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Phase-Based Control of the Central Pattern Generator for Locomotion

R. Jacob Vogelstein and Ralph Etienne-Cummings
Johns Hopkins University
Department of Electrical and Computer Engineering
Baltimore, MD USA
Email: {jvogelst, retienne}@jhuapl.edu

Avis H. Cohen
Institute for Systems Research
University of Maryland, College Park
College Park, MD, USA
Email: avis@isr.umd.edu

***Abstract*—We have previously shown that the lamprey's central pattern generator (CPG) for locomotion can be manipulated by applying electrical stimuli to the spinal cord at precise phases within the CPG cycle. Here we demonstrate how these so-called phase dependent responses (PDR) can be used to repeatably and reliably manipulate individual parameters of locomotion in the lamprey. In particular, we show that: (1) the PDR for an arbitrary stimulus prescribes the phases at which to stimulate in order to effect specific modifications of the locomotor output; (2) ipsilateral and contralateral burst lengths can be controlled separately; and (3) the responses predicted by a single-cycle PDR plot remain stable over many cycles of stimulation. All of these properties suggest that phase-dependent stimulation may be an effective means of controlling the CPG in a future spinal locomotion neuroprosthesis.**

I. Introduction

Every year, more than 10,000 individuals in the United States suffer from a spinal cord injury (SCI) that affects their ability to walk [1], [2]. Historically, the most widely applied therapy for restoring locomotion after SCI has been functional electrical stimulation (FES) of peripheral motor axons [3]. However, this technique is known to produce a steep recruitment of muscle force, causing muscle fibers to fatigue quickly and generating inelegant movements [4], [5]. It also requires large stimulation currents, on the order of milliamperes, which poses problems for a portable (battery powered) prosthetic device. Partially because of these limitations, commercial implementations of FES-based locomotor prostheses have not been implantable. Instead, they've relied upon external electrodes and surface stimulation, and have used manual hand-switches to control the output [6], [7]. These products have not been widely adopted, but to date, FES is the only intervention shown to produce adequate contractions in the target muscles and to generate enough force for locomotory tasks.

Over the course of the past decade, a number of alternative therapies to peripheral motor axon stimulation have been developed. The most promising in the long-term may be spinal cord regeneration [8]–[11], but so far, no regenerated fibers have been able to completely restore function [12]. Moreover, studies in primitive vertebrates with natural regeneration abilities have shown behavioral anomalies that are highly maladaptive after SCI [13]. Therefore, it seems likely that even if regeneration is eventually more successful, patients will need a combination of therapies to fully restore functional locomotion.

We have previously proposed an alternative approach to restoring locomotion after SCI that relies upon control of the so-called central pattern generator (CPG) for locomotion [14]. In this approach, the neuroprosthesis will first initiate (and maintain) activity in the CPG, and then conform that activity to a specific motor program of our choosing. Because a number of groups have demonstrated therapies for activating the CPG [15]–[24], here we focus on controlling the motor program after activation. Motor control is required because all existing CPG activation methods provide only coarse control over the CPG behavior that they initiate. Specifically, they are able to turn the CPG on and off, but they cannot select the pattern of motor output or alter the phase relationship of the motor components within a locomotor cycle. Additionally, they cannot guarantee generation of "normal" locomotion, or even stable output [25]. In order to generate functional locomotion, as well as to guide and adapt movements, a mechanism for more precise control is needed. In an intact animal, this mechanism is integrated with the activation circuits and performed by descending supraspinal inputs. In the neuroprosthesis, we intend to achieve this task by phasic application of electrical stimuli.

In the following sections, we show how a baseline CPG output can be manipulated into a desired motor program by applying electrical stimuli to the locomotor circuits within the spinal cord at specific phases of the locomotor cycle. The motivation for this design comes from previous studies showing that spinal reflex networks are dynamically reorganized based on the phase of locomotion [26]–[29]. The underlying assumption is that if the functional connections within the CPG are varying in time, then the effects of any particular stimulus will also vary with time. Consequentially, with a judicious choice of electrodes and stimuli, it should be possible to effect a wide range of modulations by applying the appropriate stimuli at the appropriate phases.

II. Methods

Three adult lampreys (*Ichthyomyzon unicuspis*), obtained from a commercial collector, were used for these experiments.

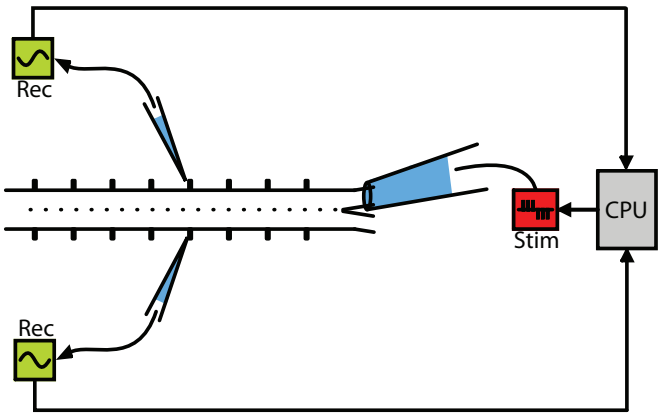

Fig. 1. Experimental setup: a custom-designed stimulator applied electrical pulses to the spinal hemicord via a suction electrode, while fictive motor output was captured by suction electrodes positioned on the ventral roots. The exact placement of electrodes varied between experiments to optimize signal quality.

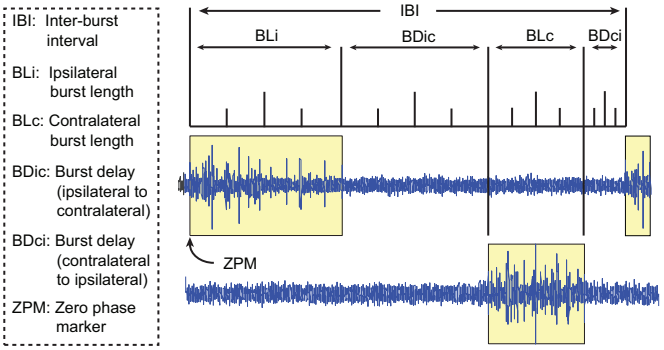

Fig. 2. Amplified, digitized, and high-pass filtered ventral root recordings from ipsilateral spinal segment 9 (top) and contralateral segment 18 (bottom) observed during a typical cycle of fictive locomotion. Bursts are highlighted by yellow rectangles.

A. Surgical Procedures

Each animal was dissected and prepared for stimulation and recording according to the methods described in ref. 14, except that motor activity was only recorded at one location on each side of the spinal cord, approximately 10 segments from the rostral end (Fig. 1). Also, because adult animals require a higher concentration of D-glutamate than ammocoetes, fictive swimming was induced by bath application of 0.50–1.00 mM D-glutamate.

B. Characterization of Phase-Dependent Responses

The effects of stimulation were characterized as functions of the phase of the CPG at which they were applied. The phase of the CPG was defined as a real-valued variable ϕ in spherical space $\mathbb{S}^1$, which takes on values in the range $\phi \in [0, 1]$ [32]. For convenience, zero phase was chosen as the beginning of S_0. During an experiment, the times at which the system entered S_0 were computed and stored as "zero phase markers" (ZPM). This allowed for a simple expression of the phase ϕ at a given time t: $\phi = \frac{t - t_{ZPM}}{T_0}$ where t_{ZPM} is the time of the most recent zero phase marker and T_0 is the average cycle period observed during unperturbed bursting.

In each experimental session, the control data was used to estimate a number of different parameters that characterize the normal bursting, including the mean values and standard deviations of burst length recorded by the electrodes contralateral and ipsilateral to the site of stimulation, the mean delay and standard deviation between bursting observed on pairs of electrodes, and the mean cycle period and its standard deviation (see Fig. 2 for acronym definitions). When a stimulus was applied, its effect on each of these parameters was calculated for the perturbed cycle and two subsequent cycles, and the results were tabulated as a function of phase. Thus, each stimulus contributed one data point to multiple different phase-dependent response (PDR) curves (Fig. 4).

C. Experimental Protocol

Each experiment consisted of an initial calibration stage followed by 10–20 stimulation "sessions". In the calibration stage, PDR characteristics were measured for a stimulus applied to one hemisegment at the rostral end of the spinal cord [14]. At the start of every session, a specific stimulation phase was selected based on the PDR curve. Next, approximately one minute of normal bursting was recorded, followed by 50–150 cycles in which a stimulus was applied at the specified phase every cycle, followed by another minute or two of control bursting. In a variation of this protocol executed in a few sessions, the same stimulus was applied at multiple different phases, with each bout of stimulation separated from the previous bout by an unperturbed period of at least one minute. The effects of the stimuli measured under this protocol were plotted as functions of time (Fig. 4).

D. Analysis

For these experiments, recordings were digitized and stored on a personal computer using a data acquisition card (NI PCI-6024E, National Instruments Corporation, Austin, TX) and custom software written in MATLAB (The Mathworks, Natick, MA). In addition to analyzing the recorded activity off-line, as described in ref. 14, this software was designed to run in real-time and to control the stimulator and apply stimuli at one or more specific phases determined by the user. This was accomplished by analyzing the recorded activity on-line, looking for the ZPM, and estimating the current phase based on the amount of time elapsed since the ZPM occurred.

III. Results

A typical example of a PDR observed during these experiments is shown in Fig. 3. Evidently, in this animal, applying this stimulus during the second half of the burst on the ipsilateral side decreased the ipsilateral burst duration, while stimulating during the second half of the burst on the contralateral side increased the contralateral burst duration. Moreover, there appeared to be a linear relationship between

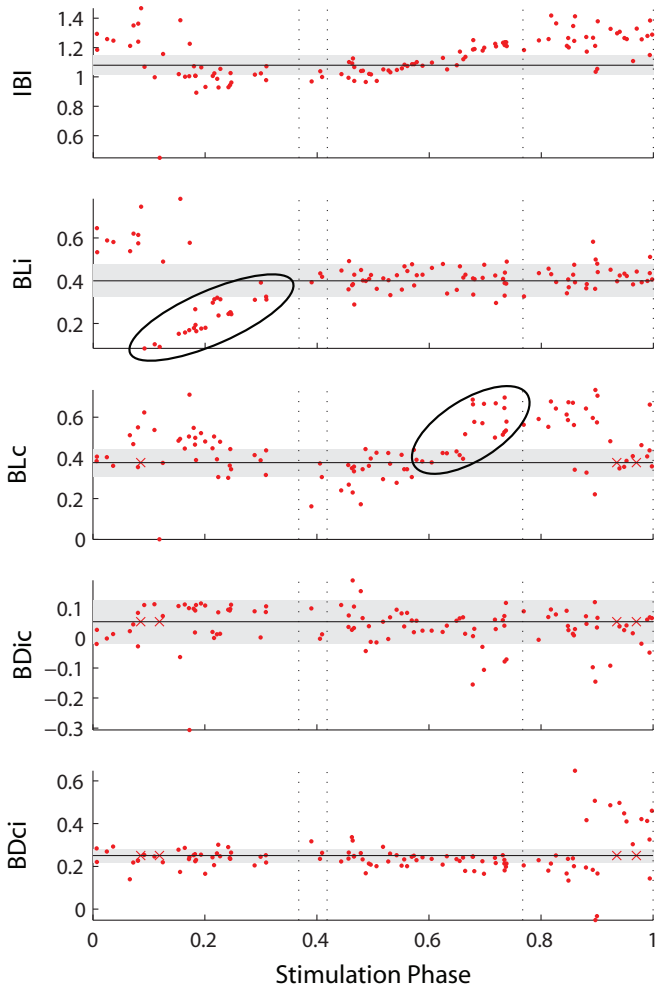

Fig. 3. PDR plots of data from experimental session #032210. Stimulus parameters were fixed throughout the experiment (PPD = NPD = 10 msec, IPI = 1 msec, PPA = NPA = 19 μA, NPB = 2). In all plots, dashed vertical lines indicate the average transition times between states during control bursting, a solid horizontal line is drawn at the mean (control) value for that burst parameter, and gray shading extends one standard deviation in each direction. Ovals highlight regions of interest for increases in BLi and decreases in BLc.

the stimulation phase and the duration of the bursts:

$$\text{BLi} = 1.24\phi - 0.03 \text{ sec}, \ R^2 = 0.79, \ \phi \in [0.1, 0.35] \quad (1)$$

$$\text{BLc} = 1.04\phi - 0.18 \text{ sec}, \ R^2 = 0.60, \ \phi \in [0.45, 0.75] \quad (2)$$

Based on this information, it is possible to choose a desired burst length for either the ipsilateral or contralateral side, and then apply stimulation at the phase specified by the equations above to constrain bursting to the desired value. For example, for the PDR shown in Fig. 3, the normal burst length on the ipsilateral side was 0.40 sec (σ = 0.08 sec); to change the ipsilateral burst length to 0.30 sec, we applied stimulation at $\phi = 0.25$ (Fig. 4). As expected, when the phase of stimulation was increased, the duration of the ipsilateral burst increased (Fig. 4); maximal impact was achieved at $\phi = 0.21$ (although

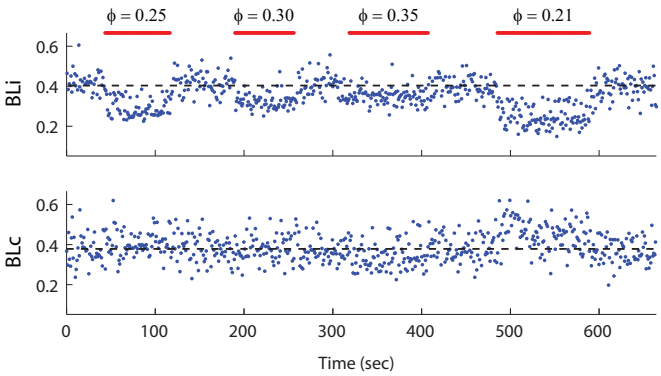

Fig. 4. Ipsilateral (BLi) and contralateral (BLc) burst lengths as a function of time. Blue dots represent the measured burst duration for each cycle. In cycles marked with a red dot, one stimulus was applied at the specified phase. Dashed horizontal lines are drawn at the average unperturbed burst length.

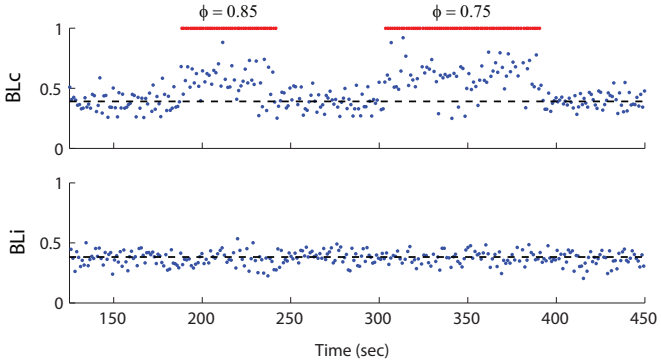

Fig. 5. Ipsilateral (BLi) and contralateral (BLc) burst lengths as a function of time. Blue dots represent the measured burst duration for each cycle. In cycles marked with a red dot, one stimulus was applied at the specified phase. Dashed horizontal lines are drawn at the average unperturbed burst length.

this caused a change in the contralateral burst length, as well). All of the changes in ipsilateral burst length were statistically different from normal ($p < 0.001$, one-sided two-sample t-tests), as well as different from each other ($p < 0.001$, one-way ANOVA).

To change the contralateral burst length, the PDR suggests applying stimuli during bursting on the contralateral side (Fig. 3). Fig. 5 illustrates the effects of stimulation at $\phi = 0.85$ and $\phi = 0.75$: the contralateral burst lengths are extended to 0.56 sec and 0.61 sec, respectively, from their normal value of 0.38 sec (σ = 0.07 sec). The altered burst lengths are statistically different from normal ($p < 0.001$, one-sided two-sample t-tests), as well as from each other ($p = 0.03$, one-sided two-sample t-test).

IV. Discussion

The data presented above show that the bursts produced by the CPG on both sides of the spinal cord can be manipulated at will according to the PDR characteristics. In most cases, stimulation through one electrode was effective at increasing the burst length on one side of the body and decreasing the burst length on the other side of the body (Fig. 3). This

implies that two stimulating electrodes, one positioned on each hemicord, should be sufficient to achieve both increases and decreases in burst length on both sides of the body. Independent control of these parameters, in conjunction with the ability to affect burst delays, is sufficient to generate arbitrary swimming gaits in the lamprey [31]. Thus, at least in lamprey, tonic chemical activation of the spinal cord in combination with phasic electrical stimulation could be used to restore "locomotion" after spinal cord injury. We expect that a similar result will apply in higher order vertebrates.

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