

Suppression and Control of Epileptiform Activity by Electrical Stimulation: A Review

DOMINIQUE M. DURAND, MEMBER, IEEE, AND MAROM BIKSON

Invited Paper

Epilepsy is a devastating disease affecting ~1% of the world's population. Although drug therapy is effective in many patients, 25% are not responsive to anticonvulsants. In addition, up to 50% of those receiving regular medication suffer major side effects. Surgical resection is another treatment also associated with serious complications. An alternative method to control seizure activity is electrical stimulation. Several electrical stimulation protocols have been developed in animal models of epilepsy that can reduce or completely suppress seizures. Moreover, in over 5000 patients worldwide, electrical stimulation has been used to control seizures. The mechanisms underlying some of the techniques of seizure control are not understood. Some stimulation protocols, such as dc stimulation, rely on the effects of fields and currents on the membrane polarization. Other methods using single pulses, such as phase-resetting, desynchronization, and chaos control rely on the modulation of the dynamic properties of the neuronal networks. Both low- and high-frequency periodic stimulation can suppress seizures not only during stimulation, but also by inducing long-term changes in brain function. The purpose of this review is to present these approaches and to discuss their underlying mechanisms and potential for clinical implementation.

Keywords—Electrical stimulation, epilepsy, suppression.

I. INTRODUCTION

Epilepsy, a chronic disorder of the nervous system affecting 1% of the population, is characterized by the abnormal synchronized firing of a large number of neurons. The large synchronized event is known as a seizure, paroxysmal discharge, or ictal event. Abnormal activity is almost always observed between seizures and is known as interictal activity. These interictal events are short in duration but occur more frequently than ictal events.

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The authors are with the Neural Engineering Center, Departments of Biomedical Engineering and Neurosciences, Case Western Reserve University, Cleveland, OH 44106 USA (e-mail: dxd6@po.cwru.edu).

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International classification of epileptic seizures [21] suggests that seizures can be defined as partial seizures (focal) with or without loss of consciousness or generalized with non-focal origin such as absence (petit mal), tonic clonic (grand mal) or atonic (drop). Epilepsy has a variety of causes. The genetic component of epilepsy has recently been recognized and studied. For example, a large pedigree displaying a variety of seizure phenotypes was linked to a point mutation of the sodium channel $\beta 1$ subunit gene located on chromosome 19q13 [114]. This subunit, when coexpressed *in-vitro* with a rat sodium channel, prolongs neural depolarization. Therefore, sodium channel dynamics are clearly involved in some clinical types of epilepsy. Potassium and calcium channels have also been found to be associated with certain types of epilepsy [100]. Head trauma, infection, stroke, hypoxia, dysplasia, and various chemical imbalances in the brain can also cause epilepsy [31].

Animal models of epilepsy have been developed and have been extremely useful both for the analysis of the mechanisms underlying epilepsy and the screening of anticonvulsant treatments [25], [31]. However, the development of epilepsy treatments has been hampered by the large number of clinical manifestations of epilepsy. Not surprisingly, there are many ways to generate epilepsy in animals and each model can reproduce some of the clinical observations in humans. The effect of electrical stimulation on several ictal and interictal animal epilepsy models, induced both *in-vivo* and *in-vitro*, are discussed in this review. The most common models involve chemical convulsants producing GABA disinhibition. Penicillin, bicuculline, and picrotoxin block the GABA-ergic inhibitory potentials and generate interictal bursting characterized intracellularly by a paroxysmal depolarization shift (PDS). PTZ, a common systemic convulsant, also interferes with the GABA inhibitory system [19]. Convulsant agents that activate the excitatory system, such as kainic acid or NMDA, are equally effective at inducing epileptiform activity. Although

electrical stimulation can suppress neuronal activity (see below), daily stimulation of the central nervous system with short trains of pulses (kindling) is also capable of generating many of the symptoms observed clinically and does not involve any chemical agent [68]. Abnormal activity persists in the absence of the stimulus. In the *in-vitro* hippocampal slice high-potassium and low-calcium models of epilepsy, neuronal excitability is enhanced and neural firing becomes synchronized, leading to the generation of large spontaneous extracellular voltages similar to interictal and ictal activity, respectively.

Since epilepsy is associated with an imbalance between excitation and inhibition, antiepileptic medications have targeted these two elements. Drugs that interfere with glutamate, the major neurotransmitter in the brain, can suppress seizures but are associated with many side effects. Similarly, anticonvulsant drugs have been designed to mimic the effect of GABA, the major inhibitory neurotransmitter in the brain, with some success. Several powerful anticonvulsants, such as Phenytoin, rely on the inhibition of the persistent sodium channel that is known to be involved in certain types of seizures.

Anticonvulsant medication is by far the most common approach for treating patients with epilepsy. However, about 25% of these patients do not respond to drugs or suffer unacceptable side effects as a result of medication [31]. Surgical resection is often indicated in such cases (100 000 patients may qualify each year in the United States), but only if the focus can be identified and removed without major impairment to the patient. Before any brain tissue is resected, possible behavioral and psychological consequences (such as loss of speech) must be considered. Therefore, alternatives to surgery and drug therapy are sought for these patients.

Electrical fields and currents applied to the nervous systems generally cause excitation and generate synchronized activity. Electrical stimulation has traditionally been used in the nervous system to excite axons and neurons for the purpose of studying basic mechanisms or to replace a function lost following injury [1], [38]. A more difficult problem is to generate inhibition and/or desynchronization using electrical techniques. Over the past two decades, researchers and clinicians have developed novel methods to treat epilepsy using electrical fields. Electrical stimulation protocols have been designed to directly suppress neuronal firing or to interfere with the synchronization of a population of neurons. Such techniques would be extremely valuable in patients suffering from conditions where the neurons and axons fire abnormally, such as epilepsy and spasticity.

The purpose of this article is to review the mechanisms by which electrical stimulation can be used to suppress abnormal neuronal activity. Some methods use subthreshold currents to inhibit action potential, whereas others suppress neural activity with superthreshold currents. Other methods rely on the dynamics of the neural networks. In all cases, electric fields interact with neural tissue and this interaction is first reviewed.

II. FUNDAMENTALS OF ELECTRICAL STIMULATION

A. Electric Fields in Volume Conductors Generated by Electrodes

Neurons in the CNS are surrounded by an extracellular medium with a relatively low resistivity (80–300 $\Omega\cdot\text{cm}$). The electrodes used for suppression of abnormal neuronal activity generally fall into two categories: 1) those generating uniform electric field (large electrodes located across a piece of tissue *in-vitro*) and 2) those generating localized fields (monopolar or bipolar electrodes). Theoretical analysis of the current flow from these different electrodes is crucial to understanding the effects of electrical fields on excitable tissue [48]. The current density, voltage and electrical field distributions can be obtained from the quasi-static formulation of the Maxwell equations since the frequencies used are usually under 10 kHz [85], [27]

Conservation of charge:

$$\nabla \cdot \mathbf{J} = 0 \quad (1)$$

Gauss' Law:

$$\nabla \cdot \mathbf{E} = \frac{\rho}{\epsilon} \quad (2)$$

Ohm's Law for conductors:

$$\mathbf{J} = \sigma \mathbf{E} \quad (3)$$

Electric field:

$$\mathbf{E} = -\nabla \phi \quad (4)$$

where

- \mathbf{E} electric field (V/m) defined as gradient of the scalar potential ϕ ;
- \mathbf{J} current density (defined as the current crossing a given surface in A/m²);
- σ conductivity (inverse of resistivity) in S/m;
- ρ charge density in C/m³;
- ϵ permittivity of the medium;
- ϕ voltage.

From these equations, it is possible to derive the expression for the voltage generated by several monopolar electrodes in a homogeneous volume conductor with conductivity σ . Assuming n electrodes generating a current I_i located at a distance r_i from the recording point, the voltage is given by

$$\phi = \frac{1}{4\pi\sigma} \sum_n \frac{I_i}{r_i} \quad (5)$$

The voltage difference across a distance Δx generated by large field electrodes producing a uniform field is given by $\Delta V = -I^* R^* \Delta x / D$ where I is the current injected, R is the resistance between the electrode, and D is the distance between the electrodes. Voltages generated in nonhomogeneous media can also be calculated using the theory of images [81], [27] or using numerical approximations such as boundary element of finite element methods [57].

B. Electric Fields and Excitable Tissue

When neurons are placed inside a volume conductor, the current flows according to the equations derived above. Some

of the current lines will pass through cell bodies, generating depolarization when current flows outward, and hyperpolarization when current flows inward across the membrane [27]. This is shown schematically for uniform fields stimulation in Fig. 1 and in Fig. 5 for a monopolar electrode. For both uniform and local fields, positive (anode near soma) stimulation will induce hyperpolarization of the soma.

Transmembrane current flow can be quantified by modeling the effect of the field on the cells analytically [106] or using compartmental analysis. A compartment of length Δx can be modeled at rest by a capacitance C_m in parallel with a series combination of a battery (E_r) for the resting potential and a resistance R_m simulating the combined resistance at rest of all the membrane channels [27]. Nonlinear ionic channel conductances can be added in parallel with the membrane resistance and capacitance. The variable of interest is the transmembrane potential V_m and is defined as the difference between the intracellular voltage V_i and the extracellular voltage V_e minus the resting potential E_r . Several membrane compartments can be connected by axial resistances. Applying Kirchoff's law at each compartment and taking the limit when the length of membrane Δx goes to zero, one obtains the following inhomogenous equation [90]:

$$\lambda^2 \frac{\Delta^2 V_m}{\Delta x^2} - \tau \frac{dV_m}{dt} - V_m = -\lambda^2 \frac{\Delta^2 V_e}{\Delta x^2}. \quad (6)$$

The space constant of the membrane depends only on the geometric and electric properties of the membrane

$$\lambda = \frac{1}{2} \sqrt{\frac{R_m^s d}{R_a^s}} \quad (7)$$

where

- R_m^s specific membrane resistance;
- R_a^s axoplasmic specific resistance;
- d diameter of the dendrite.

τ_m is the time constant of the membrane and is given by

$$\tau_m = R_m C_m. \quad (8)$$

The term on the right side of (6) is called the source term or forcing function and is the product of the square of the space constant with the second spatial derivative of the extracellular voltage. The equation clearly shows that the transmembrane voltage depends on the extracellular voltages generated along the membrane and is sensitive *only* to longitudinal fields. Therefore, as confirmed by experiments (see below), the orientation of cell bodies with respect to the electric field affects the longitudinal field amplitude, and thus the efficacy of the applied field. Moreover, a cell structure extending perpendicular to the induced field lines would not be affected by stimulation.

The forcing function indicates that the membrane voltage is affected by the external field only if the voltage has a nonzero second-order spatial derivative. Thus, a uniform field along an ideal cylindrical cell body would have no effect. However, if the membrane terminates, branches, or bends (as with dendrites and axons), then uniform applied electric fields can generate a nonzero driving force and

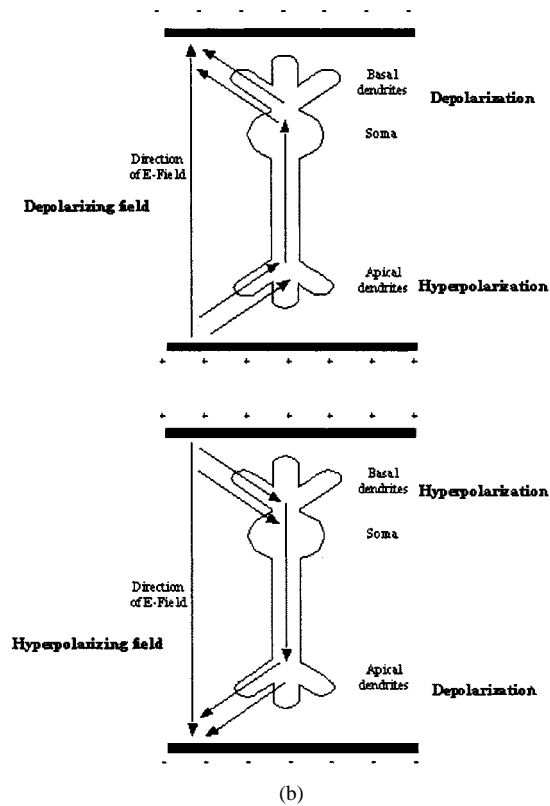
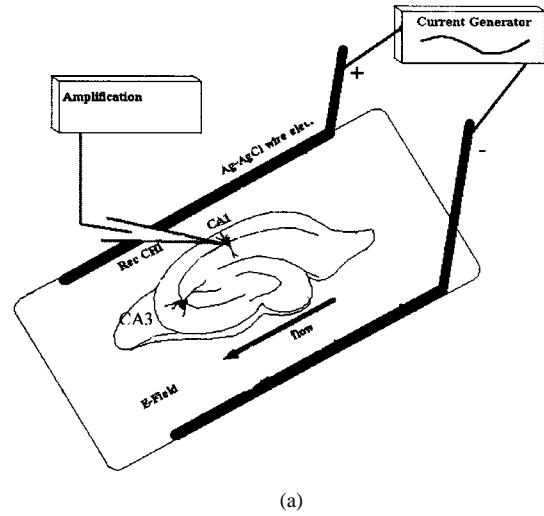


Fig. 1. Membrane polarization with a uniform field. (a) Uniform electric fields are generated using two wire electrodes located on either side of the neural tissue (hippocampal slice). (b) Top panel: A cathode is located close to the basilar dendrites and the anode close to the apical dendrites. Current enters the apical dendrites generating membrane hyperpolarization and leaves the cell in the somatic and basilar region generating membrane depolarization. Bottom panel: the current direction or cell orientations is reversed, generating hyperpolarization in the soma and therefore suppression of neuronal firing.

produce excitation or inhibition. At a boundary (cell body, bending site, or sealed end), the driving function is not proportional to the second spatial derivative but to the first spatial derivative of the extracellular voltage. Therefore, these boundaries have low thresholds and the membrane is preferentially polarized at these locations. These results

apply to electric fields induced by electrodes [106] but also to electrical fields induced indirectly by magnetic stimulation [77].

III. MEMBRANE POLARIZATION BY UNIFORM DC ELECTRIC FIELDS

Electric fields are generated endogenously by the nervous system whenever current flows in (current sink) or out (current source) of cell bodies. Those fields can, in turn, cause current to flow through neighboring cells. Electric fields generated by the nervous system can directly modulate neuronal activity [29] and are functionally important [32], [33], [29]. Endogenously generated extracellular potentials are often large enough to recruit neighboring cells. For example, experiments in solutions with low-calcium concentration have shown that neurons can synchronize in the absence of synaptic transmission [43], [54], [92], [97], [103], [104]. This synchronization of neuronal firing is thought to be mediated in part by electric fields generated by neuronal firing.

Externally applied currents or fields can also influence neural excitability in many neuronal systems such as turtle cerebellum [14], [15], hippocampal dentate granule [53] pyramidal [7], [6], and cortical neurons [20], [87]. Uniform fields were applied with large field electrodes placed on the surface of the cortex for *in-vivo* experiments or across the tissue for *in-vitro* studies [see Fig. 1(a)]. These studies have shown that dc electrical fields (with amplitudes similar to those generated endogenously) can produce both excitation or inhibition of neuronal activity depending on the orientation of the applied field with respect to the dendritic tree, as described in Section II. The mechanism of the effect is illustrated in Fig. 1(b). A cathode located near the basal dendrites produces depolarization of the dendrites and cell body, thereby generating excitation. However, an anode in the same location produces hyperpolarization in that region and can inhibit electrical activity. The effect of the exogenous uniform dc electric fields on the epileptiform activity has been tested using both the high-potassium and low-calcium *in-vitro* models of epilepsy.

A. DC Uniform Fields in the High-Potassium Model

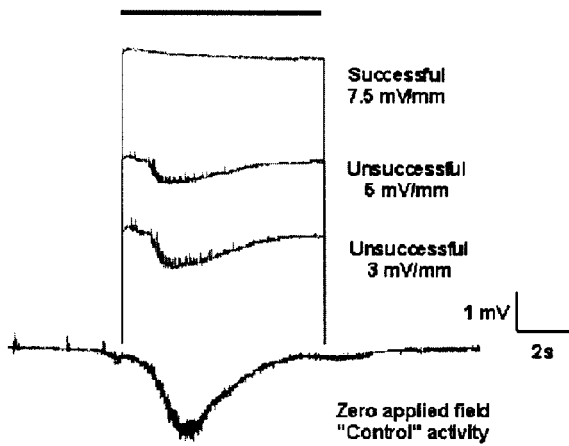
Hippocampal slices bathed in an elevated potassium concentration artificial cerebro-spinal fluid (8–10 mM) can generate epileptiform activity approximating the interictal activity observed in humans with epilepsy [107]. This activity is spontaneous and occurs in short bursts of about 100 ms duration at an average frequency of 1 Hz. Using the *in-vitro* hippocampal preparation and the high-potassium model of epilepsy, Gluckman *et al.* [35] showed that anodic electrical fields (as low as 5 mV/mm) applied with field electrodes can completely suppress interictal bursting. Reversal of the field polarity (cathodic stimulation) enhanced the activity as indicated by the number of bursts/min. The mechanism for activity suppression and enhancement involves membrane polarization, as described above. Similar results were obtained by Duong and Chang [22].

B. Uniform Fields in the Low-Calcium Model of Epilepsy

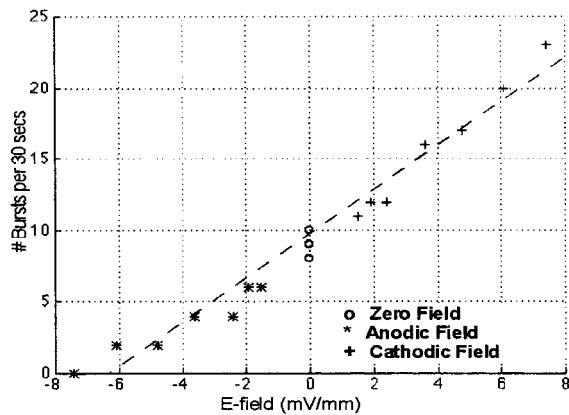
Experiments performed *in-vitro* and *in-vivo* have shown that extracellular Ca^{2+} levels can decrease to concentrations as low as 0.2–0.6 mM during sustained spiking activity and seizures [47], [86], [65], [80], [99]. In brain slice preparations, lowering $[\text{Ca}^{2+}]_o$ is known to effectively block chemical synaptic transmission (Jones and Heinemann, [58]) and leads to the development of spontaneous nonsynaptic epileptiform activity that closely approximates ictal epileptiform activity [4], [43], [95], [96], [123]. Low- $[\text{Ca}^{2+}]_o$ nonsynaptic bursts are characterized extracellularly by prolonged negative potential shifts, with superimposed high-frequency population spikes. In this model, because synchronization is largely dependent upon field effects (as opposed to synaptic connectivity), it is expected that applied currents would be highly effective in modulating low $[\text{Ca}^{2+}]_o$ ictal events.

Ghai *et al.* [34] studied the effects of exogenous dc fields applied via field electrodes on spontaneous low- Ca^{+2} bursting. Application of dc fields [Fig. 1(a)] resulted in a step increase in the extracellular field potential. This stimulus artifact is generated by the tissue resistance and can be significantly reduced by subtracting the voltage recorded by an electrode on an equipotential line of the electric field. Increasing the amplitude of the anodic fields caused greater attenuation of the individual events until complete suppression of the activity was achieved [Fig. 2(a)]. Activity was suppressed for the duration of the stimulus. However, in a majority of the slices, the trailing edge of the suppressing field pulses caused excitation of the tissue through an “anodic rebound” effect. The mean minimum field required to suppress spontaneous activity in low-calcium was 1.8 mV/mm ($n = 30$) and a field amplitude of approximately 5 mV/mm could suppress 100% of the activity in 90% of the slices. Suppression efficacy was highly orientation dependant. Busting frequency increased linearly with amplitude during cathodic stimulation and decreased with increasing anodic fields [Fig. 2(b)]. The mechanism underlying suppression is similar to the one previously discussed and involves the polarization of the membrane by electric fields.

The results obtained with applied uniform fields show that the minimum field amplitudes required for full suppression of low- Ca^{++} activity (1.8 mV/mm) are considerably lower than those required to suppress high-potassium induced epileptiform activity [35]. It was then hypothesized that the effects of the applied fields are enhanced in the “low-calcium” environment by an increase in the extracellular volume caused by cellular swelling. Since cellular swelling can increase the resistance of the tissue by shrinking the volume of the extracellular space (ECS), [43], [49] swelling can also increase the efficacy of applied currents. This hypothesis was confirmed by showing that changes in the osmolarity of the extracellular solution can directly affect electric field efficacy. A 10% decrease in osmolarity resulted in an average 50% decrease in the minimum field required for full suppression, while a 14% increase in osmolarity



(a)



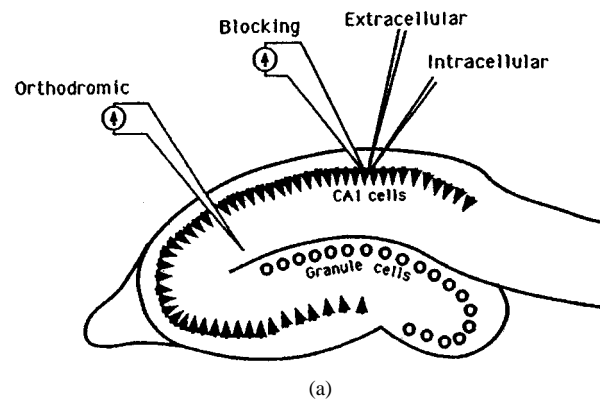
(b)

Fig. 2. Effect of applied uniform field on epileptiform activity generated in the low-calcium model. (a) An electric field applied across the slice (bar) generates a step stimulus artifact. The amplitude of low-calcium events is completely suppressed with a field of 7.5mV/mm. (b) The frequency of low-calcium events is increased or decreased when cathodic or anodic fields are applied. (Modified from Ghai *et al.* [34].)

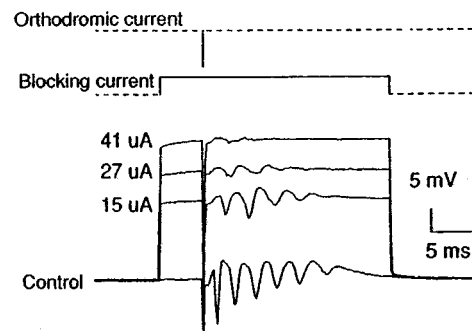
resulted in an average 76% increase in the minimum electric field amplitude required for full suppression [34].

IV. MEMBRANE POLARIZATION BY LOCALIZED DC ELECTRIC FIELDS

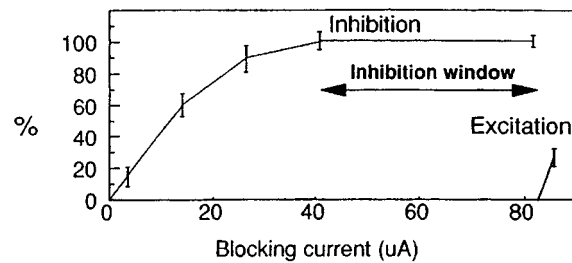
Uniform fields can affect membrane polarization and suppress neuronal firing. However, (by definition) these fields are not localized and their effect depends on the orientation of the neurons with respect to the field lines [34], [35]. Localized fields, produced by point source electrodes, should be more effective than uniform fields since the second spatial derivative of the extracellular voltage near the electrode can produce large transmembrane currents [89], [27]. The effects of localized fields have been tested on three *in-vitro* models of epilepsy: penicillin [61], high-potassium [79], and low-calcium [115], and on the *in-vivo* kindling model [117].



(a)



(b)



(c)

Fig. 3. Effect of applied localized fields on epileptiform activity induced by penicillin. (a) Schematic of hippocampal slice and electrodes. Epileptic activity was triggered by an orthodromic electrode in the stratum radiatum and recorded by an extracellular microelectrode located in the CA1 region. The blocking electrode was located on the surface of the slice close to the recording electrode. (b) With no current applied in the blocking electrode, the extracellular response shows the characteristic multiple spike evoked potential. As the current is increased, the activity is attenuated until complete suppression is obtained with a current of 41 μ A. (c) As the current is further increased, excitation is generated at the onset of the pulse. Therefore, the plot of percent inhibition as a function of current from 20 slices shows a window of current for which suppression is obtained without excitation. (Modified from Kayyali and Durand [61].)

A. Effect of Localized Fields on the Penicillin Model

Penicillin applied in low doses can induce epileptiform activity by blocking the GABA-mediated inhibitory pathways. In the presence of penicillin, using the hippocampal slice preparation [61] [Fig. 3(a)], orthodromic stimulation (stimulation electrode) of the stratum radiatum generated epileptiform field spikes in the somatic layer. Another electrode (blocking electrode) was placed on the surface of the slice in the somatic region and a low-amplitude dc anodic field was

applied. The dc stimulus was started before the orthodromic pulse and was maintained for the duration of the epileptiform event [Fig. 3(a)]. Recordings obtained during the simultaneous application of the dc field and orthodromic pulse showed that, as the dc current amplitude was increased, the amplitude of the evoked potentials decreased [Fig. 3(b)]. Intracellular recordings confirmed that the suppression mechanism was membrane polarization [61] by showing that the neuronal membrane was hyperpolarized as the amplitude of the blocking current increased. Another important conclusion to be drawn from these data is that the applied dc current pulse can block neuronal firing without exciting the tissue (i.e., triggering additional action potentials) since the amplitude of the applied current is subthreshold [61]. Increasing the amplitude of the suppressing field further can generate excitation at the onset of the stimulus. Therefore, these data showed that there exists a window of amplitude where applied dc current could generate inhibition without causing excitation [Fig. 3(c)]. Reversal of the amplitude of the dc current (cathodic stimulation) produces the opposite effect.

B. Effect of Localized Fields on the High-Potassium Model

The results generated with the penicillin model of epilepsy (see above) were obtained using neuronal activity triggered by a stimulation pulse. However, epileptic activity is often spontaneous. The effect of local dc fields on spontaneous high-potassium activity was analyzed in the hippocampal slice preparation [79]. Spontaneous events were detected using computer algorithms. Step anodic dc current was then applied with a monopolar blocking electrode positioned in the CA1 somatic layer. As previously noted, step current applied into the extracellular space caused a step increase in the extracellular potential (stimulus artifact) due to the tissue resistance. However, the amplitude of the superimposed epileptiform activity was clearly decreased [see Fig. 4(b)]. Larger anodic current amplitudes increased the size of the stimulus artifact and further decreased the bursting magnitudes until complete suppression of the activity was obtained. As in the penicillin model, inhibition was generated by subthreshold current levels. Current amplitudes beyond the level of maximal inhibition sometimes resulted in a subsequent increase in activity. Complete inhibition was generated in 94% of the slices with a mean minimum current amplitude $12.5 \pm 3.8 \mu\text{A}$. Intracellular recordings confirmed that the membrane of the neurons was hyperpolarized by the anodic current and neuronal firing was, in fact, eliminated in these neurons [Fig. 4(c), bottom right panel].

These data show that spontaneously occurring epileptiform activity generated by a high-potassium model of epilepsy can be suppressed by the application of a computer initiated and controlled anodic current dc field. As in the case of the penicillin model, the mechanism for this suppression is an inhibitory polarization effect caused by the transmembrane currents generated by the applied field. The inhibition was generated at subthreshold current amplitudes showing that there is a window of current amplitude for which inhibition of spontaneous neuronal activity can be generated without excitation.

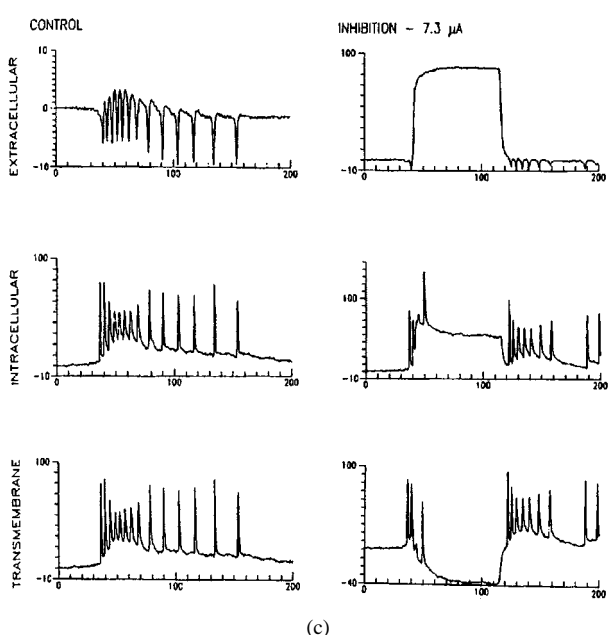
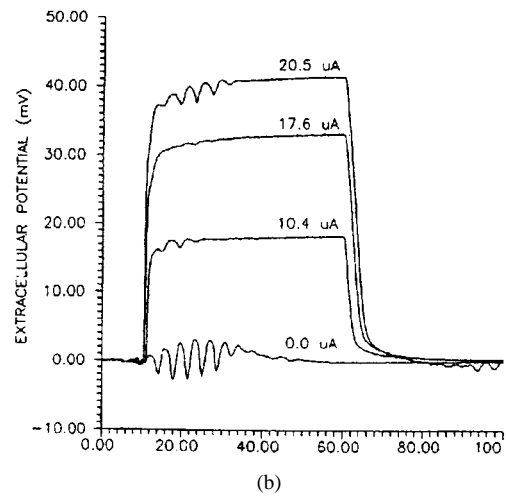
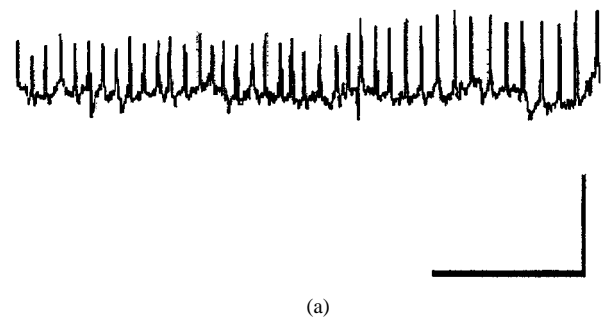


Fig. 4. Effect of localized fields on epileptiform activity generated in high-potassium solutions. (a) The high-potassium activity consists of a short burst of activity generated spontaneously at a frequency between 0.5 and 2 Hz (scale: 30 s and 1 mV). (b) Application of a localized field to the CA1 layer, generates complete suppression of the activity at a current of $17.5 \mu\text{A}$. As the current is further increased, excitation is generated at the onset of the applied pulse. (c) Simultaneous intracellular and extracellular currents show that during the application of the pulse, the transmembrane potential is hyperpolarized. (Modified from Nakagawa and Durand [79].)

C. Localized Fields in the Low-Calcium Model

Localized fields should also be effective at modulating spontaneous activity in low-calcium bursting since electric fields are thought to play a significant role in the generation of this activity. Warren and Durand [115] tested the hypotheses that: 1) locally applied current pulses can inhibit epileptiform activity induced by low-calcium solution and 2) the current amplitudes required for total inhibition are lower than those required to block penicillin- or high-potassium-induced activity. Electrical fields were applied with a single monopolar electrode located in the somatic layer. The results (not shown) indicated that the spontaneous neural activity generated by the low-calcium solution is slower and has a longer duration than the events generated in the high-potassium solution. Anodic localized electric field can also inhibit these events. The minimum current for fully blocking an event was as low as $1 \mu\text{A}$ and spontaneous events were fully blocked in 90% of the slices with a current amplitude of $9 \mu\text{A}$.

The amplitude of the electric field generated by the blocking current electrode can be estimated assuming that the resistivity is homogeneous and isotropic. For a resistivity of $200 \Omega\cdot\text{cm}$ and a current of $1 \mu\text{A}$, the electric field $200 \mu\text{m}$ from the source is 4 V/m . This number is similar to the minimum electric field required to suppress neural activity using uniform fields (see above). Taken together, these results show that epileptiform activity induced with low $[\text{Ca}^{2+}]_o$ can be blocked by lower currents than those required to block similar activity induced by other means, such as elevated $[\text{K}^+]_o$.

As with uniform fields, in all of these models, the mechanism underlying the effect of the applied localized fields can be attributed to the membrane polarization generated by the induced current flow through the cells. The spatial extent of the suppression generated by the localized fields has not been studied. Using both field and local stimulation, an anode located near the somatic layer produces hyperpolarization in the soma and depolarization in the dendrites [27], (Fig. 5). Since sodium channels are mostly located in the soma, the hyperpolarization inhibits neuronal firing, while membrane depolarization in the dendrites does not cause excitation. Thus, subthreshold dc currents can suppress neuronal activity. However, the activity is suppressed only when the current is applied and is a function of cell orientation and stimulation polarity (see discussion).

D. Effect of Low-Level DC Current on the Kindling Model

Low-level dc currents have also been tested *in-vivo* on the kindling model of epilepsy [117]. Currents as low as $5\text{--}15 \mu\text{A}$ applied 15 min/day for 14 days to amygdala-kindled animals significantly increased seizure threshold. The effect, called “quenching,” was initially erroneously attributed to a low-frequency stimulus applied with the dc current. DC currents are known to generate tissue damage through non-reversible chemical reactions that take place at the electrode

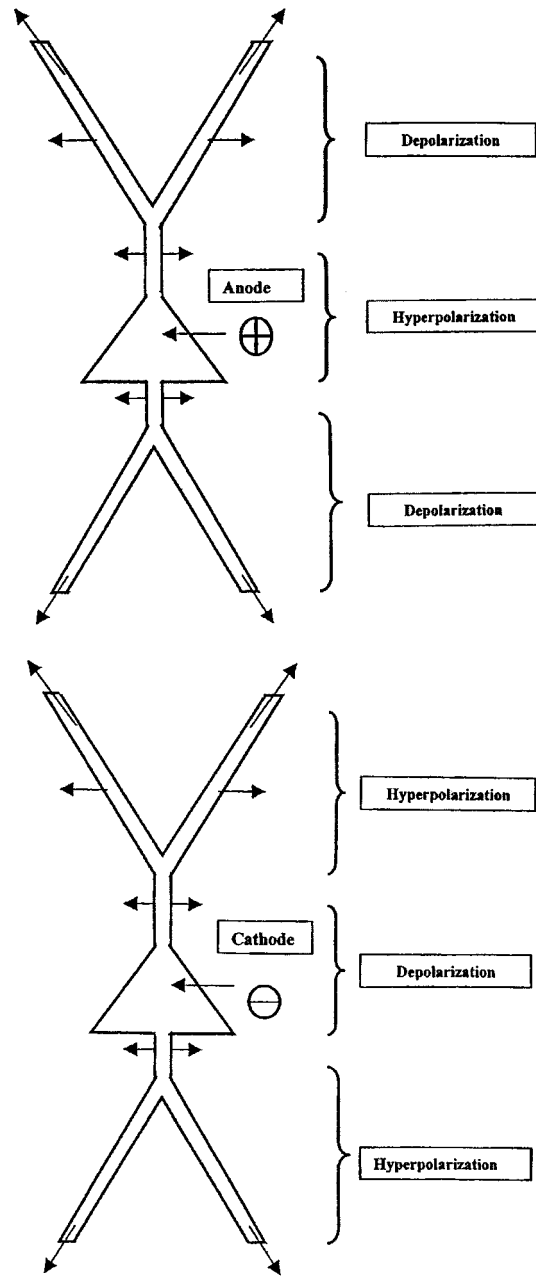


Fig. 5. Membrane polarization by a localized electrode. The current flow generated by a localized field electrode is different than that one generated in the uniform case [see Fig. 1(b)]. (Top): The electrode is localized in the somatic layer and generating a positive current (anode). The current enters the cell in the somatic region thereby producing hyperpolarization and leaves the cell in the dendrite causing depolarization. Since most of the sodium channels are located in the somatic region, the cell is moved away from threshold, and the firing of the cell is suppressed. (Bottom): The polarity is reversed and the cell is moved closer to threshold.

surface [93]. However, Weiss *et al.* [117] reported that the effect of dc stimulation was reversible and stimulation itself did not result in any anatomically evident cell damage. The mechanisms involved in the suppression of the neuronal activity *in vivo* by these dc currents are unknown. Simple experiments such as reversing the polarity of the current (see above) could be carried to test the hypothesis that the membrane polarization mediates suppression.

Although both local and uniform dc field techniques can clearly suppress neuronal activity, these methods require that the field be applied during the whole duration of the event. Moreover, the orientation of the neural structure with respect to the applied field is crucial to the suppression. Other potential anticonvulsant stimulation methods employing single narrow pulses that disrupt the dynamics of the neuronal activity could overcome these limitations.

Three stimulation methods that involve the modulation of the dynamics of the neural network have been proposed for the control of synchronized activity. The first, phase resetting/desynchronization, relies on the existence of multiple stable states in the system dynamics such as quiescent (or desynchronized) and oscillation (or synchronized). An electrical pulse applied at a precise time can switch the network from one state (periodic oscillation/synchronized) to the other (quiescent/desynchronized). The parameters for the singular pulse (current amplitude and timing) can be determined using phase resetting analysis (see below). The second method involves controlling the chaotic activity of the population dynamics. By monitoring the time interval between events, it is possible to apply current pulses to control the activity of the neural network. The third method relies on periodic low-frequency stimulation of the neural tissue generating the epileptiform activity. This stimulation can potentially interfere with neuronal excitability or synchronization, contributing to the generation of the activity. All three methods have been tested in the high-potassium *in-vitro* model of epilepsy.

A. Phase Resetting and Singularity

Perturbation studies of oscillatory systems known as phase resetting use small pulses applied at various intervals following an event to analyze the dynamics of the system. Although phase resetting analysis has been extensively used to study cardiac rhythms and predict singularities [40], [120], [119], surprisingly little has been published in the field of phase resetting analysis of epileptic activity. Using a topological theorem, Winfree [118], [119] showed that, under special conditions, one can predict the existence of a “singular stimulus” capable of disrupting periodic oscillatory behavior for an unpredictable period of time. An example of such a “singular” response is shown in Fig. 6 [44]. The Hodgkin–Huxley model is modified to simulate the high-potassium bursting conditions previously discussed. Raising the reversal potential of potassium to account for the increased potassium concentration generates repetitive firing behavior. Injecting a current at various delays (old phase) from the action potential and various amplitudes generates either delays or advances of the next action potential. This latency can be plotted as a function of both the current amplitude and phase [Fig. 6(a)]. The plot reveals that for some values of amplitude and delay, [dark blue region in Fig. 6(a)] the latency of the next event is unpredictable [Fig. 6(b)]. An example of a singular response

is shown in Fig. 6(b) where the neuronal firing is annihilated. The mechanism for the suppression of the neural activity is obtained from the concept of bistability. The singular stimulus (arrow) has moved the system from a stable oscillation to a stable fixed point [46]. This stable fixed point is shown in the phase plot of the transmembrane potential V_m and the two gate parameters, h and n [Fig. 6(c)]. Bifurcation analysis of the equations revealed that the presence of a subcritical Hopf bifurcation and bistability for a narrow range of parameters [101].

Other theoretical studies on Hodgkin–Huxley models [9], as well as experiments on squid axons [42] and Purkinje fibers [51] have shown that a singular stimulus can annihilate action potentials. The main difference between the dc field effects described in the previous section and phase resetting is that the application of a single short stimulus during a vulnerable phase of the activity can cause a suppression of the entire event, as well as subsequent ones.

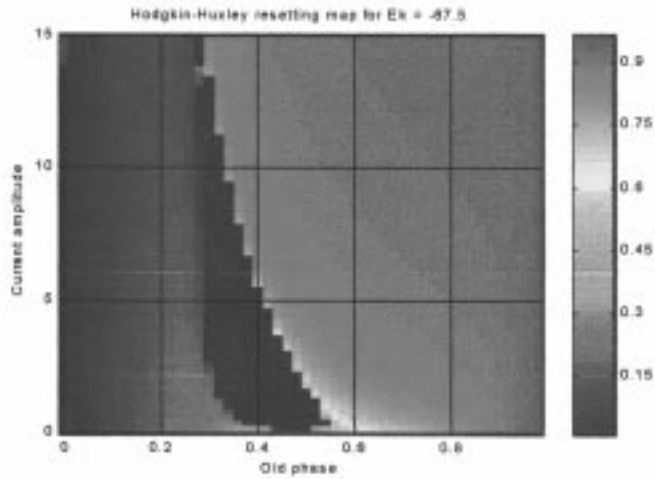
B. Phase Resetting and Desynchronization

In the hippocampus, *in-vitro* experiments have shown that electrical stimulation with a single pulse applied in the somatic region of the CA1 can generate a large decrease in the amplitude of the evoked population spikes [25]. Using the penicillin *in-vitro* epilepsy model, Durand and Warman [24] showed that a small brief current pulse (100 μ S), applied during a critical time window [Fig. 7(a)], produced a large reduction in the amplitude of an orthodromic evoked response in the CA1 region of the hippocampus [Fig. 7(b)]. The effect could not be explained by membrane polarization (as with dc fields) since the pulse was clearly not long enough to suppress the activity. Moreover, both cathodic and anodic currents were equally capable of producing the effect and the timing of the pulse was crucial to the suppression of the activity. The mechanisms underlying this effect were determined using intracellular recordings. These experiments showed that neural firing was not suppressed, and double intracellular recordings revealed that, although the neurons were still firing, their activity was desynchronized by the application of the pulse [Fig. 7(c)]. Phase resetting analysis was also applied to the high-potassium model of epilepsy [51] but with limited success.

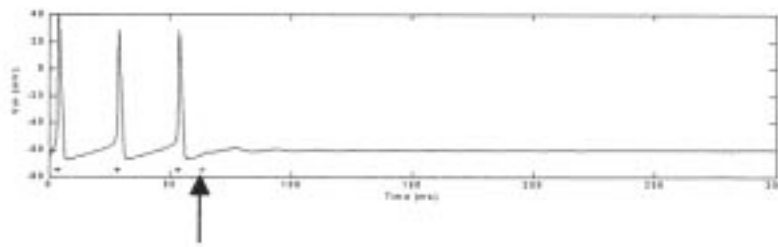
It is, therefore, possible to interfere with the dynamics of a hyperexcitable system with a single stimulus that shifts the system from a stable periodic synchronized oscillation into a stable unsynchronized fixed point. However, this method, to be successful, requires first that the activity be somewhat periodic and second the existence of stable modes. Chaos control could potentially overcome these problems.

C. Chaos Control

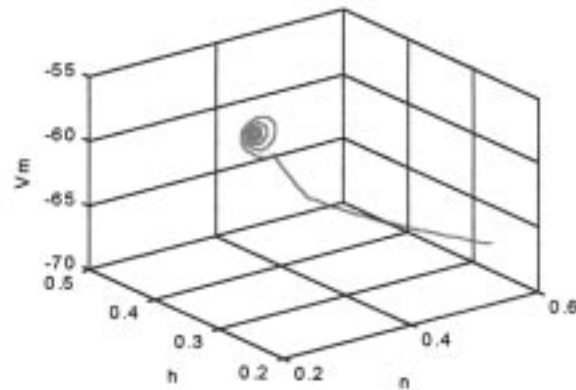
Schiff *et al.* [45] employed low-frequency pulsed stimuli, whose timing was derived from a chaos control algorithm, with the aim of reducing the periodicity of high-potassium activity in the CA3 region. Using the hippocampal slice preparation and the high-potassium model, they first showed the presence of chaos by establishing the existence of unstable fixed points in the extracellular recordings. Periodic



(a)



(b)



(c)

Fig. 6. Phase singularity and singularity. (a) Phase resetting analysis of the Hodgkin–Huxley model with high potassium. The model generates periodic spiking. A variable amplitude stimulus is applied at a variable time (old phase) between two pulses and the latency of the next pulse is measured. This latency (delay or advance) is plotted as a function of amplitude and old phase. The dark blue region indicates a region of unpredictable latency (singularity). (b) Response generated within this the singular region. A stimulus (arrow) generates complete annihilation of the periodic firing of the cell. (c) The phase trajectory of the response for three variables (V_m , h and n) indicates the presence of a fixed stable point. (Modified from Hahn and Durand [44].)

stimulation coupled with chaos control algorithms was used to control the neuronal activity. Their results showed that the system could be made more periodic or more chaotic by using a strategy of anti-control. Therefore, the dynamics of the neuronal network can be affected by applied current pulses chosen appropriately. However, it is not known to what extent the neuronal firing of the cells that generate the epileptic events was affected by the stimulus.

D. Low-Frequency Periodic Stimulation

Jerger and Schiff [45] also applied periodic stimulation to the mossy fiber pathway to force CA3 to fire periodically within specified frequency ranges during high-potassium bursting. A range of stimulation frequencies (0.1–10 Hz) was applied to the CA3 region of the slice. They report a reduction in the frequency of occurrence of tonic phase

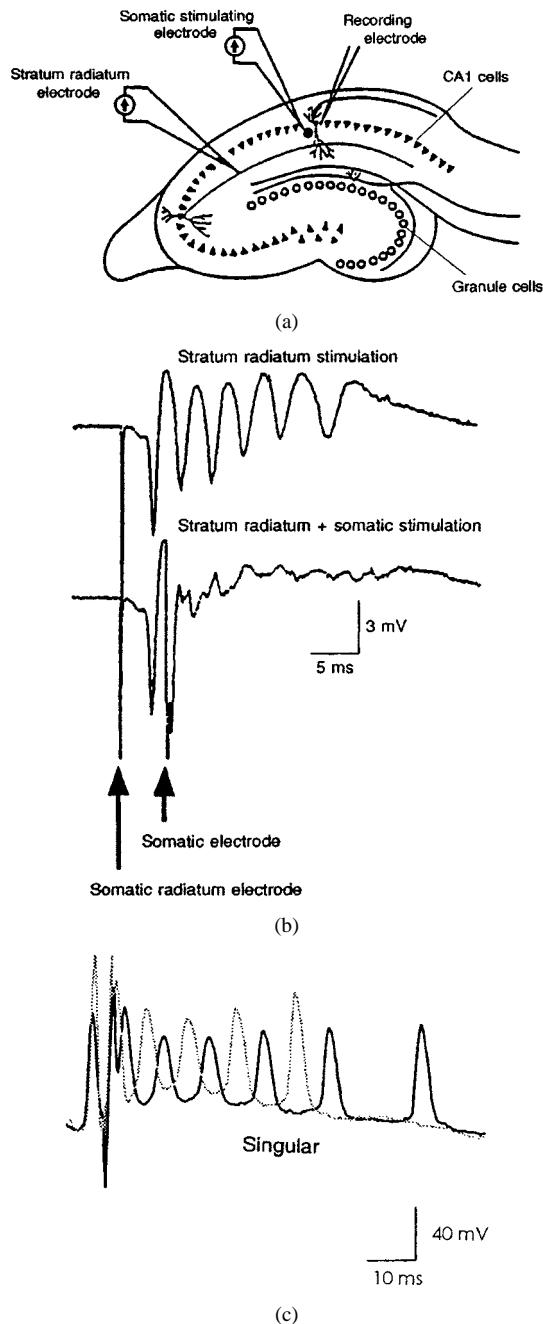


Fig. 7. Phase resetting and singularity in the penicillin model of epilepsy. (a) Penicillin event is induced by an orthodromic electrode located in the stratum radiatum and monitored with an extracellular electrode located in the CA1 region of the hippocampal slice. A narrow pulse is applied with a stimulating electrode located close to the recording electrode in the somatic region. (b) Activation of the somatic electrode with just the right delay and amplitude (singular pulse) produces nearly complete suppression of the penicillin induced population spikes. (c) The mechanism for this suppression was attributed to a desynchronization of the neuronal population. Dual intracellular recordings showed that, during the application of the singular pulse, the relative phase of the neuronal firing is changed producing a more uniform firing distribution and suppression of the extracellular activity. (Modified from Durand and Warman [24].)

seizure episodes in the CA1 region for a very narrow range of frequencies (1.0 and 1.3 Hz). This suppression was observed when either the Schaffer collaterals or the mossy fibers were stimulated. This suggests that the timing of

coherent synaptic input from CA3 to CA1 is relevant in the transition from interictal to ictal activity.

Ebert and Ziemann [28] studied the effect of low-frequency periodic stimulation applied via transcranial magnetic stimulation (TMS) on the susceptibility of amygdala kindling in rats. Transcranial stimulation is a noninvasive method to induce electric fields in the brain. They found that two weeks after a single TMS train (120 A/ μ s, 20 Hz for 3 s), rats had a 55% higher threshold for the induction of epileptic afterdischarges. Low-frequency stimulation by magnetic stimulation has also been implemented with some efficacy in patients with intractable epilepsy. Tergau *et al.* [105] used transcranial magnetic stimulation, applied noninvasively in two trains of 500 pulses at 0.33 Hz with a round coil for five consecutive days. This stimulation protocol was able to significantly decrease seizure frequency in these patients. Thus, low-frequency periodic TMS can suppress seizures for a long time after termination of stimulation.

The mechanism underlying the effect of low-frequency stimulation is not known but could involve long-term depression (LTD). Long-term depression is a synaptic plasticity phenomenon first observed in the hippocampal slice whereby an orthodromic stimulation at low frequency (1 Hz) generates a long-lasting decrease in synaptic efficacy [17]. This effect is observed only at low frequencies and could underlie the results described above.

All of the stimulation techniques discussed above, though effective and well characterized using animal models, have rarely been applied clinically. In contrast, while high-frequency stimulation of various brain structures has been used clinically for almost two decades, animal studies have only recently begun to shed light on its mechanism of action.

VI. HIGH-FREQUENCY STIMULATION IN THE CNS AND PNS

High-frequency stimulation (50–200 Hz) can activate neural tissue as well as induce secondary effects on CNS function, such as extracellular potassium accumulation [11], [12] not observed during low-frequency stimulation. High-frequency stimulation applied globally using scalp electrodes (electroconvulsive therapy) or via implanted electrodes targeting specific CNS (deep brain stimulation) or PNS structures, is used in clinical settings to treat the symptoms of epilepsy. Using these paradigms, both during stimulation and post-stimulation (i.e., after stimulation is discontinued) anticonvulsant effects have been reported. Furthermore, the antiepileptic effects of high-frequency stimulation have also been characterized in several *in-vitro* and *in-vivo* animal epilepsy models. While it is unclear if all of these paradigms share a common mechanism, in all cases, decreasing stimulus frequency either eliminates any therapeutic effect or aggravates the seizure.

A. Electroconvulsive Therapy

Electroconvulsive therapy (ECT), which is generally performed to treat refractory major depression, was first suggested as a method to reduce seizure frequency over 50 years ago [59]. Modern ECT usually involves bilateral

current controlled stimulation (Mecta Corp., Portland, OR; Somatics, Inc., Lake Bluff, IL) applied via electrodes placed on the patients head. Patients are anesthetized and stimulus intensity is increased iteratively (“dose titration”) until an electrographic seizure is induced. Typical stimulus parameters are 40–90-Hz pulse trains, 0.8 A for up to 2 s. Stimulation “dosage” is often only reported as total charge delivered. Patients will usually receive 3–4 ECT treatments over a period of 6–9 days. There are conflicting reports as to whether ECT is anticonvulsant as indicated by either an increase in ECT threshold [67], [18] or a decrease in spontaneous seizure rate [13], [37]. While stimulation efficacy increases with train duration, concerns about induced cognitive defects and short-term memory loss limit stimulation to 2-s intervals.

B. High-Frequency Stimulation of the CNS: Clinical Studies

High-frequency stimulation of the brain with depth electrodes known as deep brain stimulation (DBS) can affect seizure frequency in patients with various types of epilepsy. In particular, deep brain stimulation of the centromedian thalamic nucleus [110] or hippocampus [111] resulted in significant decreases in seizure frequency and the amount of interictal EEG discharges. These studies used a fully implantable electrode and stimulator design developed by Medtronic (Minneapolis, MN) that allows adjustment of stimulation parameters via telemetry. For centromedian thalamic nucleus (CM) stimulation, stimulation parameters were usually in the range of 450–800 μA , 65 Hz, applied in 1-min trains every 4 min, for 2 h/day for a total of 3 months. CM stimulation improved symptoms in 12 of 23 patients tested (Fig. 8). Interestingly, seizure frequency remained improved after the end of the stimulation period for up to three months. In contrast, low-frequency stimulation (3 Hz) of the CM could induce an absence attack [112]. For hippocampal stimulation, stimulation parameters of 200–400 μA , 130 Hz delivered 23 of every 24 h for 2–3 weeks improved symptoms in seven of ten patients tested. DBS at either site induced a dc shift in the EEG similar to that observed in *in-vitro* preparations (see next section).

Over 700 patients have been treated with chronic high-frequency cerebellar stimulation (CCS) for cerebral spasticity and seizure disorders [126]. These studies used both radio frequency-linked stimulators (Avery Laboratories, Inc., Farmingdale, NY; Clinical Technology Corp., Kansas City, MO; Medtronic, Inc., Minneapolis, MN) and fully implantable stimulator designs (Neurodyne Corp., Sylmar, CA; Medtronic, Minneapolis, MN). A majority of patients (85%) experienced some improvements during stimulation. Effective stimulation parameters were in the range of 150-Hz, 0.5-ms pulsewidth, 1.5–2.5 $\mu\text{C}/\text{cm}^2/\text{ph}$, 4 min ON and 4 min OFF. Furthermore, as with CM stimulation, patients using CCS continued to show improvements in seizure reductions even after discontinuing stimulation [126].

Lesser *et al.* [70] showed that a brief high-frequency pulse train (600 μs biphasic, 50 Hz for 0.5–2 s) could suppress ongoing epileptic afterdischarges in various areas of the cortex.

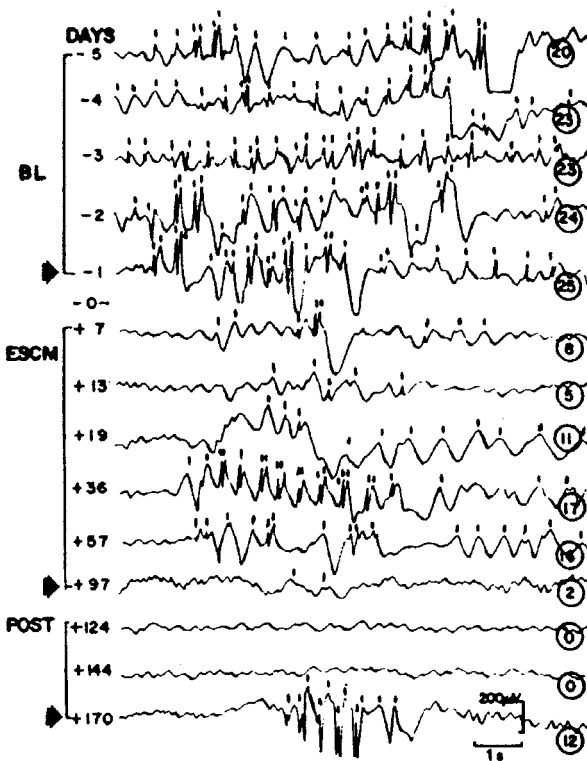


Fig. 8. Effects of electrical stimulation of centromedian thalamic nuclei on EEG activity (individual patients). EEG recording during baseline (BL), electrical stimulation (ESCM), and post-stimulation (POST) periods. Numbers (left) indicate date before (–) or after (+) initiation of stimulation. Numbers (right) indicate the number of epileptiform waves per 10 s. (Reprinted with permission from Velasco *et al.* [125].)

C. High-Frequency Stimulation of the CNS: Animal Studies

Vercueil *et al.* [113] reported that high-frequency ($\sim 100 \mu\text{A}$, 130 Hz) stimulation of the subthalamic nucleus was able to suppress ongoing seizures in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) strain. Their results showed that high-frequency stimulation could disrupt an ongoing seizure (Fig. 9). However, continuous stimulation (10 min) transiently suppressed seizures, which reappeared within the first 2 min of stimulation. Mirski and Fisher [75] reported that high-frequency stimulation (50–200 μA , 100 Hz) of the mammillary nuclei (MN) of rat posterior hypothalamus significantly increased the threshold of the seizure induced by pentylenetetrazol (PTZ). Low-frequency (5-Hz) stimulation tended to decrease, rather than increase, PTZ seizure threshold.

Bawin *et al.* investigated the effect of high-frequency sinusoidal currents on evoked epileptiform activity *in-vitro* using the penicillin model [5], [6]. They reported that high-frequency fields (20–50 mV/mm, 60 Hz) could depress evoked responses for several minutes after the termination of stimulation. In contrast, dc fields suppressed activity only for the duration of stimulation (see Section III). Furthermore, while the effect of dc fields was highly orientation specific (see above), the efficacy of sinusoidal fields was not affected by orientation. Bikson *et al.* [10], [11] studied the effect of high-frequency sinusoidal fields

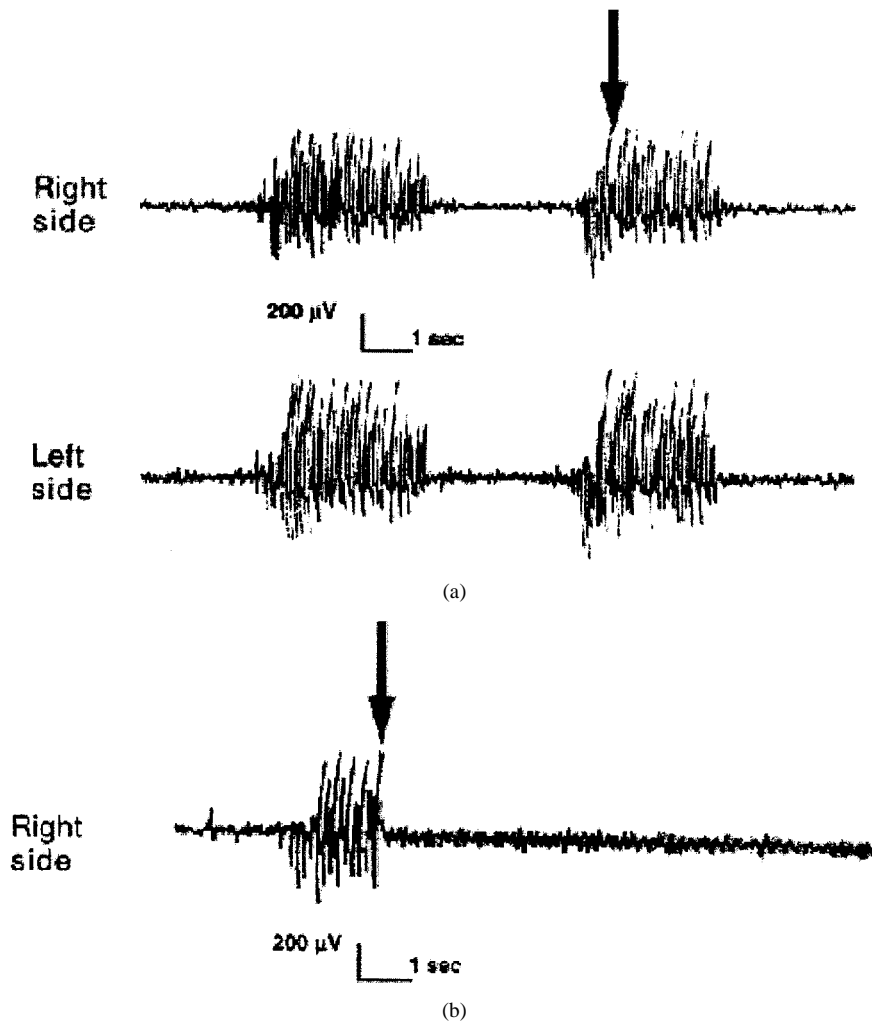


Fig. 9. Effect of triggered bilateral high-frequency stimulation of the subthalamic nuclei (at time indicated by arrow) on ongoing spontaneous epileptiform activity. (a) Low-intensity stimulation. (b) High-intensity stimulation. (Reprinted with permission from Vercueil *et al.* [113].)

(20–50 Hz, 50–250 mV/mm) on spontaneous epileptiform activity *in-vitro* using the zero- Ca^{+2} , low- Ca^{+2} , high- K^{+} , and Picrotoxin models. They found that high-frequency stimulation could suppress activity for the duration of stimulation and for up to several minutes after termination of stimulation (Fig. 10). Successful suppression of low- Ca^{+2} activity indicated neurotransmitter release was not required for suppression. In each model, suppression efficacy was not orientation dependant. Intracellular and ion-selective recordings [26] showed that suppression was caused by an extracellular potassium rise, which induced depolarization block of neurons. A similar mechanism of block was recently reported during high-frequency stimulation of thalamic slices [62].

D. High-Frequency Stimulation of the PNS

Zabara [124] first demonstrated that high-frequency vagal nerve (VN) stimulation inhibits seizures in canines. Subsequent studies showed this paradigm to be effective in other animals including rats [122] and monkeys [71]. Animal studies have shown that while high-frequency

(>70 Hz) VN stimulation can generate EEG desynchronization, low-frequency (20–50 Hz) stimulation induced EEG synchronization [16]. Similarly, high-frequency (>30 Hz) stimulation of the nucleus of the solitary tract (NTS), a structure innervated by the VN, resulted in EEG desynchronization, while low-frequency (1–17 Hz) stimulation causes synchronization [74].

There are now close to 3000 patients implanted with high-frequency vagus nerve stimulation systems for the treatment of epilepsy. The neurocybernetic prosthesis (NCP, Cybernetic, Houston, TX) VN stimulator received FDA approval in July 1997. Because of the pattern of vagus nerve innervation of the heart, the vagus nerve can only be stimulated unilaterally (i.e., the left side only). Typically the treatment routine consists of adjusting the current amplitude to tolerance (0.25–4 mA in 0.25-mA steps), using a 30-Hz frequency, 0.5-ms pulsewidth, for 30 s ON time and 5 min OFF time. In addition, the patient or a companion may trigger stimulation by placing an external magnet over the patient's chest. In multicenter, randomized, double mask studies, patients receiving high-intensity NCP stimulation (30 Hz, 0.25–4mA, 0.5 ms pulsewidth, 30 s ON time and 5 min OFF time) experi-

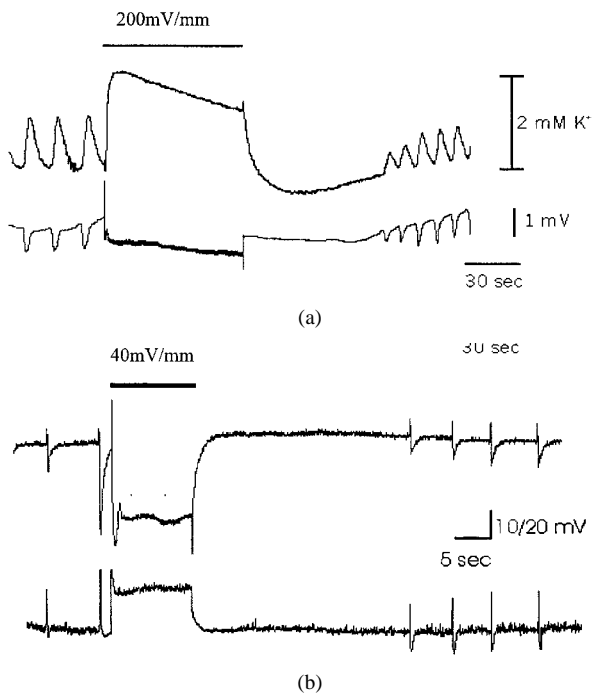


Fig. 10. Intracellular and extracellular potassium measurements during suppression of spontaneous epileptiform activity in hippocampal slices with high-frequency fields. (a) Top trace: [K] recording. Bottom trace: extracellular field recording. During spontaneous low- Ca^{+2} epileptiform activity high-frequency stimulation resulted in a large potassium increase during stimulation and suppression of activity. Post-stimulation suppression of activity was associated with a decrease in potassium below baseline levels. (b) Top trace: Field recording. Bottom trace: transmembrane potential. During spontaneous Picrotoxin epileptiform activity suprathreshold high-frequency stimulation resulted in the depolarization block of CA1 pyramidal cells and suppression of spontaneous activity. (Adapted from [11].)

enced a $\sim 30\%$ reduction in seizure frequency [3], [109]. In contrast, patient receiving low-intensity NCP stimulation (1 Hz, 0.13 ms pulsewidth, 30 s ON time and 180 min OFF time) experienced a 10% reduction.

Recently, Fanselow *et al.* [30] showed a reduction of pentylenetetrazole-induced seizure frequency in rats during high-frequency stimulation (3–11 mA, 100–333 Hz, 0.5 ms, 1 min ON, 1 min OFF) of the trigeminal nerve. Stimulation frequencies less than 50 Hz did not significantly reduce seizure initiation rate. Bilateral stimulation was significantly more effective than unilateral stimulation. Furthermore, they demonstrated seizure duration and frequency could be reduced using only stimulation triggered by a field potential recorded during a seizure.

VII. DISCUSSION

In this review, several approaches to controlling epileptiform activity with electrical stimulation were presented. This discussion focuses on addressing the mechanism and clinical usefulness of each approach.

A. Membrane Polarization (DC fields) Versus Pulsed Electrical Stimulation Paradigms

Low-amplitude dc current or electric fields can suppress neuronal activity without generating excitation. The main ad-

vantage of this method is that the current amplitude is very low (a few microamperes). The stimulus is subthreshold and still produces inhibition. This suppression mechanism (polarization) is well established from *in-vitro* studies. The efficacy of the dc suppression method was recently demonstrated with *in-vivo* experiments [117]. However, there are several drawbacks to this method: 1) nonreversible chemical reactions generated by dc currents potentially harmful to tissue can damage the electrode and the tissue [1]; 2) the efficacy of any dc field is dependant on cell orientation with respect to the electrode (for a uniform field, the dendrites must be aligned with the field; for the localized electrode, the cells body must be close to the electrode); 3) dc fields can produce both excitation and inhibition depending on cell location and orientation; 4) excitation rebound of spontaneous activity occurs at the termination of the dc pulse; and 5) dc fields must generally be applied for the whole duration of the event thereby requiring long pulses. To limit the duration and intensity of stimulation, dc fields can be triggered by the initiation of spontaneous activity [34]. The amplitude of the stimulus could be minimized by monitoring the size of the events and applying a field proportional to the event amplitude. Thus, dc stimulation has some potential for clinical implementation, provided that the stimulation can be shown to be effective in patients without significant electrochemical damage. Because the alternative to electrical stimulation is often complete tissue resection, some damage may be acceptable.

B. Localized Versus Uniform Electrical Field Suppression

There is no evidence to suggest that either monopolar and uniform field stimulation is more effective in suppressing epileptiform activity in any epilepsy model. Both methods can completely suppress spontaneous activity generated in the low-calcium, penicillin, and high-potassium models. Field electrodes need not be in direct contact with the targeted tissue thereby minimizing the electrochemical damage. The volume of tissue affected by the field is limited only by the size of the electrode. Clinical implementation of this method would require that two large electrodes to be placed on either side of the targeted structure, for example the hippocampus. Monopolar stimulation allows much more localized fields since the field effect is inversely proportional to the square of the distance [27]. Most clinical monopolar electrode designs employ multiple contacts and stimulators can be programmed to stimulate a subset of available leads.

C. Single Pulse and Low-Frequency Stimulation

The approaches being developed for the control of seizures using single pulses or low-frequency stimulation possess the greatest potential for clinical benefit since the effect of the stimulation can last well beyond the duration of the pulse (thereby minimizing the amount of charge required and electrochemical damage). Moreover, unlike dc stimulation, low-frequency stimulation is not necessarily orientation dependant. Implementation of low-frequency techniques experimentally, however, has been the most difficult. The phase resetting/singularity approach requires

that the system be bistable (or multistable) with at least one stable fixed point and periodic oscillation existing at the same time. Although bistability has been demonstrated in simple systems such as the squid giant axon (see Section IV), there is no guarantee that any complex neuronal network will be bistable, especially in the presence of noise. Moreover, this method requires a precise timing for the applied pulse. A similar precise timing is required for the chaos control and the algorithm for the prediction of the timing of the pulse must be robust even as environmental conditions change (such as changes in extracellular ionic composition). The largest potential limitation of both of these approaches is that they do not necessarily affect the overall excitability of the neural system. Phase resetting in the penicillin model has been shown to produce desynchronization [26], but did not reduce the underlying firing rate of a single neuron. Although it is possible that desynchronization of neuronal populations is sufficient to suppress the symptoms of epilepsy *in-vivo*, this effect has not yet been demonstrated.

Low-frequency stimulation protocols designed to induce LTD could potentially lead to reduced neuronal firing but there is no direct evidence for this effect in epilepsy treatment. Although TMS induced suppression of seizures in patients was somewhat successful, [105] it is difficult to know whether this effect was in fact caused by a decrease of synaptic efficiency. However, because magnetic stimulation is noninvasive, this method could have great clinical potential, especially if the magnetic stimulators can be made smaller and portable. Different magnetic stimulation protocols or novel coil designs for increased localization could improve the efficacy of this method [50].

D. High-Frequency Stimulation: Clinical Approaches

Electroconvulsive therapy, while not requiring surgery, is complicated by risks associated with general anesthesia and potential psychological and memory defects that results from intense stimulation of the entire brain. Controlled clinical studies in a significant patient population must be conducted before any conclusion about the efficacy of ECT can be drawn. Targeted high-frequency electrical stimulation of either deep brain structures (such as the thalamus and cerebellum) or peripheral nerves (such as the trigeminal and vagus), can produce a reduction in the severity and frequency of seizures. Deep brain stimulation offers several advantages over PNS stimulation: 1) electrodes implanted in the brain can directly activate any targeted structure with significantly more specificity than PNS stimulation and 2) with PNS stimulation there is concern about activation of additional afferent (pain, sensory) and efferent fibers (modulating cardiovascular and abdominal visceral functions). Multiple lead cuff electrodes and novel fiber selective stimulation techniques [39], [108] might be adapted to address these concerns. The main advantages of PNS stimulation is a significantly less costly and complicated implantation surgery. Although traditionally the vagus nerve was targeted for PNS stimulation, other structures could potentially be targeted in the future [30].

High-frequency stimulation of the numerous deep brain structures [111], [112] has been reported to reduce seizure frequency. To our knowledge, no controlled data exists comparing the effectiveness of each stimulation protocol in humans or animal models for any type of seizure activity. Both during-stimulation and post-stimulation anticonvulsant effects have been reported for each high-frequency stimulation technique. It is likely that short-term modulation of neuronal dynamics, environment, and excitability mediate during-stimulation effects while post-stimulation effects are mediated by persistent changes in cell connectivity. Interestingly, studies involving long term tonic electrical stimulation have found that the minimum stimulation intensity required for suppression either does not change or decreases over time. This is in contrast to pharmacologic approaches where patients tend to develop resistances to treatment and hence require incrementally higher doses over time.

E. High-Frequency Stimulation: During-Stimulation Mechanisms

Several lines of evidence suggest that high-frequency stimulation of deep brain structures inhibits neuronal activity. In treating human epilepsy and in animal models [113], high-frequency stimulation of a deep brain structure mimics the effect of lesioning that structure. Recordings from the subthalamic nucleus (STN) of rats have shown that immediately after high-frequency stimulation, neuronal firing rates are depressed [8]. Bikson *et al.* [11], [12] showed *in-vitro* that high-frequency stimulating inhibits neuronal firing by inducing potassium efflux and depolarization block. They proposed that an increase in extracellular potassium could thus mediate suppression of epilepsy by high-frequency stimulation. Because an increase in extracellular potassium levels cannot be maintained indefinitely, tonic stimulation would be ineffective and intermittent stimulation (i.e., 4 min ON, 4 min OFF) or triggered stimulation would be required. Consistent with this hypothesis, *in-vivo* animal studies have shown that triggered but not chronic stimulation is effective in suppressing seizures. Empirically determined clinical stimulation protocols for high-frequency cerebellar, thalamic, and vagal nerve stimulation all employ ON-OFF paradigms.

Several other mechanisms such as neurotransmitter buildup, loss of information transfer [76], and specific activation of inhibitory pathways have been proposed to underlie the during-stimulation effects of high-frequency stimulation. However, none of these mechanisms has been shown experimentally to mediate the suppression of epileptiform activity during high-frequency stimulation, clinically or in an animal model.

F. High-Frequency Stimulation: Post-Stimulation Mechanisms

It is well established that high-frequency stimulation induces changes in cell connectivity but these changes usually increase synaptic efficacy and, thus, would be expected to

be epileptogenic. ECT is known to induce changes in muscarinic and glutamatergic receptors [69], [116] potassium channel expression [83], microtubule-associated proteins [84], as well as modulate entorhinal-dentate projections excitability [36] and NPY transmission [64]. It is unclear if DBS and PNS stimulation protocols would induce similar long-term changes.

Although high-frequency stimulation is the only electrical stimulation paradigms currently being used extensively in a clinical environment, it is also the most poorly understood. Future basic research studies examining the short and long-term effects of high-frequency field on CNS tissue should improve this understanding and lead to improved stimulation protocols.

VIII. CONCLUSION

Several electrical stimulation protocols can either suppress or interfere with abnormal neuronal activity. This suppression has been demonstrated in several animal models of epilepsy and in humans. Unlike surgical resection, the effect of electrical stimulation is generally reversible. Unlike drugs, electrical stimulation can be applied to specific regions of the brain and the "dosage" of stimulation can be varied easily and instantaneously. By simply changing stimulation parameters, clinicians could potentially screen different protocols using a single implanted electrode. However, there are serious problems to be overcome before these techniques can be implemented routinely. The mechanisms involved in most clinically used methods are not known. For other methods, the mechanisms are known but clinical implementation seems difficult. However, electrical stimulation is a powerful tool to control seizures. Novel approaches in neural imaging, modeling and electrode design should allow researchers to unravel unknown mechanisms and design new effective methods to control abnormal activity in the brain.

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Dominique M. Durand (Member, IEEE) was born in Monbazillac, France, in 1951. He received the Eng. degree from Ecole Nationale Supérieure d'Electronique, Hydrolique, Informatique et Automatique de Toulouse, France, in 1973, the M.S. degree in Biomedical Engineering from Case Reserve University, Cleveland, OH, in 1974, and the Ph.D. degree in electrical engineering from the Institute of Biomedical Engineering, University of Toronto, Canada, in 1982.

He worked for several years at the Addiction Research Foundation of Toronto, Canada before earning his doctorate. He is currently Professor in the Departments of Biomedical Engineering and Neurosciences at Case Western Reserve University, Cleveland, OH. His research interests are in neural engineering and include computational neuroscience, neurophysiology and control of epilepsy, nonlinear dynamics of neural systems, neural prostheses, and applied magnetic and electrical field interactions with neural tissue.

Prof. Durand received a NSF Young Investigator Presidential Award as well as undergraduate and graduate teaching awards. He is a Fellow of the American Institute for Medical and Biomedical Engineering.



Marom Bikson was born in Tel-Aviv, Israel, in 1975. He received the B.S. degree in biomedical engineering from Johns Hopkins University, and the Ph.D. in biomedical engineering from Case Western Reserve University in 2001.

He worked at Sontra Medical, Cambridge, MA. He is currently a post-doctoral fellow in the Department of Neurophysiology, Division of Neuroscience, University of Birmingham, U.K. His research interests include nonsynaptic interactions in the CNS and the effects of

exogenous electric fields on CNS function.