Optimizing stimulus waveforms for suppressing epileptic activity reveals a counterbalancing mechanism

Joshua Chang, *Member, IEEE,* and David Paydarfar

***Abstract*— Electrical stimulation is used to treat drug-resistant epilepsy, and excessive stimulation can lead to adverse effects for patients. In this article, we use an extrema featured stochastic search algorithm to find energy-efficient stimulus waveforms that suppress seizure activity in two different computational models of epilepsy. We infer general principles that may provide insight into future design of energy efficient stimulus for epilepsy treatments.**

I. Introduction

Epilepsy affects 2.3 million adults and over 450,000 children under the age of 18 in the United States [1], [2]. Physicians diagnose roughly 150,000 new cases each year, and the total financial burden of this disease in both direct and indirect costs was estimated at $9.6 billion in 2009 [3]. While the primary form of treatment for epilepsy is anti-seizure medication, nearly 30% of these patients do not respond to drug therapies [4], and although some patients can undergo surgery to treat refractory epilepsy, not all medically refractory patients are candidates for these procedures. As an alternative, electrical stimulation of specific regions of the nervous system, whether the brain or peripheral nerves, have been shown to aid in the suppression of seizure frequency and severity [5]–[9].

One of the key features of epileptic seizures is dysfunctional neurological oscillatory activity. Treatment for epilepsy via electrical stimulation has focused on the suppression of these dysfunctional oscillations. To that end, three different types of treatments have been developed: vagus nerve stimulation [10]–[12], deep brain stimulation of the thalamus, the subthalamic nucleus, the caudate nucleus and the cerebellum [13], [14], and responsive neural stimulation of cortical epileptogenic regions [6]–[8]. In each of these treatments, a simple waveform is used (e.g. rectangular biphasic waveform), and physicians tweak a few basic parameters including frequency, pulse duration and amplitude based on how the patient responds in order to improve performance.

An important computational challenge arises with regards to finding customized patient-specific stimulus waveforms, which not only successfully suppress seizures, but also use the least amount of energy possible. Overstimulation can lead to a number of adverse side effects seen in patients including coughing, voice alteration, paraesthesia, dyspnea, headache, depression, memory impairment, anxiety, and dysesthesia [7], [11], [12].

In this paper, we apply an extrema feature stochastic search algorithm[15] to two separate mathematical models of epilepsy examining both activity at an ionic level as well as a population level. Using this algorithm, we can iteratively search for optimality, gaining therapeutic insights into the optimal treatment for epilepsy with electrical stimulation.

II. Methods

A. Extrema Feature Stochastic Search Algorithm

The extrema feature stochastic search algorithm finds optimal stimulus waveforms without requiring any *a priori* knowledge of the underlying mechanisms or mathematical equations defining the system's behavior [15]. This approach works by taking a randomly generated starting waveform and iteratively adding noise to its extrema points (local minimum and maximum amplitudes). As the waveform is distorted, it is applied to the system and evaluated for both its ability to cause the desired outcome (e.g. suppression of epilepsy) as well as its energy requirements, in our case computed through the L^2-norm or the sum of the squares of the stimulus amplitudes over time. The best solution seen becomes the starting waveform for the next iteration.

We constrained the electrical stimulus to be charge neutral due to the fact that charge unbalanced stimuli can cause cellular damage. This reaction is thought to be either due to the formation of toxic electrochemical reaction products from the charge deposition in the cell or due to the movement of charged particles within the cell itself [16], [17]. This constraint was accomplished by removing the average from the stimulus after each iteration, projecting the stimulus onto a zero-mean stimulus solution space. The computational experiments were performed 20 times with unique starting seeds each time.

B. Single Cell Repetitive Firing

Regarding the modeling of epileptogenesis, one hypothesis has been that seizure activity arises from a derangement in the neuron's intrinsic properties resulting in repetitive firing [18], [19]. A subset of epilepsies fall in the category of channelopathies, mutations in genes that encode various voltage-sensitive ionic channels. Among these channelopathies, forms of generalized epilepsy with febrile seizures have been linked to mutations in genes encoding voltage-gated sodium channel α, leading to persistent inward current which likely causes increased excitability of the neuron's membrane [19]. To model this, a 9 $\mu A/cm^2$ persistent current was added to the Hodgkin-Huxley model

*Research supported by the Clayton Foundation for Research and NIH R01 GM104987.

J. Chang is with the Department of Neurology, Dell Medical School, The University of Texas, Austin, TX 78712 (phone: 512.495.5302, email: joshua.chang@austin.utexas.edu)

D. Paydarfar is with the Department of Neurology, Dell Medical School, and The Institute for Computational Engineering and Sciences, The University of Texas, Austin, TX 78712 US (e-mail: david.paydarfar@austin.utexas.edu)

[20], essentially increasing the excitability of the neuron's membrane. The equations for our Hodgkin-Huxley model are as follows:

$$C\dot{V} = -120m^3h(V-115) - 36n^4(V+12) \\ -0.3(V-10.613) - 9 - u$$
$$\dot{m} = -m\big(\alpha_m(V)+\beta_m(V)\big) + \alpha_m(V)$$
$$\dot{n} = -n\big(\alpha_n(V)+\beta_n(V)\big) + \alpha_n(V)$$
$$\dot{h} = -h\big(\alpha_h(V)+\beta_h(V)\big) + \alpha_h(V)$$
$$\alpha_m(V) = \frac{0.1\phi(25-V)}{e^{0.1(25-V)}-1},\ \beta_m(V) = 4\phi e^{-V/80}$$
$$\alpha_n(V) = \frac{0.01\phi(10-V)}{e^{0.1(10-V)}-1},\ \beta_n(V) = 0.125\phi e^{-V/80}$$
$$\alpha_h(V) = 0.07\phi e^{-V/20},\ \beta_m(V) = \frac{\phi}{e^{0.1(30-V)}+1}$$

where u represents the exogenous stimulation. This model represents a space-clamped Hodgkin-Huxley neuron which assumes that every point on the neuron is getting the exact same input. Furthermore, this is a representation of a single axon, and thus synaptic inputs are not modeled. The addition of the persistent current causes the Hodgkin-Huxley model to be bistable allowing us to model the cell in either a repetitive firing state or a quiescent state. Using the stochastic search algorithm, we sought the optimal 31-ms stimulus (the duration of two cycles of repetitive firing) that successfully switched off epileptiform repetitive firing, resulting in sustained subthreshold activity.

C. *Population-based systemic bursting*

While the first model approached the problem of epilepsy at a single-cell level examining the ionic mechanisms, our second model examines epilepsy at a population level [21]. Because epilepsy affects extremely large networks, it is difficult and time-intensive to calculate the ionic mechanism underlying each individual neuron. As such, researchers have developed population-based models that lump together groups of neurons into their mean-field components, modeling the interactions between groups of neurons as opposed to individual neurons.

Here, we studied a simple bistable system developed by Suffczynski et al [22]. This model examines absence epilepsy through the interactions of four populations of neurons: pyramidal neurons, interneurons, thalamocortical neurons and reticulothalamic neurons. The pyramidal neurons qualitatively mimic EEG activity. The model parameters match experimental data collected from the Wistar albino Glaxo from Rijs-wijk (WAG/Rij) rat, which is a genetic animal model of absence epilepsy. Fig 1 shows a diagram with the various interconnections modeled between the four populations of neurons.

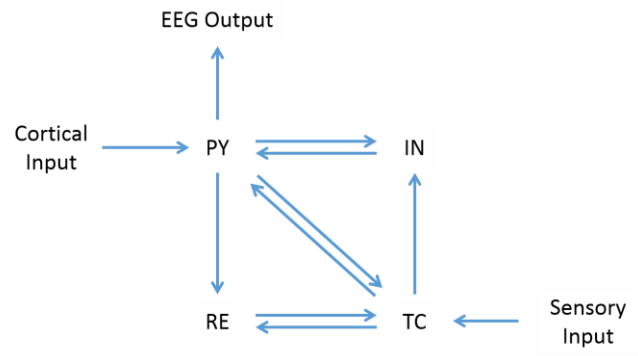

Figure 1. Conceptual model of absence epilepsy in a population-based neuronal system. The four systems are the pyramidal neurons (PY), the interneurons (IN), the reticulothalamic neurons (RE) and the thalamocortical neurons (TC).

In this model, there exist two states, a quiescent state, and a seizure state delineated by the strength of the pyramidal neurons' mean-field voltage. The system can spontaneously transition on its own from one state to the other due to a low level of sensory noise programmed into the model. We found a set of initial conditions for the system such that the system begins in the quiescent state, but then spontaneously transitions into a seizure state a second later. The extrema feature stochastic search algorithm was used to find the optimal 100-ms waveform that was sufficient to switch off the epileptic state back to the normal state within 100 millisecond of the end of the stimulus.

III. Results

A. *Single Cell Repetitive Firing*

Fig 2 shows the optimal stimulus found for the single cell model. As seen in this figure, the optimal stimulus is multi-phasic with a prominent biphasic component in the center.

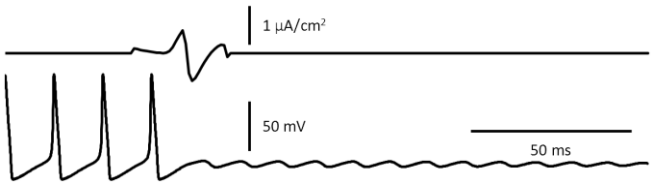

Figure 2. Optimal stimulus for suppressing repetitive firing in a bistable Hodgkin-Huxley model neuron. Both the stimulus (top) and the system response (bottom) are shown

As a point of comparison, we ran a grid search of biphasic rectangular pulses with varying stimulus duration (1-ms to 20-ms per phase) and stimulus amplitude (-10 μA/cm^2 to 10 μA/cm^2 for the first phase, the inverse for the second phase, in 0.1 μA/cm^2 increments). The optimal rectangular pulse that we found was 2-ms duration per phase, 1.4 μA/cm^2 and -1.4 μA/cm^2 for the first and second phase respectively and had a total energy usage of 7.84 μJ. The optimal stimulus waveform found using our stochastic search had a total energy usage of 2.63 μJ.

One interesting observation we noted was that the stimulus appears to have an inverse relationship with the system response in that the trough of the stimulus almost lines up with a crest in the system's response, and the following crest

in the stimulus lines up with the following trough in the system's response.

B. Population-Based Systemic Bursting

Fig 3 shows the optimal stimulus waveform found for the population-based model of systemic bursting. The optimal stimulus suppresses the seizure activity. Again, it is interesting to note the inverse relationship the stimulus has with the membrane voltage potential of the pyramidal neurons.

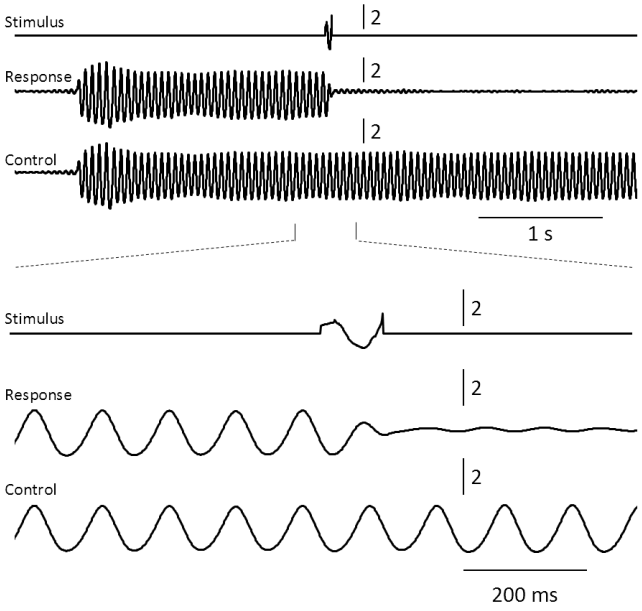

Figure 3. Optimized stimulus that switches off a epileptic activity in the population-based model system. The bottom set shows a magnification of the transition due to the stimulus.

IV. DISCUSSION

With the increasing use of electrical stimulation for the treatment of epilepsy, there is growing interest in finding energy-efficient stimulus waveforms tailored specifically to the patient. This study applied the use of an extrema featured stochastic search algorithm to finding optimal waveforms for two computational models of epileptic behavior in order to gain greater insight into suppressing seizure activity.

There has been some prior work in examining the use of non-standard pulsatile stimulation in the treatment of epilepsy. Some of this work was done in the form of utilizing a delayed feedback mechanism to suppress epileptic activity in a population of neurons [23], [24], though energy efficiency was not a factor in their studies. Others like Wilson and Moehlis have used mathematical techniques and principles to analytically solve computational models of epilepsy to find energetically efficient stimuli to terminate seizure-like bursting behavior [25], but the epileptic activity needed to be defined as a system of equations.

Here, we have captured the optimal stimulus waveform using our algorithm on two separate computational models of epilepsy: suppression of epileptiform activity at both the single cell level and at the population level. We have shown that the optimal solution performs much better than optimal rectangular waveforms, thus allowing for potentially large reductions in energy consumption. This reduction can be explained from the perspective that the biological world responds more to signals bandlimited by certain frequencies. The sharp edges in rectangular biphasic stimuli require extremely high frequencies, and thus these frequencies add to the energy requirements of the stimulus when applied to a system that does not respond to such extreme rates of change.

One interesting observation that has been true across both of these models is that there appears to be an inverse relationship between the stimulus and the system's response. The stimulus appears to act as a counter balance to the system's response, pushing back on the system so as to prevent the continuation of large oscillations. While this counter balancing force has not been described as such in the literature, there is evidence indicating that the efficacy of the stimulus is dependent on the phase of the system. Taylor et al showed computationally, and referred to experimental work, that the timing of when short discrete pulses were delivered was crucial to its success [26]. Given at the wrong phase, the stimulus could potentially do nothing to the system or in the worst case exacerbate the seizure activity. Using our hypothesis that the stimulus is acting as a counterbalancing force to the system, we can explain these findings based on the phase dependency of the stimulus. If the stimulus was in phase with the system's response, acting in synchrony, it would perpetuate, if not accentuate, the seizure activity.

There has been other work in suppressing epileptic activity by using delayed feedback stimulation. Here, the stimulus is not short discrete pulses, but instead a continuous stimulus with an oscillatory behavior. Rosenblaum and Pikovsky, as well as others later, demonstrated how synchronization can be controlled via a delayed-feedback stimulus that is out of phase with the system [24], [27], [28].

What's interesting with our work is that we are now examining a longer duration stimulus compared to discrete pulses. By stretching the pulse, this counter balancing force is distributed across time, and reduces the L^2-norm, or the energetics of the stimulus. Previous work has shown that the spreading of the stimulus reduces the energetics required to fire an action potential, but only to a certain point [29]. After a certain duration, there was no longer any energy savings. Future studies may shed light on the relationship between the optimal duration of the stimulus and the dynamics of the system itself.

While we have looked at two different computational models of epileptic behavior, there are other mechanisms that have been hypothesized in the literature. One of the main theories of interest currently is the idea that seizure activity is due to the synchronization of populations of neurons, and thus the suppression of epileptic activity is accomplished through desynchronization. We explored this concept previously in [15] , and similar concepts of counterbalancing also play a role in the coupled oscillator network that we constructed. The fact that the oscillator network that we created was not bistable implies that the existence of this counterbalancing phenomenon does not require necessarily a bistable system, but an oscillatory system. Future work may further our understanding of the ionics underlying this

phenomenon and unify it with the ionics in the bistable model that we have examined in this paper.

Finally, this paper has used the assumption that seizure activity exists in a repetitive firing state. There has been some work that has shown that there may be more of a bursting behavior that exists in epileptiform activity [25], [30]. These bursting models incorporate both fast and slow dynamics in one system. Examining the optimal stimulus waveforms in these bursters may give us further insight into the suppression of seizure activity. In light of the results of this study, does the optimal stimulus waveform for suppressing bursting activity counter the slow dynamics or the fast dynamics or both? How does the optimal duration for bursters relate to the ionic mechanisms of these model?

From both the models examined here, and in previous work [15], we see a pattern of optimal stimuli having an counter balancing relationship with the system's response. Future work is necessary to better understand the dynamics, explaining why this pattern emerges across different models of epilepsy. Armed with this greater understanding, we may hopefully one day be able to develop therapeutic devices that capture the phase and frequency of epileptic dysfunctional oscillations and administer the proper counterbalancing force so as to suppress seizure activity while minimizing adverse effects due to overstimulation. Furthermore, by using an adaptive algorithm, these devices could potentially even adapt to changes in the phase or frequency of the system due to physiologically changes in the patient.

REFERENCES

[1] R. Kobau, Y. Luo, M. Zack, S. Helmers, and D. Thurman, "Epilepsy in adults and access to care - United States, 2012," *Morb. Mortal. Wkly. Rep.*, vol. 61, no. 45, pp. 909–913, 2012.

[2] S. a. Russ, K. Larson, and N. Halfon, "A National Profile of Childhood Epilepsy and Seizure Disorder," *Pediatrics*, vol. 129, pp. 256–264, 2012.

[3] J. Y. Clark *et al.*, "Economic impact of epilepsy in the United States," *Epilepsia*, vol. 50, no. 10, pp. 2186–2191, 2009.

[4] P. Kwan and M. J. Brodie, "Early identification of refractory epilepsy.," *N. Engl. J. Med.*, vol. 342, pp. 314–9, 2000.

[5] V. Salanova and R. Worth, "Neurostimulators in epilepsy," *Curr. Neurol. Neurosci. Rep.*, vol. 7, no. 4, pp. 315–319, Jul. 2007.

[6] F. T. Sun, M. J. Morrell, and R. E. Wharen, "Responsive cortical stimulation for the treatment of epilepsy," *Neurotherapeutics*, vol. 5, no. 1, pp. 68–74, 2008.

[7] M. J. Morrell, "Responsive cortical stimulation for the treatment of medically intractable partial epilepsy," *Neurology*, vol. 77, pp. 1295–1304, 2011.

[8] E. H. Kossoff *et al.*, "Effect of an external responsive neurostimulator on seizures and electrographic discharges during subdural electrode monitoring.," *Epilepsia*, vol. 45, no. 12, pp. 1560–7, Dec. 2004.

[9] W. Penfield and H. Jasper, *Epilepsy and the functional anatomy of the human brain.* Oxford, England: Little, Brown & Co, 1954.

[10] K. Vonck, K. Van Laere, S. Dedeurwaerdere, J. Caemaert, J. De Reuck, and P. Boon, "The mechanism of action of vagus nerve stimulation for refractory epilepsy: the current status.," *J. Clin. Neurophysiol.*, vol. 18, no. 5, pp. 394–401, 2001.

[11] E. Ben-Menachem, "Vagus-nerve stimulation for the treatment of epilepsy," *Lancet Neurol.*, vol. 1, no. December, pp. 477–482, 2002.

[12] G. L. Morris and W. M. Mueller, "Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy," *Neurology*, vol. 53, no. 8. pp. 1731–1731, 1999.

[13] P. Boon *et al.*, "Deep brain stimulation in patients with refractory temporal lobe epilepsy," *Epilepsia*, vol. 48, no. 8, pp. 1551–1560, 2007.

[14] T. Loddenkemper and A. Pan, "Deep brain stimulation in epilepsy," *J. Clin. Neurophysiol.*, vol. 116, no. 6, pp. 217–34, Jan. 2001.

[15] J. Chang and D. Paydarfar, "Evolution of extrema features reveals optimal stimuli for biological state transitions," *Sci. Rep.*, vol. 8, no. 1, p. 3403, 2018.

[16] J. C. Lilly, J. R. Hughes, E. C. Alvord, and T. W. Galkin, "Brief, Noninjurious Electric Waveform for Stimulation of the Brain," *Science (80-.).*, vol. 121, no. 3144, pp. 468–469, 1955.

[17] D. R. Merrill, M. Bikson, and J. G. R. Jefferys, "Electrical stimulation of excitable tissue: Design of efficacious and safe protocols," *J. Neurosci. Methods*, vol. 141, no. 2, pp. 171–198, 2005.

[18] P. J. Hahn and D. M. Durand, "Bistability dynamics in simulations of neural activity in high-extracellular-potassium conditions," *J. Comput. Neurosci.*, vol. 11, no. 1, pp. 5–18, 2001.

[19] C. Lossin, D. W. Wang, T. H. Rhodes, C. G. Vanoye, and A. L. George, "Molecular basis of an inherited epilepsy," *Neuron*, vol. 34, pp. 877–884, 2002.

[20] A. L. Hodgkin and A. F. Huxley, "A quantitative description of membrane current and its application to conduction and excitation in nerve," *J. Physiol.*, vol. 52, no. 4, pp. 500–544, Aug. 1952.

[21] S. J. Schiff and G. Ullah, "Models of Epilepsy," *Scholarpedia*, vol. 4, no. 7, p. 1409, 2009.

[22] P. Suffczynski, S. Kalitzin, and F. H. Lopes Da Silva, "Dynamics of non-convulsive epileptic phenomena modeled by a bistable neuronal network," *Neuroscience*, vol. 126, no. 2, pp. 467–484, Jan. 2004.

[23] O. V. Popovych, C. Hauptmann, and P. A. Tass, "Effective desynchronization by nonlinear delayed feedback," *Phys. Rev. Lett.*, vol. 94, no. 16, pp. 2–5, 2005.

[24] M. G. Rosenblum and A. S. Pikovsky, "Controlling synchronization in an ensemble of globally coupled oscillators," *Phys. Rev. Lett.*, vol. 92, no. MARCH, p. 114102, 2004.

[25] D. Wilson and J. Moehlis, "A Hamilton-Jacobi-Bellman approach for termination of seizure-like bursting," *J. Comput. Neurosci.*, pp. 345–355, 2014.

[26] J. Ruths, P. Neal, and T. Justin, "Optimal Control of an Epileptic Neural Population Model ⋆ ," *19th World Congr. Int. Fed. Autom. Control*, pp. 3116–3121, 2014.

[27] C. Hauptmann, O. Popovych, and P. A. Tass, "Effectively desynchronizing deep brain stimulation based on a coordinated delayed feedback stimulation via several sites: A computational study," *Biol. Cybern.*, vol. 93, no. 6, pp. 463–470, Dec. 2005.

[28] P. A. Tass, "A model of desynchronizing deep brain stimulation with a demand-controlled coordinated reset of neural subpopulations," *Biol. Cybern.*, vol. 89, no. 2, pp. 81–88, Aug. 2003.

[29] J. Chang and D. Paydarfar, "Switching neuronal state: optimal stimuli revealed using a stochastically-seeded gradient algorithm," *J. Comput. Neurosci.*, vol. 37, no. 3, pp. 569–582, Aug. 2014.

[30] W. Barnett, G. O'Brien, and G. Cymbalyuk, "Bistability of silence and seizure-like bursting.," *J. Neurosci. Methods*, vol. 220, no. 2, pp. 179–89, Nov. 2013.