

# Bio-inspired Hardware Central Pattern Generator (hCPG) as a Therapy for Cardiorespiratory Disease

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## ABSTRACT

We report on a hCPG device, which is a network of silicon neurons, and its applications to cardiorespiratory therapy. We study the chaotic dynamics of neurons that compete through mutually inhibitory synapses and demonstrate the emergence of multistable behavior. We were able to select the spatio-temporal sequences associated with stable modes of oscillation by imparting different initial conditions with timed current steps mimicking delayed stimuli. We constructed the phase lag maps of the hCPG for various connectivities of the network. We also describe a simpler two neuron hCPG which generates a two-phase rhythmic pattern for vagus nerve stimulation and modulation of heart rate by respiration to obtain artificial respiratory sinus-arrhythmia (RSA).

## Categories and Subject Descriptors

B.7.1 [Integrated Circuit]: Types and Design Styles – VLSI (very large scale integration), input/output circuits, algorithms implemented in hardware.

## General Terms

Experimentation

## Keywords

Hardware central pattern generator (hCPG), silicon neurons.

## 1. INTRODUCTION

Biological central pattern generators (CPGs) are networks of neurons that generate rhythmic motor patterns [1]. Within the human body these rhythmic patterns are used to control and coordinate various activities like; digestion [2], locomotion [3], respiration [4, 5], heart rate [4, 6], etc. Networks of competing neurons have been studied for their adaptation to physiological feedback with the aim of introducing useful changes in rhythmic patterns [7, 8].

Two different approaches prevail in obtaining modified rhythmic patterns: (1) through small changes in network connectivity and (2) the different timings of external electrical stimulation to rings of nonlinear oscillators [9, 10, 11]. Within the second approach, stable patterns evolve based on the initial conditions. This approach suggests that nature can control the CPG motor patterns through the timing of current pulses applied by external sensory receptors or command neurons.

Our hCPG consists of a network of three Hodgkin-Huxley neurons. Each neuron models the Na, K and leakage channel conductances [12]. The network acquires chaotic dynamics when mutually inhibitory synapses are given asymmetric conductances. In this situation, the network becomes multistable. We probe its dynamics by varying the delay of current steps applied to individual neurons. We then mapped the phase lag trajectories evolving from different initial. The dynamic state of the system is found to converge towards limit cycles consisting of triphasic sequences carrying clockwise and anticlockwise momentum. We find that rhythmic sequences self-organize into stable patterns of two consecutive pulses firing out of phase with the third one. As a result our oscillation patterns are shaped by the ratio of the pulse width to the oscillation period, and not only the number of neurons in the hCPG.

The motivation behind developing hCPG is to generate and control motor patterns for restoring biological functions, for example, controlling limb motion in prosthetics and restoring cardiorespiratory coupling. The realization of hCPG has two key advantages over software CPG; (i) demonstration of dynamic attractors in hardware as prescribed by the principle of competition without a winner [13], and (ii) probing large networks as the outcomes are computed instantaneously and independently of the size and complexity of the network. There is no unifying theory for winnerless networks [14, 15]. Also the simulations incur prohibitive simulation costs when the number of neurons in the network increases which is a reason why detailed studies are only available up to a network of three neurons [15].

We used the hCPG with two neurons and a single neuron to generate artificial respiratory sinus arrhythmia (RSA) [16, 17]. Basically RSA is an oscillatory signal with two different but periodic frequencies of oscillations, both out of phase with each other. In human body RSA is the heart rate variability in synchrony with respiration. In heart failure patients RSA is distorted or lost with time and restoring this capability could provide an alternative therapy.

Respiration signals are obtained from the phrenic nerve (PN) and generally high in noise giving a signal-to-noise ratio (S/N) of the order of ~ 8dB. It is quite challenging to use this signal as input to hCPG as information could be lost by too much signal processing (filtering and amplification stages). We were able to tune the hCPG to obtain stable mode of oscillations in response to PN signal and generate artificial sinus-arrhythmia (RSA) signals. We also modulated the RSA amplitude by varying the rate of oscillation during inspiratory and expiratory phases which covers the clinically accepted human RSA range (0.1-7%) [18, 19]. The variability and robustness in modulating the RSA opens up possibilities of new therapies for heart patients.

## 2. EXPERIMENTAL

Our experiments could be categorized in two parts; (1) Construction of phase lag maps of three neurons to study the attractor dynamics, by controlling the timings of current stimulation to individual neurons, and (2) Generation of RSA for treating cardiorespiratory disease such as heart failure.

The silicon neurons used in our hCPG accurately models the Hodgkin-Huxley equations by varying the channel conductances [1, 16]. These silicon neurons were realized using analogue VLSI circuits, to obtain the spiking oscillations. The relative conductances of Na, K and leakage ion channels were optimized to mimic relative opening and closing of these channels in physiological systems [12].

### 2.1 Phase lag study

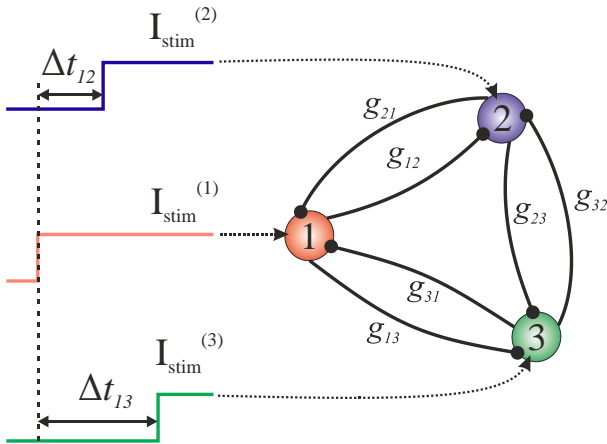


Figure 1. Neurons are made to compete with each other through mutually inhibitory synapses. The competition causes the electrical activity to bounce from one neuron to the next. The neuronal oscillations propagate through the network according to a trajectory that depends on the current stimulus ( $I_1$ ,  $I_2$ , and  $I_3$ ).  $I_1 = I_2 = I_3 = 100 \mu\text{A}$ . The typical conductance values are;  $g_{12} = g_{23} = g_{31} = 16 \mu\text{S}$ ,  $g_{21} = g_{13} = g_{32} = 45 \mu\text{S}$

We used a three neuron hCPG for studying the attractor dynamics using phase lag maps. In order to construct a phase lag map, the phases of two neurons (neuron 2 and neuron 3) were varied relative to neuron 1, as shown in fig.1. The amplitude of the stimulating current was kept just above threshold ( $100 \mu\text{A}$ ).

The network connectivity was set to allow competition between neurons to produce chaotic dynamics. We used unbalanced reciprocal synapses to achieve this [13]. Equally balanced reciprocal synapses caused the network to collapse in a state of collective synchronization where all neurons oscillate in phase for all initial conditions.

### 2.2 Generation RSA using hCPG

We used PN signal as an input to generate corresponding RSA signal using hCPG. The output of the hCPG could be used to stimulate the vagal nerve, thus completing a feedback loop and controlling the HR (fig. 2). We achieved this by first using a two neuron hCPG and then just using a single neuron hCPG.

In a two neuron hCPG we used PN signal as a stimulating signal for neuron 1 (N1) whereas neuron 2 (N2) oscillates continuously. By inducing an imbalance in the reciprocal synapses connecting the

two neurons, we inhibit the oscillations of neuron 2 (N2), thus allowing it to oscillate only during expiratory phases. Fundamentally we are using the competition between N1 and N2 oscillators to obtain switching under appropriate stimulation, as discussed in the section above.

In a single neuron hCPG we used the neuron to oscillate in response to PN signal during inspiration while keeping the hCPG frequency of oscillations fixed during expiration.

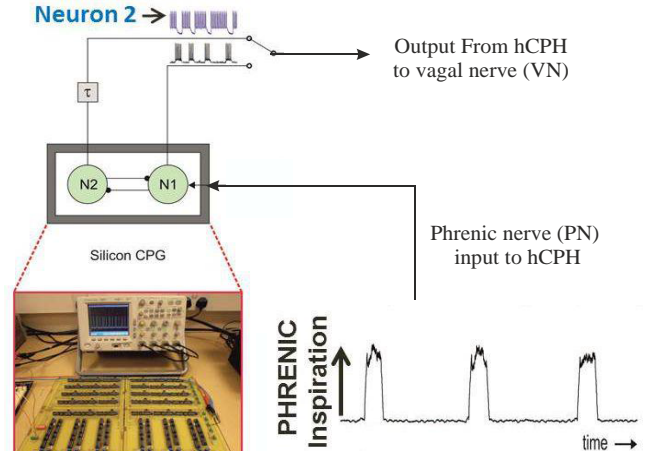


Figure 2. A feedback loop created by a two neuron hCPG with input from phrenic nerve (PN) and a corresponding output rhythmic pattern stimulating the vagal nerve (VN). This arrangement allows inducing artificial respiratory sinus arrhythmia (RSA) to control the heart rate.

## 3. RESULTS

### 3.1 Phase lag map using three neuron hCPG

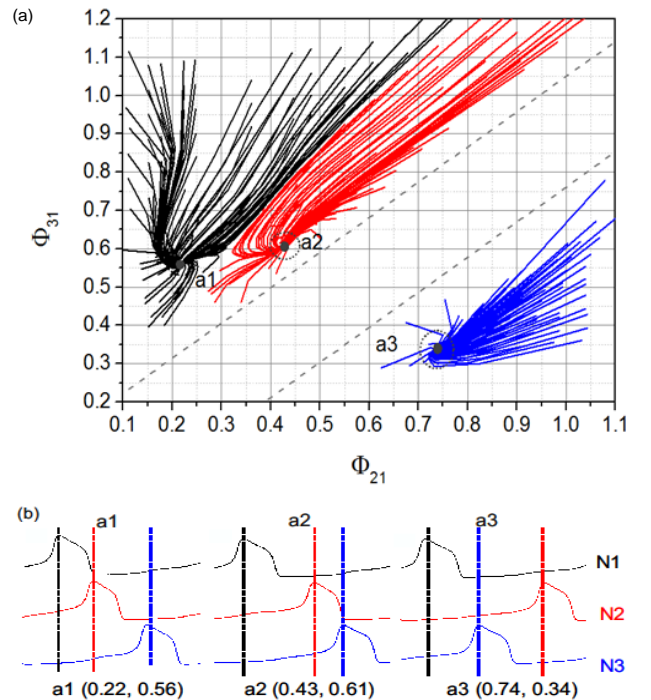
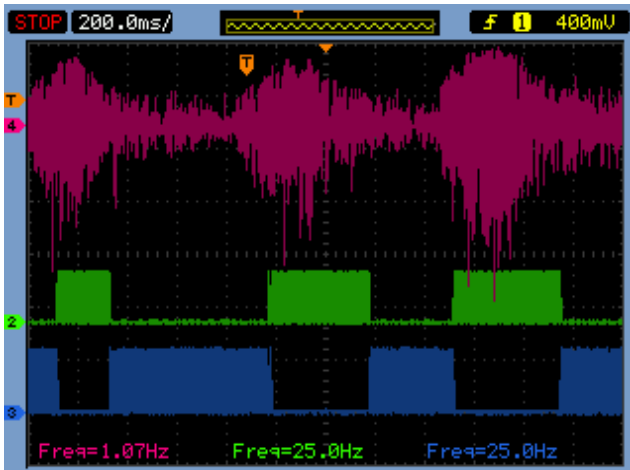


Figure 3. (a) Example of phase lag map of three neuron hCPG obtained when inhibition stronger in the anticlockwise direction stabilizes clockwise firing sequences a1 & a2. Three attractors a1, a2 and a3 are observed at coordinates (0.22, 0.56), (0.43, 0.61) and (0.74, 0.34) respectively. (b) Spatio-temporal oscillations of the three attractors.

The phase lag map of CPG was constructed by recording the dephasing of neuron2 ( $\Phi_{21}$ ) and neuron 3 ( $\Phi_{31}$ ) relative to neuron 1. Fig.3 (a) shows the phase lag map of our three neuron hCPG and fig.3 (b) shows the timing of the oscillations corresponding to the attractors. The state of coordinates ( $\Phi_{21}$ ,  $\Phi_{31}$ ) follows a trajectory in phase space that starts at a point set by the initial conditions and terminates in a steady state. The steady state points in the phase diagrams are marked as  $\mathbf{a}_1$ ,  $\mathbf{a}_2$  and  $\mathbf{a}_3$  and are called attractors. Different steady state oscillations may be induced by different initial conditions. Letting synaptic couplings become looser and more symmetrical, prolongs the transient interval needed to converge to an attractor.

### 3.2 RSA Generation Using Two Neuron hCPG

In order to generate RSA using a two neuron hCPG, the neurons were allowed to oscillate by keeping the reciprocal synapses balanced. Neuron1 (N1) was coupled to the PN signal and therefore oscillates during inspiration, whereas neuron2 (N2) oscillates continuously. We then induced imbalance in the reciprocal synapses by inhibiting the oscillations of N2 during inspiration. As a result we have N1 oscillating during inspiration and N2 oscillating during expiration, as shown in Fig. 4 (PN input signal is shown in violet, neuron 1 (N1) and neuron2 (N2) signals are represented in green and blue respectively). By increasing the frequency of oscillation of N1 relative to N2 we could generate an in-phase respiratory sinus arrhythmia (RSA) signal and vice-versa.



**Figure 4.** Two neuron hCPG using multistability in chaotic winnerless dynamics to generate a two phase signal as a response to phrenic nerve (PN) signal. PN input signal is shown in violet, neuron 1 (N1) and neuron2 (N2) signals are represented in green and blue respectively.

### 3.3 RSA Generation Using Single Neuron hCPG for Cardiorespiratory Disease

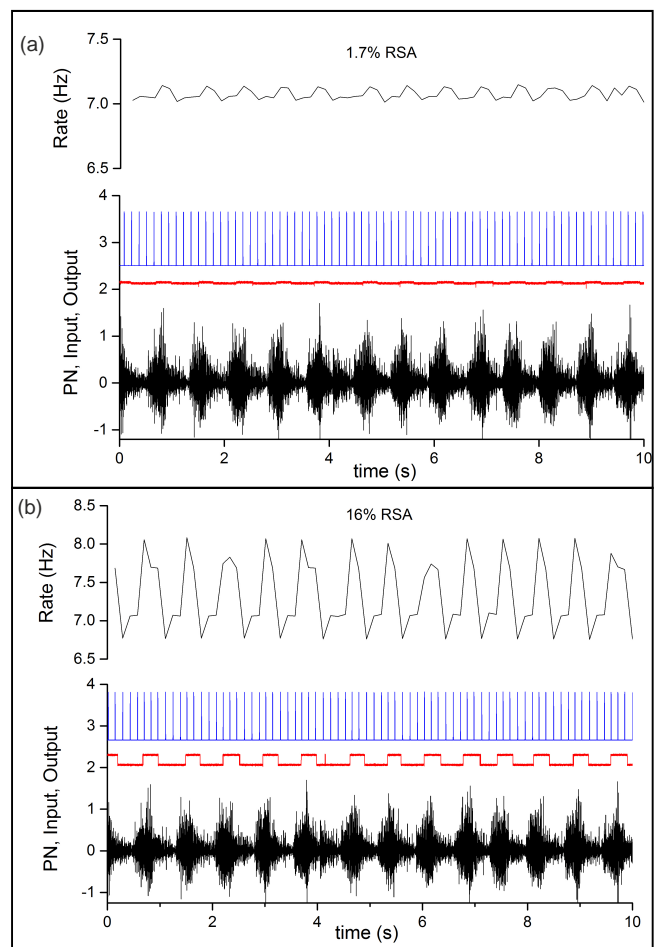
We further advanced the technology to generate RSA signal by using a single neuron hCPG. In order to achieve this, we kept the oscillations during expiration constant and just using a single neuron to adapt to the PN signal.

The PN signal is the stimulating the neuron and therefore allows it to oscillate during inspiration periods only. The hCPG was designed to independently control the frequency during the expiration period. This provides a greater flexibility to control the amplitude of RSA signal. Fig. 5 (a) and (b) respectively shows that

we can control the RSA to 1.7% and 16% and covers the clinically acceptable range (0.1-7%).

Figure 5 (a) & (b) shows the PN signal in the bottom panel, which was then amplified and filtered to generate a square signal (in red), called input signal. This signal stimulates the neuron during inspiration, whereas the frequency of oscillation was fixed during expiration ( $\sim 7\text{Hz}$  in fig. 5 (a) and  $\sim 6.7\text{Hz}$  in fig. 5 (b)). The corresponding output rhythmic pattern generated by hCPG is shown in blue. The RSA signal is a plot of the rate of oscillation of neurons during inspiration and expiration. We can control the amplitude of RSA independently of the base heart rate. The modulation automatically adapt to the breathing rate.

The RSA signal could be used to control the HR in response to the respiration in real time. As the hCPG provides the flexibility to modulate the HR using RSA, various therapies could be developed to modulate an unhealthy heart.



**Figure 5.** Generation of respiratory sinus arrhythmia (RSA) in response to phrenic nerve (PN) signal, using excitatory response of a single neuron hCPG. Input and corresponding output of hCPG is shown in red and blue respectively. By increasing the frequency of oscillation during inspiration (N1) as compared to oscillation during expiration (N2) we can modulate the amplitude of RSA (a) 1.7% and (b) 16%, and therefore the heart

We have demonstrated the realization of a bio-inspired hCPG that incorporates Hodgkin-Huxley based Na-K-I neurons. Using chaotic winnerless dynamics we can generate multiple spatio-temporal

sequences that are switched by initial conditions. The observed multistability is consistent with existing theories. We also demonstrated the use of the multistability in a two neuron hCPG to generate a two phase rhythmic pattern in response to breathing signal (PN signal).

We have also demonstrated the use of hCPG with two neurons and a single neuron to generate an RSA signal in response to breathing signal (PN) covering clinically accepted human range (0.1-7%). This advancement has a great potential to provide new therapies for cardiorespiratory diseases like heart failure.

## 5. ACKNOWLEDGMENTS

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