

Past and Recent Endeavours to Simulate *Caenorhabditis elegans*

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Abstract: Biological nervous systems are robust and highly adaptive information processing entities that excel current computer architectures in almost all aspects of sensory-motor integration. While they are slow and inefficient in the serial processing of stimuli or data chains, they outperform artificial computational systems in seemingly ordinary pattern recognition, orientation or navigation tasks. Even one of the simplest nervous systems in nature, that of the hermaphroditic nematode *Caenorhabditis elegans* with just 302 neurons and less than 8,000 synaptic connections, gives rise to a rich behavioural repertoire that – among controlling vital functions - encodes different locomotion modalities (crawling, swimming and jumping). It becomes evident that both robotics and information and computation technology (ICT) would strongly benefit if the working principles of nervous systems could be extracted and applied to the engineering of brain-mimetic computational architectures. *C. elegans*, being one of the five best-characterized animal model systems, promises to serve as the most manageable organism to elucidate the information coding and control mechanisms that give rise to complex behaviour. This short paper reviews past and present endeavours to reveal and harvest the potential of nervous system function in *C. elegans*.

1 INTRODUCTION

Caenorhabditis elegans, a tiny roundworm (L: 1 mm, Ø 80 µm) with a life span of a few weeks, is among the five best characterized organisms in nature (Epstein and Shakes, 1995). With only 2% of its population being males, the nematode proliferates predominantly as a quasi-clone through hermaphrodites. These are comprised of exactly 959 cells, including 95 body wall muscle cells and 302 neurons that fall into 118 classes (Altun and Hall, 2009; 2015). Their nervous system has been completely mapped by electron microscopy (J. G. White et al., 1986). The nematode's behaviour and its underlying operation principles are the subject of numerous past and ongoing studies (Bono and Villu Maricq, 2005; Corsi et al., 2015), which has led to an extensive body of knowledge on this creature. This inspired biologists and neurocomputational researchers at the end of the last century to simulate not only the *C. elegans* nervous system, but the organism and its development in its entirety. We will briefly summarize and discuss the outcome of these projects to then focus on the scope of three recent simulation initiatives, the **OpenWorm**, the **NEMALOAD** and the **Si elegans** projects.

2 PAST PROJECTS ON SIMULATING *C. elegans*

With the advent of sufficiently powerful computational resources in the 80's of the last century, researchers discovered computers for the simulation of all kinds of natural phenomena, among them the events in nervous systems. Modelling neural systems has diverse roots and inspirations, most of them being inductively derived from first principles (*e.g.*, (Hodgkin and Huxley, 1952)) or deduced from direct observation. The nematode *C. elegans* was considered as an ideal system to start with (Achacoso and Yamamoto, 1992). In 1997, researchers at the University of Oregon (USA) proposed **NemaSys**. It aimed at developing a computer simulation environment for *C. elegans* to support basic research and education in *C. elegans* and systems computational neuroscience. Due to *C. elegans*'s simplicity, an anatomically detailed model of the entire body and nervous system was perceived as an attainable goal. In a concerted effort employing electrophysiology, calcium imaging, quantitative behavioral analysis, laser ablation and mathematical modelling, one outcome was the

identification of the mechanism and simple computational rules by which *C. elegans* computes the time derivative of chemosensory input (Ferree and Lockery, 1999). The results were transcribed into a phototaxis response algorithm to control and analyse the trajectories of a custom-made robot (Morse et al., 1998).

In 1998, ‘The Perfect *C. elegans* Project’, a collaboration between researchers with Sony, the Keio University in Japan and the University of Maryland in the USA, targeted at introducing synthetic models of *C. elegans* to further enhance our understanding of the underlying principles of its development and behaviour, and life in general. Initial efforts focused on a realistic simulation of a subset of biological observables by providing a Java-based visualization tool for embryogenesis including cell position, kinematic interactions between cells, cell division, cell fate, neural connections and thermotaxis. Ultimately, a complete synthetic model of the nematode’s cellular structure and function, including genetic interactions, was envisioned. The concepts and first steps were outlined in an initial report (Kitano et al., 1998).

In 2004, researchers at the Hiroshima and Osaka universities in Japan aimed at developing a virtual *C. elegans* in the ‘Virtual *C. elegans* Project’. Based on data on the spatial and structural layout of the nematode, they proposed a dynamic body model with muscles to analyse motor control. It was founded on a neural oscillator circuit to generate rhythmic movement. It could be shown that the model qualitatively generates rhythmic movements similar to wildtype and mutant nematodes. Another demonstration was a real-coded genetic algorithm to drive a kinematic locomotion model that responded to gentle-touch stimuli (Suzuki et al., 2005; Suzuki, et al., 2005a).

3 ONGOING PROJECTS ON SIMULATING *C. elegans*

The OpenWorm project (USA, 2011-present) is an international open science project to simulate *C. elegans* at the cellular level as a bottom-up simulation on standard computers. The long-term goal is to model all 959 cells of the *C. elegans* hermaphrodite. The first stage is to describe the worm’s locomotion by simulating the 302 neurons and 95 muscle cells (Szigeti et al., 2014). Among the currently available modules are a realistic flexible worm body model including the muscular system

and a partially implemented ventral neural cord (A. Palyanov *et al.*, 2011; OpenWorm Browser, 2014). It is based on the location dataset compiled by the ‘Virtual Worm Project’, an initiative at the California Institute of Technology that creates an interactive atlas of the hermaphrodite’s cell-by-cell anatomy (Grove and Sternberg, 2011).

Around the same time, **NEMALOAD** (‘nematode upload’; USA, 2012-present) initiated the integration of a number of recent experimental imaging technologies (Marblestone et al., 2013; Schrödel et al., 2013) to learn how one neuron affects another in *C. elegans*. The project is structured in four subsequent stages that build on one another. In the molecular biology stage, *C. elegans* strains shall be functionalized with optogenetically encoded sensors and actuators (*e.g.*, calcium indicators, photo-stimulators and inhibitors) for the tracing and manipulation of neural activity. In the imaging stage, this activity flow shall be recorded in freely behaving worms at neuronal resolution. In the perturbation stage, individual neurons shall be excited optically by means of a custom-made two-photon digital holography system to map their contributions to a certain behaviour. In the final modelling stage, automation tools for the correlation of neural activity with behaviour shall allow the development of a dynamic model of the worm’s behaviour in a simulated environment to mirror the experimentally observed behaviour in its natural or laboratory environment. This shall elucidate the underlying information processing structure.

The most recent concerted effort in emulating *C. elegans* is the *Si elegans* project (EU, 2013-present). It will provide a closed-loop, open-access/open-source, peer-contribution platform being based on brain-mimetic principles for the emulation and reverse-engineering of *C. elegans* nervous system function in a behavioral context. Thus, the overall objectives are very similar to previous endeavours. The chosen approach is slightly different, though. The nervous system will consist of a dedicated hardware infrastructure. It will be based on 302 field-programmable gate arrays (FPGAs), a parallel architecture by nature. The FPGAs will accommodate distinct neural response models represented by freely reconfigurable electronic circuits, one for each *C. elegans* neuron. These models may be dynamic (Machado et al., 2014; Machado et al., 2015). The nematode’s connectome will be implemented by a light-projection scheme to warrant interference-free, parallel information transfer with high temporal

fidelity (Petrushin et al., 2014; Petrushin et al., 2015). This biomimetic hardware nervous system emulation will be controlling a virtually embodied and physically realistic representation of the nematode (via soft body physics) in an equally realistic virtual behavioral arena (e.g., an agar Petri dish) (Mujika et al., 2014). In there, the virtual *C. elegans* will encounter commonly tested stimuli (e.g., touch, chemicals and/or temperature gradients) at any pre-defined time. Its sensory experience will be transmitted to the sensory neurons in the FPGA network. Based on published knowledge on network-internal circuitry and signal processing pathways, the sensory input (and proprioceptive information) will generate a motor output to instruct the muscles of the virtual worm on what to do next. In this closed-loop scenario, it will furthermore be possible to read out any network state (e.g., synaptic weights) at any given time for the reverse-engineering of network function. To make the *Si elegans* framework user-friendly for novice and expert users alike, several model generation (e.g., drag-and-drop) and import functionality (e.g., from existing simulation engines) will be provided (Krewer et al., 2014). Once the chosen models generate an output that is comparable to observations in real laboratory experiments, the platform will allow the neuroscience community to better understand, if not anticipate, the neural mechanisms underlying behaviour. A first version of the *Si elegans* platform is expected to go online in late 2016 for public access and use.

4 SELECTIVE LITERATURE SURVEY ON RECENT *C. elegans* LOCOMOTION MODELS

The most accessible circuit in *C. elegans* is its body-wall muscle control system responsible for locomotion consisting of 75 motor neurons (out of a total number of 113 motor neurons) of 8 classes that innervate 79 body wall muscle cells arranged along the dorsal and ventral cords (Riddle et al., 1997; Altun and Hall, 2009; Gjorgjieva et al., 2014; Zhen and Samuel, 2015). Its output can be visualized rather easily and is thus verifiable by direct comparison with time-lapse images of worm movements. Therefore, the majority of publications on simulating *C. elegans* focuses on various aspects of the sensory-motor loop (Lockery, 2011; Cohen and Sanders, 2014; J. Gjorgjieva et al., 2014; Zhen and Samuel, 2015) and its driving inputs (W. R. Schafer, 2015). Diverse strategies have been

proposed of which only a few are mentioned. Among them are event-driven models, an asynchronous system based on pulse modulation (Claverol et al., 1999), compartmental conductance-based models exclusively for muscle cells (Boyle and Cohen, 2008), neuromuscular control systems that rely on a sensory feedback mechanism based on bistable dynamics without the need for a modulatory mechanism except for a proprioceptive response to the physical environment (Boyle et al., 2012), dynamic neural networks based on a differential evolution algorithm in the head and body with a central pattern generator in between acting on a locomotion model with 12 multi-joint rigid links (Deng and Xu, 2014), evolutionary algorithms for the identification of a minimal klinotaxis network (Izquierdo and Beer, 2013) and genetic algorithms to train 3680 synaptic weights within the motor connectome to replicate behaviours based on sensory-motor sequences (Portegys, 2015). At this point, we still lack some of the electrophysiological and biochemical data (e.g., on the role and effect of neuromodulators) to decide which of these approaches (or a combination thereof) best reflect the biological events that drive locomotion.

5 DISCUSSION

When Sydney Brenner proposed *C. elegans* as a model organism to the Medical Research Council (MRC) in the U.K. in 1963, he stated that 'We intend to identify every cell in the worm and trace lineages' (Brenner, 1963). While this goal has been accomplished, it became clear that this information is not sufficient to deduce the cells' contributions to behaviour. Several key questions are still unanswered. One of them is our lack of biological knowledge that would instruct us to what level of detail a simulation has to drill down to let realistic behaviour emerge. Will we need to uncover and formalize the entirety of the molecular machineries that underpin worm biology or will a more abstracted, thermodynamics-inspired description faithfully elicit the observed behaviour *in silico*? Although we know most of the neurons' role and purpose (e.g., sensory, interneuron, motor, projection, local/solitary), little is known about the identity (excitatory or inhibitory) and relevance of the individual connections (including gap junctions). Furthermore, evidence suggests the existence of parallel, sometimes opposing (inhibitory vs. excitatory) circuits. Similarly challenging are divergent circuits from a common starting point to different endpoints. In addition, the neural dynamics

of different neurons are not uniform and even vary between individuals. Moreover, they may be modulated by extrasynaptic neural activation mechanisms including diffusible biochemical regulators (e.g., neuromodulators) or physical parameters (e.g., temperature, proprioception) (Bargmann and Marder, 2013). These, in turn, may vary with internal states (e.g., starved vs. satiated) and the environmental conditions. On top of that, synapses are constantly remodelled not only in response to behavioral experience, but in a context-sensitive and time- or activity-dependent manner on the timescale of milliseconds to weeks (Friston, 2011). Thus, *C. elegans*'s neural circuit, despite its quasi-static wiring diagram, features many dynamic and difficult to capture mechanisms that encode different behavioral outcomes.

Due to this complexity and the many unknowns, any simulation approach is almost doomed to start with naïve and oversimplified assumptions. No matter how a simulation framework is conceptualized, the above findings strongly suggest keeping it as flexible, extensible and scalable as possible to accommodate new insights into the mechanisms that govern nervous system function underlying a particular behavioral phenotype. This may include the deviation from standard reasoning: instead of building population or neuron-specific response models (E. Marder & A. L. Taylor, 2011), an even more fine-grained approach may become necessary that provides a variety of adaptive models for one and the same neuron each responding to context-specific events.

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