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Real-Time Interaction Between a Neuromorphic Electronic Circuit and the Spinal Cord

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Abstract

We present a novel demonstration of real-time dynamic interaction between an oscillatory spinal cord (isolated lamprey nervous system) and electronic hardware that mimics the spinal motor pattern generating circuitry. The spinal cord and the neuromorphic circuit were interfaced in unidirectional and bidirectional modes. Bidirectional coupling resulted in stable, persistent oscillations. This experimental platform offers a unique paradigm to examine the intrinsic dynamics of neural circuitry. The neuromorphic analog very large scale integration (aVLSI) design and real-time capabilities of this approach may provide a particularly powerful means of restoring complex neuromotor function using neuroprostheses.

Index Terms

Analog very large scale integration (aVLSI); lamprey; locomotor control; neural engineering; neuromorphic design; neuroprostheses; pattern generator; spinal cord

I. Introduction

In several vertebrate species, neural circuits within the spinal cord are capable of producing rhythmic motor output for controlling locomotion in the absence of external periodic forcing [1]. During locomotion, however, these spinal pattern generators are continuously influenced by supraspinal and sensory inputs. Thus, motor control occurs through a dynamic interaction of the spinal pattern generator activity, descending inputs, sensory inputs, the mechanical structure of the body, and the environment [2]. Injury to the spinal cord may result in a variety of medical complications, one of which is an impaired ability to control locomotion. The degree of impairment will depend upon several factors: the location of the injury, the severity of the injury, and the medical care that is received in the acute and

chronic stages after injury. The mechanisms underlying the locomotor impairment may include damage to the spinal pattern generators, sensory feedback circuitry or motor output circuitry. In many cases, however, the primary mechanism for the impairment may be a disruption of communication between the neural circuits that are above the level of injury (brain and rostral portions of the spinal cord) and the spinal pattern generator with its associated circuitry. Over the past several years, two general approaches have been used to address this problem.

The first approach [3] seeks to repair the injured spinal cord by promoting regeneration using tissue transplants and other pharmacological interventions. In this approach, the fundamental problem is to enable regeneration of spinal-cord neurons. However, the secondary problem, and perhaps the more difficult one, will be to ensure that regeneration and reorganization result in connectivity that is functional without producing adverse side effects [4].

A second approach seeks to replace the functionality of the nervous system with neuroprostheses that electrically activate neural tissue. Most neuroprosthetic systems directly activate motoneurons to cause muscle contraction that will effect a desired movement [5]. For control of stepping movements, these systems have utilized predetermined patterns of stimulation that are delivered to drive each step [6], [7]. Recently, an adaptive control system was designed that utilizes a pattern generator (PG) module in cascade with an adaptive filter, or pattern shaper (PS) module [8], [9]. This PG/PS control system and other pattern generator-based control systems have many features of neurophysiological control systems that may substantially enhance the functionality of neuroprostheses for locomotion [10]–[12]. In other systems, sensory fibers have also been stimulated to trigger spinal reflexes that produce limb flexion movement for stepping [7]. Whereas most systems have interfaced with the nervous system at the peripheral level, several recent efforts have investigated the possibility of interfacing at the level of the spinal cord [13]–[18]. Stimulation in the spinal cord may facilitate the use of existing spinal circuitry to improve the quality of control that can be provided by neuroprosthetic systems.

The success of both of these approaches (functional regeneration and neuroprostheses) will depend greatly on the development of an improved understanding of spinal circuitry and on the development of new approaches to interface with spinal circuits in a functional manner. In this work, we demonstrate real-time interaction between actual spinal circuits and a neuromorphic electronic device that is based on a model of spinal circuitry. The neuromorphic analog very large scale integrated (aVLSI) electronic circuit incorporates key aspects of biological neuron behavior and spinal architecture. It can be configured to interact in real time with an active spinal cord in a unidirectional mode in which the spinal cord provides input to the electronic circuit or *vice versa*, or in a bidirectional mode in which each system influences the other. This platform presents unique opportunities to characterize the role of specific neural mechanisms in shaping the output of the biological system and, therefore, may be particularly useful in investigating the complex organization of spinal circuits. The neuromorphic design of the electronic device may also play a role in the development of advanced neuroprostheses that interface directly with spinal circuits or that

provide enhanced functionality by mimicking the operation of neurophysiological locomotor control systems.

II. Methods

A. Overview

The experimental system utilized in this study provides real-time interaction between active spinal circuits that generate locomotor signals and an electronic device that is designed to mimic the behavior of the spinal cord circuitry. We chose the lamprey spinal cord as the model for the implementation of the neuromorphic circuit and experimental paradigm. The comparatively simple nervous system of the lamprey has been extensively investigated from the cellular to the systems level for understanding the basic mechanisms of the origin and control of locomotion in vertebrates [19]. The spinal cord is amenable for utilization in a robust *in vitro* preparation in which fictive motor output that retains the characteristics of normal swimming can be obtained. Because as few as four of the 100 segments of the isolated lamprey spinal cord can produce fictive locomotion, the distributed spinal pattern generator can be represented as a chain of coupled unit pattern generators (uPGs). Based on histological, electrophysiological, and neuropharmacological identification of spinal neural populations, several investigators have developed mathematical models representing the uPG neural network with neurons modeled with different levels of biophysical detail [19]–[21].

Our neuromorphic electronic circuit [22], [23] is based on one of these mathematical models [20] and, thus, mimics the segmental motor pattern generating circuitry of the lamprey spinal cord. The circuit was implemented using a VLSI technology and discrete devices; a VLSI circuit technology has been used to implement various aspects of biological neurons or activity of small neural circuits [24]–[26]. This technology allows real-time implementation with larger circuit density than attainable with discrete devices and has low power requirements [27].

B. Mathematical Model of Spinal Unit Pattern Generator

The design of the electronic circuit was based on a mathematical model of the spinal uPG network of the lamprey that we have extensively characterized [20]. Our mathematical model was adapted from previous neural network models of the lamprey spinal uPG [21], [28]. In the model, the uPG is a bilaterally symmetric network whose connectivity is based on the known architecture of the lamprey spinal cord. The three spinal neural classes that have been proposed to form the kernel of the uPG are excitatory (E), inhibitory (L), and crossed inhibitory (C) [19], [29]. In the model, a single neuron represents a class of neurons. Each neuron is modeled with constructs to represent the biophysical properties of the neuron membrane: passive leakage currents, tonic drive synaptic currents, and interneuronal synaptic currents. The maximal synaptic conductances are fixed and no active conductances are present, with spike generation being implicit. The electrical equivalent for the passive cell membrane is a resistive–capacitive circuit while the tonic and synaptic currents are modeled as parallel conductances with associated driving potentials [30], [31]. The total

flow of current across the neuron membrane is given by the Kirchoff's current law as follows:

$$C_M^i \frac{dv_i}{dt} = G_R^i (V_R^i - v_i) + G_T^i (V_T^i - v_i) + \sum_j G_{ji} h(v_j) (V_{syn}^j - v_i)$$

where

v_i	membrane voltage of neuron i ;
C_M^i	membrane capacitance;
G_R^i	maximum conductance across the membrane for passive currents flowing at rest;
V_R^i	resting potential for neuron i ;
G_T^i	maximum conductance for tonic synaptic input into the neuron i ;
V_T^i	reversal (driving) potential for the tonic current input;
G_{ji}	maximal synaptic conductance for phasic synaptic input from neuron j to neuron i ;
V_{syn}^j	synaptic reversal (driving) potential for the synaptic current from neuron j to i .

Each neuron's output represents the firing frequency. Unlike the sigmoidal function (often used in artificial neural networks) and other piecewise linear models for the neuron output function [21], [28], in our model, each neuron's output is assumed to be related to its membrane voltage by a nonlinear function given by a seventh-order polynomial $h(v)$ with a strict threshold (0) and saturation (1) and a continuous third derivative. The strict threshold can be thought of as the minimum threshold of the neuron pool below which no neuron fires while the saturation level indicates the maximum firing rate of the entire pool. A seventh-order polynomial gave us continuous derivatives up to the third order, which are necessary to determine the nature of some of the bifurcations observed (e.g., Hopf and pitchfork bifurcations [32])

$$h(v) = \begin{cases} -20v^7 + 70v^6 - 84v^5 + 35v^4, & \text{for } 0 \leq v \leq 1 \\ 0, & \text{for } v \leq 0 \\ 1, & \text{for } v \geq 1. \end{cases}$$

C. Electronic Circuit Implementation of uPG

The neuromorphic uPG circuit architecture (see Fig. 1) contains neurons, tonic drive synapses, and interneuronal synapses [22]. Fig. 2 shows the layout for the different components. Each neuron is a capacitor in parallel with a resistor-voltage source series combination [see Fig. 2 (a)] and each tonic drive synapse is a resistor-voltage source series combination [see Fig. 2(b)]. The interneuronal synapses were implemented in aVLSI with

an operational amplifier and a single-quadrant multiplier [see Fig. 2(c) and (d)]. The electronic synapses are nonlinear current functions of the pre- and postsynaptic voltages and are either excitatory or inhibitory. The inhibitory synapse removes current from the neuron i based on the voltage of neuron j , whereas the excitatory synapse adds current to the neuron i based on the voltage of neuron j . The aVLSI circuit was fabricated using the 2.0- μm complementary metal–oxide–semiconductor process through MOSIS, a low-cost prototyping and small-volume production service for VLSI circuits. The excitatory and inhibitory synapses use 200 transistors and the aVLSI circuit occupies an area of $520 \times 1150 \mu\text{m}^2$. To allow implementation of the mathematical model in an electronic form, the operating voltage level for each neuron was shifted to a center of 2.5 V to accommodate a +5-V power supply. Thus, each neuron voltage could swing from 0 to +5 V. Also, the synaptic conductance (G_{ji}) and capacitance (C_M^i) parameters were scaled for appropriate implementation in an electronic circuit. In order to implement the pattern generator circuit shown in Fig. 1, the electronic circuit required six neurons, six tonic synapses, four excitatory synapses, and eight inhibitory synapses.

D. Sensitivity Analysis of the Neuromorphic Electronic Circuit

Detailed sensitivity analysis to assure suitable operation and characterize the behavior of the circuit was performed. This complemented the bifurcation analysis previously performed on the mathematical model [20]. The effect of altering tonic drive to all the neurons of the circuit was determined. As the parameters of a system are changed, the number of stable states and their stability properties may change. The circuit exhibited stable fixed points (states in which the membrane voltage of each circuit neuron fluctuated ~ 35 mV) or a stable limit cycle (an oscillatory state that is a periodic solution of the system to which trajectories converge). A small positive swing in voltage was always present and occurred due to noise and small measurement errors. A fixed point was considered symmetric if the difference between membrane voltages of the corresponding class of left and right neurons was ~ 35 mV. A limit cycle was considered symmetric if the corresponding left and right neurons had the same voltage waveform but with a half-cycle phase shift. For symmetric circuits such as ours, asymmetric fixed points and asymmetric limit cycles always occur in pairs. At a given set of parameter values, more than one stable behavior could be observed. A stable fixed point could coexist with a stable limit cycle oscillation or another stable fixed point, thus exhibiting a region of parameter space that supported multiple attractors. In these cases, past history (membrane voltage trajectories) determines the attractor to which the system will converge.

E. In Vitro Brain–Spinal Cord Preparation

Young adult lampreys (*Ichthyomyzon unicuspis*, $n = 4$) were anesthetized (tricaine methane sulphonate MS 222), the brain and spinal cord (attached to the ventral cranium and notochord) excised, and the preparation pinned with the dorsal surface up to a Sylgard-lined recording chamber filled with a physiological saline solution cooled to 8–10 °C. The bath surrounding the brain was separated from that surrounding the spinal cord by a Vaseline barrier at the spinoreticular junction and the cord transected at the seventieth segment [33]. Fictive locomotion was induced by bathing the spinal cord with N-methyl-DL-aspartate

(NMA, 0.2 mM). Neural activity was recorded *en passant* from ventral roots at around segment 45–60 using bipolar glass suction electrodes (tip 80–100 μm). The activity was bandpass filtered (100 Hz–1 KHz), amplified, full-wave rectified, and moving averaged with a three-pole Paynter filter with a 50-ms time constant (CWE). The extracellular ventral root recordings reflect both the increases in the firing rate of motoneurons and the number of motoneurons active. By performing full-wave rectification and moving average, a scaled and dynamic reflection of the integrated response of the entire population of motoneurons recorded is obtained.

F. Interfacing the Electronic Circuit With the In Vitro Preparation

The caudal end of the spinal cord was split for about 2 mm, and one split end was suctioned into a bipolar glass suction electrode for stimulation. The caudal end was selected because it provided a convenient access point to the spinal circuitry. By stimulating the caudal end, it is possible to entrain the activity of several spinal segments. Alternatively, the spinal cord surface or dorsal roots could have been stimulated. When the output of a specified neuron of the aVLSI circuit crossed a preset voltage threshold, a stimulator (A.M.P.I., Jerusalem 91163, Israel) provided 4 or 10, 2-ms-long constant-current (0.2 mA or 0.3 mA) pulse stimuli at 125 Hz. To entrain the circuit by the spinal cord rhythm, current in proportion to the voltage level of the full wave rectified moving averaged output from one of the ventral roots was injected into the left and right C, E, or L neurons. The proportionality constant was set such that the maximum current injected was approximately 3 μA or 6 μA . This intracellular current was injected in addition to the tonic drive current received by each neuron. The circuit (ckt) and the spinal cord (sc) were interfaced in either a unidirectional open-loop mode (ckt $\rightarrow$ sc or sc $\rightarrow$ ckt) or a bidirectional closed-loop mode (ckt $\leftrightarrow$ sc).

To assess the degree of entrainment between the aVLSI circuit and the spinal cord rhythm, the phase relationship between a circuit neuron oscillatory activity and the ventral root oscillatory activity was determined during the entire duration for which the circuit and spinal cord were interfaced. Thus, we denoted the moments of time at which the moving averaged ventral root activity increased above a fixed threshold as t_k , $k = 0, 1, 2, \dots, N$ and, similarly, we denoted the times at which a neuron of the aVLSI circuit crosses a preset threshold to be τ_i , $i = 0, 1, 2, \dots, M$. Then, in the unidirectional open-loop mode with the circuit neuron (E neuron) driving the spinal activity (or in the closed-loop mode), the phase of the k th cycle of the ventral root activity was calculated as [34]

$$\phi(t_k) = \frac{(t_k - \tau_i)}{(\tau_{i+1} - \tau_i)}, \quad \tau_i < t_k < \tau_{i+1}.$$

Defined in this way, the phase varied between 0 and 1 and was defined at discrete moments of time. In the unidirectional open-loop mode with the ventral root activity driving the circuit, t_k was determined from the circuit neuron into which current was injected (C neuron), whereas τ_i was determined from the moving averaged ventral root activity to calculate the phase.

III. Results

A. Sensitivity Analysis of the Circuit (Fixed Points and Limit Cycles)

Nonlinear dynamic interactions among the neurons of the circuit result in robust stable oscillatory output over a wide range of device parameter values. Fig. 3(a) illustrates the oscillatory behavior observed for a set of nominal values of tonic drive. The C neuron voltage slightly leads the L and E neuron voltages. This behavior is qualitatively similar to that reported for the corresponding classes of neurons in *in vitro* spinal preparations of the lamprey during fictive locomotion [35] as well as that exhibited by the mathematical model [20]. The left and right neuron voltages for each of the C, E, and L neurons are symmetric and 180° out of phase, reflecting the left–right symmetry of the circuit.

Fig. 3(b) is a bifurcation diagram illustrating the effect of scaling the tonic drive to all three sets of neurons (the relative amounts of the tonic drives being given by the default values). The scaling factor for the tonic drive (the bifurcation parameter) is given on the abscissa and the membrane voltages of the left and right C neurons (as one representative pair of neurons of the network) are shown on the ordinate. Stable nonoscillatory voltage levels (fixed points) are illustrated by an asterisk. The maximum and minimum voltage levels during oscillatory behavior (limit-cycles) are presented as filled circles, thereby indicating the amplitude of the oscillation for different parameter values. Based on the different behaviors exhibited by the circuit, Fig. 3(b) is divided into six panels (marked 1–6). The circuit exhibited nonoscillatory and oscillatory states and, for some parameter ranges, the system exhibited bistable states. In panels 1 and 3, bistability exists between two nonoscillatory states whereas, in panel 6, bistability exists between a nonoscillatory and an oscillatory state. Stable symmetric oscillations with substantial amplitude swing can be obtained over a wide range of tonic drive values. Fig. 3(c) shows that the frequency of the symmetric stable oscillation is higher with higher tonic drive. The behaviors exhibited by the hardware circuit are similar to the oscillatory behaviors exhibited by the mathematical model [20]. The circuit can be 1 : 1 entrained with no phase difference to the frequency of an external input by injecting oscillatory current into one or more of its neurons. This capability of entrainment allows the circuit behavior to change dynamically when it is interfaced with an *in vitro* lamprey spinal cord preparation in which fictive locomotion has been induced (see Section III-C and Section III-D).

B. Unidirectional Connections From the Circuit Control Spinal Locomotor Rhythm

The circuit (set into a stable oscillatory state) and the spinal cord (exhibiting fictive locomotion) were interfaced in two unidirectional (open-loop) modes and in a bidirectional (closed-loop) mode. In the first unidirectional mode [Fig. 4(a), ckt → sc], the output of a circuit neuron (E) provided constant current stimulation pulse trains to the spinal cord. The spinal rhythm recorded from the ventral root was entrained to the circuit frequency. Entrainment, a locking together of frequencies such that for every N cycles of stimulus there are M cycles of response ($N : M$ entrainment), can occur with or without a stable phase relationship [36]. Thus, in Figs. 4(a), 5(a), and 6(a), we see that, although a fixed periodic perturbation from the circuit was maintained, the stable phase relationship in the entrainment of the spinal rhythm was lost. The phase between the circuit neuron and ventral root activity

was initially close to zero (nearly synchronized cyclic activity) but, within 40 s, a slow phase-drift developed [see Fig. 6(a)]. Additionally, 1 : 1 entrainment was occasionally lost and ventral root activity was absent for some cycles of oscillatory circuit activity, i.e., $N > M$ [missing cycles indicated by + in Fig. 6(a)].

By changing the tonic drive to one or more neurons of the circuit, the cycle period of the electronic circuit was altered. This permitted periodic perturbation of the spinal cord at frequencies both above and below the control period of the fictive spinal locomotor rhythm. The ability of the circuit to entrain the spinal locomotor rhythm at seven different frequencies (obtained by scaling the tonic drive to the neurons) is illustrated in Fig. 5(c). On the plot, 1 : 1 entrainment with phase locking would be indicated by points lying on the diagonal, and perfect entrainment would result in standard deviation = 0. As indicated by the lower standard deviation, entrainment was more reliably achieved at cycle periods that were shorter than the mean control cycle periods (data points to the left of the vertical dashed line).

C. Unidirectional Connections From the Spinal Cord Dynamically Alter Circuit Behavior

In the second unidirectional mode [ckt $\rightarrow$ sc, Fig. 4(b)], a current proportional to the voltage of the moving averaged ipsilateral caudal ventral root output was directly injected into the E, L, or C pair of circuit neurons. In response to the injected current, the voltage output of the circuit neurons with direct inputs from the spinal cord were altered dynamically both in amplitude and frequency (C neuron shown). Other neurons without direct inputs from the spinal cord were also influenced and the oscillatory frequency of the circuit changed from cycle to cycle. Although the circuit was 1 : 1 entrained to the rhythm of the spinal cord, in some instances, as seen in Fig. 6(b), the phase relationship between the ventral root output and circuit neurons was quite dispersed. Often, more than one cycle of circuit activity was obtained for a given cycle of ventral root activity ($N < M$; phase of multiple response cycles indicated by different symbols) and there were occasional missed cycles of the circuit activity ($N > M$; missed cycles indicated by +). The ability to entrain the electronic device depended on the strength of the current input, the choice of circuit neurons into which the current was injected, and the intrinsic relative frequencies of the driving (spinal locomotor rhythm) and driven (circuit rhythm) systems. If the voltage output from the ventral root was not sufficient, the circuit neurons were not affected and the circuit continued to oscillate at its nominal intrinsic frequency.

D. Bidirectional Connections Result in Stable Phase-Locked Rhythms

In the bidirectional mode [sc $\leftrightarrow$ ckt, Fig. 4 (c)], the circuit provided input to the spinal cord and the spinal ventral root recordings were used to determine the amplitude of current injected into the circuit neurons. As in the unidirectional sc $\rightarrow$ ckt mode, current was injected into the C neuron and other circuit neurons (E neuron shown) were affected. Similarly, as in the unidirectional ckt $\rightarrow$ sc mode, the ventral root activity was altered. Thus, in this mode, the spinal cord and the neuromorphic circuit acted as dynamically coupled nonlinear oscillators. Although the frequency attained by the coupled system was not constant over time, the circuit and the spinal cord activity remained phase-locked quite well [for example, Figs. 4(c), 5(b), and 6(c)]. Unlike the unidirectional sc $\rightarrow$ ckt mode, the

entrainment was primarily 1 : 1 with a fairly stable phase relationship with synchronization (phase ≈ 1 or 0) and unlike the unidirectional ckt $\rightarrow$ sc mode, there were fewer cycles of missed ventral activity and no phase drift was observed. The bidirectional mode enabled stable oscillations of the coupled system at mean frequencies lower than during control. While not illustrated, the contralateral ventral roots were coordinated with an approximately 180° phase shift.

IV. Discussion

A. Real-Time Circuit–Spinal Cord Interaction: A Platform for Basic Science Investigations or Neuroprosthetic Applications

These results demonstrate real-time dynamic interaction between an electronic circuit and a living spinal cord. This type of real-time interaction between a neuromorphic electronic circuit and a living system has potential utility in two settings. First, the coupling between the electronic circuit and the spinal cord provides a novel experimental paradigm for investigating mechanisms for neural control. Mathematical models have often been used as effective tools to study physiological systems. The experimental paradigm described here extends the potential utility of these models. The neuromorphic structure of the model (which is implemented in the electronic circuit) provides the ability to investigate the roles of specific system model parameters in determining the behavior of the entire system. Although the electronic neurons that were implemented do not have the details of biological neurons, they capture nonlinear biophysical properties such as voltage dependent synaptic currents and reversal potentials. Implementation of the circuitry in aVLSI provides the ability to greatly increase the complexity of the model at both the individual neuron and network levels while still maintaining the ability to perform the required calculations in real time. As neural interface technology advances, this complexity would allow, if necessary, multiple sites of circuit–living system interaction.

A second potential use for a system that provides real-time interaction between an electronic circuit and a living neurophysiological system is in medical devices that replace impaired neural system function (i.e., neuroprostheses). Motor neuroprostheses are designed to restore neuromotor function to people with neurological disorders such as spinal cord injury, head injury, or stroke. VLSI implementation of the circuitry would be particularly well suited for development of lightweight, low-powered, implantable devices. The neuromorphic design and the real-time capabilities for control of the system described here may provide a powerful means of restoring complex neuromotor function using neuroprosthetic technology. In one possible open-loop configuration, the neuromorphic circuit could be used to mimic spinal pattern generator function in a system that uses direct stimulation of peripheral neurons [8], [9]. In an alternate open-loop configuration, the neuromorphic circuit could be used to activate spinal neurons and potentially take advantage of the organization of spinal circuits below the level of the lesion [13]–[17]. Intravenous, intraperitoneal, or intrathecal delivery of appropriate pharmacological drugs have been used in acutely and chronically spinalized cats with complete spinal transection to induce rhythmic output from the pattern-generating circuitry below the level of the lesion and obtain hindlimb locomotion [37], [38]. Such pharmacological interventions could be used to at least initiate a locomotor

pattern that could then potentially be modified or maintained with the use of a closed-loop configuration in which the neuromorphic circuit and spinal circuits below the level of lesion are phase-locked. Extrinsic user-generated inputs or intrinsic inputs from spinal circuits above the level of the lesion could then be utilized to alter the frequency or reset the rhythm of the coupled interface system. For the development and viability of such future neuroprosthetic systems, several additional demonstrations and assessments of the reliability and long-term stability of silicon–neural interfaces will be required in an *in vivo* system.

B. Entraining Chains of Spinal Oscillators: Open-Loop Versus Closed-Loop Nonlinear Control

In the unidirectional periodic perturbation mode, the phase-locked entrainment was lost even though the periodic perturbation was continued. In contrast, in the bidirectional mode, the phase-locked entrainment (but not constant frequency) was maintained. The cyclic burst activity of spinal neurons during locomotion exhibits an inherent variability. It appears that external periodic stimuli in the unidirectional mode are able to contain this variability for short durations, thereby allowing phase locking. We hypothesize that with the passage of time, the processes for burst generation escape from the fixed period stimulation and entrainment is lost. In the bidirectional mode, the inherent variability is still present, and endogenous mechanisms and the nonlinear dynamics of the circuit permit phase-locked coordination.

We also observed that phase locking at a lower mean frequency was more readily obtained in the bidirectional mode than in the unidirectional mode. From Fig. 4(a), we see that the periodic perturbation tended to initiate a new burst of activity. In the unidirectional mode, once phase locking had been achieved, the stimulus affected the rhythm at a particular phase of the cycle at which phase advance occurred. In the bidirectional mode, however, the nonlinear analog nature of the electronic circuit neurons and the spinal pattern generator neurons allowed for changes in the voltage output waveforms of both the circuit neurons and the ventral root output. Thus, the threshold voltage at which the circuit neuron triggers the stimulator and the threshold voltage at which the ventral root output provides sufficient current input to the circuit neurons did not occur cyclically at fixed intervals of time. This spread the effects of the mutual perturbations between the circuit and the spinal cord over the entire cycle, and enabled both phase-dependent lengthening and shortening of their respective cyclic activity. This, in turn, allowed for dynamic changes in frequency and permitted phase locking. In the chain of coupled oscillators formed among the spinal neural oscillators and the neuromorphic electronic circuit oscillator, the intersegmental connectivity among the spinal neural oscillators had a dominant influence. Hence, the mean frequency achieved by the coupled system was closer to the mean frequency of the isolated rhythmically active spinal cord (i.e., prior to establishing the bidirectional coupling).

The circuit we have developed presents only a single segment of the distributed spinal pattern generator. Neuromorphic electronic circuits representing multiple segments [39] could be developed using the aVLSI technology and utilized for providing the appropriate stimuli. Such a biomimetic model would provide a platform for examining mechanisms for intersegmental coordination. A spatially distributed stimulation with an appropriate delay

may be needed to maintain phaselocked coordination along long spinal cords. Phase-delayed multiple outputs from the multisegment neuromorphic circuit implementation could be used to provide the spatiotemporally distributed input.

In summary, this work provides a unique demonstration of real-time dynamic interaction between an oscillatory spinal cord and electronic hardware that was designed to mimic the neurophysiological system. The coupled neural–electronic system exhibited stable oscillations. Bidirectional coupling enhanced the stability, versatility, and persistence of the oscillations. The behavior of the coupled system was altered by adjusting the parameters of the electronic circuit. This type of interaction offers a unique paradigm to examine the intrinsic dynamics of neural circuitry. The neuromorphic aVLSI design of the circuit and the real-time capabilities of this type of system may provide a particularly powerful means of restoring complex neuromotor function using neuroprostheses.

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Fig. 1.

Neuromorphic electronic circuit–spinal cord interface. An *in vitro* preparation of the lamprey spinal cord was interfaced unidirectionally or bidirectionally with an electronic neural network circuit mimicking the architecture of a uPG of the lamprey spinal cord (neuromorphic pattern generator). Arrows indicate the direction of flow of activity. E: excitatory interneurons; C: crossed inhibitory interneurons; L: lateral inhibitory interneurons. The dotted line represents the tonic excitatory drive. —| represents an excitatory connection. —● represents an inhibitory connection.

Fig. 3.

Oscillatory activity and sensitivity analysis of the neuromorphic pattern generator. (a) Membrane voltage output of the left and right neurons of the circuit for a nominal set of parameter values. The voltage output of each neuron can change from 0 to 5 V. (b) The tonic drive to the E, L, and C neurons of the circuit was scaled and the response of the circuit determined. Panels 1–6 represent the stable behaviors observed for different tonic drives. The circuit can exhibit asymmetric fixed points (panels 1 and 3), symmetric fixed points (panels 2, 5, and 6), symmetric limit cycle (panels 4 and 5). Thus, panels 1 and 3 show

bistability between two asymmetric nonoscillatory states and panel 5 shows bistability between an oscillatory and a nonoscillatory state. Stable fixed points are represented by an asterisk (*). For the limit cycle, the maximum and minimum voltage levels are presented by a filled circle (●), thereby indicating the amplitude of the oscillation. (c) Effects of altered tonic drive on the frequency of the symmetric limit cycle shown in panels 4 and 5.

Fig. 4.

Real-time coupling between the neuromorphic pattern generator circuit and an *in vitro* spinal cord preparation with 68 spinal segments. Before establishing the interface, the circuit was set to exhibit stable limit cycle behavior [shown in Fig. 3(a)] and fictive locomotion induced in the spinal cord. (a) Effects of unidirectional coupling from the circuit (ckt) to the spinal cord (sc). Output voltage of the left E (excitatory) neuron in the circuit was used to determine the timing of the stimulation of the spinal cord (10 0.3-mA pulses at 125 Hz, E neuron preset threshold voltage = 2.3 volts). The full-wave rectified moving-averaged spinal motor output recorded from the left caudal ventral root (VR) at segment 31, ipsilateral to the spinal stimulation site, illustrates that the electronic circuit was able to achieve transient entrainment of the fictive locomotor rhythm. (b) Effects of unidirectional coupling from the spinal cord to the circuit. Current in proportion to the moving-averaged left caudal VR activity was injected into the left and right C neurons of the circuit. Small changes in membrane voltage output of the VR did not provide sufficient current to alter the circuit neuron waveform. (c) Effects of bidirectional coupling between the circuit and the spinal cord. Almost immediately after establishing coupling, the ventral root and electronic circuit neuron activities are phase-locked.

Fig. 5.

Entrainment and stability of phase-locked coupling. (a) Loss of entrainment with unidirectional ckt → sc coupling 40 s after initiation of coupling shown in Fig. 4(a). (b) Maintenance of phase-locked entrainment with bidirectional coupling 120 s after initiation of coupling shown in Fig. 4(c). (c) Entrainment of spinal rhythm at different frequencies by unidirectional ckt ↔ sc coupling maintained for approximately 1 min. cnt_pd: mean control period of 25 cycles pre-perturbation; resp_pd: mean response period over entire duration of stimulation; stim_pd: stimulation period. Trials with normalized stim_pd less than 1 (left of

the vertical dashed line) indicate attempts to entrain the spinal locomotor rhythm to a frequency higher than control. VR: ventral root; E: left excitatory neuron in the circuit; C: left inhibitory neuron of the circuit.

Fig. 6.

Phase between the circuit neurons and the ventral root activity while they are interfaced.

Phase relationships were calculated from data that is presented in part in Figs. 4 and 5. (a)

Phase during unidirectional open-loop connection from the E neuron of circuit to the spinal

cord. (b) Phase during unidirectional open-loop connection from the spinal ventral root to

the C neuron of the circuit. (c) Phase during bidirectional closed-loop connection between

the circuit and spinal cord; phase calculations based on activities of E neuron of circuit and

the spinal ventral root. The phase of the first response cycle is given by ●, the second by *,

the third by ∇, the fourth by ○, and the fifth by ◇. The + symbols indicate the absence of a

response cycle for a given stimulus cycle.