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Synthesis of high-complexity rhythmic signals for closed-loop electrical neuromodulation

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ABSTRACT

We propose an approach to synthesizing high-complexity rhythmic signals for closed-loop electrical neuromodulation using cognitive rhythm generator (CRG) networks, wherein the CRG is a hybrid oscillator comprised of (1) a bank of neuronal modes, (2) a ring device (clock), and (3) a static output nonlinearity (mapper). Networks of coupled CRGs have been previously implemented to simulate the electrical activity of biological neural networks, including *in silico* models of epilepsy, producing outputs of similar waveform and complexity to the biological system. This has enabled CRG network models to be used as platforms for testing seizure control strategies. Presently, we take the application one step further, envisioning therapeutic CRG networks as rhythmic signal generators creating neuromimetic signals for stimulation purposes, motivated by recent research indicating that stimulus complexity and waveform characteristics influence neuromodulation efficacy. To demonstrate this concept, an epileptiform CRG network generating spontaneous seizure-like events (SLEs) was coupled to a therapeutic CRG network, forming a closed-loop neuromodulation system. SLEs are associated with low-complexity dynamics and high phase coherence in the network. The tuned therapeutic network generated a high-complexity, multi-banded rhythmic stimulation signal with prominent theta and gamma-frequency power that suppressed SLEs and increased dynamic complexity in the epileptiform network, as measured by a relative increase in the maximum Lyapunov exponent and decrease in phase coherence. CRG-based neuromodulation outperformed both low and high-frequency periodic pulse stimulation, suggesting that neuromodulation using complex, biomimetic signals may provide an improvement over conventional electrical stimulation techniques for treating neurological disorders such as epilepsy.

1. Introduction

Neuromodulation by electrical stimulation was initially conceived to treat debilitating pain (Gildenberg, 2006). Nowadays, the definition of electrical neuromodulation has expanded to encompass varieties of electrical stimulation targeting motor control, sensory perception and cognition, whereby stimulation is delivered to counter the effects of disability or pathology compromising such functions. For example, functional electrical stimulation (FES) is a technique that modulates nerve activity in the extremities in order to restore lost motor function due to paralysis (Popovic et al., 2011; Thrasher & Popovic, 2008; Thrasher, Zivanovic, McIlroy, & Popovic, 2008). Similarly, pathological motor traits caused by Parkinson's and dystonia have been successfully treated using deep brain stimulation (DBS) (Lozano, 2001; Toda, Hamani, & Lozano, 2004), which involves surgical implantation of electrodes delivering electrical pulses to limbic and midline structures of the brain, such as the subthalamic nucleus. DBS has also been favorably indicated for disorders that can alter or otherwise impair cognition, such as epilepsy and depression (Loddenkemper et al., 2001; Mayberg et al., 2005).

For the treatment of epilepsy, most studies involving DBS have implemented open-loop periodic pulse stimulation in which the waveform and frequency of stimulation do not vary over time (Hamani, Andrade, Hodaie, Wennberg, & Lozano, 2009), and whose programmable parameters include amplitude, pulse width, duty cycle and frequency. Recently, however, several groups turned to investigating closed-loop modes of electrical pulse stimulation. Closed-loop systems require a brain–computer interface (BCI) to record and process data on-line and to subsequently deliver an appropriately modified stimulus back to the subject. The increased complexity of the stimulator appears to be compensated for by superior performance. In several studies by Osorio and colleagues, patients were administered closed-loop high-frequency stimulation (HFS)($>$ 100 Hz) at the seizure focus, with stimulation being activated automatically when a seizure was detected (Osorio et al., 2001, 2005; Peters, Bhavaraju, Frei, & Osorio, 2001). Patients with bilateral seizure foci had stimulation delivered to the anterior thalamic nucleus (AN). A mean decrease of 55% in the locally-stimulated group (ranging from 100% at best

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to −36.8% at worst) was achieved, with of 3 of the 4 patients collectively experiencing an 86% reduction in seizure frequency, whereas the AN stimulated group had a 40.8% mean reduction in seizure occurrence (ranging from 75.6% to −1.4%) (Osorio et al., 2005). In several longitudinal studies, similar benefits were noted in patients who had responsive stimulators implanted for several months or longer (Fountas & Smith, 2007; Fountas et al., 2005; Kossoff et al., 2004; Sun, Morrell, & Wharen, 2008).

These promising results provide an impetus for further investigation and development of closed-loop stimulation paradigms. However, the variability in individual patient outcomes, coupled with a moderate overall effectiveness of responsive stimulation using pulse trains, suggests there is room for improvement. Better efficacy might be achieved by not only making the stimulation responsive, but by making the stimulus properties biomimetic such that the signal emulates the waveforms, complexity and multi-banded nature of biological neural electrical activity.

A study by Wyckhuys and colleagues compared two forms of open-loop (non-responsive) stimulation: (1) conventional periodic-pulse HFS, as used in clinical DBS, and (2) Poisson-distributed pulse stimulation (PDS) with the same 130 Hz mean stimulation frequency (Wyckhuys et al., 2010). PDS is biomimetic in the sense that it emulates the observed distribution of neuronal inter-spike intervals, which approximates a Poisson point process (Shadlen & Newsome, 1998). Despite the non-responsiveness of PDS, the efficacy of PDS in seizure suppression was significantly improved over that of periodic HFS. In periodic HFS-improved rats, a 50% decrease in seizure occurrence was observed, whereas in PDS-improved rats, seizure frequency declined to 33% of the baseline rate. The only difference between the two forms of stimulation was the complexity of the interval timing of the pulses.

The advantage offered by PDS suggests that biocompatible structuring of the stimulation in terms of signal complexity, waveform and/or rhythmic constituents may be as relevant to neuromodulation performance as the responsiveness of the stimulation. To explore this concept, we constructed a cognitive rhythm generator (CRG) model (Zalay & Bardakjian, 2009; Zalay, Serletis, Carlen, & Bardakjian, 2010) comprising a therapeutic network connected in a closed loop with a spontaneously-seizing epileptiform network. The epileptiform network model was utilized previously as a platform for testing artificial neural network (ANN) based strategies for seizure control (Colic, Zalay, & Bardakjian, 2011). Presently, we extend the application of CRG networks to neuromodulator design, with the objective of investigating neuromodulation utilizing dynamic, biomimetic stimulation signals of non-trivial complexity and rhythmicity. Coupled CRGs are suitable because they can produce outputs that are comparable in waveform and dynamic complexity to activity recorded from biological neural networks (Zalay & Bardakjian, 2008, 2009; Zalay et al., 2010). Furthermore, whereas ANN-based neuromodulator design involves discrete input–output mapping of the feedback and stimulus, a coupled oscillator approach synthesizes rhythms intrinsically and dynamically, analogous to way in which rhythms are generated by biological oscillatory networks in the brain. In this paper, we evaluate the proposed therapeutic CRG network for its ability to suppress seizure-like events (SLEs) and restore dynamic complexity in the target epileptiform network, and we compare its performance to low-frequency and high-frequency periodic pulse stimulation simulating standard clinical DBS.

2. Methods

2.1. Cognitive rhythm generator model

For the model presented in this paper, the nth cognitive rhythm generator in the epileptiform or therapeutic network consists of (1) an input bank of neuronal modes, whose mode outputs are combined by mixing functions; (2) a ring device, whose instantaneous amplitude and phase are modulated by the mode outputs feeding it; and (3) a mapper, which constitutes the output static nonlinearity of the CRG (Zalay & Bardakjian, 2009; Zalay et al., 2010). The neuronal modes are filters that code for different component input–output dynamics depending on the mode shape and decay profile, and in their most general form are obtained by eigen-decomposition of the Volterra kernels estimated from measurements of the biological system response to input noise (Kang, Zalay, Serletis, Carlen, & Bardakjian, 2012). The mode outputs at time t are generated by convolution of the nth CRG input, $f_n(t)$, with the kth mode, $m_{kn}(t)$:

$$u_{kn}(t) = m_{kn}(t) * f_n(t) = \int_0^\infty m_{kn}(\tau) f_n(t-\tau)\, d\tau. \tag{1}$$

For our modeling purposes, two modes are utilized, and are selected to have the following analytical expressions:

$$m_{1n}(t) = \beta_n t \exp(-\beta_n t) \tag{2a}$$

$$m_{2n}(t) = \beta_n(\exp(-\beta_n t) - m_{1n}(t)) \tag{2b}$$

where $1/\beta_n$ is the modal time constant. The convolution operation $u_{1n}(t) = m_{1n}(t) * f_n(t)$ can be represented in equivalent differential form by first taking the Laplace transform such that

$$\begin{aligned} U_{1n}(s) &= M_{1n}(s) F_n(s) \\ &= \frac{\beta_n}{(s+\beta_n)^2} F_n(s) \\ &= \frac{\beta_n}{s^2 + 2\beta_n s + \beta_n^2} F_n(s). \end{aligned} \tag{3}$$

Rearranging (3) and making use of the Laplace transform identity for derivatives, and letting $u_{1n}(0) = \dot{u}_{1n}(0) = 0$, the following equivalent second-order differential equation is obtained:

$$\ddot{u}_{1n} + 2\beta_n \dot{u}_{1n} + \beta_n u_{1n} = \beta_n f_n \tag{4}$$

which upon noting from (2a) and (2b) that $m_{2n} = \dot{m}_{1n}$, can be converted to the following expressions:

$$\dot{u}_{1n} = u_{2n} \tag{5a}$$

$$\dot{u}_{2n} = \beta_n f_n - 2\beta_n u_{2n} - \beta_n^2 u_{1n}. \tag{5b}$$

The form of (5a) and (5b) enables the convolutions of input f_n with the two modes given by (2a) and (2b) to be computed dynamically from the system of first-order differential equations. The mode outputs, u_{1n} and u_{2n}, which are the solutions of the equations, dictate how the CRG responds dynamically to coupling inputs or external stimuli through f_n, which for a network of M CRG units can be written as

$$f_n = \sum_{m=1}^{M} c_{mn} y_m + x_n \tag{6}$$

where y_m is the output of the mth CRG, $\{c_{mn}\}$ are the associated coupling coefficients, and x_n is the external input. The mode functions given by (2a) and (2b) have integrating and differentiating character, respectively, in the sense that convolution of m_{1n} with a step input produces an accumulation effect due to its monophasic exponential form, similar to capacitor charging. (This is not to say the mode performs integration of the input in a mathematically rigorous sense of the definition.) Mode m_{2n} on the other hand is biphasic and has differentiating character because convolution of the mode with a step input generates a positive output on the rising edge and negative output on the falling edge, and is everywhere else zero where the input is a constant (Kang et al., 2012; Zalay & Bardakjian, 2009). In this way, the mode codes for rate of change of the input, which is akin to taking the derivative.