

# Maintenance and termination of neocortical oscillations by dynamic modulation of intrinsic and synaptic excitability

FLAVIO FRÖHLICH<sup>1,2</sup>, MAXIM BAZHENOV<sup>1</sup>, IGOR TIMOFEEV<sup>3,4</sup> AND TERRENCE J. SEJNOWSKI<sup>1,2</sup>

<sup>1</sup>The Salk Institute, Computational Neurobiology Laboratory, La Jolla, CA, 92037, <sup>2</sup>Division of Biological Sciences, Section of Neurobiology, University of California, San Diego, USA, <sup>3</sup>Department of Anatomy and Physiology, School of Medicine, Laval University, Québec, Canada G1K 7P4 and <sup>4</sup>The Centre de Recherche Université Laval Robert-Giffard, Québec, Canada G1J 2G3

*Mechanisms underlying seizure cessation remain elusive. The Lennox-Gastaut syndrome, a severe childhood epileptic disorder, is characterized by episodes of seizure with alternating epochs of spike-wave and fast run discharges. In a detailed computational model that incorporates extracellular potassium dynamics, we studied the dynamics of these state transitions between slow and fast oscillations. We show that dynamic modulation of synaptic transmission can cause termination of paroxysmal activity. An activity-dependent shift in the balance between synaptic excitation and inhibition towards more excitation caused seizure termination by favoring the slow oscillatory state, which permits recovery of baseline extracellular potassium concentration. We found that slow synaptic depression and change in chloride reversal potential can have similar effects on the seizure dynamics. Our results indicate a novel role for synaptic dynamics during epileptic neural activity patterns.*

**Keywords:** neocortex, synaptic plasticity, extracellular potassium concentration, intracellular chloride concentration, computational model

## INTRODUCTION

A prominent feature of cortical circuits is their propensity for rhythmic activity (Buzsaki and Draguhn, 2004; Steriade, 2006). This oscillatory activity might exist in either normal forms, such as during sleep (Steriade *et al.*, 1993a; Steriade *et al.*, 1993b; Steriade and Contreras, 1995; Contreras *et al.*, 1997; Steriade and Amzica, 1998; Amzica and Steriade, 2000; Steriade *et al.*, 2001; Timofeev *et al.*, 2001; Bazhenov *et al.*, 2002; Steriade, 2003; Steriade, 2004a; Steriade, 2004b; Steriade and McCarley, 2005), or paroxysmal forms, such as during epilepsy (Steriade *et al.*, 1986; Neckelmann *et al.*, 1998; Steriade *et al.*, 1998; Steriade and Contreras 1998; Timofeev *et al.*, 1998; Timofeev *et al.*, 2002a; Grenier *et al.*, 2003; Timofeev *et al.*, 2004; Bazhenov *et al.*, 2004; Timofeev and Steriade, 2004). Epileptic seizures are characterized by epochs of hypersynchronous neural oscillations that are accompanied by firing. Experimental animals exhibit electrographic seizures that closely mimic the dynamics of clinical seizures. Here, we focus on the paroxysmal activity that closely resembles Lennox-Gastaut seizures (Niedermeyer, 2002; Markand, 2003), which are characterized by slow bursting (spike-wave or polyspike-wave complexes) intermixed with epochs of fast runs (Frohlich *et al.*, 2006; Neckelmann *et al.*, 1998; Timofeev *et al.*, 1998).

Recently, we proposed a mechanism for the slow state transitions between two different oscillatory regimes using a computational model of a cortical network with

extracellular potassium dynamics (Frohlich *et al.*, 2006). Pyramidal cells exhibited bistability with hysteresis between tonic firing and slow bursting for elevated extracellular potassium concentration  $[K^+]_o$  (Frohlich and Bazhenov, 2006). In a model that included  $[K^+]_o$  as a dynamic variable, this bistability caused persistent oscillations with slow transitions between slow bursting and fast run. We concluded that activity-dependent modulation of intrinsic excitability can mediate slow patterning of sustained neural oscillations. Activity-dependent changes of synaptic and intrinsic properties can modulate excitability through positive- and negative-feedback mechanisms. Thus, an increase in  $[K^+]_o$  during sustained neural activity (Heinemann *et al.*, 1977; Amzica *et al.*, 2002) upregulates excitability by decreasing the driving force on potassium currents and, hence, forms a positive-feedback loop (Yaari *et al.*, 1986). By contrast, depression of excitatory recurrent coupling between pyramidal cells mediates negative feedback, whereas depression of inhibition constitutes positive feedback. Little is known about the combined effect of different dynamic mechanisms that modulate excitability. Here, we study network oscillatory states in the presence of dynamic mechanisms that shift the balance between excitation and inhibition towards more excitation. The positive-feedback nature of activity-dependent increase in excitability would indicate the occurrence of some form of self-amplifying ‘runaway dynamics’ by a global loss of stability. We found the opposite, namely that a dynamic shift in balance towards more excitation can force the network back to its silent state after a period of patterned oscillatory activity. We discuss the resulting dynamics as a model for seizure cessation.

### Corresponding author:

M. Bazhenov  
Email: bazhenov@salk.edu

## OBJECTIVES

The key objective of this study was to investigate how slow activity-dependent changes of synaptic transmission modulate paroxysmal network activity. Specifically, we studied the effect of slow synaptic depression and of change in GABAergic reversal potential mediated by chloride accumulation on the oscillatory network dynamics.

## METHODS

### Computational model

The model neocortical network with extracellular potassium dynamics has been described in detail elsewhere (Bazhenov *et al.*, 2004; Frohlich and Bazhenov 2006; Frohlich *et al.*, 2006). In short, individual neurons were modeled with an axo-somatic and a dendritic compartment, each endowed with Hodgkin-Huxley type conductances including fast transient sodium, delayed-rectifier potassium, persistent sodium, high-threshold calcium, calcium-activated potassium, and a mixed cationic leak conductance. Passive and active ion-transport mechanisms and glial buffering regulated the extracellular potassium concentration. The two-layered network consisted of a line of 80 pyramidal cells (PYs) and 16 inhibitory interneurons (INs). PYs were recurrently coupled through excitatory synapses (both AMPA and NMDA) to their local neighbors (five PYs on each side). Each PY excited three neighboring INs, which, in turn, inhibited 11 neighboring PYs through GABA(A) synapses. Synaptic transmission was modeled with first-order gating kinetics (Destexhe *et al.*, 1994). Maximal conductances denoting the total excitation and inhibition received by a given cell were set to  $G(\text{AMPA})(\text{PY-PY}) = 200$  nS,  $G(\text{NMDA})(\text{PY-PY}) = 13$  nS,  $G(\text{AMPA})(\text{PY-IN}) = 100$  nS,  $G(\text{NMDA})(\text{PY-IN}) = 14$  nS, and  $G(\text{IN-PY}) = 50$  nS. All synapses included spontaneous release of neurotransmitter resulting in miniature postsynaptic potentials (Bazhenov *et al.*, 2002). All synapses included short-term depression (STD) modeled with depression factor ( $D = 0.07$ ) denoting the fraction of synaptic resources lost per presynaptic action potential and with first-order recovery dynamics with time-constant of 700 msec (Markram *et al.*, 1998). Slow, activity-dependent synaptic depression ('slow depression') was modeled similarly to STD but with different parameters. Depression factor  $D$  was set to a low value ( $D = 0.001$ ) and recovery time-constant was very slow ( $T = 1000$  sec). In some simulations, intracellular chloride concentration was computed for each cell by integration of the inhibitory currents mediated by GABA(A) receptors. The reversal potential for chloride was dynamically updated using Nernst equation with extracellular concentration  $[\text{Cl}^-]_o = 130$  mM:  $E_{\text{Cl}} = 26.64 \text{ mV} \ln([\text{Cl}^-]_i/[\text{Cl}^-]_o)$ .

### *In vivo* experiments

The details of *in vivo* electrophysiological experiments involving intracellular recordings during paroxysmal activities have been described before (Timofeev *et al.*, 2002b; Timofeev *et al.*, 2004). Briefly, intracellular recordings from neocortical neurons were performed in 15 cats anesthetized with ketamine-xylazine ( $10-15 \text{ mg kg}^{-1}$  and  $2-3 \text{ mg kg}^{-1}$ ; i.m.) Following ketamine-xylazine anesthesia,  $\sim 30\%$  of cats

( $n = 6$ ) displayed spontaneous electrographic seizures consisting of SW/PSW complexes at  $1.5-3$  Hz, often associated with fast runs at about  $10-15$  Hz. In cats that did not display spontaneous electrographic seizures, the electrographic seizures were elicited by 3-4 pulse-trains ( $10-20$  stimuli at  $100$  Hz) applied to cortical areas in the vicinity of the intracellular recording pipette.

Field potential recordings and stimulation were obtained by using bipolar coaxial macroelectrodes inserted into the cortex. The outer pole of the electrode was placed at the cortical surface or  $0.1$  mm deeper, whereas the inner pole was placed at  $0.8-1$  mm in the cortical depth.

Intracellular recordings were obtained with sharp glass micropipettes filled in the majority of cases with a solution of  $2.5-3.0$  M potassium acetate (KAc). Electrophysiological identification of recorded neurons was achieved by intracellular application of depolarizing current pulses of  $0.2-1.0$  nA lasting for  $200-300$  msec. Because the intrinsic firing patterns of neurons are influenced by the network state (Steriade *et al.*, 1998; Steriade, 2004b), formal identification was performed during active phases of slow oscillation in seizure-free periods. In this study, we only report data on regular-spiking neurons that revealed spike-frequency adaptation and on fast-spiking neurons that exhibited both thin spikes and high-frequency tonic discharge without spike-frequency adaptation upon direct depolarization. In some experiments with dual intracellular recordings, one pipette was filled with KAc and the other with potassium chloride (KCl,  $2.0-3.0$  M). Intracellular pipettes had a DC resistance of  $30-80$  M $\Omega$ . A high-impedance amplifier (bandpass,  $10$  kHz) with an active bridge circuitry was used to record and inject current into the neurons. All electrical signals were sampled at  $20$  kHz and digitally stored on Vision (Nicolet). To simplify data processing, occasionally the data were downsampled to  $2$  kHz.

All experimental procedures were performed in accordance with the guidelines of the Canadian Council on Animal Care and were approved by the Committee for Animal Care of Laval University.

## RESULTS

### Persistent oscillatory activity in the cortical network model

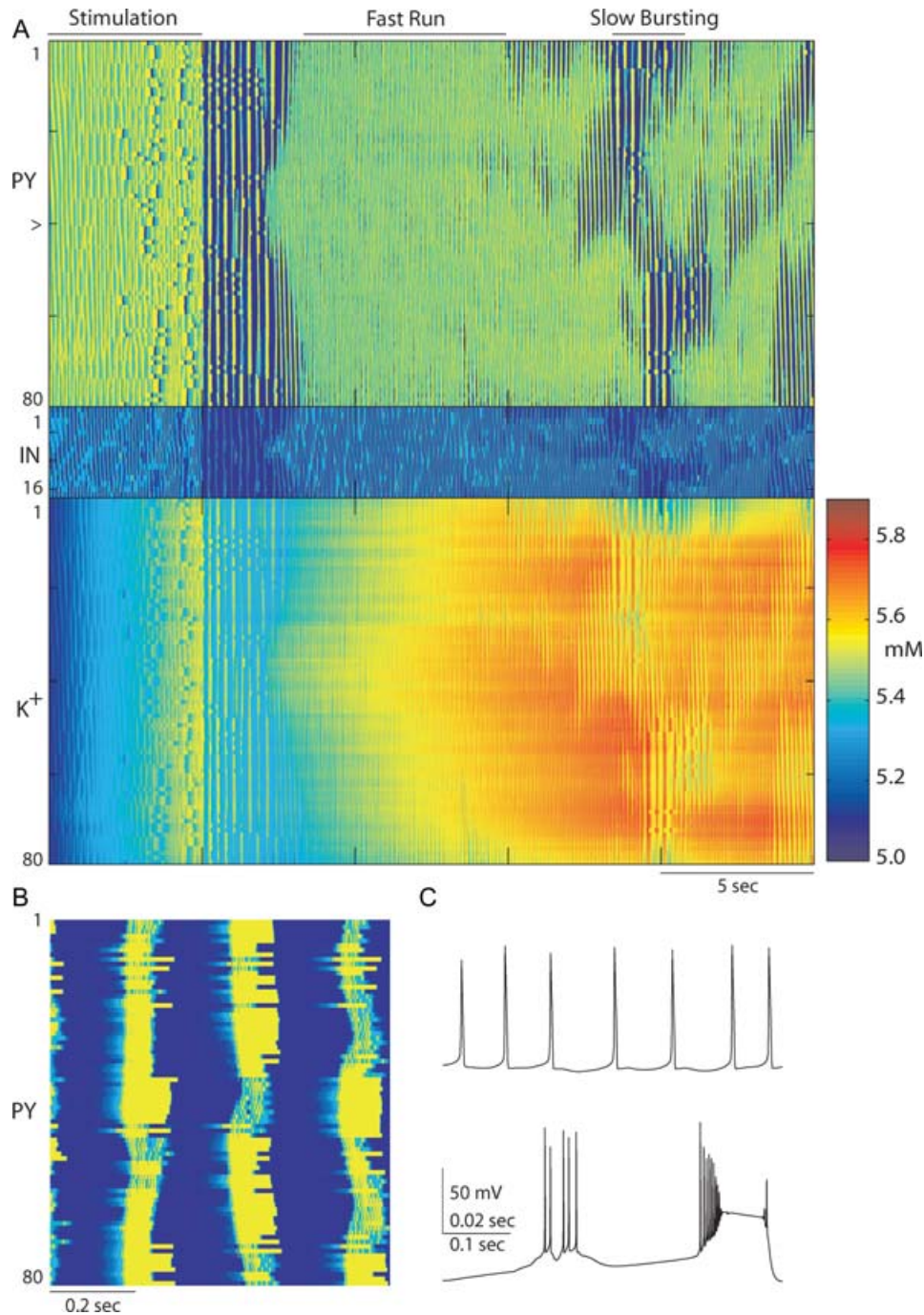
Step depolarization of all 80 pyramidal cells in the network induced high-frequency firing that resulted in a gradual increase in  $[\text{K}^+]_o$  (Fig. 1A). At the end of the stimulation, potassium concentration reached  $5.5$  mM, for which activity-dependent potassium outflow was approximately balanced by mechanisms for removal of excess extracellular potassium. Therefore,  $[\text{K}^+]_o$  remained elevated, causing sustained oscillations in absence of stimulation. The persistent activity was structured into epochs of tonic firing (fast runs) and slow bursting (sample epochs labeled in Fig. 1A, top panel). Both the pyramidal cells (Fig. 1A, top panel) and the inhibitory interneurons (Fig. 1A, middle panel) were subject to this slow patterning. Previously, we showed that these slow state transitions between the two oscillatory regimes are mediated by a bistability with hysteresis of the two modes for elevated  $[\text{K}^+]_o$  (Frohlich *et al.*, 2006). At the offset of external

stimulation, the network started slow bursting during which  $[K^+]_o$  decreased (Fig. 1A, bottom panel) to a level at which only fast run is a stable mode. At this point the network switched to fast run and  $[K^+]_o$  started to increase because of the higher overall activity during fast run compared with slow bursting (Fig. 1A, bottom panel). Eventually, the system reached a  $[K^+]_o$  value at which fast run becomes unstable and the system switched to slow bursting again.

Slow bursting was synchronized throughout the network and occurred at frequencies of few bursts per second

(Fig. 1B). In individual neurons, fast run denotes firing patterns similar to tonic firing (Fig. 1C top panel shows sample epoch of fast run in PY 40, marked in Fig. 1A, top panel). During slow bursting, pyramidal cells exhibited both bursts with and without spike inactivation (Fig. 1C bottom panel shows sample epoch of slow bursting in PY 40).

Here, we investigate possible mechanisms for the termination of the persistent oscillatory firing. In the model, transitions between fast run and slow bursting last indefinitely in presence of balanced synaptic excitation and inhibition.



**Fig. 1. Cortical network oscillation patterned into alternating epochs of slow bursting and fast run following stimulation of PYs.** (A) Top: Activity of all 80 PYs as a function of time. Middle: INs. Bottom:  $[K^+]_o$  time-course. After an initial transient increase,  $[K^+]_o$  increases and decreases during fast run and slow bursting, respectively. (B) Activity of all 80 PYs during slow bursting. (C) Membrane voltage time-course during fast run (top) and slow bursting (bottom). Scale bars: top, 20 msec; bottom, 100 msec.

In case of strong recurrent excitation and weak inhibition, however, the network exhibited only bursting followed by silence (Frohlich *et al.*, 2006). In other words, if the excitatory coupling is sufficient to prevent the network from switching to fast run, the network is bound to return to the silent state because  $[K^+]_o$  only decreases during slow bursting. Therefore we asked if a dynamic mechanism can shift the balance between excitation and inhibition such that a network that initially exhibits transition dynamics eventually reaches the regime where only bursting is stable and the persistent activity eventually terminates. In the following, we discuss two alternative dynamic mechanisms mediating an activity-dependent shift in the balance of excitation and inhibition towards more excitation. As we show below, both differential synaptic depression of excitation and inhibition with slow recovery time-constant ('slow depression') and increase in intracellular chloride concentration terminated the oscillatory activity.

### Effect of synaptic depression on seizure cessation

First, we consider depression of both excitatory coupling between pyramidal cells and inhibitory coupling between interneurons and pyramidal cells. We used a generic model of synaptic depression with a low depression rate and a long recovery time-constant causing activity-dependent depression for synaptic coupling without recovery on the time-scale of a seizure. In presence of such slow depression, a transient increase in  $[K^+]_o$  initiated a series of alternating epochs of fast run and slow bursting with eventual return to the silent state in a network with 80 PYs and 16 INs (Fig. 2A, activity map of pyramidal cells). As in the case without slow depression (Fig. 1),  $[K^+]_o$  decreased during slow bursting and increased during epochs of fast run (Fig. 2B); this regime would persist in the network with balanced excitation and inhibition. However, depression rates of excitatory and inhibitory synaptic conductances were chosen such that inhibition decreased faster than excitation [ $D(PY-PY) = 0.0005$  and  $D(IN-PY) = 0.001$ ]. This resulted in a net shift of the balance between excitation and inhibition towards more excitation. The phase plane representing the normalized synaptic coupling strengths (Fig. 2C) shows that during the development of the seizure both excitation and inhibition decreased. However, because of the different depression rates, the trajectory moved away from the diagonal band (blue lines) corresponding to persistent oscillations mediated by balanced excitation and inhibition (red arrow in Fig. 2C). The persistent oscillations ended with an epoch of slow bursting during which  $[K^+]_o$  decreased to a value where all cells eventually became silent (membrane voltage time-course in Fig. 2D).

We next analyzed 10 seizures triggered by a transient increase in  $[K^+]_o$  for two values of the slow-depression rate for the inhibitory coupling [Fig. 3A for  $D(IN-PY) = 0.001$  and Fig. 3B for  $D(IN-PY) = 0.0011$ , all activity maps aligned on onset of oscillatory firing]. Slow bursting is shown in black, fast run in gray, and silence in white. The difference between the firing patterns for a given value of  $D(IN-PY)$  was mediated by the random modulation of the membrane voltages by miniature postsynaptic potentials evoked by spontaneous release of neurotransmitter vesicles. For  $D(IN-PY) = 0.001$ , three out of ten seizures did not

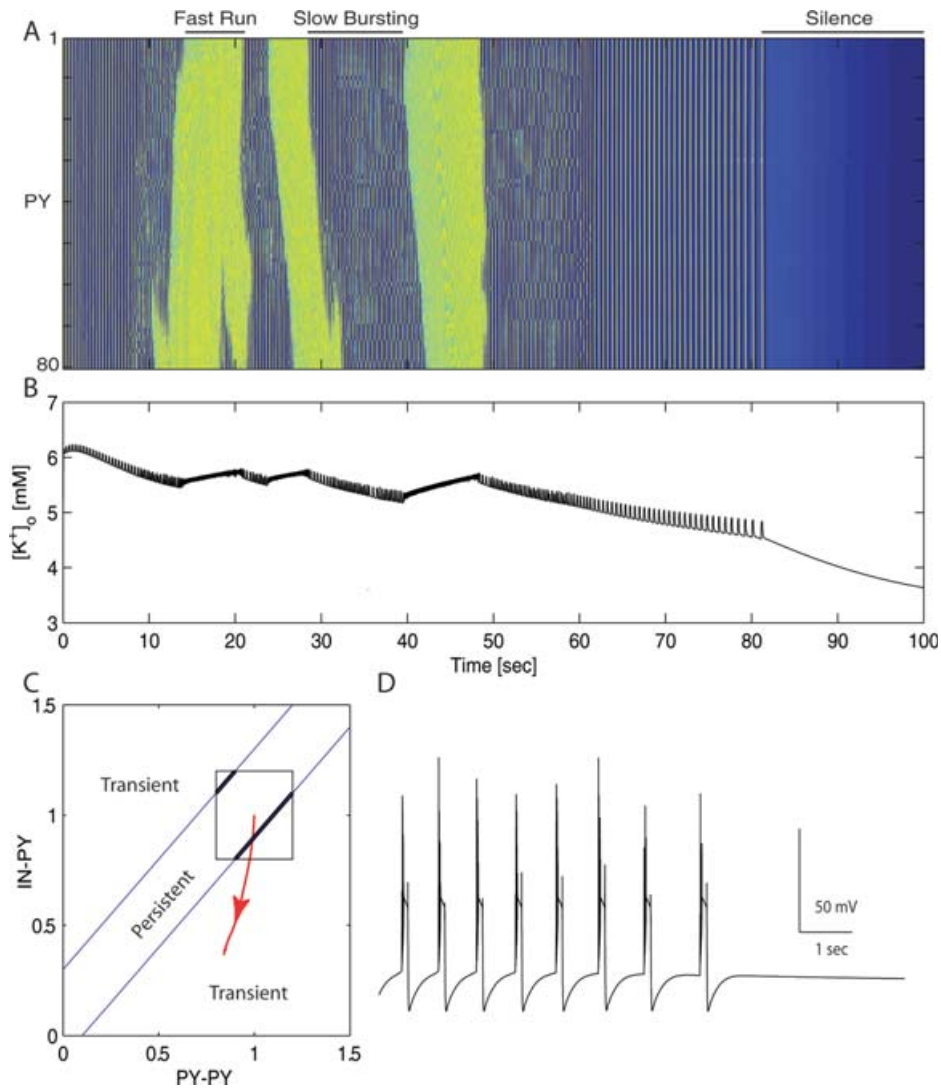
terminate within the time-window simulated (150 sec). All cases exhibited a series of transitions between fast run and slow bursting. In case of  $D(IN-PY) = 0.0011$  (Fig. 3B), only one out of ten seizures did not terminate within 150 sec. In one case, the seizure consisted only of slow bursting with no epoch of fast run. In all cases for which the network returned to the silent state, the oscillatory pattern ended with an epoch of slow bursting. In phase space, the normalized synaptic conductances diverged from the diagonal band that corresponds to persistent activity. We found a statistically significant difference in seizure duration for the two values of  $D(IN-PY)$  (Fig. 3D, left panel,  $P = 0.02$ ). Accordingly, the number of epochs of fast run decreased for increased  $D(IN-PY)$  (Fig. 3D, right panel). All this can be explained by faster depression for  $D(IN-PY) = 0.0011$  that moved the system further away from the region of balanced excitation and inhibition where oscillation could persist infinitely (Fig. 2C). Our results also indicate that the same network might produce a different pattern of paroxysmal oscillations as a result of random fluctuations of the membrane voltages.

### Effect of chloride reversal potential on seizure cessation

Our simple model of slow depression with differential scaling of synaptic excitation and inhibition represents a general principle of activity-dependent shift in the balance between excitation and inhibition. Next, we focused on a specific experimentally determined physiological mechanism, which can mediate such a shift in balance of excitation and inhibition. We previously found that the reversal potential for fast GABAergic synaptic currents mediated by chloride ions changes over the time-course of an electrographic seizure (Timofeev *et al.*, 2002b). Specifically, chloride influx caused a depolarization of the chloride reversal potential from  $-69.7$  mV before seizure onset to  $-46.7$  mV at the end of the seizure. The resulting decrease in inhibitory currents is, therefore, a potential candidate mechanism for a slow, activity-dependent shift in the balance between synaptic excitation and inhibition during a seizure. We included these data in our model by adding simplified intracellular chloride dynamics in the form of a simple, activity-dependent accumulation mechanism that integrates the inhibitory currents targeting a cell. When using the dynamically updated chloride concentration to compute the reversal potential for the currents mediated by GABA receptors, the persistent neural oscillations terminated (Fig. 4A). Over the duration of the patterned oscillatory activity, the chloride concentration increased from 8.0 mM (corresponding to a reversal potential  $E_{Cl} = -74.3$  mV) to 16.4 mM ( $E_{Cl} = -55.1$  mV) (Fig. 4B). This led to a weakening of inhibition without affecting synaptic excitation (Fig. 4C). As in the case of slow depression, the seizure ended with an epoch of slow bursting (Fig. 4D).

### Differences in activities of regular-spiking neurons and fast-spiking interneurons during seizures *in vivo*

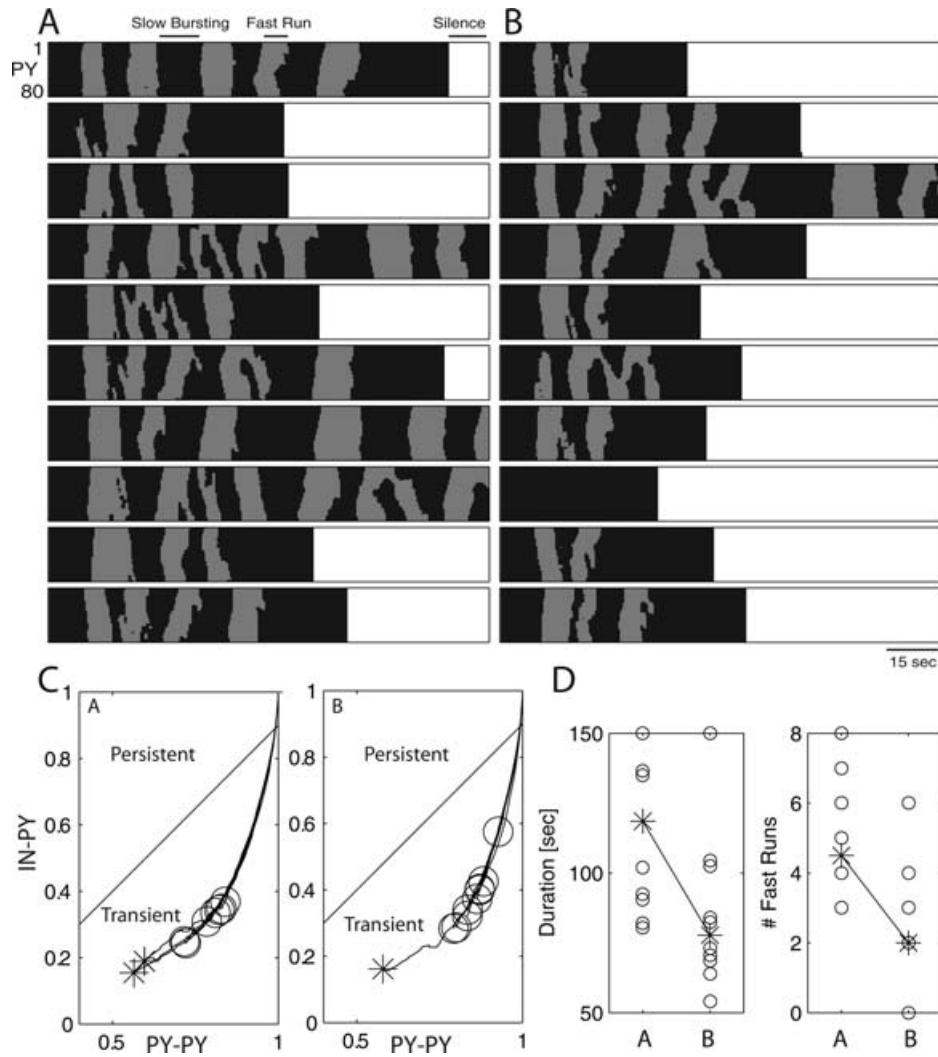
For the depolarization of the chloride reversal potential to have an effect on the seizure dynamics, inhibitory interneurons need to be active throughout the seizure. Fast-spiking neurons constitute an important class of inhibitory interneurons in



**Fig. 2. Patterned cortical network oscillations of finite length for slow depression of synaptic transmission.** (A) Activity of all 80 PYs as a function of time. (B) Time-course of changes in  $[K^+]_o$ . (C) Phase-space representation of normalized synaptic coupling strength. Dynamic change in balance between excitation and inhibition (red line). Arrowhead indicates direction of time. Blue diagonal lines delimit the region for which alternating epochs of fast run and slow bursting can occur infinitely. The box corresponds to the values of synaptic coupling strengths for which we found persistent oscillations in a small network with the same dynamics (Frohlich *et al.*, 2006). (D) Time-course of membrane voltage before termination of oscillations shows slow bursting.

the CNS. For this study, we recorded from 120 regular-spiking and 15 fast-spiking neurons (cell-type classification based on electrophysiological properties). In five simultaneous dual intracellular registrations, at least one regular-spiking and one fast-spiking neuron was recorded during electrographic seizures (Fig. 5). The observed seizures evolve from the slow oscillation and consist of spike-wave complexes with frequency 1–3 Hz (mainly 1.5–2.5 Hz) interrupted with periods of fast runs (8–20 Hz). On all occasions, the first 3–5 initial paroxysmal discharges were characterized by high-frequency firing of fast-spiking neurons (50–300 Hz, sometimes reaching 500 Hz). Regular-spiking neurons also increased their firing frequency (Fig. 5B). During later stages of seizure spike-wave components, the fast-spiking inhibitory interneurons continued to maintain high-frequency firing during each burst, often reaching 500 Hz (Fig. 5C). However, despite large depolarization, the regular-spiking neurons displayed mainly one or two action potentials per paroxysmal spike (Fig. 5C). The loss of ability to fire spikes

by regular-spiking neurons is probably caused by depolarization block. Thus, in these experiments, the fast-spiking neurons maintained high firing rate and, therefore, were in a position to exhibit a strong influence on their postsynaptic target neurons during both initial and spike-wave components of seizure. Combined with our earlier findings that chloride reversal potential increases over the duration of the seizure to an extent that chloride mediated synaptic currents mediate depolarizing postsynaptic potentials (Timofeev *et al.*, 2002), our experiments imply – in agreement with our modeling results – a crucial shift in the balance between inhibition and excitation towards excitation over the time-course of the seizure. The relative increase in firing for the fast-spiking interneurons over the time-course of the seizure can be explained by depolarizing GABAergic postsynaptic potential from synaptic connectivity between fast-spiking interneurons and further amplifies the divergence from balanced excitation and inhibition towards more excitation in the case of elevated intracellular chloride concentration.



**Fig. 3.** (A,B) Ten instances of patterned oscillatory firing for slow synaptic depression rate  $D = 0.001$  (A) and  $D = 0.0011$  (B). Black, gray, and white denote slow bursting, fast run and silence, respectively. (C) Phase-space representation of normalized excitation and inhibition (Left,  $D = 0.001$ ; right,  $D = 0.0011$ ). Circles, endpoints with termination of oscillations; stars, endpoint with no termination of oscillations within 150 sec. (D) Left, duration of seizures. Right, number of epochs of fast runs. Stars, median values.

## CONCLUSIONS

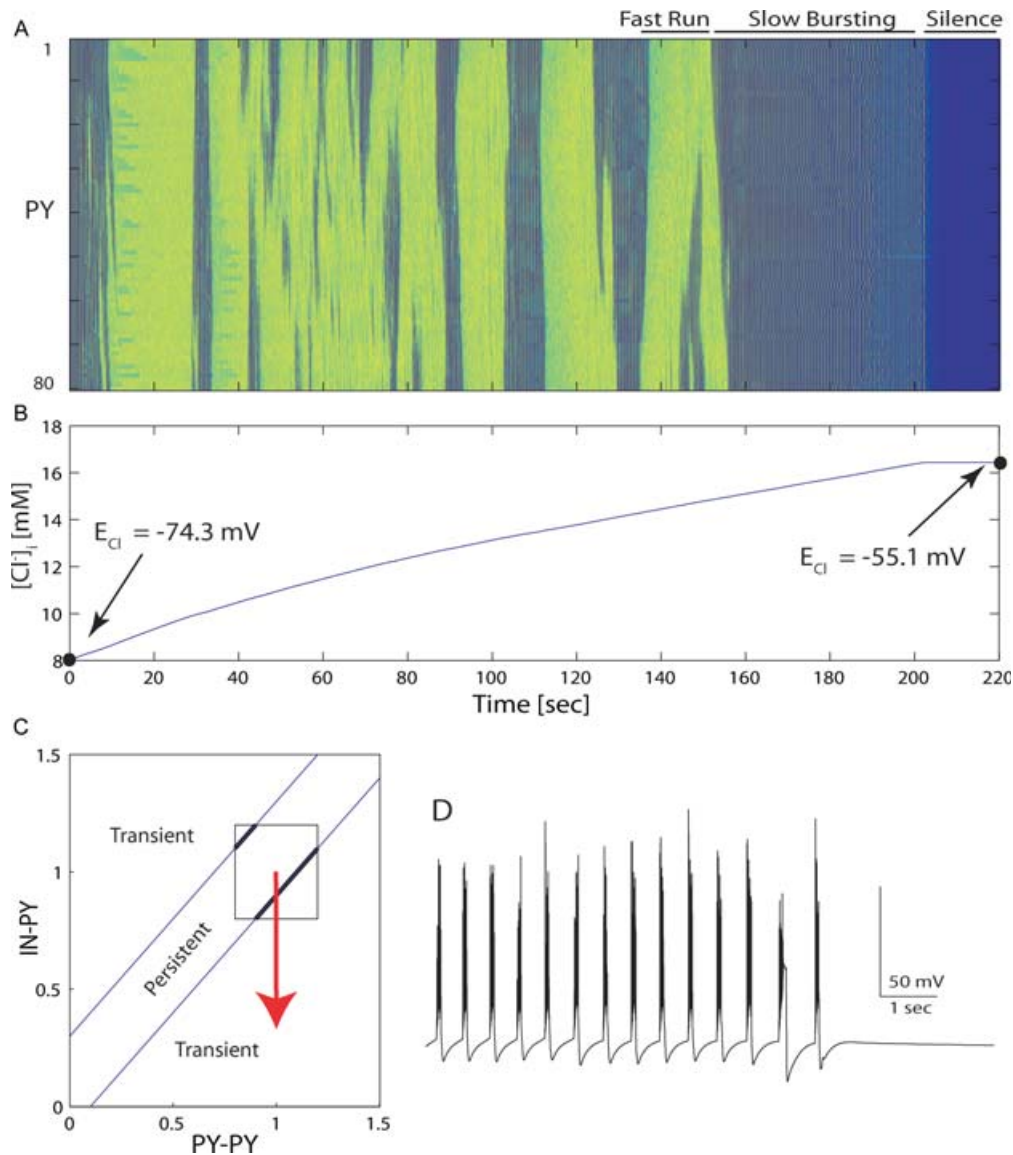
- We have shown that a cortical network model that includes ion-concentration dynamics exhibits both seizure maintenance and termination dynamics in qualitative agreement with experimental results on electrographic seizures in experimental animals (Timofeev and Steriade, 2004) and human clinical EEG recordings (Niedermeyer, 2002).
- We suggest that the same shift towards more excitation that initiates and maintains a seizure will eventually also permit seizure cessation.

## DISCUSSION

Little is known about the mechanisms underlying seizure cessation (Timofeev and Steriade, 2004). Here, we found in the model of neocortical seizures with epochs of slow bursting and fast run mediated by extracellular  $K^+$  dynamics that an activity-dependent shift towards more excitation can mediate seizure cessation. For both activity-dependent

scaling of synaptic conductances (slow depression) and change in chloride reversal potential, the transition dynamics was followed by silence that is qualitatively similar to *in vivo* intracellular recordings in anesthetized cats (Timofeev *et al.*, 1998). Using a computational model, we first identified the general mechanism of a relative increase in excitation as a potential cause of seizure cessation. Then, based on experimentally established chloride-concentration dynamics (Timofeev *et al.*, 2002b) as a physiological candidate mechanism for differential weakening of inhibition, we verified the hypothesis that a collapse in the chloride gradient can mediate seizure cessation. Synaptic inhibition is a highly efficient mechanism for cortical synchronization and therefore we suggest that a decrease in inhibitory efficiency (more depolarizing reversal potential for inhibitory postsynaptic potentials, IPSPs) would terminate hypersynchronous activities such as seizures.

It is widely accepted that the development of epileptiform activity results from a shift in the balance between excitation and inhibition towards excitation (Dichter and Ayala, 1987; Galarreta and Hestrin, 1998; Nelson and Turrigiano, 1998). The easiest way to elicit acute seizures is to block inhibition

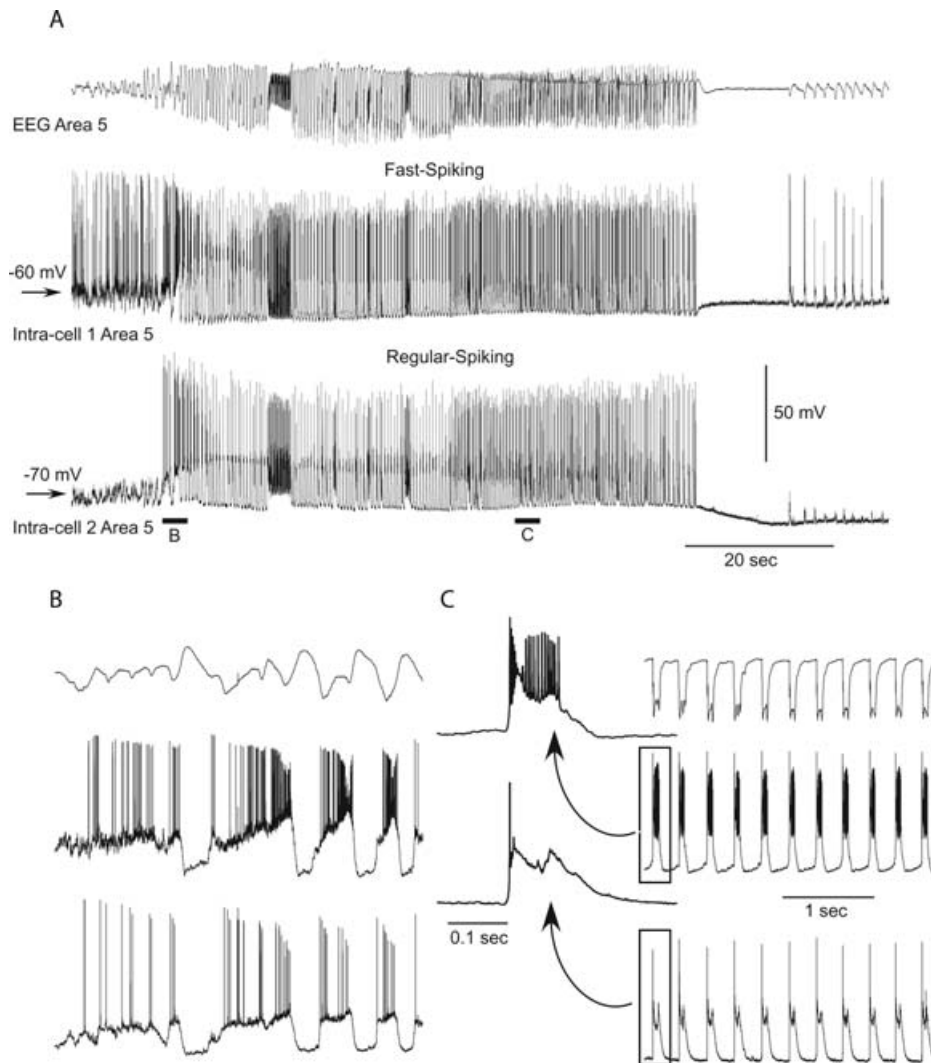


**Fig. 4. Patterned cortical network oscillations of finite length for dynamically updated intracellular chloride concentration.** (A) Activity of all 80 PYs as a function of time. (B) Time-course of changes in intracellular chloride concentration ( $[Cl^-]_i$ ). Corresponding reversal potentials are shown for the onset and the end of oscillations. (C) Symbolic phase-space representation of dynamic change in balance between excitation and inhibition (red line). Arrowhead indicates direction of time. Blue diagonal lines delimit the region for which alternating epochs of fast run and slow bursting can occur infinitely. (D) Time-course of membrane voltage before termination of oscillations.

(Matsumoto and Ajmonemarsan, 1964; Prince, 1978; Gutnick *et al.*, 1982; Chagnac-Amitai and Connors, 1989a; Chagnac-Amitai and Connors, 1989b), which is a well known approach to elicit experimental seizures (Reviewed in McNamara, 1994; Traub *et al.*, 1996; Steriade *et al.*, 1998; Timofeev and Steriade, 2004). Chloride concentration has been implicated previously in seizure dynamics because it directly affects synaptic inhibitory currents mediated by GABA(A) receptors (Cohen *et al.*, 2002). Contrary to expectation, the model implementing activity-dependent increase of  $[Cl^-]_i$  showed that seizure cessation was mediated by a relative increase in excitation over the course of paroxysmal oscillations. This provides a new interpretation for the changes in intracellular chloride concentration that occur during a seizure. Although a decrease in inhibition can promote seizure initiation in normal cortex, we propose here that an actual increase in excitability during paroxysmal run itself can lead to seizure cessation.

Importantly, our model predicts that the termination of a seizure is preceded by an epoch of slow bursting. This finding is confirmed by experimental recordings (I. Timofeev, unpublished observations).

Our model of chloride dynamics is relatively simple, and other mechanisms that we have not included in our model also affect intracellular chloride concentration (Thompson and Gahwiler, 1989; Kaila *et al.*, 1997; Taira *et al.*, 1997). For example, an increase in  $[K^+]_o$  in mature neocortical PYs would result in further increase in  $[Cl^-]_i$  via activation of the neuron-specific protein  $K^+Cl^-$  (KCC2) co-transporter (DeFazio *et al.*, 2000). Although we have not included this mechanism in our model, our result indicates that adding another activity-dependent mechanism of intracellular chloride dynamics might affect the duration of a seizure and contribute further to seizure cessation. Chloride concentration dynamics have also been implicated in the field of pain research where



**Fig. 5. Spontaneous firing patterns of regular-spiking and fast-spiking cortical neurons during electrographic seizure *in vivo*.** (A) EEG and simultaneous dual intracellular recordings of regular-spiking and fast-spiking neurons (indicated) during seizure that is composed of spike-wave components and fast runs. The seizure evolves from slow oscillation. The fast-spiking inhibitory interneuron is active throughout the seizure. (B,C) Expansions of underlined fragments. (B) Intracellular activities during transition from slow oscillation to seizure. The fast-spiking neuron fires much more spikes than the regular-spiking neuron. (C) During spike-wave complexes the regular-spiking neuron displays one spike, whereas the fast-spiking neuron maintains ability to fire high-frequency trains of spikes.

a change from inhibitory to excitatory GABAergic transmission has been associated with neuropathic pain (Coull *et al.*, 2003)

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Correspondence should be addressed to:

Dr Maxim Bazhenov

The Salk Institute for Biological Studies

10010 North Torrey Pines Rd.

La Jolla, CA 92037, USA

phone: +1 858 453 4100 Ext. 1965

fax: +1 858 587 0417

email: bazhenov@salk.edu