Robust Sigmoidal Control Response of *C. elegans* Neuronal Network

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Abstract. Biological systems are known to evolve mechanisms for acquiring robust response under uncertainty. Brain is a complex adaptive system characterized with system specific network features, at global as well as local level, critical for its function and control. We studied controllability response in *C. elegans* neuronal network with change in number of functionally important feed-forward motifs, due to synaptic rewiring. We find that this neuronal network has acquired a sigmoidal control response with a robust regime for saturation of feed-forward motifs and an extremely fragile response for their depletion. Further we show that, to maintain controllability this neuronal network must rewire following a power law distance constraint. Our results highlight distance constrained synaptic rewiring as a robust evolutionary strategy in the presence of sigmoidal control response.

Keywords: *C. elegans* neuronal network · Controllability · Feed-forward motifs · Synaptic rewiring · Optimization

1 Introduction

Brain networks are characterized with non-trivial topological features, on global as well as local level, that are key to their function and control [1]. Typical to a complex adaptive system, the neuronal map is known to be plastic, and undergoes synaptic rewiring [2]. Under such dynamic synaptic reorganizations, it is important to know how the brain maintains functionally important topological features. We investigated this question in *C. elegans* neuronal network (CeNN), the most complete neuronal wiring diagram available till date [3, 4]. CeNN is a small world network, characterized with over-representation of feed-forward motifs (FFMs) and distributed control architecture [5–8]. FFMs represent functional building blocks of this system, a fine-grained feature that potentially gives rise to coarse-grained properties specifying network control [9].

A system is said to be controllable if it can be driven from any initial state to a desired final state in finite amount of time. For a linear time-invariant system, the necessary conditions to achieve structural control were specified by Lin in 1974 [10].

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To achieve full control with least efforts, minimum input theorem requires identification of a minimal subset of 'driver nodes'. Maximal matching algorithm facilitates computation of the number of driver nodes (D_n) in a network [7]. Lesser the number of inputs, the more centralized is the control [8].

CeNN is known to have distributed control with higher number of driver neurons than its random counterpart [7, 8, 11]. By studying genotypic and phenotypic aspects of CeNN, in our earlier study we have shown that 'driver neurons' are associated with important biological functions such as reproduction, signaling processes and anatomical structural development [11]. The CeNN has been shown to have a bimodal control architecture which is sensitive to edge plasticity [8]. Synaptic plasticity can influence the number of driver neurons and hence control mechanisms in CeNN. Hence, we probed relationship between number of FFMs and number of driver neurons under synaptic rewiring. While the saturation of feed-forward motifs in CeNN is of functional consequence [6, 12, 13], it is not clear whether the system optimizes for the number of FFMs.

Interestingly, our studies suggest that the controllability (number of driver neurons) is sensitive to not 'the absolute number of FFMs' but to 'change in FFMs', exhibiting an asymmetric, sigmoidal response. We also find that the distance constrained synaptic rewiring can explain preservation of FFMs as well as robust controllability response of the network.

2 Materials and Methods

Towards investigations done as part of this work, we compiled data of *C. elegans* nervous system to construct its network model as well as its controls. Apart from enumerating its motifs and driver nodes, we also designed an algorithm for implementing motifs tuning.

2.1 *C. elegans* Neuronal Network

The nervous system of *C. elegans* consists of around 302 neurons which are interconnected via chemical synapses and gap junctions [3, 14]. We constructed CeNN, a network model of *C. elegans* neuronal network, using neuronal connectivity data of 277 somatic neurons [4]. Multiple synaptic connections between two neurons were merged to represent a single edge between them. Thus neuronal connectivity data were represented as a directed unweighted graph, where neurons represent nodes and synaptic connections represent links between them. We also constructed a random control of CeNN viz. Erdős-Rényi random control (ER) in which the number of nodes and edges were kept identical but wiring pattern was randomized [15]. Among topological properties of CeNN, we computed clustering coefficient and characteristic path-length which represent global features of the network [5, 9].

2.2 Analysis of Motifs

Network sub-structures that are significantly over-represented in networks compared to their random counterparts are known as motifs [6]. Some of these motifs are known to be of functional significance to the system [6, 12, 16]. A directed binary graph can have 13 types of three node sub-structures. These three node sub-graphs could further be divided into angular and triangular motifs. Angular motifs are linear three node sub-structures, whereas triangular motifs comprise of three nodes sub-graphs with either unidirectional or bidirectional edges. Following the methodology of Milo *et al.*, we computed the number of sub-structures and their over-representation using $Z\text{-score} = \frac{\mathrm{X}-\mu}{\sigma}$ [6].

2.3 Number of Driver Neurons

In a network where every node can be in one of the multiple states, it has been shown that the state of the network can be controlled with the help of driver nodes [7, 11, 17]. Aligned with this notion, driver neurons are those neurons which when controlled with an external input can provide full control over the state of the network [7]. Due to their role in control of network 'number of driver neurons' (D_n) are of functional relevance to the neuronal network [11]. To find the minimum number of driver neurons we used maximum matching criterion [7]. A pair of edges were matched if they share start and end nodes [18]. A node is said to be matching if any matching edge points towards it and is unmatched if no matching edge is directed towards it.

2.4 Motif Tuning Algorithm

Feed forward motifs are three neuron sub-graphs composed of two input neurons, one of which regulates the other and both jointly regulating a third target neuron. FFMs are known to be of critical functional relevance for CeNN [6]. To observe the effect of increase/decrease (MTA +/MTA-) of FFMs on controllability of CeNN, we devised a Motif Tuning Algorithm (MTA). This strategy achieves maximum increase/decrease in the number of FFMs (n_{FFM}) with minimal rewiring. Starting from a random neuron in CeNN, MTA looks for a three node linear chain $(A \rightarrow B \rightarrow C)$. In case of finding such a linear chain, it adds a feed-forward link from $A \rightarrow C$ if it doesn't exist already. To preserve the number of edges, it removes an edge randomly from the network, while ensuring the connectedness of CeNN. An inverse procedure of searching for an FFM and removing the feed-forward link was implemented to decrease the number of motifs. The detailed logic of motif tuning algorithm is depicted in Fig. 1. Through monotonous increase/decrease of number of FFMs, MTA achieves the desired tuning of motifs in the network. The motif tuning was implemented enough number of times till the saturation of the number of FFMs.

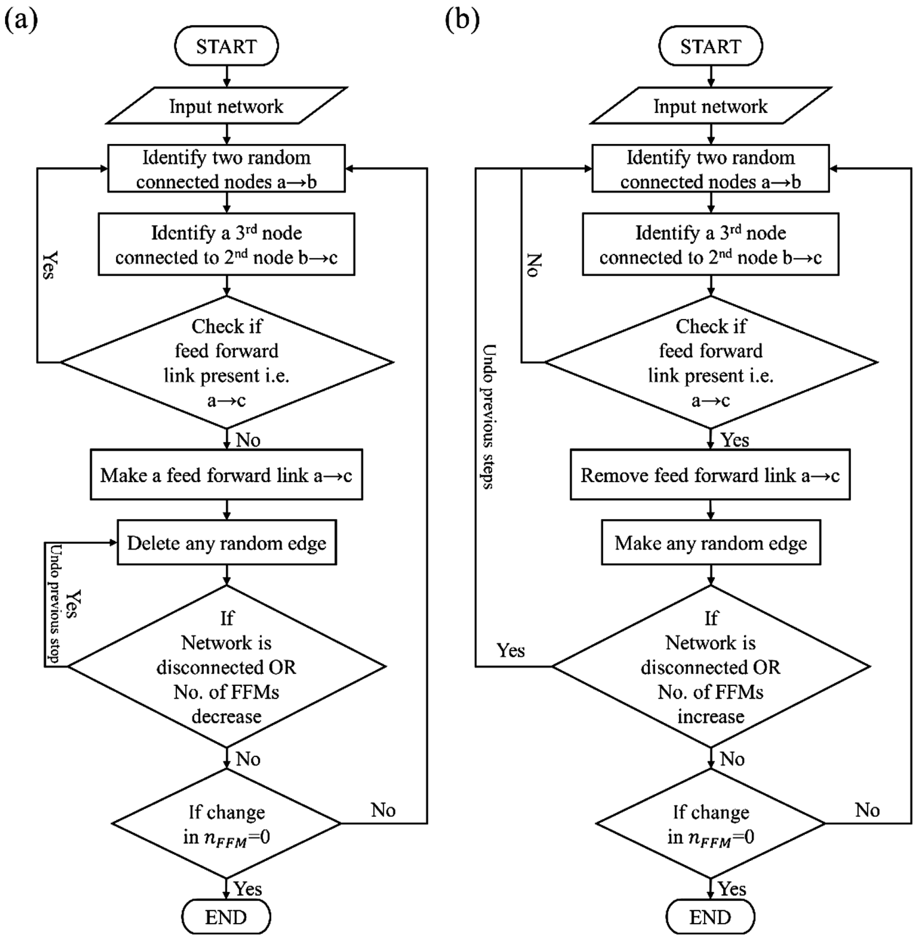

Fig. 1. Motif tuning algorithm. Strategy implemented to (a) increase and to (b) decrease the number of feed-forward motifs.

2.5 Strategies for Synaptic Rewiring

Two types of strategies were implemented for simulating the synaptic rewiring: (a) Random rewiring and (b) Distance constrained rewiring (DC).

(a) **Random Rewiring:** In this strategy it was assumed that, neurons rewire completely randomly under the influence of synaptic plasticity. Every synapse was swapped randomly without affecting the number of nodes and edges [15].

(b) **Distance Constrained Rewiring:** In this strategy, while maintaining the number of synapses of each neuron, the synapses were rewired such that the probability of two neurons being connected to each other is proportional to $d^{-\beta}$, where d is the distance between two nodes and β is the distance constrain parameter. Despite randomization of synapses, this strategy imposes a power law distance constraint.

3 Results and Discussion

A networked entity could be studied as a linear time invariant system to assess its control architecture. A system could have centralized control with a small number of nodes critical for driving its dynamics. The structural features of CeNN could be probed at the coarse grained as well as fine grained levels to adjudge their connection to control of the system. We investigated the control response of CeNN for change in in number of feed-forward motifs to identify rewiring mechanisms that render it robust.

3.1 Topological Properties of CeNN

CeNN encodes the structural and functional correlates of the neuronal wiring of *C. elegans* which are reflected in its topological features. These features could be enumerated at coarse-grained level as well as at a fine-grained level. Consistent with previous observations [5, 9, 11, 19, 20], we found that *C. elegans* neuronal network is a small world network by virtue of high average clustering coefficient ($\bar{C} = 0.172$) and small characteristic path length ($L = 4.02$), when compared to its randomized counterpart ($\overline{C_{rand}} = 0.028 \pm 0.001$ and $L_{rand} = 2.97 \pm 0.01$).

CeNN is characterized with a distributed control architecture with higher number of driver neurons compared to its random control. Knowing that driver neurons are of biological significance to *C. elegans* [11] and that CeNN is over represented with feed-forward motifs (Fig. 2) [6], we investigated their interrelationship that could be of central importance for control of CeNN.

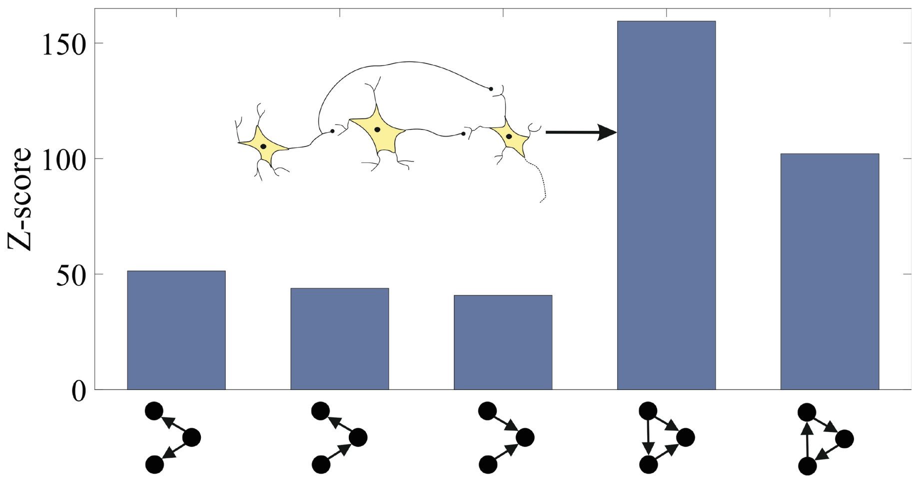

Fig. 2. Feed-forward motifs are significantly over-represented in CeNN, followed by feedback motifs, as measured in terms of Z-score against a background of random networks.

CeNN has significantly large number of driver neurons ($D_n = 34$) compared to that of its randomized counterpart (0.26 ± 0.44). Connectivity of neurons is one of the key factors in specification of number of driver neurons, as preservation of degree distribution leads to its increases (22.38 ± 1.15) [7, 11]. Driver neurons in CeNN are genotypically and phenotypically associated with various functions such as reproduction and maintenance of cellular processes of the organism [11]. CeNN is characterized with distributed control with a large number of driver neurons [8]. Synaptic rewiring, a common features in neuronal systems, could alter the motif saturation in CeNN with repercussions for control mechanisms. To probe the response of CeNN with increase/decrease of FFMs, we devised the motif tuning algorithm.

3.2 CeNN Shows Sigmoidal Controllability Response with Change in FFMs

We used motif tuning algorithm (see Methods) to simulate monotonous increase/decrease in number of FFMs due to synaptic plasticity. Interestingly, we observed that the CeNN shows an asymmetric, sigmoidal response with a clear division between a robust regime in which the number driver neurons (hence, the distributed control) is maintained with monotonic increase in FFMs, and a fragile regime in which it rapidly loses the distributed control with decrease in FFMs (Fig. 3). This implies that to maintain the distributed control (through large number of driver neurons), the neuronal system would need to maintain the number of FFMs. Prevalence of certain connectivity patterns is associated with evolution and development [21]. Starting from the random counterpart of CeNN, systematic monotonic increase/decrease was found to have no

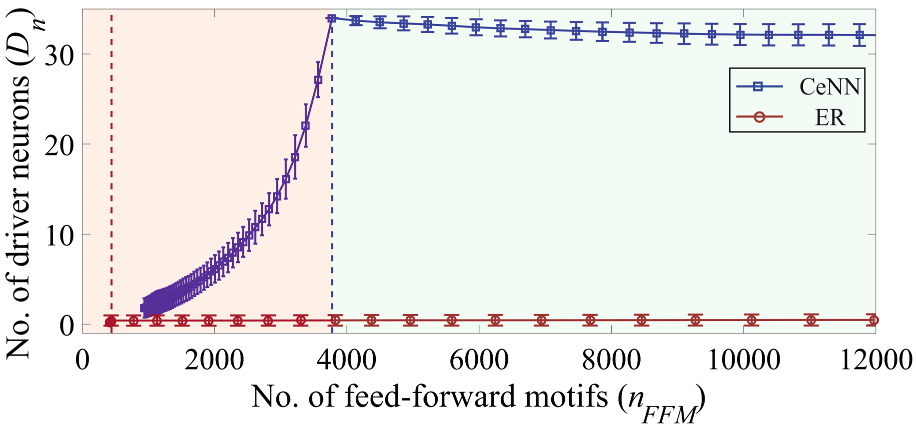

Fig. 3. Asymmetric controllability response (enumerated with the number of driver neurons, D_n) of *C. elegans* neuronal network with monotonic increase/decrease in number of FFMs (n_{FFM}). The random control (ER), on the other hand, does not show any change in D_n. This implies that while CeNN exhibits robust control response to systematic increase in FFMs, it is extremely sensitive to systematic depletion of FFMs. Dashed lines represent the starting points for the models. Error bars indicate standard deviation over 1000 instances.

impact on number of driver nodes (Fig. 3), indicating that neuronal architecture of *C. elegans* has evolved to achieve an optimum structure with distributed control as well as asymmetric response to change in number of key network motifs (FFMs).

Aligned with our observations, we hypothesize that the synaptic rewiring mechanisms in *C. elegans* must have adapted a robust strategy to avoid depletion of FFMs, and hence to maintain distributed control. Rooted in our distance constraint synaptic plasticity model [9], we propose that the mechanisms of synaptic rewiring are not random, but are dictated by distance constraint. We investigated effect of random rewiring versus distance constrained rewiring on change in number of feed-forward motifs (Δn_{FFM}), for which the network control was found to have sensitive dependence (Fig. 3).

3.3 Response of CeNN to Random Versus Distance Constrained Rewiring

Neuronal networks evolving under cognitive stresses show a remarkable property of forming new synapse and deleting older obsolete ones known as neuronal rewiring [22]. To simulate neuronal plasticity in CeNN we implemented different strategies to identify the best strategy the system may have evolved.

To assess the control response of different kind of rewiring mechanisms (MTA+, MTA−, random and distance constrained), we measured the change in number of feedforward motifs for every step of rewiring, Δn_{FFM} (Fig. 4). Positive value of Δn_{FFM} indicates that such a mechanism yields robust control response by maintaining the number of driver neurons (see Fig. 3). On the contrary, negative values suggest fragile response. This is corroborated by observations made with MTA + and MTA- rewiring strategies. MTA + and MTA- are artificial strategies implementing monotonous increase and decrease of FFMs, respectively. While the rewiring mechanisms of CeNN are not expected to follow such artificial processes, any process the brain network may have evolved is expected to show robust controllability response.

Random Rewiring

The easiest way to simulate a natural phenomenon, such as synaptic rewiring, is to assume that it is dictated by random processes. We observed that random rewiring is expected to induce loss of FFMs over time, hence is fragile (Fig. 4). Such a strategy is also expected to cause loss of clustering, an important topological feature which renders the network small-world [5, 9]. Randomized synaptic rewiring has been reported to result in loss of number of driver neurons as well as FFMs [9]. Hence, we conclude that such a mechanism could not have evolved through natural selection as it yields loss of structurally important features as well as leads to fragile control response.

Distance Constrained Rewiring

The neuronal connectivity of CeNN is known to follow a scale free distribution suggesting a deviation from random connectivity pattern [23, 24]. Further, it is also observed that, in this spatially laid network, distance between two neurons is critical in specifying probability of they being connected with a synapse [9]. The probability of two neurons being linked with each other, interestingly, decreases as a power law. This suggests that while increasing distance between neurons is a constraint in their

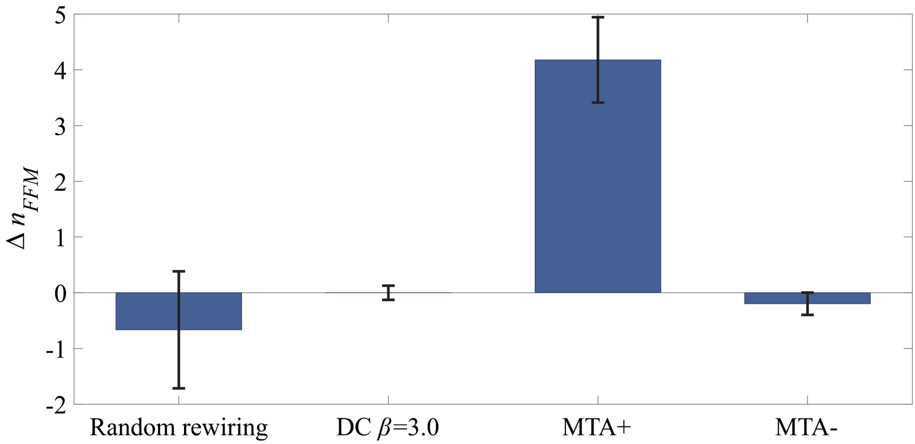

Fig. 4. Change in n_{FFM} per rewiring for different strategies. DC and MTA + show a positive Δn_{FFM}, whereas random and MTA- were presented with negative Δn_{FFM}. This implies that MTA + and distance constrained rewiring induce robust response.

connection, it still allows for more number of neuronal connections than expected by exponential decay. Such a distance constraint has also been reported to be central in determining the location of neurons in the body of organism [25–27].

With this premise, we modeled the synaptic rewiring in CeNN following the power law distance constraint. In this model every neuron maintains its connections (degree) and every synapse is rewired following power law distribution, $P(k) \sim k^{-\beta}$. We implemented the model for varying values of the exponent $\beta (0 \leq \beta \leq 3)$, such that with increasing value of β, chances of observing a synaptic connection are higher for a given distance between neurons. We find that distance constrained rewiring is expected to maintain the FFMs yielding robust response, unlike random rewiring (Fig. 4, DC for $\beta = 3$).

To further probe the response to distance constrained rewiring, we studied the change in number of FFMs (n_{FFM}) and number of driver nodes (D_n) with increasing number of rewiring for different values of exponent β (Fig. 5(a) and (b)). We also computed the average change in number of FFMs (Δn_{FFM}) with changing β (Fig. 5(c)). Consistent with the observation made from Fig. 4, we find that number of FFMs drops marginally regardless of the value of exponent, with better response observed for higher values of β (Fig. 5(a)). Despite large number of rewirings, the number of driver nodes is preserved to maintain the distributed control (Fig. 5(b)). The performance improves with increasing values of β, suggesting that following a strong power law in synaptic rewiring promotes robust controllability response.

In summary, we investigated the control response of CeNN, measured in terms of the number of driver neurons, with varying number of FFMs known to be of functional relevance. By implementing MTA, we surmise that monotonous increase or decrease of FFMs shows an interesting asymmetric, sigmoidal response divided into robust and fragile regimes, respectively. We find that, while random synaptic rewiring would lead to fragile control response, distance constrained rewiring is expected to yield robust response.

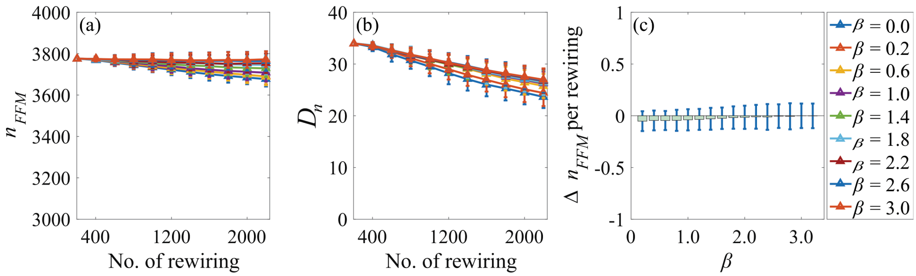

Fig. 5. Robust control response of CeNN under distance constrained rewiring. (a) With increasing extent of rewiring, the number of FFMs are preserved. The stronger the constraint, the better is the response. (b) Correspondingly, the number of driver nodes is preserved with distance constrained rewiring. (c) With increasing power law exponent the average change in number of FFMs (Δn_{FFM}) is diminished.

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