Review

Potassium diffusive coupling in neural networks

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Conventional neural networks are characterized by many neurons coupled together through synapses. The activity, synchronization, plasticity and excitability of the network are then controlled by its synaptic connectivity. Neurons are surrounded by an extracellular space whereby fluctuations in specific ionic concentration can modulate neuronal excitability. Extracellular concentrations of potassium ($[K^+]_o$) can generate neuronal hyperexcitability. Yet, after many years of research, it is still unknown whether an elevation of potassium is the cause or the result of the generation, propagation and synchronization of epileptiform activity. An elevation of potassium in neural tissue can be characterized by dispersion (global elevation of potassium) and lateral diffusion (local spatial gradients). Both experimental and computational studies have shown that lateral diffusion is involved in the generation and the propagation of neural activity in diffusively coupled networks. Therefore, diffusion-based coupling by potassium can play an important role in neural networks and it is reviewed in four sections. Section 2 shows that potassium diffusion is responsible for the synchronization of activity across a mechanical cut in the tissue. A computer model of diffusive coupling shows that potassium diffusion can mediate communication between cells and generate abnormal and/or periodic activity in small (§3) and in large networks of cells (§4). Finally, in §5, a study of the role of extracellular potassium in the propagation of axonal signals shows that elevated potassium concentration can block the propagation of neural activity in axonal pathways. Taken together, these results indicate that potassium accumulation and diffusion can interfere with normal activity and generate abnormal activity in neural networks.

Keywords: potassium diffusion; modelling; synchronization

1. INTRODUCTION

Known non-synaptic mechanisms such as osmolarity, ephaptic interactions and extracellular ionic waves are considered critical for neural network synchronization. They are essential in non-synaptic epileptogenesis, but also important in the generation of synaptic seizures (Yaari & Jensen 1988). More importantly, non-synaptic diffusion has been shown to be an energy efficient neurotransmission mechanism (Aiello & Bach-y-Rita 2000). Experimental studies have shown that a diffusion coupling signal can propagate in the hippocampus under normal extracellular calcium concentration (Perreault & Avoli 1992) and under low extracellular calcium concentration (Lian *et al.* 2001; see §2). Computational model studies have also confirmed that diffusive coupling can play an important role in the synchronization of oscillators (Hale 1996). Furthermore, the slow waveform and low frequency of ictal

epileptiform activity are consistent with potassium dynamics known to underlie non-synaptic bursting (Bikson *et al.* 1999, 2001; Lian *et al.* 2003; Bihi *et al.* 2005). In most models of epilepsy, ictal activity originates almost exclusively in the CA1 and entorhinal cortex regions (Dreier & Heinemann 1990; Bragdon *et al.* 1992; Patrylo *et al.* 1994; Jensen & Yaari 1997) where the tight packing of cell bodies promotes non-synaptic interactions such as extracellular potassium build-up. In contrast, inter-ictal activity originates in the CA3 region where recurrent synaptic connections are abundant (Prince & Connors 1986). Traditionally, non-synaptic bursting was thought only to occur in the low- Ca^{2+} and zero- Ca^{2+} models. However, experimental data show that it is also possible to generate non-synaptic activity associated with increases in potassium concentration in the presence of normal synaptic transmission (Bikson *et al.* 2002). Therefore, besides synaptic transmission, potassium diffusion and its subsequent coupling effect can work together to modulate synchronization in neural networks.

(a) Potassium coupling

Although potassium coupling is best observed while synaptic transmission is blocked (low-calcium concentration), the effect of the synchronization by potassium

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diffusion has been observed in preparations with intact synaptic transmission (Perreault & Avoli 1992). These *in vitro* experiments using rat hippocampal slices perfused with potassium channel blocker 4-aminopyridine (4-AP) showed that γ -aminobutyric acid (GABA) released from interneurons activates post-synaptic GABA-A receptors that are located in the dendrites and this process produces a long-lasting depolarization (LLD) response. These LLDs are generated both in the CA1 and in the dentate gyrus (DG), and the LLD signals are synchronized across the hippocampus fissure. Synchrony is lost, however, when the two regions (CA1 and DG) are physically separated. Although it has been shown that GABAergic interneurons located in the CA1 region send both axonal and dendritic branches across the fissure towards the dentate granule cell layer (Lacaille & Schwartzkroin 1988), the speed of propagation of these events ($4\text{--}17\text{ mm s}^{-1}$) is similar to the activity generated in low-calcium potassium, suggesting that 'non-synaptic mechanisms' are probably involved in the propagation mechanism. These findings, taken together with the fact that potassium can cross a cut along a cell layer (Lian *et al.* 2001; §2), strongly suggest that potassium lateral diffusion can synchronize activity across two layers of neurons. Electrophysiology, pharmacology and computer simulations have been used to test this hypothesis further. Since it is not possible to remove lateral diffusion in experiments, computer simulations are essential to test the effects of lateral diffusion by adding and removing the mechanism.

(b) Potassium accumulation

Elevation of potassium concentration in the extracellular space has been shown to be a crucial factor in several types of epilepsy such as status epilepticus (SE). SE is the most severe form of epilepsy and it is often associated with considerable morbidity and mortality. The cause of SE is related in part to the failure of seizure termination (Coulter & DeLorenzo 1999). SE is very unlikely to be generated in *in vitro* normal extracellular medium, suggesting that the termination of seizure is robust (Coulter & DeLorenzo 1999). In recent *in vivo* low- Ca^{2+} experiments performed in the anaesthetized rat, SE-like activity (characterized by periodic double spikes) in the hippocampus has been observed (Feng & Durand 2005). Computer simulation studies have predicted that potassium lateral diffusion could explain this phase-synchronized state of individual cell activity leading to production of rhythmical SE-like activity (§4). Moreover, it has been shown *in vitro* (Lian *et al.* 2004) that phase synchrony could be destroyed by single site sub-threshold sinusoidal stimulation which is known to generate potassium accumulation. The mechanism underlying the control of phase synchronization is still unknown. However, it has to involve potassium diffusion coupling since this form of coupling is shown to be able to pass through a complete mechanical cut.

(c) Source of potassium

The source of the increasing extracellular potassium is often assumed to be intracellular compartment of neurons and glia. However, another important source

of potassium resides within blood where potassium concentration (5 mM) is higher than that in cerebrospinal fluid (CSF; 2.9 mM). Normally, the blood–brain barrier (BBB) prevents potassium in blood from reaching the brain tissues. Advances in radiology have enhanced our ability to image and study the human BBB, and the persistent problem of multiple drug resistance to antiepileptic drugs has amplified the significance of the BBB's relationship to epilepsy (Oby & Janigro 2006). The same concept of BBB breakdown for therapeutic purposes (generally for the purpose of increasing drug delivery to the brain) has also revealed a previously unrecognized role for BBB breakdown (Oby & Janigro 2006) as a possible aetiological mechanism in epileptogenesis. Several studies have shown that mechanisms such as the Na^+/K^+ pump and glial cell uptake play an important role in the regulation of $[\text{K}^+]_o$ (Janigro *et al.* 1997; D'Ambrosio *et al.* 1999; Ransom *et al.* 2000; Walz 2000).

(d) Neural network synchronization by diffusion

A first important question is: how can neurons be synchronized without synaptic transmission? Many studies on synchronization of oscillators in general and synchronization within networks of neurons in particular (Pikovsky *et al.* 2001) have been published. These studies show that coupling is a necessary but not sufficient condition for synchronization. In cases of globally coupled oscillators (all to all) with weak coupling, interesting behaviour between oscillators can emerge. An important contribution was made in 1975 whereby an analytical solution to the problem of globally coupled oscillators was obtained (Kuramoto 1975). One of the most publicized examples is that of fireflies which tend to fire in unison under certain conditions (Strogatz 2003). Analysis of global coupling showed that an arbitrary number of oscillators globally coupled would almost always synchronize (Mirollo & Strogatz 1990). However, the situation is not as simple for networks that are locally (nearest-neighbour) coupled. This type of coupling is also known as diffusive coupling. Diffusive coupling can be observed in chemical oscillators (Bar-Eli 1985) or in neural networks (Rossini *et al.* 2005). In some simulation studies, it has been shown that diffusively coupled neuronal oscillators are not necessarily completely synchronized but show various patterns of phase locking mode (Park *et al.* 1996). Diffusive coupling can also lead to dephasing of neuronal oscillators (Han *et al.* 1995). Noise has also been shown to enhance synchronization in coupled networks (a phenomenon known as coherence resonance; Stacey & Durand 2000, 2001; Balenzuela & Garcia-Ojalvo 2005). Therefore, it is difficult to predict the effect of a non-synaptic coupling mechanism on the synchronization of neural networks. The second important question to answer is: what is the coupling mechanism between cells when synaptic transmission is absent. There are several mechanisms to couple neurons non-synaptically within neural tissue, such as ephaptic transmission, gap junctions, field effect interactions and ionic and neurotransmitter diffusion. The diffusion coupling mechanism is to be distinguished

from ephaptic interactions since it does not require the close apposition of the two membranes (ephapse). Diffusion of potassium ions between neurons is such a possible answer to this question in the hippocampus as shown by computer simulations and experiments.

2. POTASSIUM DIFFUSION AS A COUPLING SIGNAL

Potassium ions can diffuse throughout neural tissue and could in principle couple neural networks not directly connected by axons or synapses. This effect was demonstrated with 4-AP preparation in which activity generated in the DG was found to cross the hippocampal fissure into the CA1 region (Perreault & Avoli 1992); this propagation was attributed to the accumulation and dispersion of potassium within the hippocampus. Therefore, one could predict that potassium diffusion should provide a coupling mechanism between two areas of the brain. To test this hypothesis, a complete mechanical cut of the CA1 region of the hippocampus was made and low-calcium solutions were applied to the slice to generate oscillations. Electrodes positioned within the CA1 layer of the hippocampus in the low-calcium concentration solution were able to record low-frequency periodic signals typical in this preparation as shown in figure 1*a*. The cross correlation between signals recorded by electrodes separated by a small distance (0.2 mm) was measured and found to be close to unity at $t = 0$ (figure 1), indicating a high level of correlation and synchronization. A complete cut through the tissue between the two electrodes did not destroy the correlation between the two signals (figure 1*b*). However, physical separation between the two sides did eliminate the coupling, which was restored by repositioning the two sides in close apposition (figure 1*c,d*). Ephaptic interaction between the two sides was eliminated as a possible mechanism since large evoked field potentials generated on one side did not elicit any response on the other. Gap junctions, synaptic and axonal transmission were also eliminated as possible coupling mechanisms since they were disrupted by the cut (Lian *et al.* 2001). These results indicate a novel coupling mechanism between the two pieces of slice and suggested that a diffusible coupling signal is responsible for the synchronization. Extracellular potassium concentration recordings did show that a wave of potassium was diffusing between the two sides (figure 2). From these experiments, it is clear that a diffusive coupling between cells exists and can contribute to the synchronization of neural activity.

Can the local diffusion of potassium resulting from the excitation of a few neurons be sufficient to depolarize neighbouring cells and thereby generate propagation of diffusion-induced activity? This question is difficult to answer experimentally since it relies on the precise measurement of potassium in the small extracellular space between cells. Potassium-sensitive microelectrodes can measure the potassium concentration in the bulk extracellular space, but not without destroying tissue, and therefore cannot give a precise measurement of the interstitial value. Computer stimulations, however, are able to provide a possible answer to this question.

3. COMPUTER SIMULATION OF LATERAL DIFFUSION IN NEURAL NETWORKS

Several decades ago it was suggested that an accumulation of potassium ions $[K^+]_o$ in a very narrow interstitial space around neurons can serve as a potential mechanism for increasing neuronal excitability leading to seizure generation (Frankenhaeuser & Hodgkin 1956; Green 1964; Fetzinger & Ranck 1970). Yet, the idea that elevated extracellular potassium concentration in the interstitial space is responsible for initiating seizure activity remains controversial. Some have concluded that $[K]_o$ is not responsible for the initiation or the termination of the seizure activity (Lux 1974; Moody *et al.* 1974; Fisher *et al.* 1976; Heinemann & Lux 1977; Kager *et al.* 2000; Somjen 2004). Others have shown that $[K]_o$ accumulation can initiate seizure activity (Zuckermann & Glaser 1968; Izquierdo *et al.* 1970; O'Connor & Lewis 1974). The latter is based on the fact that neurons sharing the same extracellular space were depolarized by the diffusion of high potassium concentration. Particularly, in several low-calcium experiments, the fluctuation of $[K^+]_o$ has been proposed as a key component for non-synaptic epileptogenesis (Jefferys & Haas 1982; Taylor & Dudek 1982; Yaari *et al.* 1983, 1986; Konnerth *et al.* 1986).

Computer models have been developed to test the role of lateral diffusion in the generation of seizure activity. Computer simulations are particularly valuable in this regard because manipulation of lateral diffusion (removing or adding the coupling) is not feasible in *in vitro* and *in vivo* experiments. The hypothesis is that sustained, spontaneous neuronal activity can be generated by potassium lateral diffusion coupling between neurons. To test this hypothesis, the effect of potassium lateral diffusion on the synchronization and generation of neuronal activity was examined using modified Hodgkin–Huxley (HH) type model neurons and more physiologically relevant CA1 pyramidal neurons (Park & Durand 2006).

(a) Model

A diffusion model consisting of three compartments is shown in figure 3*a* for the cell, the interstitial space, and the bath. Two modified Hodgkin & Huxley (1952) type cells were juxtaposed in the potassium bathing solution. One of the cells was electrically stimulated. Each cell was surrounded by interstitial space where potassium ions accumulate. Potassium pump dynamics (Tuckwell & Miura 1978; Bazhenov *et al.* 2004) and a glial uptake mechanism (Kager *et al.* 2000; Bazhenov *et al.* 2004) were included in the model to remove the excess potassium ions from the interstitial space. Equations, variables, and parameters for each HH type cell can be found in Park & Durand (2006).

The mechanism for generating potassium lateral diffusion-induced activity was also applied to a more physiologically relevant zero- Ca^{2+} 16-compartment CA1 pyramidal neuron model initially developed for simulating non-synaptic epileptiform activity (Shuai *et al.* 2003). The 16-compartment neuron model includes a single compartment soma, 10 compartments for apical dendrites and five compartments for basal

Figure 1. Synchrony of spontaneous low-calcium activity across a mechanical lesion. Neural activity is induced by a low-calcium solution in the hippocampal slice and recorded by two electrodes separated by 200 μm. (a) Before a cut: the cross variance between the activity recorded from the two electrodes indicates a high degree of synchrony between the two sites and periodicity. (b) After a cut (placed side-by-side): a cut is made between the two electrodes and the synchronization between the two sites is still present. (c) After a cut (separated by approx. 300 μm): the two sites are separated and the synchrony is lost. (d) After a cut (put two halves back together): the two cut sides are repositioned side by side and the synchrony is returned. These data indicate that a diffusible coupling mechanism exists between the two sides (Modified from Lian *et al.* 2001).

dendrites (figure 4a). In the simulation study, four CA1 pyramidal neurons were coupled through potassium lateral diffusion and each pyramidal model neuron was modelled by 25 variables. For integration of the differential equations, a Runge–Kutta fourth-order algorithm with time step of 0.01 ms (for HH type cell) and 0.005 ms (for CA1 pyramidal neuron) was used.

To estimate the synchronization, a ‘synchronization index (γ)’ was calculated and γ is described as follows:

$$\gamma^2 = \left[\frac{1}{N} \sum_{m=1}^N \cos(\Psi_m) \right]^2 + \left[\frac{1}{N} \sum_{m=1}^N \sin(\Psi_m) \right]^2 \\ = \langle \cos \Psi_m \rangle^2 + \langle \sin \Psi_m \rangle^2$$

where Ψ indicates relative phase and $\langle \rangle$ denotes average over time (or a large number of firing events N ; Pikovsky *et al.* 2001; Rosenblum *et al.* 2001; Park

et al. 2005). The relative phase Ψ is the instantaneous phase of one cell at the time when the other cell fires and it is expressed as follows:

$$\Psi_i(t_1) = 2\pi \times \left(\frac{t_1 - t_{2(i)}}{t_{2(i+1)} - t_{2(i)}} \right), \\ (t_{2(i)} \leq t_1 < t_{2(i+1)}; i = 0, 1, 2, 3 \dots).$$

The synchrony index scales between phase-locked and phase-unlocked state ($\gamma = 0$) with $\gamma = 1$ being the fully synchronized state.

(b) Sustained neuronal activity induced by potassium lateral diffusion

To examine the role of potassium lateral diffusion in the generation of neuronal activity, simulations with two HH type cells were performed in the presence and in the absence of the lateral diffusion process.

Figure 2. Extracellular potassium measurements in low-calcium activity. (a) Before a mechanical cut: potassium concentration in the CA1 region of the hippocampus is oscillating between 7 and 9 mM. (b) After a mechanical cut (placed side-by-side): potassium recordings are made after a cut has been made and obtained from an electrode located before the cut, within the cut and on the other side of the cut. The recording indicates that potassium concentration increases in the solution between the two sides. (c) After a mechanical cut (separated by approx. 300 μ m): when the two sides are separated, the potassium coupling signals disappear. These data suggest that a potassium wave is a possible coupling mechanism (Modified from Lian *et al.* 2001).

One of the cells (cell-1) was electrically stimulated with a current pulse (1 nA for 840 ms) to initiate activity. During stimulation cell-1 stopped firing as $[K^+]_o$ increased (up to approx. 40 mM) due to sodium inactivation. Following the termination of stimulus cell-1 resumed firing but not until $[K^+]_o$ decreased to approximately 20 mM. In the absence of lateral diffusion coupling, no activity was generated in cell-2 (figure 3b(i,ii)). However, when lateral diffusion coupling was present, spontaneous *sustained activity* was generated in cell-1 and cell-2 with the same level of stimulation as previously injected to cell-1 (1 nA for 840 ms; figure 3b(iii,iv)). When the lower level of stimulation was applied (1 nA for 825 ms), the activity lasted about 1 s. This transient activity is shown in figure 3b(v,vi). The results suggest that potassium lateral diffusion is responsible for the generation of sustained neuronal activity in this model.

(c) Effect of potassium lateral diffusion on synchronization

Since the potassium lateral diffusion process mediates a coupling, the role of lateral diffusion on synchronization was quantified using a synchrony index (γ). To estimate the index, the relative phases extracted from the spike times across the threshold were used (see

methods and fig. 5a in Park & Durand (2006) for details). Difference between cells was generated by varying potassium delayed-rectifier conductance (g_{KDR}) by 1 to 3 per cent: $\Delta g_{KDR} = (|g_{KDR,2} - g_{KDR,1}| / g_{KDR,1}) \times 100(\%)$. The index γ as a function of the lateral diffusion time constant (τ_{ss}) is shown in figure 3c. The synchrony index decreased as the lateral diffusion time constant was increased. Additionally, it has been shown that τ_{ss} can be expressed as the effective space constant x_{eff} (i.e. $x_{eff} \propto \sqrt{\tau_{ss}}$) and this space constant reflects a level of complexity of the path between cells (see appendix B in Park & Durand (2006) for details). The results show that an increase in the lateral diffusion time constant (or the space constant) weakens the coupling strength and decreases the synchrony level. Since the space constant depends on the extracellular space and therefore on the potassium concentrations, synchronization by potassium diffusion is a complex function of variables of the networks.

(d) Spontaneous activity generated by potassium diffusive coupling

Since it has been shown that synchronization of non-synaptic epileptiform activity observed from low-calcium hippocampal slice experiments is due to

Figure 3. Effect of potassium lateral diffusion on the generation and synchronization of neuronal activity in a two Hodgkin–Huxley (HH) type cell model system. Schematic of three compartment diffusion model where two HH type cells were embedded in the potassium bath is shown in (a). Each cell was inactive without electrical stimulation. Potassium ions released during neuronal firing were able to accumulate in the interstitial space (grey shadow around cells), diffuse to neighbouring interstitial spaces (lateral diffusion) and diffuse to the bath (dispersion). Excessive potassium concentration was cleared by potassium pump and glial buffer. Particularly, role of lateral diffusion in the generation of spontaneous sustained activity is shown in (b). In the absence of lateral diffusion, little activity in cell-1 (solid black line) but no activity in cell-2 (grey line) was observed during the supra-threshold stimulation (840 ms, 1 nA). Following the stimulation, self-regenerating activity was observed in cell-1 and still no activity was observed in cell-2; scale bar, 1 s (b(i,ii)). When lateral diffusion enabled excitation of cell-1 with the same supra-threshold current sustained activity was generated in both cells (b(iii,iv)). With sub-threshold current pulse (825 ms, 1 nA), however, the activation of cell-1 was able to generate transient activity in both cells. The parameter values used for the simulations were $r_v = 0.15$, $[K^+]_{bath} = 5$ mM, $\tau_{bs} = 500$ ms and $\tau_{ss} = 50$ ms. For sustained activity of two non-identical neurons, effect of lateral diffusion time constant τ_{ss} on synchronization is shown in (c). Difference between cells was generated by varying g_{KDR} by 1–3%. The details on synchronization index and other methodologies can be found in the methods in Park & Durand (2006). For the simulation, $r_v = 0.15$, $[K^+]_{bath} = 5.0$ mM and $\tau_{bs} = 500$ ms were used. (Modified from Park & Durand 2006)

Figure 4. Neuronal activity generated by potassium lateral diffusion in CA1 pyramidal neuronal network exposed to zero calcium solution. Schematic diagram of 16-compartment CA1 pyramidal neuronal network consisting of four neurons is shown in (a). The model neuron consists of five compartments for the basal dendrite, 10 compartments for the apical dendrite, and one compartment for the soma. Neuron-1 was excited by long pulse stimulation (40 s, 2 nA). With the volume ratio $r_v = 0.15$ and the radius of soma $R = 8.9 \mu\text{m}$, the distance between the first and the last was estimated as $74.56 \mu\text{m}$. The membrane potential of each neuron plotted in three different time-frames (b). While the neuron-1 was inactivated during the stimulation, neuron-2 started firing first, and then neuron-3 and finally neuron-4 fired consecutively showing propagation in time. Immediately following stimulation, neuron-1 was activated and the activity for all neurons lasted about 50 s. The bursting patterns observed in experiments and in simulations are compared and shown in (c). The spontaneous triplet bursting observed from experiments (see fig. 3A in Shuai *et al.* (2003)) is shown on the right and the bursting pattern obtained from the simulation is shown on the left. (Modified from Park & Durand 2006)

potassium diffusion (Lian *et al.* 2001), a network of more physiologically relevant CA1 pyramidal neurons exposed to zero calcium solution was used to validate the simulation results obtained from the two-HH type cell model. A model consisting of four neurons with their surrounding network structure is shown in figure 4a. One of the neurons was stimulated by a 2 nA pulse for 40 s. In the absence of lateral diffusion only the stimulated cell was activated, whereas the

other three neurons remained silent (data not shown). In the presence of potassium lateral diffusion, spontaneous activity was generated in neurons (neuron-2, neuron-3 and neuron-4) with a time delay in response to stimulation applied to neuron-1. The potassium-induced activity propagated with the velocity of approximately 1 mm s^{-1} which is well within the physiological range (figure 4b). The simulated triplet bursting shown in the grey inset of

figure 4b is quite similar to the pattern observed in low-calcium experiments (Konnerth *et al.* 1986; Shuai *et al.* 2003).

(e) Model validation

- An increase in potassium concentration to about 11 mM observed in the model is well within the physiological ‘ceiling level’ (9–12 mM; Moody *et al.* 1974; Heinemann & Lux 1977; Heinemann *et al.* 1983).
- Spontaneous bursting activity can propagate throughout the network and corresponding potassium wave propagation velocity ($74.56 \mu\text{m}$ (distance from neurons 1–4)/4 neurons/20 ms (lateral diffusion time constant) approx. 1 mm s^{-1}) falls within the range of experimentally obtained values: $0.44\text{--}4.2 \text{ mm s}^{-1}$ in Konnerth *et al.* (1984); $0.43\text{--}3.64 \text{ mm s}^{-1}$ in Lian *et al.* (2001); $0.2\text{--}5 \text{ mm s}^{-1}$ in Yaari *et al.* (1986) in low Ca^{2+} . More importantly, in normal Ca^{2+} , propagation velocity of seizure activity has been confirmed to be similar to that of potassium wave ($0.18\text{--}0.83 \text{ mm s}^{-1}$; Weissinger *et al.* 2000).
- The triplet spontaneous bursting pattern observed in experiments (Konnerth *et al.* 1986; Shuai *et al.* 2003) was also successfully reproduced by the model (Park & Durand 2006).

In this diffusive coupling model of a neural network without gap junctions or synaptic transmission, the results show that the potassium lateral diffusion process alone is necessary and sufficient to generate and synchronize sustained neuronal activity in a simple two-HH type cell model system. The synchronization level is dependent upon the lateral diffusion time constant. Additionally, neuronal activities are desynchronized as the time constant increased or as the space constant increased. The simulations performed with a CA1 pyramidal neuron network suggest that potassium lateral diffusion may serve as a potential mechanism to explain the non-synaptic activity observed in *in vitro* and *in vivo* experiments performed in low- Ca^{2+} solution (Feng & Durand 2003).

4. DIFFUSIVE COUPLING CAN INDUCE PERIODIC ACTIVITY IN NEURAL NETWORKS

Consistent with the experimental observations, computer simulations with a three compartment diffusion model wherein two HH type cells are placed side by side and coupled through potassium diffusion have also shown that the synchronized activity could be attributed to *potassium lateral diffusion* (Park & Durand 2006). In general, synchronization is achieved through a mutual interaction due to a coupling between two or more oscillatory systems. One of the most extensively studied coupling mechanisms is *global coupling* (or *all-to-all coupling*) through which each individual oscillator interacts with equal strength with all the other oscillators in the system (Ostborn 2004). Another type of coupling mechanism in many physical systems is *local coupling* or *diffusive coupling* (or *nearest-neighbour coupling*). Diffusive coupling mediates a local interaction only between an individual

Figure 5. *In vivo* non-synaptic SE-like activity and distribution of inter-event intervals. Thirty second long *in vivo* SE-like activity observed in the rat hippocampus exposed to EGTA, low extracellular calcium and high extracellular potassium solution is shown in (a). As shown in the inset, time intervals ΔT are estimated by the interval between consecutive two maximum peaks (events). (b) A distribution of the mean inter-event intervals for six other *in vivo* data sets including the data shown in (a) demonstrates that the structure of distribution with a local maximum around 0.25 s (4 Hz) is stable. Each dataset was recorded for 1 to 2 min with the sampling rate of 20 KHz following 60, 65, 70, 75, 80, 85 min the use of EGTA. (Modified from Park & Durand 2006)

component of the network and its nearest neighbours. Therefore, in the current context of computer model simulation studies, *potassium dispersion* where each cell is coupled with all other cells in the network through the same potassium bath can be characterized as *global coupling*. *Potassium lateral diffusion* through which each cell interacts only with its neighbouring cells can be characterized as local coupling or *diffusive coupling*.

Recently, extracellular potassium concentration has also been suggested as a causative factor in the generation of non-synaptic epileptiform activity in *in vivo* experiments with anesthetized rats (Feng & Durand 2006). The results showed that an increase of extracellular potassium concentration from 6 to 12 mM was responsible for a transformation from a typical non-synaptic burst ($0.34 \pm 0.14 \text{ Hz}$) into a regular type of epileptiform activity ($3.77 \pm 1.28 \text{ Hz}$), which lasted longer than 30 min. The physiological properties of the activity such as frequency and duration are consistent with those of SE reported in the literature (Coulter & DeLorenzo 1999).

However, a fundamental mechanism underlying the specific periodic activity (see figure 5) is not clear. Since synaptic transmission was blocked by lowering Ca^{2+} concentration in this *in vivo* experiment, a non-synaptic mechanism such as potassium lateral diffusion could explain the results. This experimental configuration includes both a potassium dispersion mechanism (global coupling) and a potassium lateral

Figure 6. Extracellular field potential activity and intracellular activity using the neuronal network model with potassium lateral diffusion. Schematic diagram of zero calcium 16-compartment CA1 pyramidal neurons arranged in two-dimensional array embedded in the potassium bath is shown in (a). Two diffusion coupling processes were incorporated into the three compartment diffusion model: potassium dispersion (global coupling) and potassium lateral diffusion (diffusive coupling). For potassium clearance mechanisms, potassium pump and glial buffer uptake were used. To calculate the field potential, the distance (r) between the virtual recording location (solid circle) and the centre of each cell was used. Field potential activity and inter-event interval distribution in the presence and absence of diffusive coupling are shown in (b(i,ii)) and (c(i,ii)), respectively. With potassium lateral diffusion coupling, field potential activity shows a periodic pattern (b(i)) and the average inter-event interval distribution for 10 realizations reveals a clear local maximum around 0.25 s (b(ii)). Without diffusive coupling, no periodicity in field potential activity can be detected (c(i)) and no clear peak can be observed in the inter-event interval distribution for 10 different realizations (c(ii)). Intracellular activity and relative phase distribution in the presence and the absence of diffusive coupling are shown in b(iii,iv) and c(iii,iv), respectively. With potassium lateral coupling, phases of neuronal firings (activities of five neurons out of sixteen are shown here) are locked (b(iii)) and this locking is confirmed by preferred phases shown in the cyclic relative phase distribution (b(iv)). Without lateral diffusion coupling, however, phases of neuronal firings keep slipping (c(iii)) and this desynchronized state is confirmed by absence of a local maximum around the preferred phase value in the relative phase distribution (c(iv)). For the simulations, parameter values used were $\tau_{ss} = 5$ ms and $n = 16$. The different types of lines indicate neuronal activity from different cells. (Modified from Park & Durand 2006)

diffusion mechanism (diffusive coupling) since CA1 pyramidal cells are embedded in the same potassium bath and concurrently the cells are aligned and packed; thus, local cell-to-cell coupling is quite feasible. Computer simulation experiments were carried out to test the hypothesis that potassium *diffusive coupling can promote network periodicity under low-calcium non-synaptic conditions in an in vivo rat preparation*. To test this hypothesis a diffusively coupled network of 16-compartment CA1 pyramidal neurons was used.

(a) Two-dimensional diffusive coupling neural network model

Sixteen-compartment CA1 pyramidal neurons modelled for zero- Ca^{2+} solution were arranged in two-dimensional array (see figure 6a) and these neurons were coupled through the potassium lateral diffusion. At the macroscopic level, the diffusion process and

potassium clearance mechanism (glial buffer and potassium pump) were implemented by the three compartment diffusion model (Park & Durand 2006). At the microscopic level, the kinetics of single cell for all channels was constructed based on the previous 16-compartment model developed for simulating low-calcium non-synaptic epileptiform activity (Shuai et al. 2003). The additional modifications were made to incorporate the diffusion process with each neuron (Park & Durand 2006). A 10 per cent reduced function of the potassium pump was used to generate spontaneous neuronal activity. Equations including variables, currents and the parameter values used in the simulations are given in tables 1–4 in Park et al. (2008). Among several parameters, potassium delayed-rectifier conductance (g_{KDR}) and sodium conductance (g_{Na}) were changed to generate the parameter disparity between the cells. Extracellular field potential periodicity was monitored by the inter-

event interval distribution obtained from *in vivo* experiments (Feng & Durand 2006) and simulations. For intracellular neuronal activity, synchronized periodic behaviour was monitored by cyclic relative phase distribution. The relative phases were estimated from each pair of neurons of the network and synchronization was identified by phase locking of the neuronal activities (see methods in Park *et al.* (2008) for details).

(b) Periodic extracellular activity in *in vivo* preparation and in computational network model

By implementing diffusive coupling between each cell and its nearest neighbours, the network model simulations were able to generate neural activity similar to that observed in *in vivo* network lacking synaptic transmission. The network activity was estimated by the field potential. As indicated in figure 6*a* and as described previously in Park *et al.* (2008), the extracellular field potential was calculated by summing the electrical activity of each cell weighted by their distance (r) to the recording site. The network periodicity was monitored by the inter-event interval distribution for which simulations were performed in 10 separate trials, and the numbers falling into each bin of the histogram were averaged for all the trials.

In the presence of diffusive coupling, the network generated *periodic* field potential activity. The periodicity observed in this simulated model was confirmed by a clear peak around 0.25 s (4 Hz) in the inter-event interval distribution shown in figure 6*b*. As shown earlier in figure 5*b*, similar periodicity in *in vivo* experimental data was detected by a well-defined peak centred at approximately 0.25 s in the inter-event interval distribution obtained from six different *in vivo* data sets. When the potassium lateral diffusion (diffusive coupling) was removed while potassium dispersion (global coupling) remained intact, the network still generated activity (figure 6*c*(i)) but with no periodic pattern as indicated in figure 4*c*. As confirmed by the distributions shown in figure 6*b,c*, the emergence of periodic activity taking place in the presence of potassium diffusion coupling is robust. Therefore, the results suggest that diffusive coupling, but not global coupling, is responsible for generating periodic activity in the network lacking synaptic transmission.

(c) Synchronized periodic intracellular activity in the presence of lateral diffusion coupling

To understand the mechanism underlying extracellular periodicity appearing with potassium lateral diffusion, the effect of diffusive coupling on intracellular activity in the network was examined. Each cell in the network independently produced a periodic burst and the bursts are much more broadly distributed in the absence of lateral diffusion coupling (figure 6*c*(iii)) compared with those in the presence of diffusive coupling (figure 6*b*(iii)), suggesting that the lateral diffusion is necessary for synchronized activity.

The firing rate of a periodic burst was about 4 Hz which is similar to the rate of *in vivo* experimental activity. Therefore, the histogram of mean frequency

values in the absence and in the presence of lateral diffusion coupling show about the same frequency distribution with a local maximum around 4 Hz (see fig. 4*b,e* in Park *et al.* (2008)). When the frequencies of the individual oscillators are only slightly different, frequency alone is not a sufficient basis for identifying true synchronization, since it is possible to falsely identify an uncoupled state as a synchronized state simply because individual frequencies of the elements in the network are similar. In this particular situation, synchronization can be revealed by a local maximum around a preferred phase in the distribution of the relative phase (Schäfer *et al.* 1999). In the presence of both diffusive coupling and global coupling, synchronization was detected by a well-defined peak in the phase distribution as shown in figure 6*b*(iv), but when diffusive coupling was removed and global coupling still remained the peak disappeared and no synchronization was observed. Therefore, the results show that lateral diffusion coupling is responsible for network periodicity based on phase locking of the intracellular activity in this model.

Taken together, these simulations indicate that potassium lateral diffusion (or diffusive coupling) is responsible for generating synchronized periodic activity in the absence of synaptic transmission in the network model and could explain the periodic non-synaptic epileptiform activity observed in the *in vivo* preparation.

5. ROLE OF POTASSIUM DIFFUSION IN AXON BUNDLES

Neural networks are a collection of interconnected neurons, and axons are usually neglected in the simulation of the behaviour of networks. Yet the nervous system is composed of both grey and white matter, with white matter fibre tracts occupying a large portion of the brain. Previous experiments have shown that electrical stimulation of axons' tracts induced potassium elevation, membrane depolarization and excitation of adjacent fibres by potassium diffusion (Eng & Kocsis 1987). Therefore, the diffusion of potassium could have an important effect on the activity of the network if neuronal activity along the axons is also modulated by potassium coupling. High frequency electrical stimulation (HFS) of the central and peripheral nervous systems (CNS, PNS) can modulate both somatic and axonal activity *in vitro*, *in vivo* and *in situ* (Benabid *et al.* 1998; Garcia *et al.* 2003; Hashimoto *et al.* 2003; Kilgore & Bhadra 2006; Hung *et al.* 2007; Tai *et al.* 2007). Historically, studies have emphasized the effect of electrical stimulation on activity at the cell body, with suppression of somatic activity during stimulation predominating (figure 7*a,b*; D'Ambrosio *et al.* 1998; Beurrier *et al.* 2001; Bikson *et al.* 2001; Garcia *et al.* 2003; Lee *et al.* 2003; Richardson *et al.* 2003; D'Ambrosio 2004). Recent studies have shown that electrical stimulation also generates changes in axonal activity (Raastad & Shepherd 2003; Soleng *et al.* 2004; Meeks *et al.* 2005; Iremonger *et al.* 2006; De Col *et al.* 2008) including a depression of excitatory synaptic currents (Iremonger *et al.* 2006; Schiller & Bankirer 2007), and conduction blockade in the PNS

Figure 7. Electrical stimulation generates suppression of spontaneous and evoked somatic and axonal activity. (a) Local electric stimulation (suprathreshold 50 Hz sinusoidal) blocks spontaneous epileptiform activity (low- Ca^{2+}). Bar indicates the duration of stimulation. Stimulation was applied to the CA1 somatic layer (filled circle; Lian *et al.* 2003). (b,c) Local stimulation (suprathreshold 50 Hz sinusoidal) blocked evoked potentials under physiological conditions (Jensen & Durand 2007). Blocking stimulation applied to the CA1 somatic layer in (b), and the alvear axon field in (c). Recording sites denoted by filled boxes. (Modified from Jensen & Durand 2007)

(Kilgore & Bhadra 2006; Ragnarsson 2007; Tai *et al.* 2007) and in the CNS (figure 7c; Jensen & Durand 2007). Thus, changes in neural activity induced by electrical stimulation provide a means to modulate abnormal communication at several levels within the target network. In the case of somatic suppression and axonal conduction block, HFS is hypothesized to cause a non-specific suppression of target structures via depolarization blockade (Benazzouz *et al.* 1995; Garcia *et al.* 2003; Meeks & Mennerick 2004; Meeks *et al.* 2005). In general, excess potassium in the extracellular space is thought to mediate development of depolarization blockade (Benazzouz *et al.* 1995; Garcia *et al.* 2003; Meeks & Mennerick 2004; Meeks *et al.* 2005). Yet, it is unclear whether the blockade observed during electrical stimulation is the direct effect of: (i) potassium upon neural elements within the target (Jensen & Durand 2007; Bellinger *et al.* 2008b); or (ii) stimulation on voltage gated channel dynamics leading to impairment of action potential

initiation and conduction (Diamond & Jahr 2000; Beurrier *et al.* 2001; Kilgore & Bhadra 2006).

(a) Effect of potassium on axonal conduction

Repetitive stimulation has long been associated with increases in extracellular potassium that, in part, produce changes in neural excitability (Gutnick *et al.* 1979; Kocsis *et al.* 1983; Poolos *et al.* 1987; Benazzouz *et al.* 1995; Kaila *et al.* 1997; Beurrier *et al.* 2001; Garcia *et al.* 2003; Jensen & Durand 2007; Shin *et al.* 2007). Excess potassium alters brain function, generating abnormal network activity and modulating the efficacy of somatic and axonal communication. As potassium concentrations increase, neurons depolarize, leading to tonic inactivation of sodium channels. As a result, sustained inactivation of sodium channels could lead to suppression of somatic and axonal communication.

In the case of axonal conduction, elevated extracellular potassium concentrations are known to reduce action potential amplitude, depress presynaptic

potentials and affect axonal signalling (Hablitz & Lundervold 1981; Meeks & Mennerick 2004; Meeks *et al.* 2005; Shin *et al.* 2007). Additionally, potassium levels sufficient to produce changes in axonal and somatic activity have been recorded using potassium selective microelectrodes (KSMs) in the presence of electrical stimulation under a number of pathological and physiological conditions (figure 8*a,b*; Garcia *et al.* 2003; Jensen & Durand 2007). These stimulus-induced changes in extracellular potassium have been correlated with block of axonal conduction (figure 8*c*; Garcia *et al.* 2003; Jensen & Durand 2007). Recent computer modelling studies show a clear role for potassium dynamics in HFS-induced conduction block during electrical stimulation (Bellinger *et al.* 2008*a*; Liu *et al.* 2008). Also, elevated potassium concentrations in the bath within the ranges observed during stimulus-induced conduction block, are sufficient to depress action potential amplitude and can affect axonal signalling (Hablitz & Lundervold 1981; Kocsis *et al.* 1983; Poolos *et al.* 1987; Peacock & Orchardson 1999; Meeks & Mennerick 2004; Shin *et al.* 2007). Of particular note, potassium concentrations required for complete conduction block are generally higher than those recorded using potassium sensitive electrodes. These differences are due, in part, to the known underestimation of extracellular potassium concentrations by KSMs (Poolos *et al.* 1987; Chvatal *et al.* 1999; Garcia *et al.* 2003), since these electrodes measure the average potassium concentration around the electrode tip.

Finally, elevated potassium concentrations (pathological, stimulus-induced) are associated with changes in voltage gated ion conductances such as I_{NaP} and I_h (Beurrier *et al.* 2001; Shin & Carlen 2008). Alternation of gating in the persistent sodium channel produces sustained depolarization, such as potassium-induced failure of inactivation as observed during hyperkalemic periodic paralysis (Cannon *et al.* 1991). An initial increase in potassium may cause depolarization which opens the persistent sodium channels leading to additional sustained depolarization during stimulation even as extracellular potassium concentration decreases. Elevations in extracellular potassium have been shown to increase the persistent sodium current amplitude in isolated cells as well as hippocampal slices (Somjen & Mueller 2000). Sustained enhancement of persistent sodium conductances could lead to prolonged depolarization-induced failure of inactivation.

(b) Sources of potassium during electrical stimulation of axons

The source of extracellular potassium concentration increases during repetitive stimulation is unclear, and could be axonal, cellular and/or glial in origin. Somata are known to release ions and neurotransmitters in response to electrical stimulation (Poolos *et al.* 1987; Mitchell *et al.* 1993; Sakatani *et al.* 1994; Garcia *et al.* 2003). While glial cells help maintain potassium homeostasis through spatial buffering (Amedee *et al.* 1997; Chvatal *et al.* 1999; Zhou & Kimelberg 2000), alterations in their ability to remove and redirect potassium could generate elevations in

Figure 8. Extracellular potassium increases during stimulation. (a*i*) Low Ca^{2+} epileptiform activity was suppressed by a locally applied suprathreshold AC field. (a*ii*) The stimulation resulted in a transient increase in extracellular potassium (Lian *et al.* 2004; scale bar, 10 s). (b*i*) Changes in extracellular potassium occurred during sinusoidal stimulation in a stimulus amplitude dependent manner. Increases in potassium were transient (Jensen & Durand 2007). (b*ii*) Axonal activity was suppressed by a local AC field. Conduction block was achieved in a stimulus amplitude dependent manner (Jensen & Durand 2007). (c) Suppression of axonal activity was correlated with stimulus induced increases in extracellular potassium (Modified from Jensen & Durand 2007).

extracellular concentrations. The role of axons in potassium homeostasis has been analysed from computational studies (Bellinger *et al.* 2008*a,b*; Liu *et al.* 2008), and is difficult to assess experimentally.

(c) Role of glia cells

In the CNS, myelinating oligodendrocytes and surrounding glia express voltage-gated potassium conductances (I_{KDr} , I_{Ka} , I_{Kir}) involved in maintaining $[K^+]_o$ homeostasis (Barres *et al.* 1990; Ritchie 1992;

Tse et al. 1992; Sontheimer & Waxman 1993; Amedee et al. 1997; D'Ambrosio et al. 1998; Chvatal et al. 1999). In addition, potassium channels are distributed not only in the dendrites and soma of CA1 pyramidal cells, but also are present along the axon (juxtaparanodal regions, Kv1.1, Kv1.2) and in its terminals (Mongilner et al. 2001; Pedraza et al. 2001; Devaux et al. 2003). Therefore, electrical stimulation may impair the ability of glia and/or axons to modulate potassium, leading to an excess build up of potassium in the extracellular and submyelin space. Prior research indicates that glia are not able to handle potassium buffering in the presence of electrical fields, specifically, the clearance of excess extracellular potassium (Chvatal et al. 1999; Bikson et al. 2001). However, it is not known whether HFS acts to modulate potassium dynamics through (i) voltage gated conductances (influx, efflux) or (ii) uptake via electrogenic pumps. The literature indicates that although glutamate release is enhanced during pulse train HFS (Lee et al. 2004), electrogenic pumps are not adversely affected, maintaining glutamate and potassium clearance during stimulation (Diamond & Jahr 2000).

6. CONCLUSIONS

Diffusive coupling has been studied extensively in the literature but its effect on neural tissue had not been identified. Both computer simulations and experiments confirm the fact that potassium diffusion can be a coupling mechanism in neural tissue affecting the activity in both cell bodies and axons within neural networks. In particular, experiments suggest that the synchronization of the neuronal activity within neural networks in the hippocampus can be increased or decreased by potassium diffusion. Moreover, potassium diffusion seems to be responsible for generating synchronized and periodic neural activity in the absence of synaptic transmission. Therefore diffusion alone can modulate the activity within the neural network. This effect of potassium is strongly enhanced by electrical stimulation. Although short pulse trains can be sufficient to generate a significant increase in potassium concentrations, HFS leads to strong depolarization of membrane in axons and cell bodies leading to depolarization block of neural activity. This effect must be reconciled with the fact that neurons can fire at high rates (at least for short periods of time) such as those used in deep brain stimulation (approx. 130 Hz). Synchronized activation of axons and cells by an applied electric field or epileptiform activity is known to produce a large increase in potassium concentration that can alter neural activity in the network. This diffusive coupling effect is observed only when the potassium concentration is higher than normal, suggesting that its importance may be limited to pathological conditions whereby many elements are firing simultaneously, such as in epilepsy. However, a high level of activity in neural networks whereby the extracellular space is limited could be sufficient to induce this effect of diffusive potassium coupling and alter the normal activity of a neural network. Lateral potassium diffusion in neuronal networks could therefore be a physiological

realization of the well-studied theoretical model system known as diffusive coupling.

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REFERENCES

- Aiello, G. L. & Bach-y-Rita, P. 2000 The cost of an action potential. *J. Neurosci. Methods* **103**, 145–149. (doi:10.1016/S0165-0270(00)00308-3)
- Amedee, T., Robert, A. & Coles, J. 1997 Potassium homeostasis and glial energy metabolism. *Glia* **21**, 46–55. (doi:10.1002/(SICI)1098-1136(199709)21:1<46::AID-GLIA5>3.0.CO;2-#)
- Balenzuela, P. & Garcia-Ojalvo, J. 2005 Role of chemical synapses in coupled neurons with noise. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **72**, 021901. (doi:10.1103/PhysRevE.72.021901)
- Bar-Eli, K. 1985 On the stability of coupled chemical oscillators. *Physica D: Non-linear oscillators* **14**, 242–252. (doi:10.1016/0167-2789(85)90182-4)
- Barres, B., Chun, L. & Corey, D. 1990 Ion channels in vertebrate glia. *Annu. Rev. Neurosci.* **13**, 441–474. (doi:10.1146/annurev.ne.13.030190.002301)
- Bazhenov, M., Timofeev, I., Steriade, M. & Sejnowski, T. J. 2004 Potassium model for slow (2–3 Hz) *in vivo* neocortical paroxysmal oscillations. *J. Neurophysiol.* **92**, 1116–1132. (doi:10.1152/jn.00529.2003)
- Bellinger, S., Miyazawa, G. & Steinmetz, P. 2008a Submyelin potassium accumulation may functionally block subsets of local axons during deep brain stimulation: a modeling study. *J. Neural Eng.* **5**, 263–274. (doi:10.1088/1741-2560/5/3/001)
- Benabid, A., Benazzouz, A., Hoffmann, D., Limousin, P., Krack, P. & Pollak, P. 1998 Long-term electrical inhibition of deep brain targets in movement disorders. *Mov. Disord.* **13**, 119–125.
- Benazzouz, A., Piallat, B., Pollak, P. & Benabid, L. 1995 Responses of substantia nigra pars reticulata and globus pallidus complex to high frequency stimulation of the subthalamic nucleus in rats: electrophysiological data. *Neurosci. Lett.* **189**, 77–80. (doi:10.1016/0304-3940(95)11455-6)
- Beurrier, C., Bioulac, B., Audin, J. & Hammond, C. 2001 High-frequency stimulation produces a transient blockade of voltage-gated currents in subthalamic neurons. *J. Neurophysiol.* **85**, 1351–1356.
- Bihi, R. I., Jefferys, J. G. & Vreugdenhil, M. 2005 The role of extracellular potassium in the epileptogenic transformation of recurrent GABAergic inhibition. *Epilepsia* **46**, 64–71. (doi:10.1111/j.1528-1167.2005.01011.x)
- Bikson, M., Ghai, R. S., Baraban, S. C. & Durand, D. M. 1999 Modulation of burst frequency, duration, and amplitude in the zero-Ca(2+) model of epileptiform activity. *J. Neurophysiol.* **82**, 2262–2270.
- Bikson, M., Lian, J., Hahn, P. J., Stacey, W. C., Sciortino, C. & Durand, D. M. 2001 Suppression of epileptiform activity by high frequency sinusoidal fields in rat hippocampal slices. *J. Physiol. (Lond.)* **531**, 181–191. (doi:10.1111/j.1469-7793.2001.0181j.x)
- Bikson, M., Baraban, S. C. & Durand, D. M. 2002 Conditions sufficient for nonsynaptic epileptogenesis in the CA1 region of hippocampal slices. *J. Neurophysiol.* **87**, 62–71.
- Bragdon, A. C., Kojima, H. & Wilson, W. A. 1992 Suppression of interictal bursting in hippocampus unleashes

- seizures in entorhinal cortex: a proepileptic effect of lowering $[K^+]_o$ and raising $[Ca^{2+}]_o$. *Brain Res.* **590**, 128–135. (doi:10.1016/0006-8993(92)91088-V)
- Cannon, S., Brown, R. & Corey, D. 1991 A sodium channel defect in hyperkalemic periodic paralysis: potassium-induced failure of inactivation. *Neuron* **6**, 619–626. (doi:10.1016/0896-6273(91)90064-7)
- Chvatal, A., Anderova, M., Ziak, D. & Sykova, E. 1999 Glial depolarization evokes a larger potassium accumulation around oligodendrocytes than around astrocytes in gray matter of rat spinal cord slices. *J. Neurosci. Res.* **56**, 493–505. (doi:10.1002/(SICI)1097-4547(19990601)56:5<493::AID-JNR5>3.0.CO;2-O)
- Coulter, D. A. & DeLorenzo, R. J. 1999 Basic mechanisms of status epilepticus. *Adv. Neurol.* **79**, 725–733.
- D'Ambrosio, R. 2004 The role of glial membrane ion channels in seizures and epileptogenesis. *Pharmacol. Therapeut.* **103**, 95–108. (doi:10.1016/j.pharmthera.2004.05.004)
- D'Ambrosio, R., Wenzel, J., Schwartzkroin, P. A., McKhann II, G. M. & Janigro, D. 1998 Functional specialization and topographic segregation of hippocampal astrocytes. *J. Neurosci.* **18**, 4425–4438.
- D'Ambrosio, R., Maris, D. O., Grady, M. S., Winn, H. R. & Janigro, D. 1999 Impaired K^+ homeostasis and altered electrophysiological properties of post-traumatic hippocampal glia. *J. Neurosci.* **19**, 8152–8162.
- De Col, R., Messlinger, K. & Carr, R. 2008 Conduction velocity is regulated by sodium channel inactivation in unmyelinated axons innervating the rat cranial meninges. *J. Physiol.* **586**, 1089–1103. (doi:10.1113/jphysiol.2007.145383)
- Devaux, J., Alcaraz, G., Grinspan, J., Bennett, V., Joho, R., Crest, M. & Scherer, S. S. 2003 Kv3.1b is a novel component of CNS nodes. *J. Neurosci.* **23**, 4509–4518.
- Diamond, J. S. & Jahr, C. E. 2000 Synaptically released glutamate does not overwhelm transporters on hippocampal astrocytes during high-frequency stimulation. *J. Neurophysiol.* **83**, 2835–2843.
- Dreier, J. P. & Heinemann, U. 1990 Late low magnesium-induced epileptiform activity in rat entorhinal cortex slices becomes insensitive to the anticonvulsant valproic acid. *Neurosci. Lett.* **119**, 68–70. (doi:10.1016/0304-3940(90)90757-Z)
- Eng, D. L. & Kocsis, J. D. 1987 Activity-dependent changes in extracellular potassium and excitability in turtle olfactory nerve. *J. Neurophysiol.* **57**, 740–754.
- Feng, Z. & Durand, D. M. 2003 Low-calcium epileptiform activity in the hippocampus *in vivo*. *J. Neurophysiol.* **90**, 2253–2260. (doi:10.1152/jn.00241.2003)
- Feng, Z. & Durand, D. M. 2006 Effects of potassium concentration on firing patterns of low-calcium epileptiform activity in anesthetized rat hippocampus: inducing of persistent spike activity. *Epilepsia* **47**, 727–736. (doi:10.1111/j.1528-1167.2006.00499.x)
- Fertziger, A. P. & Ranck Jr, J. B. 1970 Potassium accumulation in interstitial space during epileptiform seizures. *Exp. Neurol.* **26**, 571–585. (doi:10.1016/0014-4886(70)90150-0)
- Fisher, R. S., Pedley, T. A. & Prince, D. A. 1976 Kinetics of potassium movement in normal cortex. *Brain Res.* **101**, 223–237. (doi:10.1016/0006-8993(76)90265-1)
- Frankenhaeuser, B. & Hodgkin, A. L. 1956 The after-effects of impulses in the giant nerve fibres of *Loligo*. *J. Physiol.* **131**, 341–376.
- Garcia, L., Audin, J., D'Alessandro, G., Bioulac, B. & Hammond, C. 2003 Dual effect of high-frequency stimulation on subthalamic neuron activity. *J. Neurosci.* **23**, 8743–8751.
- Green, J. D. 1964 The hippocampus. *Physiol. Rev.* **44**, 561–608.
- Gutnick, M. J., Heinemann, U. & Lux, H. D. 1979 Stimulus induced and seizure related changes in extracellular potassium concentration in cat thalamus (VPL). *Electroencephalogr. Clin. Neurophysiol.* **47**, 329–344. (doi:10.1016/0013-4694(79)90284-0)
- Hablitz, J. J. & Lundervold, A. 1981 Hippocampal excitability and changes in extracellular potassium. *Exp. Neurol.* **71**, 410–420. (doi:10.1016/0014-4886(81)90099-6)
- Hale, J. 1996 Diffusive coupling, dissipation, and synchronization. *J. Dyn. Differential Equations* **9**, 1–52. (doi:10.1007/BF02219051)
- Han, S., Kurrer, C. & Kuramoto, Y. 1995 Dephasing and bursting in coupled neural oscillators. *Phys. Rev. Lett.* **75**, 3190–3193. (doi:10.1103/PhysRevLett.75.3190)
- Hashimoto, T., Elder, C. M., Okun, M. S., Patrick, S. K. & Vitek, J. L. 2003 Stimulation of the subthalamic nucleus changes the firing pattern of pallidal neurons. *J. Neurosci.* **23**, 1916–1923.
- Heinemann, U. & Lux, H. D. 1977 Ceiling of stimulus induced rises in extracellular potassium concentration in the cerebral cortex of cat. *Brain Res.* **120**, 231–249. (doi:10.1016/0006-8993(77)90903-9)
- Heinemann, U., Neuhaus, S. & Dietzel, I. 1983 Aspects of K^+ regulation in normal and gliotic brain tissue. In *Cerebral blood flow, metabolism and epilepsy* (eds M. Baldy-Moulinier, D. Ingvar & B. Meldrum), pp. 271–278. London, UK: John Libbey.
- Hodgkin, A. L. & Huxley, A. F. 1952 A quantitative description of membrane current and its application to conduction and excitation in nerve. *J. Physiol.* **117**, 500–544.
- Hung, S. W. et al. 2007 Long-term outcome of bilateral pallidal deep brain stimulation for primary cervical dystonia. *Neurology* **68**, 457–459. (doi:10.1212/01.wnl.0000252932.71306.89)
- Iremonger, K. J., Anderson, T. R., Hu, B. & Kiss, Z. H. 2006 Cellular mechanisms preventing sustained activation of cortex during subcortical high frequency stimulation. *J. Neurophysiol.* **96**, 613–621. (doi:10.1152/jn.00105.2006)
- Izquierdo, I., Nasello, A. G. & Marichich, E. S. 1970 Effects of potassium on rat hippocampus: the dependence of hippocampal evoked and seizure activity on extracellular potassium levels. *Arch. Int. Pharmacodyn. Ther.* **187**, 318–328.
- Janigro, D., Gasparini, S., D'Ambrosio, R., McKhann II, G. & DiFrancesco, D. 1997 Reduction of K^+ uptake in glia prevents long-term depression maintenance and causes epileptiform activity. *J. Neurosci.* **17**, 2813–2824.
- Jefferys, J. G. & Haas, H. L. 1982 Synchronized bursting of CA1 hippocampal pyramidal cells in the absence of synaptic transmission. *Nature* **300**, 448–450. (doi:10.1038/300448a0)
- Jensen, A. & Durand, D. 2007 Suppression of axonal conduction by sinusoidal stimulation in rat hippocampus *in vitro*. *J. Neural Eng.* **4**, 1–16. (doi:10.1088/1741-2560/4/2/001)
- Jensen, M. S. & Yaari, Y. 1997 Role of intrinsic burst firing, potassium accumulation, and electrical coupling in the elevated potassium model of hippocampal epilepsy. *J. Neurophysiol.* **77**, 1224–1233.
- Kager, H., Wadman, W. J. & Somjen, G. G. 2000 Simulated seizures and spreading depression in a neuron model incorporating interstitial space and ion concentrations. *J. Neurophysiol.* **84**, 495–512.
- Kaila, K., Lamsa, K., Smirnov, S., Taira, T. & Voipio, J. 1997 Long-lasting GABA-mediated depolarization evoked by high-frequency stimulation in pyramidal

- neurons of rat hippocampal slice is attributable to a network-driven, bicarbonate-dependent K^+ transient. *J. Neurosci.* **17**, 7662–7672.
- Kilgore, K. L. & Bhadra, N. 2006 High frequency mammalian nerve conduction block: simulations and experiments. In *Conf. Proc. IEEE Eng. Med. Biol. Soc.* **1**, 4971–4974.
- Kocsis, J., Malenka, R. & Waxman, S. 1983 Effects of extracellular potassium concentration on the excitability of the parallel fibres of the rat cerebellum. *J. Physiol. (Lond.)* **334**, 225–244.
- Konnerth, A., Heinemann, U. & Yaari, Y. 1984 Slow transmission of neural activity in hippocampal area CA1 in absence of active chemical synapses. *Nature* **307**, 69–71. (doi:10.1038/307069a0)
- Konnerth, A., Heinemann, U. & Yaari, Y. 1986 Nonsynaptic epileptogenesis in the mammalian hippocampus *in vitro*. I. Development of seizurelike activity in low extracellular calcium. *J. Neurophysiol.* **56**, 409–423.
- Kuramoto, Y. 1975 *International symposium on mathematical problems in theoretical physics*. Lecture Notes in Physics, no. 30, p. 140. New York, NY: Springer.
- Lacaille, J. C. & Schwartzkroin, P. A. 1988 Stratum lacunosum-moleculare interneurons of hippocampal CA1 region. II. Intracellular and intradendritic recordings of local circuit synaptic interactions. *J. Neurosci.* **8**, 1411–1424.
- Lee, K., Robers, D. & Kim, U. 2003 Effect of high-frequency stimulation of the subthalamic nucleus subthalamic neurons: an intracellular study. *Stereotact. Funct. Neurosurg.* **80**, 32–36. (doi:10.1159/000075157)
- Lee, K., Chang, S., Roberts, D. & Kim, U. 2004 Neurotransmitter release from high-frequency stimulation of the subthalamic nucleus. *J. Neurosurg.* **101**, 511–517.
- Lian, J., Bikson, M., Shuai, J. & Durand, D. M. 2001 Propagation of non-synaptic epileptiform activity across a lesion in rat hippocampal slices. *J. Physiol. (Lond.)* **537**, 191–199. (doi:10.1111/j.1469-7793.2001.0191k.x)
- Lian, J., Bikson, M., Sciortino, C., Stacey, W. C. & Durand, D. M. 2003 Local suppression of epileptiform activity by electrical stimulation in rat hippocampus *in vitro*. *J. Physiol.* **547**, 427–434. (doi:10.1113/jphysiol.2002.033209)
- Lian, J., Shuai, J. & Durand, D. M. 2004 Control of phase synchronization of neuronal activity in the rat hippocampus. *J. Neural Eng.* **1**, 46–54. (doi:10.1088/1741-2560/1/1/007)
- Liu, H., Roppolo, J., de Groat, W. & Tai, C. 2009 The role of slow potassium current in nerve conduction block induced by high-frequency biphasic electrical current. *IEEE Trans. Biomed. Eng.* **56**, 137–146.
- Lux, H. D. 1974 The kinetics of extracellular potassium: relation to epileptogenesis. *Epilepsia* **15**, 375–393. (doi:10.1111/j.1528-1157.1974.tb04015.x)
- Meeks, J. P. & Mennerick, S. 2004 Selective effects of potassium elevations on glutamate signaling and action potential conduction in hippocampus. *J. Neurosci.* **24**, 197–206. (doi:10.1523/JNEUROSCI.4845-03.2004)
- Meeks, J. P., Jiang, X. & Mennerick, S. 2005 Action potential fidelity during normal and epileptiform activity in paired soma/axon recordings from rat hippocampus. *J. Physiol. (Lond.)* **566**, 425–441. (doi:10.1113/jphysiol.2005.089086)
- Mirollo, R. & Strogatz, S. 1990 Synchronization of pulse-coupled biological oscillators. *SIAM J. Appl. Math.* **50**, 1645–1662. (doi:10.1137/0150098)
- Mitchell, J., Miller, K. & Dunwiddie, T. 1993 Adenosine-induced suppression of synaptic responses and the initiation and expression of long-term potentiation in the CA1 region of the hippocampus. *Hippocampus* **3**, 77–86. (doi:10.1002/hipo.450030108)
- Mongilner, A., Benabid, A. & Rezaei, A. 2001 Brain stimulation: current applications and future prospects. *Thalamus Rel. Syst.* **1**, 255–267.
- Moody, W. J., Futamachi, K. J. & Prince, D. A. 1974 Extracellular potassium activity during epileptogenesis. *Exp. Neurol.* **42**, 248–263.
- Oby, E. & Janigro, D. 2006 The blood–brain barrier and epilepsy. *Epilepsia* **47**, 1761–1774. (doi:10.1111/j.1528-1167.2006.00817.x)
- O'Connor, M. J. & Lewis, D. V. 1974 Recurrent seizures induced by potassium in the penicillin treated hippocampus. *Electroencephalogr. Clin. Neurophysiol.* **36**, 337–345.
- Ostborn, P. 2004 Frequency entrainment in long chains of oscillators with random natural frequencies in the weak coupling limit. *Phys. Rev. E Stat. Nonlin. Soft Matter Phys.* **70**, 016120.
- Park, E. H. & Durand, D. M. 2006 Role of potassium lateral diffusion in non-synaptic epilepsy: a computational study. *J. Theor. Biol.* **238**, 666–682. (doi:10.1016/j.jtbi.2005.06.015)
- Park, S., Han, S., Kim, S., Ryu, C., Kim, S. & Yim, T. 1996 Switching among alternate synchronization patterns in an electrical coupled neuronal model. *ETRI J.* **18**, 161–170. (doi:10.4218/etrij.96.0196.0034)
- Park, E. H., Barreto, E., Gluckman, B. J., Schiff, S. J. & So, P. 2005 A model of the effects of applied electric fields on neuronal synchronization. *J. Comput. Neurosci.* **19**, 53–70. (doi:10.1007/s10827-005-0214-5)
- Park, E. H., Feng, Z. & Durand, D. M. 2008 Diffusive coupling and network periodicity: a computational study. *Biophys. J.* **95**, 1126–1137. (doi:10.1529/biophysj.108.129239)
- Patrylo, P. R., Schweitzer, J. S. & Dudek, F. E. 1994 Potassium-dependent prolonged field bursts in the dentate gyrus: effects of extracellular calcium and amino acid receptor antagonists. *Neuroscience* **61**, 13–19. (doi:10.1016/0306-4522(94)90055-8)
- Peacock, J. & Orchardson, R. 1999 Action potential conduction block of nerves *in vitro* by potassium citrate, potassium tartrate and potassium oxalate. *J. Clin. Periodontol.* **26**, 33–37. (doi:10.1034/j.1600-051X.1999.260106.x)
- Pedraza, L., Huang, J. K. & Colman, D. R. 2001 Organizing principles of the axoglial apparatus. *Neuron* **30**, 335–344. (doi:10.1016/S0896-6273(01)00306-3)
- Perreault, P. & Avoli, M. 1992 4-Aminopyridine-induced epileptiform activity and a GABA-mediated long-lasting depolarization in the rat hippocampus. *J. Neurosci.* **12**, 104–115.
- Pikovsky, A. S., Rosenblum, M. G. & Kurths, J. 2001 *Synchronization. A universal concept in nonlinear sciences*. Berlin, Germany: Cambridge University Press, Springer.
- Poolos, N. P., Mauk, M. D. & Kocsis, J. D. 1987 Activity-evoked increases in extracellular potassium modulate presynaptic excitability in the CA1 region of the hippocampus. *J. Neurophysiol.* **58**, 404–416.
- Prince, D. A. & Connors, B. W. 1986 Mechanisms of interictal epileptogenesis. *Adv. Neurol.* **44**, 275–299.
- Raastad, M. & Shepherd, G. 2003 Single-axon action potentials in the rat hippocampal cortex. *J. Physiol. (Lond.)* **548**, 745–752. (doi:10.1113/jphysiol.2002.032706)
- Ragnarsson, K. 2008 Functional electrical stimulation after spinal cord injury: current use, therapeutic effects, and future directions. *Spinal Cord.* **46**, 255–274.
- Ransom, C. B., Ransom, B. R. & Sontheimer, H. 2000 Activity-dependent extracellular K^+ accumulation in rat optic nerve: the role of glial and axonal Na^+ pumps. *J. Physiol.* **522**, 427–442.

- Richardson, K. A., Gluckman, B. J., Weinstein, S. L., Glosch, C. E., Moon, J. B., Gwinn, R. P., Gale, K. & Schiff, S. J. 2003 *In vivo* modulation of hippocampal epileptiform activity with radial electric fields. *Epilepsia* **44**, 768–777. (doi:10.1046/j.1528-1157.2003.35402.x)
- Ritchie, J. 1992 Voltage gated ion channels in Schwann cells and glia. *Trends Neurosci.* **15**, 345–351.
- Rosenblum, M. G., Pikovsky, A. S., Kurths, J., Schäfer, C. & Tass, P. 2001 Phase synchronization: from theory to data analysis. In *Handbook of biological physics, neuro-informatics and neural modeling*, vol. 4 (eds F. G. Moss & S. Gielen), pp. 279–321. Amsterdam, The Netherlands: Elsevier Science.
- Rossini, E., Chen, Y. & Ding, M. 2005 Stability of synchronous oscillations in a system of Hodgkin–Huxley neurons with delayed diffusive and pulsed coupling. *Phys. Rev.* **71**, 11.
- Sakatani, K., Hassan, A. Z. & Chesler, M. 1994 Effects of GABA on axonal conduction and extracellular potassium activity in the neonatal rat optic nerve. *Exp. Neurol.* **127**, 291–297. (doi:10.1006/exnr.1994.1105)
- Schäfer, C., Rosenblum, M. G., Abel, H. H. & Kurths, J. 1999 Synchronization in the human cardiorespiratory system. *Phys. Rev. E Stat. Phys. Plasmas Fluids Relat. Interdiscip. Top.* **60**, 857–870. (doi:10.1103/PhysRevE.60.857)
- Schiller, Y. & Bankirer, Y. 2007 Cellular mechanisms underlying antiepileptic effects of low- and high-frequency electrical stimulation in acute epilepsy in neocortical brain slices *in vitro*. *J. Neurophysiol.* **97**, 1887–1902. (doi:10.1152/jn.00514.2006)
- Shin, D. S.-H. & Carlen, P. L. 2008 Enhanced I_h depresses rat entopeduncular nucleus neuronal activity from high-frequency stimulation or raised K_e^+ . *J. Neurophysiol.* **99**, 2203–2219. (doi:10.1152/jn.01065.2007)
- Shin, D., Samoilova, M., Cotic, M., Zhang, L., Brochie, J. & Carlen, P. 2007 High frequency stimulation or elevated K^+ depresses neuronal activity in the rat entopeduncular nucleus. *Neuroscience* **149**, 68–86. (doi:10.1016/j.neuroscience.2007.06.055)
- Shuai, J., Bikson, M., Hahn, P. J., Lian, J. & Durand, D. M. 2003 Ionic mechanisms underlying spontaneous CA1 neuronal firing in Ca^{2+} -free solution. *Biophys. J.* **84**, 2099–2111. (doi:10.1016/S0006-3495(03)75017-6)
- Soleng, A., Baginskas, A., Andersen, P. & Raastad, M. 2004 Activity-dependent excitability changes in hippocampal CA3 cell Schaffer axons. *J. Physiol. (Lond.)* **560**, 491–503. (doi:10.1113/jphysiol.2004.071225)
- Somjen, G. G. 2004 *Ions in the brain. Normal function, seizures, and stroke*. New York, NY: Oxford University Press.
- Somjen, G. G. & Mueller, M. 2000 Potassium-induced enhancement of persistent inward current in hippocampal neurons in isolation and in tissue slices. *Brain Res.* **885**, 102–110. (doi:10.1016/S0006-8993(00)02948-6)
- Sontheimer, H. & Waxman, S. 1993 Expression of voltage-activated ion channels by astrocytes and oligodendrocytes in the hippocampal slice. *J. Neurophysiol.* **70**, 1863–1873.
- Stacey, W. C. & Durand, D. M. 2000 Stochastic resonance improves signal detection in hippocampal CA1 neurons. *J. Neurophysiol.* **83**, 1394–1402.
- Stacey, W. C. & Durand, D. M. 2001 Synaptic noise improves detection of subthreshold signals in hippocampal CA1 neurons. *J. Neurophysiol.* **86**, 1104–1112.
- Strogatz, S. 2003 *Sync: the emerging science of spontaneous order*. New York, NY: Hyperion Press.
- Tai, C., Wang, J., Wang, X., Roppolo, J. & de Groat, W. 2007 Voiding reflex in chronic spinal cord injured cats induced by stimulating and blocking pudendal nerves. *NeuroUrol. Urodyn.* **26**, 879–886. (doi:10.1002/nau.20430)
- Taylor, C. P. & Dudek, F. E. 1982 Synchronous neural after-discharges in rat hippocampal slices without active chemical synapses. *Science* **218**, 810–812. (doi:10.1126/science.7134978)
- Tse, F., Fraser, D., Duffy, S. & MacVicar, B. 1992 Voltage-activated K^+ currents in acutely isolated hippocampal astrocytes. *J. Neurosci.* **12**, 1781–1788.
- Tuckwell, H. C. & Miura, R. M. 1978 A mathematical model for spreading cortical depression. *Biophys. J.* **23**, 257–276. (doi:10.1016/S0006-3495(78)85447-2)
- Walz, W. 2000 Role of astrocytes in the clearance of excess extracellular potassium. *Neurochem. Int.* **36**, 291–300. (doi:10.1016/S0197-0186(99)00137-0)
- Weissinger, F., Buchheim, K., Siegmund, H., Heinemann, U. & Meierkord, H. 2000 Optical imaging reveals characteristic seizure onsets, spread patterns, and propagation velocities in hippocampal-entorhinal cortex slices of juvenile rats. *Neurobiol. Dis.* **7**, 286–298. (doi:10.1006/nbdi.2000.0298)
- Yaari, Y. & Jensen, M. S. 1988 Non-synaptic mechanisms and interictal-ictal transitions in the mammalian hippocampus. In *Mechanisms of epileptogenesis: the transition to seizures* (ed. M. A. Dichter), pp. 183–198. New York, NY: Plenum Press.
- Yaari, Y., Konnerth, A. & Heinemann, U. 1983 Spontaneous epileptiform activity of CA1 hippocampal neurons in low extracellular calcium solutions. *Exp. Brain Res.* **51**, 153–156.
- Yaari, Y., Konnerth, A. & Heinemann, U. 1986 Nonsynaptic epileptogenesis in the mammalian hippocampus *in vitro*. II. Role of extracellular potassium. *J. Neurophysiol.* **56**, 424–438.
- Zhou, M. & Kimelberg, H. K. 2000 Freshly isolated astrocytes from rat hippocampus show two distinct current patterns and different $[K^+]_o$ uptake capabilities. *J. Neurophysiol.* **84**, 2746–2757.
- Zuckermann, E. C. & Glaser, G. H. 1968 Hippocampal epileptic activity induced by localized ventricular perfusion with high-potassium cerebrospinal fluid. *Exp. Neurol.* **20**, 87–110. (doi:10.1016/0014-4886(68)90126-X)