A Simplified Cell Network for the Simulation of C. elegans' Forward Crawling

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Abstract

We simulate *C. elegans'* forward crawling with a cell network composed of the AVB interneuron pair, 18 B-type and 19 D-type motorneurons and 95 body muscles, considering three key hypotheses; I. AVB interneurons get activated from their upstream neurons, and excite B-type motor neurons. II. Simultaneously, a central pattern generator (CPG) in the head, produces periodic stimuli for the B-type motorneuron network. Input stimuli from the CPG is injected into the first dorsal and ventral motor neurons (DB01 and VB01). These signals then propagate in a coordinated manner through the rest of the B-type motorneurons. III. At the same time, a proprioceptive feedback function is assumed amongst B-type motorneurons that establishes synchronized traveling waves in the muscles. Simulation of the cell network and the worm's crawling is performed in the c302 and Sibernetic platforms of the OpenWorm project. See a video demonstration here `https://youtu.be/iyV7y8nFdDU`.

Introduction

There are several hypotheses on how the nervous system of *C. elegans*, the nematode worm, gives rise to crawling and swimming behavior. A central pattern generator (CPG) mechanism in the head could generate traveling waves in the muscles that propagate from head to tail [1]. It could be local oscillatory circuits all along the body that communicate with each other to form the worms' body bends [2]. Another hypothesis argues that there are no CPGs, and only synchronization of direct activation of muscles together with sensory feedback from environment to the muscles (proprioception), results in the crawling behavior [3].

We test a simple assumption in which stimulation of the command neurons, AVB, which is known to modulate the forward locomotion, together with a proprioceptive mechanism in B-type motor neurons, and a CPG signal to them makes the worm crawl forward. We show this in the OpenWorm simulation platform [4], where a cell circuit exposed to a head-CPG signal, is simulated within c302 and Sibernetic simulation platforms. Details of the work are discussed as follows.

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c302 the worm's nervous system simulator

c302 [5], a sub-platform of the OpenWorm project, is a Python framework for simulation of multi-scale cell and network models of the *C. elegans* nervous system. c302 incorporates various neuron model types ranging from simple integrate-and-fire cells to more complex multi-compartmental conductance-based Hodgkin-Huxley (HH) cell models. Therefore, it provides us with a comprehensive substrate for testing hypotheses and assumptions about the dynamics of the worm's nervous system. For our simulation, we utilized an HH single compartmental model which additionally, incorporates dynamics of the intracellular calcium concentration of the cell.

Sibernetic platform for physical simulation of the worm's body

Sibernetic [6], is the platform implemented for simulating the body of the worm and its interactions with environment. Sibernetic is a physical simulation framework which implements the PCI SPH algorithm, a modified version of the smoothed-particle hydrodynamics algorithm, in C++, OpenCL, and uses OpenGL for 3D visualization. Sibernetic integrates c302 so that it can use the output of the simulated nervous system as an input for the simulation of the body movement of the worm. For simulating the body in Sibernetic, only intracellular calcium concentration dynamics of the muscle cells, which are simultaneously generated by c302, are required.

Forward Crawling Neural Circuit

In this section we discuss the structural and functional basis of the cell circuit that is hypothesized to perform the worm's forward crawling.

The circuit comprises the following cells: left and right pair command neurons AVB (AVBL, AVBR), 18 B-type motorneurons including 7 dorsal (DB1-DB7) and 11 ventral (VB1-VB11), 19 inhibitory D-type motorneurons consist of 6 dorsal (DD1-DD6) and 13 ventral (VD1-VD13), as well as 95 body-wall muscle cells.

Connectome(Figure 1B)**-** We used the wiring data provided for the hermaphrodite *C. elegans* in [7]. Note that weights of the synaptic connections in the *C. elegans* connectome has not yet been defined [8]. Thus, we simplified the network by assuming that all the synaptic connections share the same weight in the network.

Structural Perspective- AVB neurons synapse into DB and VB motorneuron groups mainly by gap-junctions. DB neurons excite/inhibit VD/DD, whereas VB neurons excite/inhibit DD/VD neurons through chemical synapses.

B-type/D-type neurons send excitatory/inhibitory chemical signals to muscle cells resulting in muscles' contraction/relaxation. Neighboring B-type neurons are connected with electrical synapses together with a functional mechanism to approximate the proprioceptive feedback a motor neuron receives from an anterior motorneuron during forward locomotion [9]. D-type motorneurons make electrical connections to neighboring neurons within the same neuronal group (Figure 1B).

Functional Perspective and Crawling simulation- Optimization of a relatively large neural circuit designed based on the HH neuron model requires a number of simplifying assumptions. Due to the large size of the parameter-space and, as a consequence, a substantial need for computing resources, it is not possible to find proper parameters to produce the desired behavior simply by applying an evolutionary-based optimization algorithm. Instead, a guided approach is needed. Here we started from a simplified network and show how crawling can be generated from the dynamics of the neural circuit simulation.

To generate the forward locomotion, we adopted the following hypotheses:

- **Assumptions on the network structure-** A symbolic representation of the hypothesized circuit for simulating the forward crawling is shown in Figure 1B. AVB makes gap junctions with B-type motor neurons. We assume that DB and VB, cholinergic motorneurons, excite their downstream muscle cells with excitatory synapses while GABAergic neurons, DD and VD groups inhibit the muscle cells. DB group excites VD neurons and inhibits the DD motor neurons. Similarly, VB motor neurons activate the DD inhibitory motorneurons and inhibit the VD motor neurons. The predictions for the polarity setting of synapses in the

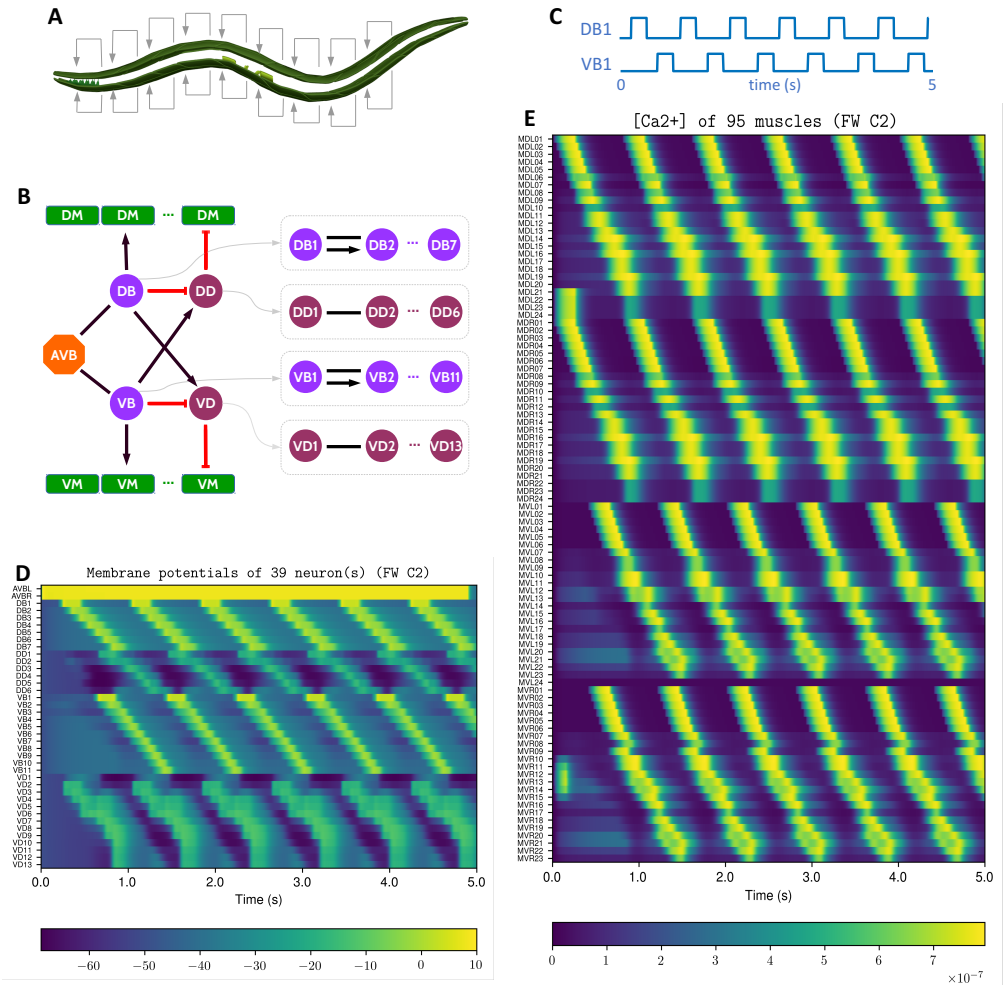

Figure 1: Simulation of the worm's forward crawling. A) Representation of the worm body wall muscle and the proprioceptive feedback effects. B) Symbolic representation of the Neural circuit composed of AVB interneuron, B-type and D-type motorneurons for generation of the forward crawling. C) Hypothetical central pattern generator modulatory inputs to DB1 and VB1 motor neurons. D) Motorneuron activity plot during 5 seconds of real time simulation of the forward-locomotion neural circuit. E) Activity of the body-wall muscles during the forward locomotion simulation.

network are preliminary assumptions to create the forward locomotion, which obviously requires experimental reports for its validation.

- **Head muscle cells are directly stimulated by synchronized periodic current pulses -** Neurons which are presynaptic to the head muscle cells are not included in the model. We therefore directly injected synchronized oscillatory current pulses to generate alternating bends of the dorsal and ventral muscles in the head (The first 7 muscle cells in each group: left/right dorsal muscles, left/right ventral muscles). We adjust the delays between dorsal and ventral muscles and between two dorsal/ventral pulses so that the muscles of the head contract with the same frequency as the rest of the body.

- **AVB neurons are active during the forward crawling period-** In a forward movement state, AVB neurons are active [10]. They modulate locomotion of the worm by inducing or accelerating forward movement. Synaptic inputs to the AVB neuron pairs from their upstream neurons were approximated by an input current pulse into the cell, in order to keep the neuron active during the forward-movement period.

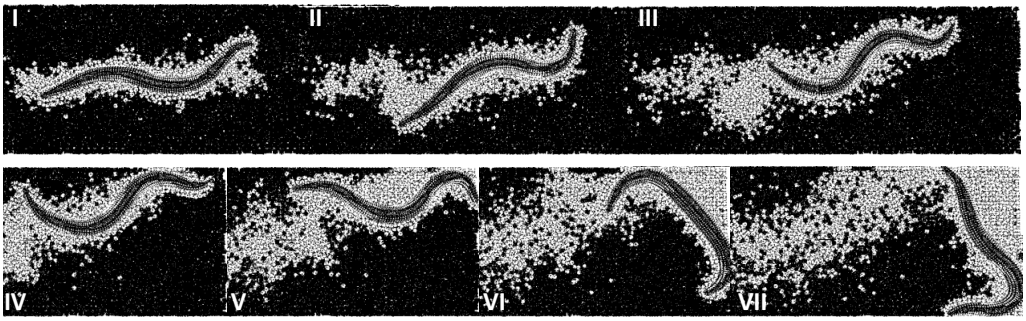

Figure 2: Simulation of the worm's crawling in Sibernetic worm simulator. Seven time-elapses in the 5-second forward crawling is represented from I to VII.

- **An external current pulse, hypothesized as a CPG system, periodically stimulates the first dorsal and ventral B-type motor-neurons -** We assumed a CPG mechanism with which the worm induces phase shifted dorsoventral body bends in the B-type motorneuron networks, from the neck posteriorly to the tail. We approximated the input from this hypothetical CPG, by injecting periodic current pulses directly into the first B motorneurons, DB1 and VB1 (Figure 1C). These currents then flow through the chain of B-type motorneurons which are linked to each other with gap junctions.
- **A proprioceptive mechanism in B-type motorneurons-** When a body segment bends, a posteriorly located motorneuron receives additional excitatory current due to stretch receptors located in some processes sensing bends of an anterior body segment [9]. As a result of such proprioceptive mechanism, the body bends get propagated along the body, coordinately. We added a functional excitatory mechanism between neighboring DB/VB neurons to approximate the propagation of this proprioceptive feedback. This is symbolically shown in Figure 1B (Left) by an arrow between the B-type motorneuron groups.

Results

The forward-crawling cell network was simulated within the c302 framework for a simulation time of 5 seconds. Figure 1D and 1E respectively represent the membrane potential dynamics of the individual motorneurons, and the intracellular calcium kinetics of all the 95 body muscles. The simplified circuit successfully generated reasonable traveling waves into the muscle cells, from head to tail. The muscle outputs were then incorporated as input in the Sibernetic platform. Figure 2 represents 7 time-elapse of a 5-second simulation of the worm's forward crawling recorded at the Sibernetic end. The environment in which the worm crawls, consists of agar particles. This simulation was run in 20 hours, on a Microsoft Azure virtual machine, NC6 series, enhanced with one NVIDIA Tesla K80 GPU instance.

Discussion

We showed the preliminary results of a global attempt to generate a realistic simulation of the worm's crawling, within the OpenWorm project. We started applying simplifications on a neural circuit model that is known to function in the forward locomotion of *C. elegans*. We made several assumptions about the network such as equal weight distribution, synaptic polarity assignments, abstraction of head bending by applying direct external inputs to the muscles and presumption of a proprioceptive mechanism amongst B-type motorneurons. Proofs for the correctness of such conditions and predictions, have to be yet investigated, either by means of lab experiments or by a more thorough and detailed modeling framework.

Our future directions are to build on top of this work by methodically removing the assumptions and ultimately develop a detailed and biophysically consistent model of a cell network, for making the worm crawl in an manner indistinguishable from a real worm.

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References

[1] Julijana Gjorgjieva, David Biron, and Gal Haspel. Neurobiology of Caenorhabditis elegans locomotion: where do we stand? *Bioscience*, 64(6):476–486, 2014.

[2] Erick Olivares, Eduardo J Izquierdo, and Randall D Beer. A ventral nerve cord CPG may underlie locomotion in C. elegans. *arXiv preprint arXiv:1705.02301*, 2017.

[3] Jordan H Boyle, Stefano Berri, and Netta Cohen. Gait modulation in C. elegans: an integrated neuromechanical model. *Frontiers in computational neuroscience*, 6, 2012.

[4] Balázs Szigeti, Padraig Gleeson, Michael Vella, Sergey Khayrulin, Andrey Palyanov, Jim Hokanson, Michael Currie, Matteo Cantarelli, Giovanni Idili, and Stephen Larson. OpenWorm: an open-science approach to modeling Caenorhabditis elegans. *Frontiers in computational neuroscience*, 8:137, 2014.

[5] c302 - multiscale simulation framework for C. elegans. `https://github.com/openworm/CElegansNeuroML/tree/master/CElegans/pythonScripts/c302`. Accessed: 2017-10-25.

[6] Andrey Palyanov, Sergey Khayrulin, and Stephen D. Larson. Application of smoothed particle hydrodynamics to modeling mechanisms of biological tissue. *Advances in Engineering Software*, 98(Supplement C):1 – 11, 2016.

[7] The connectome of the C. elegans hermaphrodite. `http://wormwiring.org/hermaphrodite/fullhermaphrodite.php`. Accessed: 2017-10-25.

[8] Gang Yan, Petra E Vértes, Emma K Towlson, Yee Lian Chew, Denise S Walker, William R Schafer, and Albert-László Barabási. Network control principles predict neuron function in the Caenorhabditis elegans connectome. *Nature*, 2017.

[9] Quan Wen, Michelle D Po, Elizabeth Hulme, Sway Chen, Xinyu Liu, Sen Wai Kwok, Marc Gershow, Andrew M Leifer, Victoria Butler, Christopher Fang-Yen, et al. Proprioceptive coupling within motor neurons drives C. elegans forward locomotion. *Neuron*, 76(4):750–761, 2012.

[10] Saul Kato, Harris S Kaplan, Tina Schrodel, Susanne Skora, Theodore H Lindsay, Eviatar Yemini, Shawn Lockery, and Manuel Zimmer. Global brain dynamics embed the motor command sequence of Caenorhabditis elegans. *Cell*, 163(3):656–669, 2015.