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Robust sigmoidal control response of *C. elegans* neuronal network

Biological systems are known to evolve mechanisms for acquiring robust response under uncertainty. Brain networks are characterized with non-trivial, system specific topological features, on global as well as local level, that are key to their function and control [Sporns, 2011]. Typical to a complex adaptive system, the neuronal map is known to be plastic, and undergoes synaptic rewiring [E.R. Kandel et al., 2000]. 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, the most complete neuronal wiring diagram available till date [Choe et al., 2004; White et al., 1986]. CeNN is a small world network, characterized with over-representation of feed-forward motifs (FFMs) and distributed control architecture [Jia et al., 2013; Y.-Y. Liu et al., 2011; R Milo et al., 2002; Watts and Strogatz, 1998]. FFMs represent functional building blocks of this system, a fine-grained feature that potentially gives rise to coarse-grained properties specifying network control [Badhwar and Bagler, 2017].

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 [Lin, 1974]. 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 [Y.-Y. Liu et al., 2011]. Lesser the number of inputs, the more centralized is the control [Jia et al., 2013].

CeNN is known to have distributed control with higher number of driver neurons than its random counterpart [Badhwar and Bagler, 2015; Jia et al., 2013; Y.-Y. Liu et al., 2011]. By studying genotypic and phenotypic aspects of this network, in our earlier study (Chapter 4) we have shown that 'driver neurons' are associated with important biological functions such as reproduction, signaling processes and anatomical structural development [Badhwar and Bagler, 2015]. The CeNN has been shown to have a bimodal control architecture which is sensitive to edge plasticity [Jia et al., 2013]. Synaptic plasticity can influence the number of driver neurons and hence control mechanisms of the neuronal network. Hence, we studied controllability response in CeNN with change in number of functionally important feed-forward motifs, due to synaptic rewiring. While the saturation of feed-forward motifs in CeNN is of functional consequence [Alon, 2007a; Mangan and Alon, 2003; R Milo et al., 2002], it is not clear whether the system optimizes for the number of FFMs.

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. 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'. We also find that the distance constrained synaptic rewiring can explain preservation of FFMs as well as robust controllability response of the network. 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.

6.1 MOTIF TUNING ALGORITHM (MTA)

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 [R Milo et al., 2002]. 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 Figure 6.1. 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.

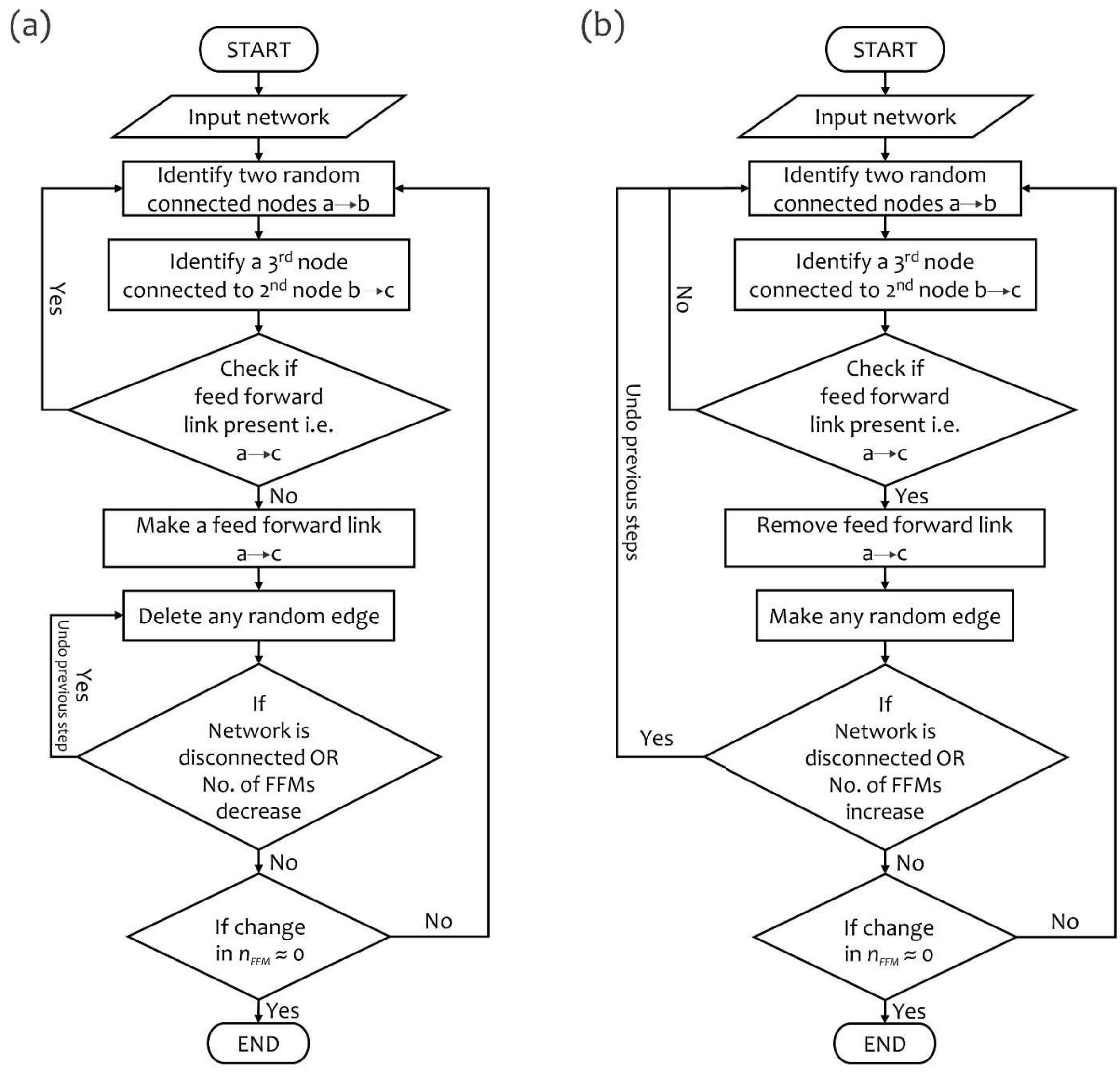

Figure 6.1 : Motif tuning algorithm. Strategy implemented to (a) increase, and to (b) decrease the number of feed-forward motifs.

6.2 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 [Erdös, P., 1984].

(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.

6.3 RESULTS

6.3.1 Distributed control architecture of CeNN

The structural features of CeNN could be probed at the coarse grained as well as fine grained levels to adjudge their connection to function and control of the system. Consistent with previous observations [Badhwar and Bagler, 2015, 2017; Chatterjee and Sinha, 2008; Pan et al., 2010; Watts and Strogatz, 1998], it was observed 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 $L_{rand} = 2.97 \pm 0.01$). This may have consequences for efficiency of neuronal communication and hence functioning of the organism.

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. On the other hand, it may have a distributed control requiring far too many nodes needed to be tapped for achieving desired system dynamics [Jia et al., 2013]. CeNN is characterized with a distributed control architecture with significantly large number of driver neurons ($D_n = 34$) compared to that of its randomized counterpart (0.26 ± 0.44) as discussed earlier in Chapter 4 and Chapter 5. Knowing that driver neurons are of biological significance to *C. elegans* [Badhwar and Bagler, 2015] and that CeNN is over-represented with feed-forward motifs (Figure 6.2) [R Milo et al., 2002], we investigated their interrelationship that could be of central importance for control of CeNN.

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) [Badhwar and Bagler, 2015; Y.-Y. Liu et al., 2011]. Driver neurons in CeNN are genotypically and phenotypically associated with various functions such as reproduction and maintenance of cellular processes of the organism [Badhwar and Bagler, 2015]. Synaptic rewiring, a common feature 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.

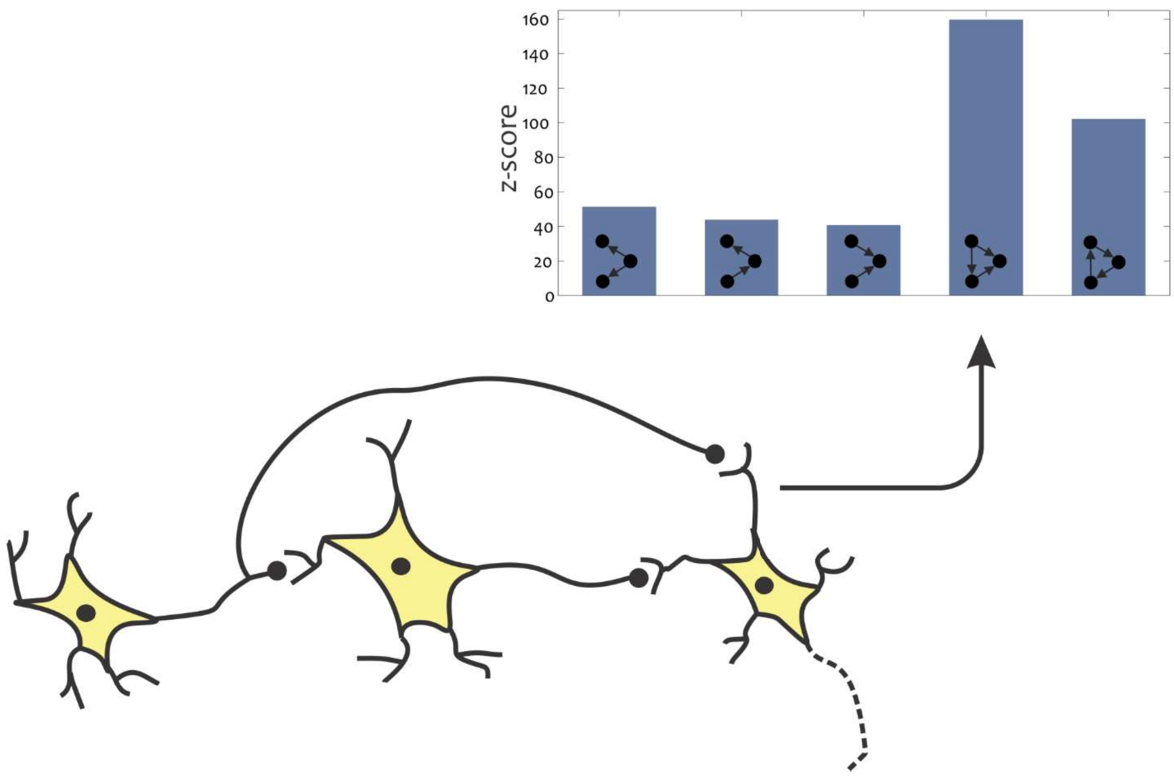

Figure 6.2 : Feed-forward motifs are significantly over-represented in CeNN, followed by feedback motifs, as measured in terms of Z-score against a background of random networks.

6.3.2 CeNN shows sigmoidal controllability response with change in FFMs

Prevalence of certain connectivity patterns is known to be associated with evolution and development of nervous system [MacKay, 1988]. We used motif tuning algorithm 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 (Figure 6.3). 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. Starting from the random counterpart of CeNN, systematic monotonic increase/decrease was found to have no impact on number of driver nodes (Figure 6.3), 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 the feed forward motifs.

Aligned with our observations, we hypothesize that the synaptic rewiring mechanisms in *C. elegans* must have adopted a robust strategy to avoid depletion of FFMs, and hence to maintain distributed control. Rooted in our distance constraint synaptic plasticity model [Badhwar and Bagler, 2017], 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 (Figure 6.3).

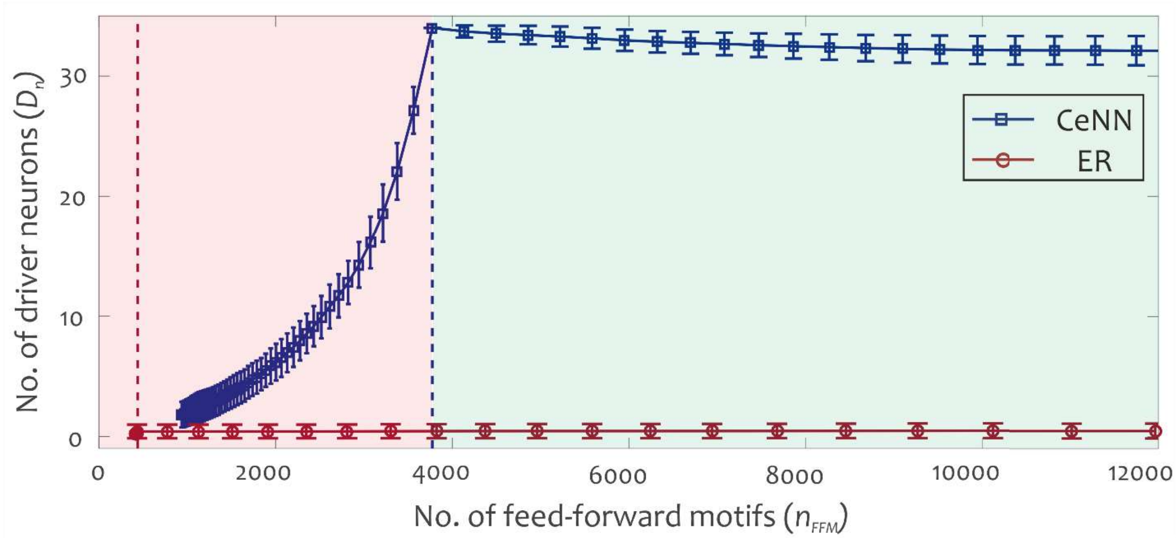

Figure 6.3 : Asymmetric controllability response (enumerated with the number of driver neurons, D_n) of *C. elegans* neuronal network with monotonic increase/decrease in number of FFMs (n_{FFM}). The random control (ER), on the other hand, does not show any change in D_n. This implies that while CeNN 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.

6.3.3 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 obsolete ones known as neuronal rewiring [Eric R Kandel et al., 2014]. 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} (Figure 6.4). Positive value of Δn_{FFM} indicates that such a mechanism yields robust control response by maintaining the number of driver neurons (see Figure 6.3). 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 (Figure 6.4). Such a strategy is also expected to cause loss of clustering, an important topological feature which renders the network small-world [Badhwar and Bagler, 2017; Watts and Strogatz, 1998]. Randomized synaptic rewiring has been reported to result in loss of number of driver neurons as well as FFMs [Badhwar and Bagler, 2017]. 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.

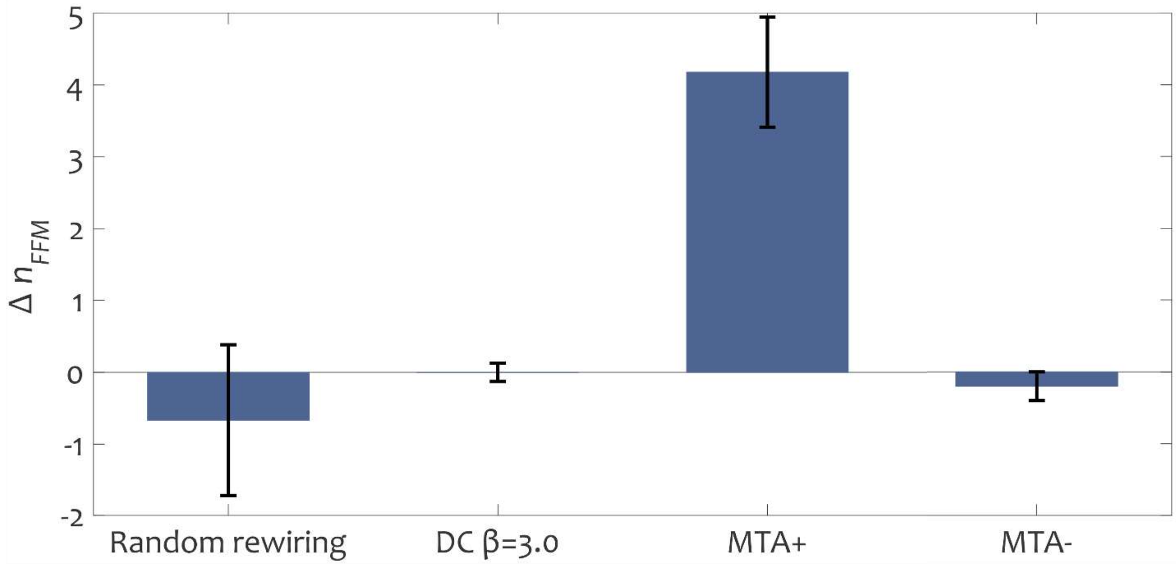

Figure 6.4 : Change in n_{FFM} per rewiring for different strategies. DC and MTA+ show a positive Δn_{FFM} whereas random and MTA- were presented with negative Δn_{FFM}. This implies that MTA+ and distance constrained rewiring lead to robust response.

Distance constrained rewiring

The neuronal connectivity of CeNN is known to follow a scale free distribution suggesting a deviation from random connectivity pattern [Esposito et al., 2014; Varshney, Chen, Paniagua, Hall, and Chklovskii, 2011]. 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 (Figure 5.5; Chapter 5) [Badhwar and Bagler, 2017]. 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 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 [Ahn et al., 2006; Beth L Chen et al., 2006; Gushchin and Tang, 2015].

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 $\beta(0 \le \beta \le 3)$, 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 (Figure 6.4, DC for β =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 (Figure 6.5(a) and Figure 6.5(b)). We also computed the average change in number of FFMs (Δn_{FFM}) with changing β (Figure 6.5(c)). Consistent with the observation made from Figure 6.4, we find that number of FFMs drops marginally regardless of the value of exponent, with better response observed for higher values of β (Figure 6.5(a)). Despite large number of rewirings, the number of driver nodes is preserved to maintain the distributed control (Figure 6.5(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.

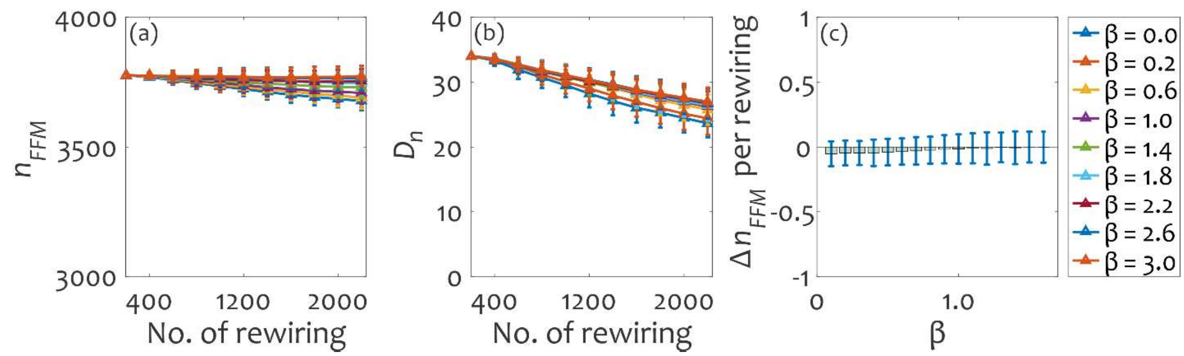

Figure 6.5 : Robust control response of CeNN under distance constrained rewiring. (a) With increasing extent of rewiring, the number of FFMs are preserved. The stronger the constraint, the better is the response. (b) Correspondingly, the number of driver nodes is preserved with distance constrained rewiring. (c) With increasing power law exponent the variation in number of FFMs (Δn_{FFM}) is diminished.

6.4 DISCUSSION

The neuronal network of *C. elegans* is responsible for various cognitive functions in this organism, including learning and memory [Ardiel and Rankin, 2010]. Functions associated to memory are important for survival and reproduction of any organism. It has been observed that specialized neuronal network structures can play a major role in basic functions including long term potentiation of reflex actions [Azulay et al., 2016; Mozzachiodi and Byrne, 2010]. This highlights the role of basic structural units that could lend important functions [R Milo et al., 2002]. Feed forward motifs are one of the critical motifs known to be over-represented and suggested to be of functional relevance in CeNN [Azulay et al., 2016; R Milo et al., 2002]. Previous studies have shown the importance of such substructures by associating them with network functions [Alon, 2007a; Azulay et al., 2016; Mangan and Alon, 2003; Miller, Feng, Li, and Rabitz, 2012; R Milo et al., 2002].

Plasticity is a natural evolutionary mechanism in neuronal networks acquired over the period of evolution and development of organism. Knowing the potential importance of FFMs to the organism, it is natural to expect that change in their numbers, due to synaptic plasticity, could affect the function of the network [Badhwar and Bagler, 2017]. In this study we probed the controllability response (measured in terms of 'number of driver neurons') with change in driver neurons that could be attributed to synaptic rewiring. Towards this we designed an algorithm (Motif Tuning Algorithm) that simulated rewiring leading to systematic population or depletion of FFMs. We also developed computational strategies to mimic random as well as distance constrained rewiring.

Interestingly, we observed that CeNN responds in a contrasting manner to systematic increase/decrease of FFMs, with a sigmoidal response, suggesting a corresponding robust/fragile control response. Random rewiring is expected to lead to depletion of FFMs (fragile control response). Hence to maintain the number of driver neurons, the worm must have adopted a non-random rewiring strategy. From our earlier studies (Chapter 5) we know that CeNN follows a distance constrained synaptic connectivity [Badhwar and Bagler, 2017; Y.-Y. Liu et al., 2011]. A distance constrained rewiring strategy was implemented, which unlike the random rewiring, was found to lead to robust control response. We propose that *C. elegans* would have evolved distance constrained rewiring mechanism with implications for controllability of its neuronal network. Our studies open up possibilities of experimental studies to investigate the role of synaptic rewiring mechanisms in specifying function.

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