

MODELING THE NEURAL ACTIVITY OF CAENORHABDITIS ELEGANS THROUGH NEURAL MESSAGE PASSING

MODELACIÓN DE LA ACTIVIDAD NEURONAL DEL CAENORHABDITIS ELEGANS MEDIANTE ALGORITMOS DE TRASMISIÓN DE MENSAJES

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The great complexity of the human connectome motivates the study of a simpler neural network. For that purpose, the Ising Model was applied on experimental data on the synaptic connectivity of *Caenorhabditis elegans* (*C. elegans*) in resting-state, assigning a binary variable (representing active or inactive states) to each neuron in the network. The dynamics of this system is postulated as a message passing network, encoded by the Belief Propagation algorithm (BP) in its criticality region. The inferences of neuronal activity maps were obtained for different times of the nematode's life cycle. We determined the network susceptibilities as a measure of correlations in the system through the Susceptibility Propagation algorithm (SP). Finally, we applied clustering methods to obtain functional clusters and analyze similarities between them and the real functional clusters (sensory, interneurons and motor). All this contributed to the analysis of structure-function relationship in the *C. elegans* neural network.

La gran complejidad del cerebro humano incentiva el estudio de una red neuronal mucho más simple. Para eso, se aplicó el modelo de Ising sobre datos experimentales de la conectividad sináptica del *Caenorhabditis elegans* en estado de reposo, asignándole a cada neurona de la red un comportamiento binario (activo o inactivo). La dinámica de este sistema se postula como una red de transmisión de mensajes dada por el algoritmo Belief Propagation (BP) en su región de criticalidad. Se obtuvieron mapas de inferencia de actividad neuronal para diferentes tiempos del ciclo de vida del nematodo. Además, determinamos las susceptibilidades de la red como medida de las correlaciones del sistema a través del algoritmo Susceptibility Propagation (SP). Finalmente, aplicamos métodos de clustering para inferir módulos funcionales en la red y analizar semejanzas entre estos y los módulos funcionales reales (sensoriales, inter-neuronas y motores). Todo esto contribuyó al análisis de la relación estructura-función en la red neuronal del *C. elegans*.

PACS: Neural networks (redes neurales), 87.18.Sn; Criticality of glass transitions (Criticalidad en transiciones vítreas), 64.70.qj; Ising model (Modelo de Ising), 05.50.+q; Biological complexity (Complejidad biológica), 87.18.-h.

I. INTRODUCTION

C. elegans is a small and transparent nematode worm; just under a millimeter long [1, 2]. Thanks to its simplicity (959 cells, 302 of which are neurons) and its simultaneous complexity (it shares many systems and structures with other complex animals) [3], *C. elegans* has become one of the most used models in neurobiology. Each neuron of the nematode has a specific function assigned [4] and the synaptic connectivity network between these neurons is already known [5].

With this information several studies have attempted to model the neural activity of *C. elegans*, including approaches based on differential equations, agent-based models, and machine learning techniques [6, 7]. However, they often suffer from limitations such as: high computational complexity, difficulty in parameter tuning, and lack of interpretability. In this paper, we propose a novel approach to modeling the neural activity of *C. elegans* using message passing algorithms. Message passing algorithms are a class of algorithms that allow for efficient computation on graph structures, making them well-suited for modeling neural networks.

Our approach starts defining, from the synaptic connectivity matrix, a graph representation of the *C. elegans* neural

network and applying message passing algorithms to simulate the activity of the network as a whole. In practice, we use in the vicinity of the critical point the message passing algorithm, Belief Propagation (BP) to quantify the activity of each neuron in the different phases of the organism's development. We also compute the response function between the different nodes in the network (susceptibilities) using another message passing technique, Susceptibility Propagation [8], as in reference [9]. Finally, we show that the information provided by this response function is a good proxy to classify the functionality of the neurons [10].

II. METHODS

C. elegans

Current experimental data about the nematode's nervous system contains information on the births times and spatial coordinates of the 279 neurons. Moreover, it also provides the synaptic connections weights (directed links) assigned to every neural pair [5]. This information is enough to generate direct graphs or networks, at different moments of the evolution of the nematode, where the vertices are the *C. elegans* neurons and the links are encoded by its synaptic connectivity matrix J .

For example, Fig. 1 is a representation of the actual positions of all the neurons scattered throughout the body of the nematode in its adult state. These neurons are identified by colours, assigned according to the functions they perform in the system. Sensory neurons are shown in red, inter neurons in yellow and motor neurons in blue.

Neurons appear at different times during the whole development of the nematode. This is represented in Fig. 2. There we see that neurons are born mainly in two time stages: one, very short, called embryonic burst; and a larval or embryonic phase larger than the first, that starts with the hatching (840 minutes) and finishes when the nematode becomes an adult worm. As can be seen in the graph, after hatching there is a time interval where neuronal growth stops. This could correspond to a laboratory-induced hibernation phase, where the nematode is able to freeze its metabolic processes.

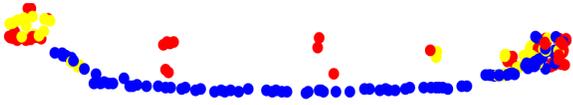


Figure 1. Red-sensory, yellow-inter-neurons, blue-motor. Functional classification of the *C. elegans* neurons according to experimental data for the nematode in its adult state.

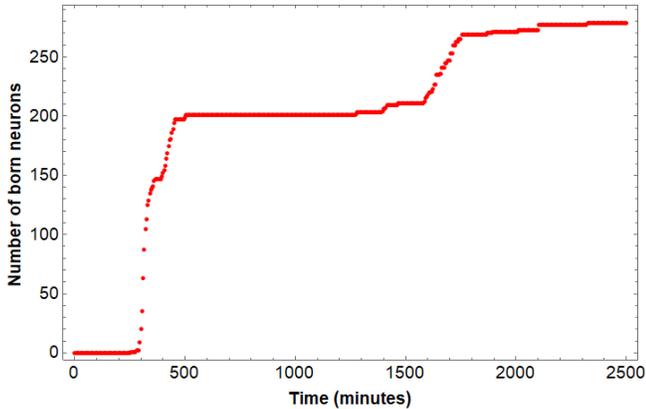


Figure 2. Neurons births during the developmental cycle of *C. elegans*

Notice moreover, that while we have access to the connectivity matrix in the late stage of development of the nematode, this information is not present during the growth of *C. elegans*. Therefore, in what follows we assume that once two neurons are present at time t , they are connected with the same connectivity strength that the adulthood of the worm. This is a strong assumption during the nematode's development.

The model

To model the dynamic activity of the *C. elegans* neural network we map it to a binary system of interacting variables in the spirit of the Ising model [9, 11, 12]. Variables have two possible values $s_i \in \{1, -1\}$ attributed to the electrical activity for each neuron (node) i of the structural network [9, 10, 13]. In practice, $s_i = 1$ means that the neuron is "on" or activated and $s_i = -1$ implies that the neuron is "off" or inactivated. Moreover, every pair of nodes (i, j) interacts with intensity J_{ij} , encoded by the synaptic connectivity matrix [5].

In short, for a specific configuration $\{s_i\}_{i=1, \dots, 279}$ the interaction occurs according to an energy function:

$$H\{s_i\} = - \sum_{i < j} J_{ij} s_i s_j - \sum_i h_i s_i \quad (1)$$

where in general h_i is the external field on the i^{th} spin and represents the presence of an external stimulus. However, in the rest of this work h_i is set to zero, mimicking the neural activity in the absence of external stimuli. To solve this problem numerically we use Belief Propagation and Susceptibility Propagation, two message passing algorithms that were previously exploited to study the human brain [9].

Belief Propagation

Message passing algorithms are computationally cheap alternatives of the Monte-Carlo method [14]. One of these efficient algorithms is Belief Propagation (BP). It is easy to program, and known to be exact in random graphs. Here it is employed to infer the stationary values or *beliefs* b_i of the electrical activity intensity of each neuron i after convergence [15].

Within this algorithm, we consider that the dynamics of the system is described by the transmission and reception of messages m_{ji} between the neurons (i, j) . Therefore, $m_{ji}(s_i)$ can take values between 0 and 1 and is interpreted as the probability, that according to j , i is in the state s_i . The probability, $m_{ji}(s_i)$ depends on the state of node i (s_i), the synaptic connectivity between them (J_{ij}) and the messages that j received from each of its neighbors other than i :

$$m_{ji}(s_i) = k \sum_{s_j} e^{\beta(J_{ji}s_i s_j + h_j s_j)} \prod_{l \in N(j) \setminus i} m_{lj}(s_l) \quad (2)$$

where k is a normalization constant, h_j is the external field over node j ($h_j = 0$ for every node in our system), $N(j) \setminus i$ refers to the set of neighbors of node j , excluding neighbor i . The parameter β is the inverse of the temperature T of the system and is a measure of the noise in the system.

The algorithm consists of iterating the eq. (2) over each edge in the network until the messages converge to a fixed point (the equilibrium configuration). In our case this convergence was achieved when the maximum relative variation of the messages between one iteration cycle and another was lower than $\delta_{max} = 10^{-7}$. Once BP converges to the fixed point, the *belief* of each node of the network is obtained. These results constitute the equilibrium values for the probabilities of each neuron to be active or inactive. We then calculate the magnetization m_i corresponding to each neuron i by means of the equation $m_i = b_i(+1) - b_i(-1)$, a measure of the activity in the system.

Susceptibility Propagation

Susceptibility Propagation (SP) is an extension of Belief Propagation. It is very useful in the reconstruction of neural networks, when solving the inverse Ising problem. In this

work, it was implemented to solve the direct problem, i.e., to infer the response (or magnetic susceptibilities χ_{ij}) between two nodes (i, j).

In short, we start by writing the equations of BP for the messages $m_{ji}(s_i)$ in an alternative way:

$$m_{ji}(s_i) = q_{ji}(s_i) = k \sum_{s_j} e^{\beta J_{ji} s_i s_j} p_{ji}(s_j), \quad (3)$$

where the messages $p_{ji}(s_j)$ are defined as those containing the influence of local external fields, as:

$$p_{ji}(s_j) = e^{\beta h_j s_j} \prod_{l \in N(j) \setminus i} q_{lj}(s_j) \quad (4)$$

If we use likelihood logarithmic notation to rewrite the eq. 3 and 4, we have:

$$h_{ij}(s_i) = \frac{1}{2} \log \frac{p_{ij}(+1)}{p_{ij}(-1)} \quad (5)$$

$$u_{ij}(s_i) = \frac{1}{2} \log \frac{q_{ij}(+1)}{q_{ij}(-1)} \quad (6)$$

We define new messages $g_{ij,k}$ and $v_{ij,k}$ as the derivatives of h_{ij} and u_{ij} , with respect to the local field h_j :

$$g_{ij,k} = \frac{\partial h_{ij}}{\partial h_k} \quad \text{and} \quad v_{ij,k} = \frac{\partial u_{ij}}{\partial h_k} \quad (7)$$

Then, there are two equations to be iterated:

$$g_{ij,k} = \beta \delta_{ik} + \sum_{l \in N(i) \setminus j} v_{li,k} \quad (8)$$

$$v_{ij,k} = g_{ij,k} \tanh(\beta J_{ij}) \frac{1 - \tanh^2(h_{ij})}{1 - \tanh^2(u_{ij})} \quad (9)$$

Once the messages have converged the susceptibilities of the system are then calculated using:

$$\chi_{ij} = \left(\beta \delta_{ij} + \sum_{l \in N(i)} v_{li,j} \right) (1 - m_i^2) \quad (10)$$

where m_i is the magnetization computed with BP.

Here the susceptibilities can be interpreted as the influences exerted by the local field acting on a node on the magnetization of other nodes [8]. In this work we were interested in the properties of resting-state network, therefore all the computations were done in the limit of small fields.

III. RESULTS

Fig. 3 shows the results of calculating, using BP, the average magnetizations of the network for different temperatures, at significant times during the development of the nematode.

The critical temperature is an important parameter in the characterization of the real network. The intuition is that around this region, the neurons have long range correlations and therefore that this is the temperature at which the system works. Far away from the critical temperature either all neurons behave in the same way (high global magnetization, $m = 1$), or they behave randomly (low global magnetization, $m = 0$), in these cases there is no flux of information through the network. Therefore, from now on, we will focus our attention on the behavior of the model near the critical temperature [12].

Fig. 4 shows, in more detail how this critical temperature changes as a function of the actual time at which the neurons are born. One can see some jumps reflecting the abrupt variations in the neuronal birth and also intervals where the function remains constant, during this time intervals the system remains identical (no neurons were born).

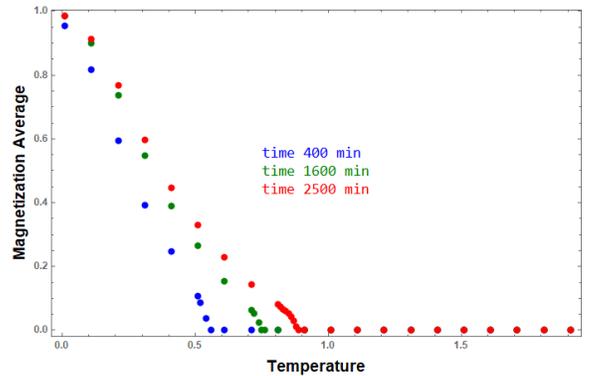


Figure 3. Variation of mean magnetization with temperature at different times of the nematode development cycle.

The information provided by Fig. 3 and 5a suggests that the changes in the critical temperatures are directly related to variations in the number of neurons. Furthermore, the Fig. 5b indicates a nearly linear dependence between these two quantities. This dependence is shown in the graph in 4b.

From now on we concentrate our efforts in studying the resting-state activation map, in adult state, and near T_c [9, 10]. In Fig. 5 the intensity of the red color indicates how likely it is that the neuron is activated. The neurons colored grey have the lowest magnetizations. This indicates that these neurons can be found on or off indistinctly, since the probability that they assume one of the two states is similar to the probability of finding them in the alternative state.

If we compare this activation maps with their functionality (Fig. 1) we may notice that gray neurons in Fig. 5 seem to

correspond to sensory neurons, that is, to those neurons that in resting state do not have a preferential on or off state.

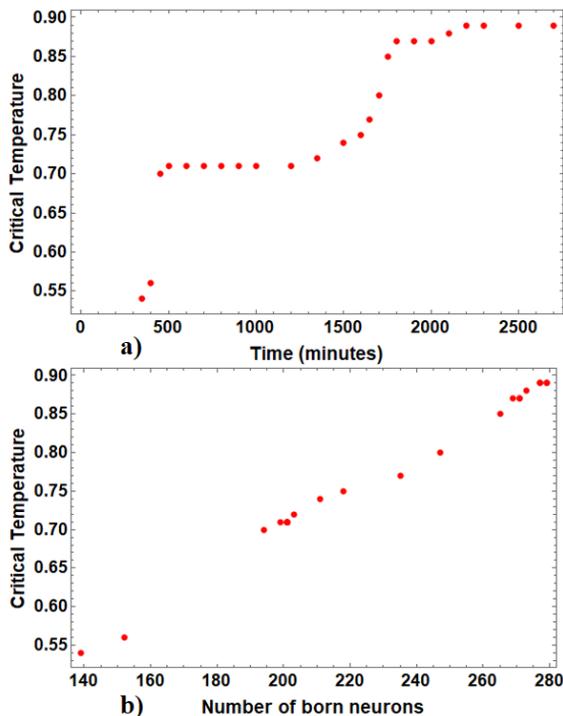


Figure 4. Behavior of critical temperature of *C. elegans* neural network. a). Variation of the critical temperature over time. b) Variation of the critical temperature with the number of born neurons. An approximately linear behavior is observed.

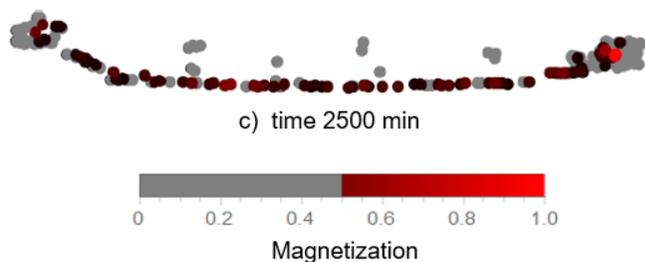


Figure 5. Magnetization of neurons in the neighborhood of critical temperatures for the adult nematode ($time = 2500 \text{ min}$). The intensity of the red color is proportional to the intensity of activation of the neurons.

With this qualitative results the next goal is to infer, from the information of the system, the functional modules in the nematode neural network. To this aim we first run SP and compute the response functions. Then, we perform three different clustering: one where the clusters of neurons were randomly constructed (null hypothesis); another generated from the synaptic connectivity matrix J , which is associated with the structural network; and a third clustering constructed from the susceptibility matrix of the system χ .

The clusterings were obtained using the *greedy_modularity* function of the Python clustering package. This function is based on the hierarchical clustering algorithm and maximizes the modularity of the network [17]. All the clusterings were performed with the same conditions (same parameters handed to the function). The comparison with the real functional character of the neurons are shown in the similarity matrices represented in figures 6.b and 6.c, respectively.

The similarity matrix obtained from the random clustering (see 6a) shows a remarkable homogeneity. This indicates that the random partitions are not related to the functionality. Logically, a null hypothesis can not provide information about the function in the system. The contrary happens when the clustering is done using J and χ . Both departure from the null hypothesis, but the best coincidence between the clustering and the actual function of the neurons is provided by the clustering made using susceptibilities. In particular, it gives a very good estimate of the sensory and motor communities. This can be seen more directly in Fig. 7 where we assign to the neurons belonging to each cluster the same colour of the analogous community in the true (experimental) clustering: red-sensory, blue-motor and yellow-interneuron. One must notice that the difficulty in predicting the inter-neurons is not surprising, on one hand their functionality is not as well-defined as the one of sensory and motor neurons, on the other, they may well suffer from changes in their functionality during the developmental cycle of the system.

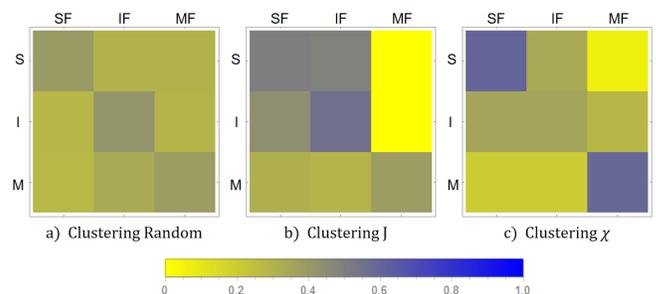


Figure 6. Similarity matrixes between real functionality modules and modules found. a) Random choice b) By clustering from J c) By clustering from χ . The rows represent the real modules of functionality and the columns represent the modules found, always sorted into sensory, inter-neuron and motor. The color scale is directly proportional to the number of coincidences between predicted and real partitionings. A blue square in the position (i, j) of the matrix indicates that the real cluster i and the "found" cluster j share a large number of nodes, while a yellow square means the opposite.

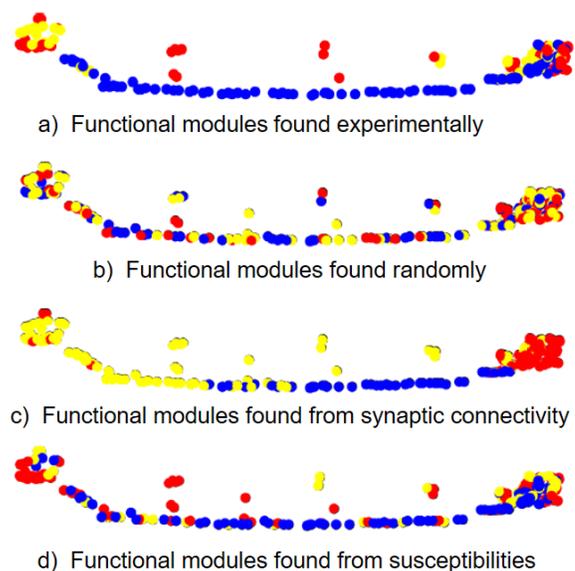


Figure 7. Functional modularity (red-sensory, yellow-inter-neuron, blue-motor) obtained from a) experimental data b) a random distribution c) the structural neural network, encoded by the matrix of synaptic connectivity J d) the matrix of susceptibilities of the system χ .

IV. CONCLUSIONS

In this work we modeled the neural activity of the *C. elegans* as binary interacting variables whose dynamics is governed by message passing algorithms. We postulate, as is usual for these systems, that the dynamics occurs at a fixed critical temperature (T_c), reflecting the noise in the system.

The results of our simulations suggest that both Belief Propagation and Susceptibility Propagation can be used as proper proxies to describe the functionality of the neurons of *C. elegans*. The results of BP near the critical temperature indicate that in the absence of external stimuli sensory neurons are not activated. Moreover, the clustering obtained from the susceptibilities matrix χ computed with SP represents the known functional character of the neurons better than the connectivity matrix.

This work may be extended in various directions. For instance, the same techniques can be used in the presence of external stimuli, and the predictions can be compared with those that could be derived from more realistic dynamics in the nervous system.

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