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Introduction

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**Author for correspondence:**
Stephen D. Larson
e-mail: stephen@openworm.org

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# Connectome to behaviour: modelling *Caenorhabditis elegans* at cellular resolution

Stephen D. Larson[1], Padraig Gleeson[1,2] and André E. X. Brown[3,4]

[1]OpenWorm Foundation, Boston, MA, USA
[2]Department of Neuroscience, Physiology and Pharmacology, University College London WC1E 6BT, UK
[3]MRC London Institute of Medical Sciences, London W12 0N, UK
[4]Institute of Clinical Sciences, Imperial College London, London SW7 2AZ, UK

SDL, 0000-0001-5397-6208; PG, 0000-0001-5963-8576

It has been 30 years since the 'mind of the worm' was published in *Philosophical Transactions B* (White *et al*. 1986 *Phil. Trans. R. Soc. Lond. B* **314**, 1–340). Predicting *Caenorhabditis elegans*' behaviour from its wiring diagram has been an enduring challenge since then. This special theme issue of *Philosophical Transactions B* combines research from neuroscientists, physicists, mathematicians and engineers to discuss advances in neural activity imaging, behaviour quantification and multiscale simulations, and how they are bringing the goal of whole-animal modelling at cellular resolution within reach.

This article is part of a discussion meeting issue 'Connectome to behaviour: modelling *C. elegans* at cellular resolution'.

## 1. Introduction

The structure and connectivity of the complete *Caenorhabditis elegans* nervous system, informally known as the 'mind of the worm', was published in 1986 in *Philosophical Transactions B* [1,2]. This was the first nervous system to be reconstructed to the level of synapses. This publication marked a critical milestone in the worldwide effort to study this nervous system and has been cited more than 3000 times. Recent work has advanced our knowledge of neurotransmitter use [3,4], the extrasynaptic connectome of neuropeptides and monoamines [4] and localization in the worm's 118 neuron classes [6]. Also, techniques such as laser ablation, optogenetics and the analysis of mutants have allowed a wealth of experimental information to be gathered on the effects of modifying neural activity on behaviour.

However, integrating these experimental advances remains a challenge because of the sheer quantity of results and because observations are made at vastly different spatial and temporal scales. Motivated by the challenge of integrating these complex datasets into a better understanding of a whole organism, an international collaboration known as OpenWorm was set up 6 years ago. Its aim is to model and simulate the functioning of *C. elegans*, including its complete nervous system, behavioural dynamics and eventually every cell in its body, in a computer [7]. This project combines biophysical neuronal modelling, detailed mechanical modelling and behavioural quantification, and applies them to the challenge of predicting the activity of the *C. elegans* nervous system and its behavioural output. This has been done in an open science manner, making all of the tools and the results of the collaboration open to all on the public Internet. The aim is to generate testable hypotheses and ultimately provide a highly detailed understanding of how ensembles of cells generate patterns of behaviour.

Achieving this aim will only be possible through the merger of experimental and computational approaches to understanding *C. elegans* physiology, especially of the nervous system [8–13], and so this special theme issue consists

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of contributions from both experimental and computational neuroscientists, computer scientists and biophysicists. The contributing disciplines are diverse, but the problem is specific: *how does* C. elegans' *well-specified nervous system function with respect to the whole organism, and how can we use digital modelling and simulation tools to help us understand it?*

Natural nervous systems are embodied and interact continuously with their external environments [14], making mechanical models a valuable way to study this relationship. Palyanov *et al.* have developed Sibernetic [15], a simulation framework that uses smoothed particle hydrodynamics [16] to perform detailed mechanical simulations of a morphologically accurate *C. elegans* moving through virtual environments. Mechanics is not only important to 'translate' neural activity to behaviour, but it also plays an important role in feeding back on neural activity as demonstrated in papers from Denham *et al.* [17] and Izquierdo & Beer [18], which use neuromechanical models to study how locomotion could be shaped by neural activity. A role for proprioception in body wave propagation does not necessarily resolve the origin of oscillations as described by Wen *et al.* [19], who review evidence for intrinsic oscillations in rhythm generation in the ventral nerve cord.

A conceptual division of the nervous system into sensory and motor systems, including command interneurons that instruct activity in the nerve code, has been proposed in *C. elegans* since at least the publication of the connectome. Recent imaging experiments suggest there may be quite a close coupling between behaviour and whole-brain activity and Kaplan *et al.* suggest in their perspective [20] that a less partitioned, more dynamic picture of the sensory-motor system could make more sense.

Patterns of oscillation lead to locomotion and differences in these patterns have been used to identify dozens of uncoordinated mutants with muscle and nervous system defects. Just as locomotion differences in real worms led to the discovery of nervous system defects, quantifying the behaviour of artificial agents might be used to constrain model parameters. Javer *et al.* [21] report a new set of features for quantifying behaviour that are useful for distinguishing mutant worms and may also be useful for comparing existing databases of worm behaviour to the output of neural simulations.

Most of the quantitative data on worm behaviour is collected from worms crawling on a smooth agar surface, but in nature they are likely to encounter heterogeneous three-dimensional environments. White [22] hypothesizes that the extra degrees of freedom of the worm's snout are important for navigating these more complex environments and looks to the neural circuitry in the head for insights into possible control mechanisms.

Network analysis of the *C. elegans* synaptic connectome has drawn significant attention in recent years because of its nearly unique status as a complete organismal nervous system wiring diagram. Branches of mathematics such as graph theory and network science have entered into the domain of neuroscience, and are bringing with them novel quantitative perspectives on the complexity of nervous systems. Along these lines, Lui *et al.* [23] present results from deriving a candidate functional connectome from Probabilistic Graphical Models built on the structural *C. elegans* connectome. Towlson *et al.* [24] present a Network Control-based perspective on predicting functions of the *C. elegans* connectome, and work to bridge the conceptual gaps between the mathematical theory from which this is derived and the experimental understanding of the neurobiologist.

Not all of the communication between neurons goes through chemical and electrical synapses. There are also 'wireless' connections between neurons that release diffusible molecules and those with receptors for those molecules. Chew *et al.* [25] use a combination of reverse pharmacology, behaviour analysis and genetics to identify a new wireless connection mediated by neuropeptides encoded by *nlp-49* and the conserved receptor SEB-3.

Neuronal systems can be modelled using many different approaches and at many levels of detail. Gleeson *et al.* [26] describe a modelling framework, c302, created specifically for *C. elegans*, which can generate network models of many different sizes, incorporating varying levels of detail in neurons, muscles and synapses depending on the research question being addressed. Use of standards enables the models to be used on many simulation platforms and in other applications. One of these is Geppetto, described by Cantarelli *et al.* [27]. This middleware platform has been used by a number of neuroscience initiatives, including OpenWorm and Open Source Brain [28], to make neuroscience models and data more accessible via web browsers.

Models need to be constrained at many levels by experimental data to be of use in making predictions about the behaviour of the biological entities being simulated. Gerkin *et al.* [29] describe a framework, SciUnit, which is being used in OpenWorm to validate models produced by the project against experimental data on ion channel kinetics, neuronal firing and worm locomotion.

While there is much still to do before a full-scale simulation of *C. elegans* is completed, the OpenWorm project has already made a number of valuable contributions towards structuring the diverse array of experimental data on *C. elegans* and facilitating modelling of it. Sarma *et al.* [30] present an overview of the aims of the project, the work completed to date, how the project interacts with and invites contributions from the community and future plans for the initiative.

The work presented in this special issue covers a broad range of topics, and approaches the problems of understanding *C. elegans* from many different perspectives. We hope that these contributions will provide a valuable resource for the community working towards a deeper understanding of the neuronal basis for *C. elegans* behaviour. We also hope that the approach in this issue of placing detailed data-driven theoretical approaches directly alongside data-generating experimental approaches, in service of understanding *C. elegans*, can provide a model for an even broader discipline of biology.

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