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Deciphering neural circuits for *Caenorhabditis elegans* behavior by computations and perturbations to genome and connectome Q5

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Abstract
Caenorhabditis elegans nematode worms are the only animals with the known detailed neural connectivity diagram, well characterized genomics, and relatively simple quantifiable behavioral output. With this in mind, many researchers view this animal as the best candidate for a systems biology approach, where one can integrate molecular and cellular knowledge to gain global understanding of worm's behavior. This work reviews some research in this direction, emphasizing computational perspective, and points out some successes and challenges to meet this lofty goal.

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Introduction

Despite diverse goals and scopes, engineering and biological sciences share a common general methodology. If engineers want to know how a device works, they usually break or decomposes it into smaller parts and study them in isolation [1]. Subsequently, they gradually put the components together and investigate their interactions, which generally leads to deciphering the workings of the device. A similar version of such a reverse engineering is used also in biology. The functions of biological circuits are usually decoded by application of either molecular or cellular perturbations in the form of genetic mutations or cell elimination (laser ablations), with simultaneous observation of their consequences on the system performance [2].

Caenorhabditis elegans worms are unique biological organisms to study the structure—function relationship across different scales, from molecules to behavior, for the three main reasons. (i) Their genome and protein networks are well characterized [3,4], which represents a microscopic level. (ii) They have a very small nervous system composed of only 302 neurons and they are the only animals on the Earth with the known wiring diagram of neural connections [5–7], called connectome, and this represents a mesoscopic level (for a comparison human brain contain 10^{11} neurons and even a small fruit fly brain has $\sim 10^5$ neurons). (iii) These worms can exhibit a broad range of behaviors (locomotion, olfaction, complex mating, sleep, learning and memory) that can be quantified, and this represents a macroscopic level [8]. It should be noted that the structure—function relationship has also been successfully studied in rodents [9] and in the fly [10]. However, these systems, despite recent progress in their connectome studies, still lack a detailed neuron-to-neuron wiring diagram.

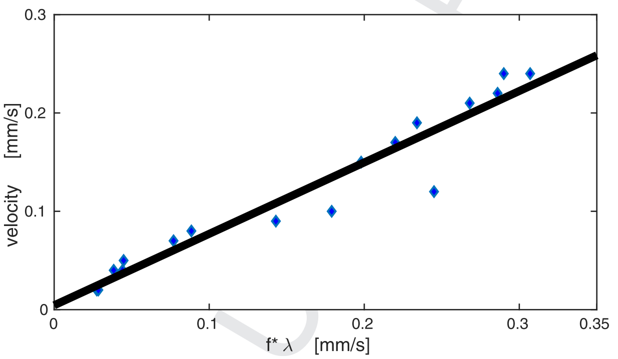
The above suggests that an integrated description of the nematode worms across different spatial scales is in principle possible by merging the tools of separate disciplines such as genomics, connectomics, behavioral neurophysiology, and computational biology. There is an expectation that such a description might provided insights not only about inner mechanisms employed by the worm to execute its behavioral program [4,8], but also can shed some light on the biological mechanisms in more complex animals because many molecular processes and their modularity are preserved across different species [2,11]. However, despite the apparent structural-behavioral simplicity of *C. elegans* nematodes, the system-level approach is not as straightforward as it might seem. Foremost it requires a collaboration of researchers with different backgrounds and skills who have to learn the basics of the other disciplines to communicate efficiently. Despite this practical difficulty there are some studies that successfully merge and apply the tools from molecular genetics, behavioral neurophysiology [12], and/or computational biology [13–16]. On the other hand, such a merging often requires a lot of guess-work, since each of the levels (i-iii), although well characterized, contains some "knowledge gaps", and moreover the levels are not easily related to one another.

The goal of this review is to give a sense and examples of how the above three levels could be potentially integrated using a system-level computational perspective, with hopes and challenges that have to be addressed and solved before systems biology of *C. elegans* worms can fully materialized. We focus mainly on locomotion as it accompanies a large part of the behavioral output of these worms [17–19]. Specifically, we consider the questions of locomotion robustness, locomotion encoding in *C. elegans* nervous system, locomotory decision making, the type of synaptic signaling between premotor command neurons, and the question about which neuronal models could be best used for behavioral description?

How robust is *C. elegans* locomotory behavior?

Sinusoidal locomotion is the basic short-term behavior of *C. elegans* nematodes, and therefore one can suppose that it must have been somehow optimized during evolution (see e.g. Refs. [20,21]). Interestingly, most genetic mutations do not have a visible effect on locomotion [22], and similarly, random elimination of neurons from the worm's network rarely alters the motion. To affect the locomotor output, e.g., to change mean velocity, frequency of body undulations, or the rate of changing direction (reversals), one has to apply targeted mutations or neural ablations [23]. But even in these cases, the proportional relationship between worm's velocity and the frequency of neural oscillation is mostly preserved (Figure 1). The exceptions that break this proportionality are rare, but if they happen they can have a very dramatic influence on motion (i.e. phenotype), including its cessation. The reason for a high degree of motor robustness against genetic mutations and neuron eliminations is that both protein and neural networks possess the so-called "rich club" architecture [24]. This means that connectivity in these two types of networks is generally sparse, with only a small fraction of proteins and neurons serving as "hubs" with dense connections [25] (For neural connectome these are primarily locomotor interneurons [24].) Thus, random mutations or ablations would most likely hit a non-hub protein or neuron, and therefore can cause only a minor (i.e. local) damage to network organization.

Figure 1



Robustness of *C. elegans* locomotion. Scaling of propulsion velocity with body wave velocity (product of undulatory frequency *f* and body wavelength λ) for *C. elegans* across wild type and several mutants. Note that most of the strains align along a common line (least square fitting; black line). Adapted and modified from Ref. [23]. Mutants included: cat-2(e112), cat-4(e1141), egl-30(tg26), goa-1(n1134), goa-1(sy192), lon-1(e185), double mutant lon-1(e185); lon-2(e678), BE109, sqt-1(sc101), sqt-1(sc103), unc-54(st130), unc-54(st132), unc-54(st134), unc-54(st135), unc-54(s95), and unc-54(s74).

Another manifestation of *C. elegans* robustness and simplicity is the fact that its locomotory output is low dimensional in a sense that at any given instant the worm's posture can be represented as a linear combination of the same four basic shapes, the so-called "eigenworms" [26], across different genotypes (for wild-type and different mutants) [14]. In sum, all this suggests a robust control mechanism of locomotion that spans the three levels, form microscopic to macroscopic, and it resembles the concept of "robust yet fragile" architecture that possess many engineering and biological systems [27].

Why is it difficult to integrate the knowledge of connectome and neural dynamics with nematode behavior?

The neural connectome is a static structure over the worm adulthood. On the other hand, the worm behavior has a temporal aspect that can change depending on environmental input or internal neuronal activity. Simply saying, the same connectome can produce a diverse behavioral output, which means that there is no a one-to-one mapping between neuronal structure and behavior, or between mesoscopic and macroscopic levels [28]. To understand a neuronal mechanism of a particular behavior one has to relate it to a corresponding neural dynamics. However, there are two problems here. One is that it is extremely difficult to record electric activity of *C. elegans* neurons because of the worm's hydrostatic skeleton that can explode under the release of internal pressure upon dissection [29]. This problem has been circumvented in recent years by the invention of optogenetic methods that enable imaging of calcium activity in many neurons simultaneously [30–33], which is possible due to *C. elegans* transparent body (see also below). Calcium level in neurons is a proxy for membrane electric voltage, and hence there is a high hope that these type of imaging methods can yield great insights about neuronal control of behavior not only in the

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