, Anatol, Penttonen, M., & Buzsáki, G. (1997). Termination of Epileptic Afterdischarge
892 in the Hippocampus. *The Journal of Neuroscience*, 17(7), 2567–2579.
893 <https://doi.org/10.1523/JNEUROSCI.17-07-02567.1997>
- 894 Bromfield, E. B., Cavazos, J. E., & Sirven, J. I. (Eds.). (2006). *An Introduction to Epilepsy*
895 [Internet]. West Hartford (CT): American Epilepsy Society.
896 <https://www.ncbi.nlm.nih.gov/books/NBK2508/>
- 897 Buchin, A., Chizhov, A., Huberfeld, G., Miles, R., & Gutkin, B. S. (2016). Reduced efficacy of
898 the KCC2 cotransporter promotes epileptic oscillations in a subiculum network model.
899 *Journal of Neuroscience*, 36(46), 11619–11633.
900 <https://doi.org/10.1523/JNEUROSCI.4228-15.2016>
- 901 Chizhov, A. V., Zefirov, A. V., Amakhin, D. V., Smirnova, E. Y., & Zaitsev, A. V. (2018).
902 Minimal model of interictal and ictal discharges “Epileptor-2.” *PLoS Computational*
903 *Biology*, 14(5), 1–25. <https://doi.org/10.1371/journal.pcbi.1006186>
- 904 Conradsen, I., Moldovan, M., Jennum, P., Wolf, P., Farina, D., & Beniczky, S. (2013).
905 Dynamics of muscle activation during tonic–clonic seizures. *Epilepsy Research*, 104(1–
906 2), 84–93. <https://doi.org/10.1016/j.eplepsyres.2012.09.004>
- 907 de Curtis, M., & Avoli, M. (2016). GABAergic networks jump-start focal seizures. *Epilepsia*,
908 57(5), 679–687. <https://doi.org/10.1111/epi.13370>
- 909 de Curtis, M., & Gnatkovsky, V. (2009). Reevaluating the mechanisms of focal ictogenesis:
910 The role of low-voltage fast activity. *Epilepsia*, 50(12), 2514–2525.
911 <https://doi.org/10.1111/j.1528-1167.2009.02249.x>

- 912 de Curtis, M., Librizzi, L., & Uva, L. (2006). In Vitro Isolated Guinea Pig Brain. In A.
913 Pitkänen, P. A. Schwartzkroin, & S. L. Moshé (Eds.), *Models of Seizures and Epilepsy*
914 (pp. 103–109). Academic Press Inc. <https://doi.org/10.1016/B978-012088554-1/50011-6>
- 915 de Curtis, M., Uva, L., Gnatkovsky, V., & Librizzi, L. (2018). Potassium dynamics and
916 seizures: Why is potassium ictogenic? *Epilepsy Research*, 143(April), 50–59.
917 <https://doi.org/10.1016/j.eplepsyres.2018.04.005>
- 918 Derchansky, M., Jahromi, S. S., Mamani, M., Shin, D. S., Sik, A., & Carlen, P. L. (2008).
919 Transition to seizures in the isolated immature mouse hippocampus: a switch from
920 dominant phasic inhibition to dominant phasic excitation. *The Journal of Physiology*,
921 586(2), 477–494. <https://doi.org/10.1113/jphysiol.2007.143065>
- 922 Devinsky, O., Vezzani, A., O'Brien, T. J., Jette, N., Scheffer, I. E., de Curtis, M., & Perucca, P.
923 (2018). Epilepsy. *Nature Reviews Disease Primers*, 4(1), 18024.
924 <https://doi.org/10.1038/nrdp.2018.24>
- 925 Doyon, N., Prescott, S. A., Castonguay, A., Godin, A. G., Kröger, H., & de Koninck, Y.
926 (2011). Efficacy of synaptic inhibition depends on multiple, dynamically interacting
927 mechanisms implicated in chloride homeostasis. *PLoS Computational Biology*, 7(9).
928 <https://doi.org/10.1371/journal.pcbi.1002149>
- 929 During, M. J., & Spencer, D. D. (1992). Adenosine: A potential mediator of seizure arrest and
930 postictal refractoriness. *Annals of Neurology*, 32(5), 618–624.
931 <https://doi.org/10.1002/ana.410320504>
- 932 Ebert, U., Cramer, S., & Löscher, W. (1997). Phenytoin's effect on the spread of seizure
933 activity in the amygdala kindling model. *Naunyn-Schmiedeberg's Archives of*
934 *Pharmacology*, 356(3), 341–347. <https://doi.org/10.1007/PL00005060>
- 935 Elahian, B., Lado, N. E., Mankin, E., Vangala, S., Misra, A., Moxon, K., Fried, I., Sharan, A.,
936 Yeasin, M., Staba, R., Bragin, A., Avoli, M., Sperling, M. R., Engel, J., & Weiss, S. A.
937 (2018). Low-voltage fast seizures in humans begin with increased interneuron firing.
938 *Annals of Neurology*, 84(4), 588–600. <https://doi.org/10.1002/ana.25325>
- 939 Evangelista, E., Bénar, C., Bonini, F., Carron, R., Colombet, B., Régis, J., & Bartolomei, F.

- 940 (2015). Does the Thalamo-Cortical Synchrony Play a Role in Seizure Termination?
941 *Frontiers in Neurology*, 6. <https://doi.org/10.3389/fneur.2015.00192>
- 942 Feng, Z., & Durand, D. M. (2003). Low-Calcium Epileptiform Activity in the Hippocampus In
943 Vivo. *Journal of Neurophysiology*, 90(4), 2253–2260.
944 <https://doi.org/10.1152/jn.00241.2003>
- 945 Fisher, R. S., Pedley, T. A., Moody, W. J., & Prince, D. A. (1976). The Role of Extracellular
946 Potassium in Hippocampal Epilepsy. *Archives of Neurology*, 33(2), 76–83.
947 <https://doi.org/10.1001/archneur.1976.00500020004002>
- 948 Fisher, Robert S., & Schachter, S. C. (2000). The Postictal State: A Neglected Entity in the
949 Management of Epilepsy. *Epilepsy and Behavior*, 1(1), 52–59.
950 <https://doi.org/10.1006/ebbeh.2000.0023>
- 951 Franaszczuk, P. J., Bergey, G. K., Durka, P. J., & Eisenberg, H. M. (1998). Time-frequency
952 analysis using the matching pursuit algorithm applied to seizures originating from the
953 mesial temporal lobe. *Electroencephalography and Clinical Neurophysiology*, 106(6),
954 513–521. [https://doi.org/10.1016/S0013-4694\(98\)00024-8](https://doi.org/10.1016/S0013-4694(98)00024-8)
- 955 Fransen, E., Alonso, A. A., & Hasselmo, M. E. (2002). Simulations of the role of the
956 muscarinic-activated calcium-sensitive nonspecific cation current INCM in entorhinal
957 neuronal activity during delayed matching tasks. *Journal of Neuroscience*, 22(3), 1081–
958 1097. <https://doi.org/10.1523/jneurosci.22-03-01081.2002>
- 959 Fröhlich, F., Bazhenov, M., Timofeev, I., Steriade, M., & Sejnowski, T. J. (2006). Slow state
960 transitions of sustained neural oscillations by activity-dependent modulation of intrinsic
961 excitability. *Journal of Neuroscience*, 26(23), 6153–6162.
962 <https://doi.org/10.1523/JNEUROSCI.5509-05.2006>
- 963 Fujiwara-Tsukamoto, Y., Isomura, Y., Imanishi, M., Fukai, T., & Takada, M. (2007). Distinct
964 types of ionic modulation of GABA actions in pyramidal cells and interneurons during
965 electrical induction of hippocampal seizure-like network activity. *European Journal of*
966 *Neuroscience*, 25(9), 2713–2725. <https://doi.org/10.1111/j.1460-9568.2007.05543.x>
- 967 Futamachi, K. J., Mutani, R., & Prince, D. A. (1974). Potassium activity in rabbit cortex. *Brain*

- 968 *Research*, 75(1), 5–25. [https://doi.org/10.1016/0006-8993\(74\)90767-7](https://doi.org/10.1016/0006-8993(74)90767-7)
- 969 Gentiletti, D., Suffczynski, P., Gnatkovsky, V., & De Curtis, M. (2017). Changes of Ionic
970 Concentrations during Seizure Transitions-A Modeling Study. *International Journal of*
971 *Neural Systems*, 27(4), 1–16. <https://doi.org/10.1142/S0129065717500046>
- 972 Gnatkovsky, V., Librizzi, L., Trombin, F., & De Curtis, M. (2008). Fast activity at seizure
973 onset is mediated by inhibitory circuits in the entorhinal cortex in vitro. *Annals of*
974 *Neurology*, 64(6), 674–686. <https://doi.org/10.1002/ana.21519>
- 975 Golomb, D., Yue, C., & Yaari, Y. (2006). Contribution of Persistent Na⁺ Current and M-Type
976 K⁺ Current to Somatic Bursting in CA1 Pyramidal Cells: Combined Experimental and
977 Modeling Study. *Journal of Neurophysiology*, 96(4), 1912–1926.
978 <https://doi.org/10.1152/jn.00205.2006>
- 979 González, O. C., Shiri, Z., Krishnan, G. P., Myers, T. L., Williams, S., Avoli, M., & Bazhenov,
980 M. (2018). Role of KCC2-dependent potassium efflux in 4-Aminopyridine-induced
981 Epileptiform synchronization. *Neurobiology of Disease*, 109(August 2017), 137–147.
982 <https://doi.org/10.1016/j.nbd.2017.10.011>
- 983 Grasse, D. W., Karunakaran, S., & Moxon, K. A. (2013). Neuronal synchrony and the
984 transition to spontaneous seizures. *Experimental Neurology*, 248, 72–84.
985 <https://doi.org/10.1016/j.expneurol.2013.05.004>
- 986 Haas, H. L., & Jefferys, J. G. (1984). Low-calcium field burst discharges of CA1 pyramidal
987 neurones in rat hippocampal slices. *The Journal of Physiology*, 354(1), 185–201.
988 <https://doi.org/10.1113/jphysiol.1984.sp015371>
- 989 Hamidi, S., & Avoli, M. (2015). KCC2 function modulates in vitro ictogenesis. *Neurobiology*
990 *of Disease*, 79, 51–58. <https://doi.org/10.1016/j.nbd.2015.04.006>
- 991 Heinemann, U., Lux, H. D., & Gutnick, M. J. (1977). Extracellular free calcium and potassium
992 during paroxysmal activity in the cerebral cortex of the cat. *Experimental Brain Research*,
993 27(3–4), 237–243. <https://doi.org/10.1007/BF00235500>
- 994 Heinemann, Uwe, & Lux, H. D. (1975). Undershoots following stimulus-induced rises of

995 extracellular potassium concentration in cerebral cortex of cat. *Brain Research*, 93(1), 63–
996 76. [https://doi.org/10.1016/0006-8993\(75\)90286-3](https://doi.org/10.1016/0006-8993(75)90286-3)

997 Ho, Y. E. C., & Truccolo, W. (2016). Interaction between synaptic inhibition and glial-
998 potassium dynamics leads to diverse seizure transition modes in biophysical models of
999 human focal seizures. *Journal of Computational Neuroscience*, 41(2), 225–244.
1000 <https://doi.org/10.1007/s10827-016-0615-7>

1001 Igelström, K. M. (2013). Is Slack an Intrinsic Seizure Terminator? *The Neuroscientist*, 19(3),
1002 248–254. <https://doi.org/10.1177/1073858412446311>

1003 Jefferys, J. G. (1995). Nonsynaptic modulation of neuronal activity in the brain: electric
1004 currents and extracellular ions. *Physiological Reviews*, 75(4), 689–723.
1005 <https://doi.org/10.1152/physrev.1995.75.4.689>

1006 Jefferys, J. G. R., & Haas, H. L. (1982). Synchronized bursting of CA1 hippocampal pyramidal
1007 cells in the absence of synaptic transmission. *Nature*, 300(5891), 448–450.
1008 <https://doi.org/10.1038/300448a0>

1009 Jefferys, J., Jiruska, P., de Curtis, M., & Avoli, M. (2012). Limbic Network Synchronization
1010 and Temporal Lobe Epilepsy. In J. Noebels, M. Avoli, M. Rogawski, R. Olsen, & A.
1011 Delgado-Escueta (Eds.), *Jasper's Basic Mechanisms of the Epilepsies*. Bethesda (MD):
1012 National Center for Biotechnology Information (US).
1013 <http://www.ncbi.nlm.nih.gov/pubmed/22787650>

1014 Jensen, M. S., & Yaari, Y. (1997). Role of intrinsic burst firing, potassium accumulation, and
1015 electrical coupling in the elevated potassium model of hippocampal epilepsy. *Journal of*
1016 *Neurophysiology*, 77(3), 1224–1233. <https://doi.org/10.1152/jn.1997.77.3.1224>

1017 Jirsa, V. K., Stacey, W. C., Quilichini, P. P., Ivanov, A. I., & Bernard, C. (2014). On the nature
1018 of seizure dynamics. *Brain*, 137(8), 2210–2230. <https://doi.org/10.1093/brain/awu133>

1019 Kager, H., Wadman, W. J., & Somjen, G. G. (2000). Simulated Seizures and Spreading
1020 Depression in a Neuron Model Incorporating Interstitial Space and Ion Concentrations.
1021 *Journal of Neurophysiology*, 84(1), 495–512. <https://doi.org/10.1152/jn.2000.84.1.495>

- 1022 Kager, H., Wadman, W. J., & Somjen, G. G. (2002). Conditions for the triggering of spreading
1023 depression studied with computer simulations. *Journal of Neurophysiology*, 88(5), 2700–
1024 2712. <https://doi.org/10.1152/jn.00237.2002>
- 1025 Kaila, K., Price, T. J., Payne, J. A., Puskarjov, M., & Voipio, J. (2014). Cation-chloride
1026 cotransporters in neuronal development, plasticity and disease. *Nature Reviews*
1027 *Neuroscience*, 15(10), 637–654. <https://doi.org/10.1038/nrn3819>
- 1028 Kalitzin, S. N., Bauer, P. R., Lamberts, R. J., Velis, D. N., Thijs, R. D., & Da Silva, F. H. L.
1029 (2016). Automated Video Detection of Epileptic Convulsion Slowing as a Precursor for
1030 Post-Seizure Neuronal Collapse. *International Journal of Neural Systems*, 26(8), 100–
1031 104. <https://doi.org/10.1142/S0129065716500271>
- 1032 Krishnan, G. P., & Bazhenov, M. (2011). Ionic dynamics mediate spontaneous termination of
1033 seizures and postictal depression state. *Journal of Neuroscience*, 31(24), 8870–8882.
1034 <https://doi.org/10.1523/JNEUROSCI.6200-10.2011>
- 1035 Krishnan, G. P., Filatov, G., Shilnikov, A., & Bazhenov, M. (2015). Electrogenic properties of
1036 the Na⁺/K⁺ ATPase control transitions between normal and pathological brain states.
1037 *Journal of Neurophysiology*, 113(9), 3356–3374. <https://doi.org/10.1152/jn.00460.2014>
- 1038 Lado, F. A., & Moshé, S. L. (2008). How do seizures stop? *Epilepsia*, 49(10), 1651–1664.
1039 <https://doi.org/10.1111/j.1528-1167.2008.01669.x>
- 1040 Lagarde, S., Buzori, S., Trebuchon, A., Carron, R., Scavarda, D., Milh, M., McGonigal, A., &
1041 Bartolomei, F. (2019). The repertoire of seizure onset patterns in human focal epilepsies:
1042 Determinants and prognostic values. *Epilepsia*, 60(1), 85–95.
1043 <https://doi.org/10.1111/epi.14604>
- 1044 Lévesque, M., Herrington, R., Hamidi, S., & Avoli, M. (2016). Interneurons spark seizure-like
1045 activity in the entorhinal cortex. *Neurobiology of Disease*, 87, 91–101.
1046 <https://doi.org/10.1016/j.nbd.2015.12.011>
- 1047 Lian, J., Bikson, M., Shuai, J., & Durand, D. M. (2001). Propagation of non-synaptic
1048 epileptiform activity across a lesion in rat hippocampal slices. *Journal of Physiology*,
1049 537(1), 191–199. <https://doi.org/10.1111/j.1469-7793.2001.0191k.x>

- 1050 Lillis, K. P., Kramer, M. A., Mertz, J., Staley, K. J., & White, J. A. (2012). Pyramidal cells
1051 accumulate chloride at seizure onset. *Neurobiology of Disease*, 47(3), 358–366.
1052 <https://doi.org/10.1016/j.nbd.2012.05.016>
- 1053 Lindén, H., Hagen, E., Leski, S., Norheim, E. S., Pettersen, K. H., & Einevoll, G. T. (2014).
1054 LFPy: A tool for biophysical simulation of extracellular potentials generated by detailed
1055 model neurons. *Frontiers in Neuroinformatics*, 7(JAN), 1–15.
1056 <https://doi.org/10.3389/fninf.2013.00041>
- 1057 Liou, J., Smith, E. H., Bateman, L. M., Bruce, S. L., McKhann, G. M., Goodman, R. R.,
1058 Emerson, R. G., Schevon, C. A., & Abbott, L. (2020). A model for focal seizure onset,
1059 propagation, evolution, and progression. *ELife*, 9. <https://doi.org/10.7554/eLife.50927>
- 1060 Lopantsev, V., & Avoli, M. (1998). Participation of GABA(A)-mediated inhibition in ictallike
1061 discharges in the rat entorhinal cortex. *Journal of Neurophysiology*, 79(1), 352–360.
1062 <https://doi.org/10.1152/jn.1998.79.1.352>
- 1063 Magistretti, J., & Alonso, A. (1999). Biophysical Properties and Slow Voltage-Dependent
1064 Inactivation of a Sustained Sodium Current in Entorhinal Cortex Layer-II Principal
1065 Neurons. *Journal of General Physiology*, 114(4), 491–509.
1066 <https://doi.org/10.1085/jgp.114.4.491>
- 1067 Magloire, V., Cornford, J., Lieb, A., Kullmann, D. M., & Pavlov, I. (2019). KCC2
1068 overexpression prevents the paradoxical seizure-promoting action of somatic inhibition.
1069 *Nature Communications*, 10(1), 1–13. <https://doi.org/10.1038/s41467-019-08933-4>
- 1070 Martinet, L.-E., Fiddymment, G., Madsen, J. R., Eskandar, E. N., Truccolo, W., Eden, U. T.,
1071 Cash, S. S., & Kramer, M. A. (2017). Human seizures couple across spatial scales through
1072 travelling wave dynamics. *Nature Communications*, 8(1), 14896.
1073 <https://doi.org/10.1038/ncomms14896>
- 1074 McBain, C., Traynelis, S., & Dingledine, R. (1990). Regional variation of extracellular space
1075 in the hippocampus. *Science*, 249(4969), 674–677.
1076 <https://doi.org/10.1126/science.2382142>
- 1077 Miri, M. L., Vinck, M., Pant, R., & Cardin, J. A. (2018). Altered hippocampal interneuron

1078 activity precedes ictal onset. *ELife*, 7. <https://doi.org/10.7554/eLife.40750>

1079 Moore, Y. E., Deeb, T. Z., Chadchankar, H., Brandon, N. J., & Moss, S. J. (2018). Potentiating
1080 KCC2 activity is sufficient to limit the onset and severity of seizures. *Proceedings of the*
1081 *National Academy of Sciences of the United States of America*, 115(40), 10166–10171.
1082 <https://doi.org/10.1073/pnas.1810134115>

1083 Nunez, P. L., & Srinivasan, R. (2006). *Electric Fields of the Brain*. Oxford University Press.
1084 <https://doi.org/10.1093/acprof:oso/9780195050387.001.0001>

1085 Payne, D. E., Karoly, P. J., Freestone, D. R., Boston, R., D’Souza, W., Nurse, E., Kuhlmann,
1086 L., Cook, M. J., & Grayden, D. B. (2018). Postictal suppression and seizure durations: A
1087 patient-specific, long-term iEEG analysis. *Epilepsia*, 59(5), 1027–1036.
1088 <https://doi.org/10.1111/epi.14065>

1089 Payne, J. A. (1997). Functional characterization of the neuronal-specific K-Cl cotransporter:
1090 Implications for [K⁺]_o regulation. *American Journal of Physiology - Cell Physiology*,
1091 273(5 42-5). <https://doi.org/10.1152/ajpcell.1997.273.5.c1516>

1092 Payne, J. A., Rivera, C., Voipio, J., & Kaila, K. (2003). Cation-chloride co-transporters in
1093 neuronal communication, development and trauma. *Trends in Neurosciences*, 26(4), 199–
1094 206. [https://doi.org/10.1016/S0166-2236\(03\)00068-7](https://doi.org/10.1016/S0166-2236(03)00068-7)

1095 Perucca, P., Dubeau, F., & Gotman, J. (2014). Intracranial electroencephalographic seizure-
1096 onset patterns: effect of underlying pathology. *Brain*, 137(1), 183–196.
1097 <https://doi.org/10.1093/brain/awt299>

1098 Pottkämper, J. C. M., Hofmeijer, J., van Waarde, J. A., & van Putten, M. J. A. M. (2020). The
1099 postictal state — What do we know? *Epilepsia*, 61(6), 1045–1061.
1100 <https://doi.org/10.1111/epi.16519>

1101 Proix, T., Jirsa, V. K., Bartolomei, F., Guye, M., & Truccolo, W. (2018). Predicting the
1102 spatiotemporal diversity of seizure propagation and termination in human focal epilepsy.
1103 *Nature Communications*, 9(1), 1088. <https://doi.org/10.1038/s41467-018-02973-y>

1104 Pumain, R., Menini, C., Heinemann, U., Louvel, J., & Silva-Barrat, C. (1985). Chemical

- 1105 synaptic transmission is not necessary for epileptic seizures to persist in the baboon *Papio*
 1106 *papio*. *Experimental Neurology*, 89(1), 250–258. [https://doi.org/10.1016/0014-](https://doi.org/10.1016/0014-4886(85)90280-8)
 1107 4886(85)90280-8
- 1108 Raimondo, J. V., Burman, R. J., Katz, A. A., & Akerman, C. J. (2015). Ion dynamics during
 1109 seizures. *Frontiers in Cellular Neuroscience*, 9, 1–14.
 1110 <https://doi.org/10.3389/fncel.2015.00419>
- 1111 Saggio, M. L., Crisp, D., Scott, J. M., Karoly, P., Kuhlmann, L., Nakatani, M., Murai, T.,
 1112 Dämpelmann, M., Schulze-Bonhage, A., Ikeda, A., Cook, M., Gliske, S. V, Lin, J.,
 1113 Bernard, C., Jirsa, V., & Stacey, W. C. (2020). A taxonomy of seizure dynamotypes.
 1114 *ELife*, 9. <https://doi.org/10.7554/eLife.55632>
- 1115 Schiff, S. J., Colella, D., Jacyna, G. M., Hughes, E., Creekmore, J. W., Marshall, A., Bozek-
 1116 Kuzmicki, M., Benke, G., Gaillard, W. D., Conry, J., & Weinstein, S. R. (2000). Brain
 1117 chirps: spectrographic signatures of epileptic seizures. *Clinical Neurophysiology*, 111(6),
 1118 953–958. [https://doi.org/10.1016/S1388-2457\(00\)00259-5](https://doi.org/10.1016/S1388-2457(00)00259-5)
- 1119 Schindler, K., Leung, H., Elger, C. E., & Lehnertz, K. (2007). Assessing seizure dynamics by
 1120 analysing the correlation structure of multichannel intracranial EEG. *Brain*, 130(1), 65–
 1121 77. <https://doi.org/10.1093/brain/awl304>
- 1122 Shivacharan, R. S., Chiang, C.-C., Zhang, M., Gonzalez-Reyes, L. E., & Durand, D. M.
 1123 (2019). Self-propagating, non-synaptic epileptiform activity recruits neurons by
 1124 endogenous electric fields. *Experimental Neurology*, 317, 119–128.
 1125 <https://doi.org/10.1016/j.expneurol.2019.02.005>
- 1126 Somjen, G. G., Kager, H., & Wadman, W. J. (2008). Computer simulations of neuron-glia
 1127 interactions mediated by ion flux. *Journal of Computational Neuroscience*, 25(2), 349–
 1128 365. <https://doi.org/10.1007/s10827-008-0083-9>
- 1129 Spencer, S. S., Guimaraes, P., Katz, A., Kim, J., & Spencer, D. (1992). Morphological Patterns
 1130 of Seizures Recorded Intracranially. *Epilepsia*, 33(3), 537–545.
 1131 <https://doi.org/10.1111/j.1528-1157.1992.tb01706.x>
- 1132 Suffczynski, P., Gentiletti, D., Gnatkovsky, V., & de Curtis, M. (2017). Extracellular

- 1133 Potassium and Focal Seizures—Insight from In Silico Study. In P. Érdi, B. Sen
1134 Bhattacharya, & A. Cochran (Eds.), *Computational Neurology and Psychiatry. Springer*
1135 *Series in Bio-/Neuroinformatics* (pp. 49–72). Springer, Cham.
1136 https://doi.org/10.1007/978-3-319-49959-8_3
- 1137 Thompson, S. M., & Gahwiler, B. H. (1989). Activity-dependent disinhibition. II. Effects of
1138 extracellular potassium, furosemide, and membrane potential on ECl⁻ in hippocampal
1139 CA3 neurons. *Journal of Neurophysiology*, 61(3), 512–523.
1140 <https://doi.org/10.1152/jn.1989.61.3.512>
- 1141 Timofeev, I., & Steriade, M. (2004). Neocortical seizures: initiation, development and
1142 cessation. *Neuroscience*, 123(2), 299–336.
1143 <https://doi.org/10.1016/j.neuroscience.2003.08.051>
- 1144 Toyoda, I., Fujita, S., Thamattoor, A. K., & Buckmaster, P. S. (2015). Unit activity of
1145 hippocampal interneurons before spontaneous seizures in an animal model of temporal
1146 lobe epilepsy. *Journal of Neuroscience*, 35(16), 6600–6618.
1147 <https://doi.org/10.1523/JNEUROSCI.4786-14.2015>
- 1148 Traub, R. D., Buhl, E. H., Gloveli, T., & Whittington, M. A. (2003). Fast Rhythmic Bursting
1149 Can Be Induced in Layer 2/3 Cortical Neurons by Enhancing Persistent Na⁺
1150 Conductance or by Blocking BK Channels. *Journal of Neurophysiology*, 89(2), 909–921.
1151 <https://doi.org/10.1152/jn.00573.2002>
- 1152 Truccolo, W., Donoghue, J. A., Hochberg, L. R., Eskandar, E. N., Madsen, J. R., Anderson, W.
1153 S., Brown, E. N., Halgren, E., & Cash, S. S. (2011). Single-neuron dynamics in human
1154 focal epilepsy. *Nature Neuroscience*, 14(5), 635–643. <https://doi.org/10.1038/nn.2782>
- 1155 Uva, L., Breschi, G. L., Gnatkovsky, V., Taverna, S., & de Curtis, M. (2015). Synchronous
1156 inhibitory potentials precede seizure-like events in acute models of focal limbic seizures.
1157 *Journal of Neuroscience*, 35(7), 3048–3055. [https://doi.org/10.1523/JNEUROSCI.3692-](https://doi.org/10.1523/JNEUROSCI.3692-14.2015)
1158 14.2015
- 1159 Uva, L., & de Curtis, M. (2020). Activity- and pH-dependent adenosine shifts at the end of a
1160 focal seizure in the entorhinal cortex. *Epilepsy Research*, 165, 106401.
1161 <https://doi.org/10.1016/j.epilepsyres.2020.106401>

1162 Velascol, A. L., Wilson, C. L., Babb, T. L., & Engel Jr, J. (2000). Functional and Anatomic
1163 Correlates of Two Frequently Observed Temporal Lobe Seizure-Onset Patterns. *Neural*
1164 *Plasticity*, 7(1–2), 49–63. <https://doi.org/10.1155/NP.2000.49>

1165 Viitanen, T., Ruusuvuori, E., Kaila, K., & Voipio, J. (2010). The K⁺-Cl⁻ cotransporter KCC2
1166 promotes GABAergic excitation in the mature rat hippocampus. *Journal of Physiology*,
1167 588(9), 1527–1540. <https://doi.org/10.1113/jphysiol.2009.181826>

1168 Voipio, J., Pasternack, M., Rydqvist, B., & Kaila, K. (1991). Effect of gamma-aminobutyric
1169 acid on intracellular pH in the crayfish stretch-receptor neurone. *The Journal of*
1170 *Experimental Biology*, 156, 349–360. <http://www.ncbi.nlm.nih.gov/pubmed/1711091>

1171 Wei, Y., Ullah, G., & Schiff, S. J. (2014). Unification of neuronal spikes, seizures, and
1172 spreading depression. *Journal of Neuroscience*, 34(35), 11733–11743.
1173 <https://doi.org/10.1523/JNEUROSCI.0516-14.2014>

1174 Wen, B., Qian, H., Feng, J., Ge, R.-J., Xu, X., Cui, Z.-Q., Zhu, R.-Y., Pan, L.-S., Lin, Z.-P., &
1175 Wang, J.-H. (2015). A Portion of Inhibitory Neurons in Human Temporal Lobe Epilepsy
1176 are Functionally Upregulated: An Endogenous Mechanism for Seizure Termination. *CNS*
1177 *Neuroscience & Therapeutics*, 21(2), 204–214. <https://doi.org/10.1111/cns.12336>

1178 Yaari, Y., Konnerth, A., & Heinemann, U. (1983). Spontaneous epileptiform activity of cal
1179 hippocampal neurons in low extracellular calcium solutions. *Experimental Brain*
1180 *Research*, 51(1). <https://doi.org/10.1007/BF00236813>

1181 Ziburkus, J., Cressman, J. R., Barreto, E., & Schiff, S. J. (2006). Interneuron and pyramidal
1182 cell interplay during in vitro seizure-like events. *Journal of Neurophysiology*, 95(6),
1183 3948–3954. <https://doi.org/10.1152/jn.01378.2005>

1184 Ziemann, A. E., Schnitzler, M. K., Albert, G. W., Severson, M. A., Howard III, M. A., Welsh,
1185 M. J., & Wemmie, J. A. (2008). Seizure termination by acidosis depends on ASIC1a.
1186 *Nature Neuroscience*, 11(7), 816–822. <https://doi.org/10.1038/nn.2132>

1187 Zubler, F., Steimer, A., Gast, H., & Schindler, K. A. (2014). Seizure Termination. In
1188 *International Review of Neurobiology* (pp. 187–207). Academic Press Inc.
1189 <https://doi.org/10.1016/B978-0-12-418693-4.00008-X>

Supplementary figures

Figure S1. Bifurcation diagram of a single PY cell. The 2D bifurcation diagram demonstrates the behavior of a single PY cell as a function of extracellular potassium concentration in the dendritic ($[K^+]_{o,dend}$) and somatic compartments ($[K^+]_{o,soma}$) used as control parameters. Concentrations of all other ions were fixed at their reference values, all ion accumulation mechanisms were blocked and all synaptic connections were removed. The legend on the right shows the PY cell activity traces for different values of the control parameters: resting (yellow, $[K^+]_{o,soma} = 4$ mM, $[K^+]_{o,dend} = 4$ mM), tonic firing (violet, $[K^+]_{o,soma} = 4$ mM, $[K^+]_{o,dend} = 6$ mM) and bursting (dark blue, $[K^+]_{o,soma} = 6$ mM, $[K^+]_{o,dend} = 6$ mM). In each panel, 2 seconds of activity is shown. The colors of the 2D diagram correspond to the types of activity shown in the

legend. For low $[K^+]_{o,dend}$ and $[K^+]_{o,soma}$ the cell was at rest. A moderate increase in either $[K^+]_{o,dend}$ or $[K^+]_{o,soma}$, or both, led to tonic firing. Subsequent increases in these parameters led to bursting.

Figure S2. A comparison of tonic firing (A) and bursting (B) of a PY cell. In each column, the membrane potential of a cell (top) and the activation gate of I_{KM} (bottom) is shown. During tonic firing, the activation gate of the M-type potassium current was closed. The prolonged depolarization of the cell during bursting led to the opening of the activation gate m and activation of the I_{KM} current, which eventually terminated the burst. The simulation was performed using an isolated PY cell model with the concentrations of all ions fixed at their reference values, except for A: $[K^+]_{o,soma} = 11$ mM, $[K^+]_{o,dend} = 3.75$ mM, B: $[K^+]_{o,soma} = 11$ mM and $[K^+]_{o,dend} = 5$ mM.