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Multilayer adaptive networks in neuronal processing

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Abstract. The connectome is a wiring diagram mapping all the neural connections in the brain. At the cellular level, it provides a map of the neurons and synapses within a part or all of the brain of an organism. In recent years, significant advances have been made in the study of the connectome via network science and graph theory. This analysis is fundamental to understand neurotransmission (fast synaptic transmission) networks. However, neurons use other forms of communication as neuromodulation that, instead of conveying excitation or inhibition, change neuronal and synaptic properties. This additional neuromodulatory layers condition and reconfigure the connectome. In this paper, we propose that multilayer adaptive networks, in which different synaptic and neurochemical layers interact, are the appropriate framework to explain neuronal processing. Then, we describe a simplified multilayer adaptive network model that accounts for these extra-layers of interaction and analyse the emergence of interesting computational capabilities.

1 Introduction

In the last years considerable efforts are being dedicated to provide insights into neural circuits in what has been called the connectome [1–4]. The connectome is a map of neural connections in the brain and may be thought of as its “wiring diagram”.

The connectome can be structural, if it describes anatomical connections between parts of the brain or neurons, or functional, if it describes statistical associations between activities in those parts. If we think of the structural connectome as a road map, then the functional connectome corresponds to the vehicles that travel the roads.

The knowledge of the neural elements and their neural connections can help understand how the cognitive function emerges from the neuronal structure and dynamics. This wiring diagram maps all the neural connections in the brain and, at the cellular level, it provides a map of the neurons and synapses in the brain.

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The ideal framework to study and model the dynamics, topology and properties of this type of synaptic connections is that of complex networks and dynamical systems. Different approaches, from artificial neural networks to biophysical models that take into account the biological reality (conductances, response times, properties of synapses and dendrites, ...), have been used to describe the dynamics of neuronal connections and information processing in the brain; see [5] for a comprehensive description of neuronal dynamic models.

However, as some neuroscientists have pointed out [6–9], knowledge and modelling of the connectome, either structural or functional, are not enough to understand how the brain processes the information, although they contribute in a prominent way. There are other biological mechanisms, such as neuromodulation, that reconfigure the connectome.

In neuromodulation [10], a given neuron uses one or more chemicals to regulate diverse populations of neurons, in contrast to classical synaptic transmission, where one presynaptic neuron directly influences a single postsynaptic neuron. Neuromodulators operate on several time scales, and modulate and configure the connectome so as to determine the processing of information. The connectome provides a minimal structure and, on top of it, neuromodulators configure and specify the functional circuits that give rise to behaviour.

Thus, neuromodulators add new computational and processing capabilities to traditional synaptic transmission. First, they add extra-layers of biochemicals that regulate or tune neuronal processing. Second, the temporal scales of these extra-layers are different from classical ones. Third, these extra-layers and classical synaptic networks interact in a complicated way.

We propose that the appropriate framework for modelling neuronal processing is that of multilayer adaptive networks. Multilayer because in the brain different synaptic and neuromodulatory networks interact to produce behaviour, and adaptive because the topology of these networks changes according to the dynamics.

The first goal of this paper is to highlight the limitations of the connectome and neurotransmission networks to understand neuronal processing, as well as to point out the need of using a new framework. We review examples in which the same structural network can have different configurations and behaviours.

The second goal is to define the characteristics that a complex network framework must have in order to provide a complete description of the different neuronal information dynamics, scales and interactions that occur in the brain. Multilayer adaptive networks, in which different synaptic and chemical layers interact, are the appropriate framework to explain neuronal processing and the emergence of interesting computational capabilities.

2 Beyond neurotransmission networks

The connectome is a wiring diagram mapping all the neural connections in the brain. At the cellular level, it provides a map of the neurons and synapses within a part or all of the brain of an organism. The structural connectome provides the basis on which functional activity is implemented and therefore shapes the functional connectivity.

On the way to unveil the connectome of the human brain, one of the ultimate goals in neuroscience, some milestones have been achieved, e.g., the complete connectome of the nematode Caenorhabditis elegans [11,12], which comprises 302 neurons.

In recent years, significant advances have also been made in the study of the connectome via network science and graph theory [13–17]. At the cellular level, the nodes of the network are the neurons, and the edges correspond to the synapses between those neurons. Therefore, graph theory is the ideal framework to study the topology and dynamics of brain networks. The combination of new tools to map and
record neuronal patterns and the computational techniques of network science has provided a new setting for the study of the brain dynamics.

Many studies have been conducted to analyze the topology and dynamics of the neuronal connectome. In [18], the authors studied the growth rules of the neuronal system of *C. elegans*. They found that the network growth undergoes a transition from an accelerated to a constant increase in the number of synaptic connections as a function of the number of neurons. The transition between different growth regimes may be explained by a dynamic economical model incorporating a trade-off between topology and cost. In [19], graph theory is used to investigate the neuronal connectome of *C. elegans*. The authors identified a small number of highly connected neurons as a rich club interconnected with high efficiency and high connection distance.

Clearly, connectome modelling and analysis play a salient role when it comes to understand neurotransmission (fast synaptic transmission) networks. However, neurons use other forms of communication as neuromodulation that, instead of conveying excitation or inhibition, change neuronal and synaptic properties.

As described in [20], neuromodulators are released in modes other than fast synaptic transmission and modify the neuronal circuit outputs. They are the main factors in shaping behaviour by changing neuronal excitability and synaptic dynamics and strength. The processes that are subject to modulation include changes in probability of neurotransmitter release, changes in transmitter receptors, modification of synaptic strength, adding or subtracting ionic currents, and changes in voltage and time dependence of channel gating. In doing so, they reconfigure the connectome and provide adaptability of the brain functions.

Although traditionally neurochemical messengers have been classified as small-molecule neurotransmitters, biogenic amines and neuropeptides, for the purposes of this paper it is more appropriate to differentiate between neurotransmitter (fast synaptic transmission) and modulator functions as in [8].

In neuronal circuits, connectivity alone does not provide enough information to predict circuits outputs [6,7]. Neuronal processing and behaviour are sensitive to intrinsic channels and electrical properties that vary within and between cell types. Fast synaptic transmission and biochemical processes interact to generate complex dynamics in neurons and circuits.

Studies of neuronal circuits in invertebrate and vertebrate animals [7] have revealed the ability of neuromodulators to reconfigure information processing. They change the composition of neuronal circuits and permit a circuit with a fixed number of neurons to produce many different patterns of activity.

Then, the greatest challenge that we face to understand the brain is to have new models that allow us to explain how the interaction of different layers of neurotransmission, neuromodulators and genetic changes gives rise to information processing. Moreover, without taking into account these different interactions, it is impossible to explain many computational functions observed in the brain.

### 3 Multilayer adaptive networks in neuronal processing

Network science has grown over the last decades to become a relevant conceptual framework for the analysis of many real systems. A tremendous progress has been made in the application of network models in neuroscience. Modelling brain networks as graphs of nodes connected by edges has provided major advances in understanding brain dynamics. From the dynamic analysis of groups of neurons to the topological characterization of large-scale human brain networks, network theory has become a fundamental tool in neuroscience; see [21] and [22] for a comprehensive description of network neuroscience.
Traditionally, the study of dynamical networks has covered either dynamics on networks or dynamics of networks. In the first approach, nodes are dynamical systems coupled through static links. This case includes dynamical systems describing the dynamics in a phase space with no topological changes between the nodes. In the second approach, network topology evolves dynamically in time. This is the case of traditional complex networks, where the focus has been put on analyzing the statistical properties that arise from exogenous topological transformations.

In recent years, there has been a growing interest in adaptive networks, i.e., networks whose links change adaptively with the states of the nodes in an interplay between node states and network topology [23–27]. Two facts make adaptive networks specially convenient for the study of natural and social systems. First, dynamical processes on a network are sensitive to the network topology, which influences the states of nodes. Second, the states of the nodes feed back to the network topology creating a dynamical feedback loop between topology and states of the network. In a neuronal network, the firing rate of a neuron depends on the synaptic connections (topology) and, in turn, the evolution of the synaptic connections and weights depends on the neuronal activity. Furthermore, both processes – neuronal activity and synaptic reconfiguration – take place at different timescales.

A typical adaptive, directed network with a fixed set of nodes is composed of the following elements:

(i) A set of \( N \) nodes \( V = \{v_1, v_2, ..., v_N\} \). Abusing notation, node \( v_i \) will be denoted by \( i \).

(ii) Each node \( i \in \{1, ..., N\} \) has a state \( s_i(t) \).

(iii) The set of evolving links is encoded in a time-dependent, weighted adjacency matrix \( A(t) \) with entries \( a_{ij}(t) \). In our case, self-links are excluded, so \( a_{ii}(t) = 0 \).

(iv) Each link weight \( a_{ij}(t) \) represents the relationship from node \( i \) to node \( j \neq i \) and is a function of \( s_i(t) \) and \( s_j(t) \).

(v) Node states \( s_j(t) \) are a function of the sum of incoming weighted nodes, that is, \( \sum_{i=1}^{N} a_{ij}(t)s_i(t) \).

These systems change their states and topologies simultaneously according to their interrelated dynamical rules. In a link removal \( a_{ij}(t) \neq 0 \) becomes \( a_{ij}(t) = 0 \) while a new link is established when \( a_{ij}(t) = 0 \) becomes \( a_{ij}(t) \neq 0 \).

In addition, until recently the majority of studies have focused on single-layer networks, usually with a single type of node connected via a single type of link. But in most biological systems multiple entities interact with each other in complicated patterns that include multiple layers of connectivity. Consequently, it became necessary to generalize network theory by developing a new setting to study multilayer systems in a comprehensive fashion [28–31]. Then, multilayer networks are the suitable framework to study different networks that interact to produce complex activities.

As we have seen, single-layer networks are represented using adjacency matrices which, in the case considered, represent directed and weighted relationships between the nodes of a network. Instead, multilayer networks represent multiple dimensions of connectivity that, in the case of neurons, can stand for different types of communication channels (neurotransmitters and neuromodulators). A typical multilayer network has the following ingredients:

(i) A number \( N \) of nodes (denoted by Latin letters \( i, j, ... \)) and a number \( L \) of layers (denoted by Greek letters \( \alpha, \beta, ... \)).

(ii) Node \( i \in \{1, 2, ..., N\} \) in layer \( \alpha \in \{1, 2, ..., L\} \) has a state \( s_{i\alpha}(t) \).
Fig. 1. A multilayer network with intra-layer edges and inter-layer edges that connect entities with their replicas in other layers.

(iii) A 4th-order, time-dependent adjacency tensor \( M(t) \) with components \( m_{ij}^{\alpha\beta}(t) \) which are the weights of the link from any node \( i \) in layer \( \alpha \) to any node \( j \) in layer \( \beta \) in the network.

In multilayer networks (see Fig. 1), nodes can be connected by different types of interactions: intra-layer links connecting nodes within the same layer, inter-layer links between the same nodes in different layers, as well as inter-layer links between different nodes in different layers. Multiplex networks are a special class of multilayer networks such that \( m_{ij}^{\alpha\beta} = 0 \) if \( \alpha \neq \beta \) and \( i \neq j \), i.e., different layers are not interconnected except from each node to itself.

An interesting example of a multilayer network can be defined by extending the connectome with synaptic and neuromodulatory layers representing alternative modes of interaction between neurons, along with the corresponding communication links between layers (see Fig. 2).

The combination of multilayer and adaptive networks describes networks with different interactions between their nodes, together with a dynamical feedback between network topology and node states.

As we pointed out before, the connectome and single synaptic networks are not enough to understand neuronal information processing. We summarize next the characteristics that make multilayer adaptive networks the right framework:

(i) In addition to fast synaptic transmission, neurons use other forms of communication such as neuromodulation that change neuronal and synaptic properties.

(ii) The extra layers of a multilayer approach regulate or tune neuronal processing and operate on temporal and spatial scales different from the fast synaptic ones.

(iii) The neuromodulatory layers interact with the fast synaptic transmission layer in a complicated way, changing neuronal excitability and synapses dynamics and strength.
The connectome represents a network of potential neurons and connections (synapses). Function, context and neuromodulatory networks shape and reconfigure the connectome network allowing different paths of information flow.

Neurotransmission is a wiring transmission that targets designated synapses and produces localized responses. On the other hand, neuromodulation is a volume transmission that diffuses through large areas of the neural tissue and affects multiple neurons. As a result, neuromodulatory networks are more complex than neurotransmission ones because neuromodulators act non-locally.

In [32], the authors hold that further understanding of brain function and dysfunction will require an integrated framework that links brain connectivity with brain dynamics. This expanded description is called “dynome” and includes the functional connectome but expands the notion to the mechanisms involved in producing and processing brain signals. Detailed biophysical models of neural activity embedded in an anatomical network may be essential to examine the effects of biological dynamics on functional connectivity.

As described in [33] for the crustacean stomatogastric nervous system, different regulatory mechanisms (synaptic and intrinsic neuronal properties, neuromodulation and gene expression regulation) influence each other to produce stable neuronal circuits.

The C. elegans connectome is considered in [34] as a multiplex network, with each node representing a neuron and with different layers of connection (synaptic and neuromodulatory). The authors found highly significant multilink motifs of
interaction between the extrasynaptic and synaptic connectomes, detecting locations in the network where the monoamines and neuropeptides modulate synaptic activity.

A simplified multilayer adaptive network model that accounts for these extra-layers of interaction can be represented as follows:

(i) A number \(N\) of neurons and a number \(L\) of layers. Each neuron is replicated in the rest of the layers, but with a different associated dynamics. An adjacency tensor \(M(t)\) with components \(m_{ij}^{\beta}(t)\) encodes the relationships from any neuron \(i\) in layer \(\alpha\) to any neuron \(j\) in layer \(\beta\).

(ii) The first layer is the neurotransmission layer. Each neuron in this layer has a state \(s_{i1}(t)\). An evolving set of synapse weights is represented by \(m_{i1}^{j1}(t)\).

(iii) The remaining layers are neuromodulatory layers. Each neuron in one of this layer has a state \(s_{i\alpha}(t)\) with \(\alpha \in \{2, \ldots, L\}\). An evolving set of neuromodulatory link weights is represented by \(m_{i\alpha}^{j\alpha}(t), \alpha \in \{2, \ldots, L\}\).

(iv) The states in the first layer \(s_{j1}(t)\) are a function of both the sum of incoming synapses \(\sum_{i=1}^{N} m_{i1}^{j1}(t)s_{i1}(t)\) and the sum of incoming interactions from neuromodulatory nodes \(\sum_{\alpha=2}^{L} m_{j\alpha}^{j\alpha}(t)s_{j\alpha}(t)\).

(v) The synapse weights in the first layer \(m_{i1}^{j1}(t)\) are a function of both \(s_{i1}(t)\) and neuromodulatory link weights in the remaining layers \(\epsilon_{\alpha} m_{i\alpha}^{j\alpha}(t), \alpha \in \{2, \ldots, L\}\), where \(\epsilon_{\alpha}\) is a coupling parameter between neuromodulatory and neurotransmission links.

(vi) The states in the remaining layers \(s_{j\alpha}(t), \alpha \in \{2, \ldots, L\}\), are a function of both the sum of incoming neuromodulatory links \(\sum_{i=1}^{N} m_{i\alpha}^{j\alpha}(t)s_{i\alpha}(t)\) and \(m_{j1}^{j\alpha}(t)s_{j1}(t)\).

(vii) The neuromodulatory link weights \(m_{i\alpha}^{j\alpha}(t), \alpha \in \{2, \ldots, L\}\), are a function of \(s_{i\alpha}(t)\).

In this directed network, the first layer is a typical neurotransmission layer with adaptive node states and synapses, where the link weights \(m_{i1}^{j1}(t)\) represent classical fast-synaptic connections. The remaining layers contain adaptive neuromodulatory states and links, where \(m_{i\alpha}^{j\alpha}(t)\) are neuromodulatory link weights within layers. The interaction between layers is of three types: node states in the first layer are influenced by the states of the same node in the neuromodulatory layers via \(m_{i1}^{j1}\). Second, synapse weights in the first layer are influenced by the same link weights in the neuromodulatory layers via \(\epsilon_{\alpha}\). Third, node states in the neuromodulatory layers are influenced by the state of the same node in the first layer via \(m_{j1}^{j\alpha}\). Adjacency weights are different from 0, \(m_{i\alpha}^{j\beta} \neq 0\), when \(\alpha = \beta\) or when \(\alpha \neq \beta, i = j, \) and \(\alpha = 1\) or \(\beta = 1\).

Within the above setting, one can formulate detailed biological models (e.g., Hodgkin–Huxley [35]) as well as more abstract models (e.g., McCulloch–Pitts [36]). For example, in an abstract model the output of a neuron in the neurotransmission layer is given by the weighted sum of its inputs. The neuromodulatory layers determine how synaptic weights are updated. In such a model, neuromodulation can change how a circuit function is achieved. The variables of a model are fixed by the level of biological detail (concentration, membrane potential, state of the neuron, etc.).

Regarding the dynamics, the evolution of a network is mostly described by differential equations (Hodgkin–Huxley, Fitzhugh–Nagumo, ...) or by difference equations (logistic maps, ...) depending on the kind and purpose of the model; see, e.g., [37,38].
As a final remark, by examining basic aspects of the multilayer adaptive models being considered, several insights can be extracted. If neuromodulatory layers do not depend on neurotransmission activity, then we have extrinsic neuromodulation. In intrinsic neuromodulation, neuromodulatory layers are not isolated from neurotransmission activity. It is also interesting to compare the temporal scale of the neurotransmission layer with that of the neuromodulatory layers. In most cases, neuromodulation is a slow process compared to neurotransmission [39].

In the next section, we consider the importance of multilayer adaptive models to analyze the computational capabilities of neuromodulators and to provide a complete description of neuronal processing beyond the connectome.

5 Computational capabilities of the multilayer connectome

As pointed out above, it is necessary to take into account the different layers of neuronal communication to complete the connectome, both functional and structural. To this end, multilayer adaptive networks build the appropriate framework to analyse how these layers interact to produce neuronal processing. Next we focus on the computational capabilities added by these interactions at the circuit level. The computational capabilities listed below can be materialized with two interacting layers, one for neurotransmission and the other one for neuromodulation. Other works have focused on aspects of neuromodulators more related to behaviour [40–42]. Among those capabilities, we underline the following:

(i) The different time scales between neurotransmission and neuromodulatory layers give rise to interesting phenomena. For example, neuromodulatory activity in a slower process may fine-tune some properties of the neurotransmission layer such as neuronal excitability and synapse dynamics.

(ii) Because neuromodulation occurs in a diffusive manner, the same neuromodulatory layer can tune different and isolated neuronal circuits (neurotransmission layers).

(iii) Neuromodulatory layers can improve the functioning of neuronal circuits. For example, in [43] the authors found that the neuromodulators trigger distinct changes in representations (through the synaptic weights) that improve the networks classification performance. In [44] the authors demonstrate that neuromodulation of a single target neuron may dramatically alter the performance of an entire network or have almost no effect depending on the state of the network.

(iv) Neuromodulatory layers can ensure a reliable neuronal circuit function despite changes in the parameters of the neurotransmission layer. These extra layers regulate the correlation between parameters, providing robustness to their variation [45,46].

(v) Neuromodulatory layers can reconfigure the neuronal circuit and even change the function performed. This provides a very useful circuit adaptability to the environment.

(vi) Neuromodulators possibly regulate the storage of new information in neuronal networks. Neuromodulatory layers can maintain memory and activity after reconfiguration of neuronal networks [47,48].

These facts show once more the limitations of the connectome to predict the output of the circuit and the need to extend the connectome with additional layers of
neuromodulation that interact dynamically to reconfigure the connectome at every moment.

This new approach will call for network theory and dynamical systems, along with large computational resources, but it will be essential to understand the complexity of the brain. Moreover, the study of neuronal circuits using multilayer adaptive networks will provide clues and evidence of why the processing of information in the brain is more complex and varied than the one observed in artificial neural networks.

6 Conclusions and future work

Important as is the study of structural and functional connectome networks, it is even more important to consider the additional neuromodulatory layers that condition and reconfigure the connectome. In line with the complex cognitive needs of the brain, there is no universal neural coding-decoding scheme but rather different layers of processes that add capabilities to information processing.

As we have seen in this paper, multilayer adaptive networks are an appropriate framework to study neuronal processing and to take into account all the communication processes that occur beyond neurotransmission (for example neuromodulation). Further work is still needed on concrete biological models of interesting phenomena via the multilayer approach.

Recent research has challenged the current premises in memory formation. The use of new techniques such as optogenetics has made it possible to differentiate between mechanisms of memory retrieval and memory storage [49–51]. New theoretical and computational models, such as the one described here, will be required to explain these new observations.

More generally, the use of multilayer adaptive networks for the study of neuronal circuits will lead to analyze the computational capabilities added by the additional layers. These computational capabilities (e.g., adaptability, regulation, robustness, degeneracy, memory, and recurrency) will be key to understand the particularities of information processing in the brain and relate them to those of computers.

Furthermore, cognitive scientists are calling for greater integration between neuroscience and artificial intelligence. This enlarged framework will allow to establish synergies and points in common between neuronal processing and current techniques such as machine learning. Machine learning needs new approaches to imitate how the brain learns and operates and, therefore, it may be relevant to consider how neuromodulation and biochemical communications condition the processing of information.

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Author contribution statement

A.H wrote the draft. J.M.A. revised the draft. Both authors discussed the contents and agreed on the final version.

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