ABSTRACT

Network representations of the nervous system have been useful for understanding of brain phenomena such as perception, motor coordination, memory, etc. Although brains are composed of both neurons and glial cells, only networks of neurons have been studied so far. Given the emergent role of glial cells in information transmission in the brain, here we develop a mathematical representation of neuron-glial networks: $\Upsilon$-graph. We proceed defining isomorphisms for $\Upsilon$-graph, generalizing the multidigraph isomorphism. Then, we define a function for unnesting an $\Upsilon$-graph, getting a multidigraph. Additionally, we found that the isomorphism between unnested forms guarantee the isomorphism between their $\Upsilon$-graph if the matrix equations has only linearly independent columns and are equal after interchanging some rows and columns. Finally, we introduce a novel approach to model the network shape. Our work presents a mathematical framework for working with neuron-glia networks.

Keywords Neuron-glia network · Multiset · Graph theory

1 Introduction

Traditionally, it was commonly accepted that only neurons are implied in the brain information processing while glial cells are relegated to support and protect them. A more updated view suggest that glial cells are also involved in the information processing. In fact, one type of glia cell - astrocytes - couples to single synapses between neurons, forming tripartite synapses \cite{13}. Astrocytes have an active role at tripartite synapse. On one hand, they can directly readout signals from the presynaptic neuron (e.g. they express receptors for GABA, dopamine, glutamate, and glycine)\cite{15,31}. On the other hand, they can modulate the activity of the postsynaptic neuron via the release of neuroactive substances called gliotransmitters \cite{13,25}.

Neuron-driven activation of astrocytes induces an increase in cytosolic calcium \cite{15,32}. This increase in calcium in turn triggers the release of gliotransmitters \cite{8}. More importantly, local increases in calcium spreads through the astrocyte syncytium, i.e astrocyte network, mainly via IP3 diffusion \cite{10,26}. Interestingly, recent studies suggest that the astrocyte network plays a role in neural network phenomena - such as burst synchronization, bursting behavior, barrage firing, gamma waves, - and in cognitive capabilities (e.g. recognition memory) \cite{6,9,18}. Therefore, studying neuron-glia networks could be critical to understand the brain dynamics of large populations of neurons.

Although, neuron-glia networks have been modelled before, finding that astrocytes modulate dynamic coordination, facilitate ultra-slow oscillation, and increase the occurrence of bursting-like spikes, they lack of a formal network representation \cite{5,29,34}. Neural networks are typically represented using graphs or digraphs \cite{2,22,27}. This
representations allows the study of its features such as connectivity, modularity, centrality, etc. [2]. So far, graph-like structures has guided the study of connectomes at all scales [2, 17, 28]. However, neuron-glia networks are more complex and they are not accurately represented by graphs nor digraphs.

In this paper we address this problem by defining a representations of a neuron-glia network and studying it. In order to achieve this goal, first, we represent synapses as binary relations whose ordered pairs represent the information flux between cells. Then, we represent a collection of synapses as a Υ-family that relates binary relations (synapses) to indexes, in order to distinguish synapses that share synaptic configuration. To simplify this representation, we define Υ-multiset that contain identical copies of repeated synaptic configuration. A set of general neurons (neurons and astrocytes) and an Υ-multiset form an Υ-graph which represent a neuron-glia network. This representation allows us to easily generalize the concept of multidigraph isomorphism to neuron-glia networks. Finally, we introduce a novel approach to model neuron-glia network shape, applying natural structure theory and topology [3, 4]. Our work could conceptually help future connectomics studies of neuron-glia networks and guide dynamic modelling.

2 Basic definitions and properties

We follow the definitions and notations of [11] and [12] about multisets (mset) and related objects. We also follow the concepts of [1] about digraphs and related objects.

Note 1. Given a binary relation r, there is another binary relation $r^{-1}$ defined as follow.

$$r^{-1} = \{(y, x) : (x, y) \in r\}.$$ 

Our first definition formalizes the concept of directed pseudograph [1] to create our multidigraph definition, using multiset theory [12, 11].

Definition 1. A finite multidigraph $A$ is a tuple $(V(A), E(A))$, where $V(A)$ is a finite vertex set and $E(A)$ is the finite edge mset with support set $E^*(A) \subset V(A) \times V(A)$.

Note that if all edges appear once, $E(A)$ is a set, and the multidigraph $A$ is equivalent to a digraph (loop allowed). In addition, note that $E^*(A)$ is a binary relation on $V(A)$.

We also formalize the multidigraphs homomorphism in the context multiset theory as follows.

Definition 2. Given two multidigraphs $M$ and $N$ with vertex set $V(M)$ and $V(N)$, respectively. An homomorphism is a bijective function $f : V(M) \to V(N)$ such that for any $(u, v) \in E(M)$ the following is true.

$$\text{Count}_{E(M)}((u, v)) = \text{Count}_{E(N)}((f(u), f(v)))$$

If $M$ is homomorphic to $N$, and $N$ is homomorphic to $M$, $M$ and $N$ are isomorphic ($M \cong N$).

3 Model formulation

As neurons, astrocytes receive and release transmitters, so we will refer to both as neural-like cells. If we had a finite set of neurons $N$ and a finite set of astrocytes $A$, both $N$ and $A$ are sets of neural-like cells (NL-sets). Additionally, we can create a NL-set $W$ that is the union of $N$ and $A$ ($W = N \cup A$). We can state that a set of neurons and a set of astrocytes are always disjoint sets i.e. $N \cap A = \emptyset$.

3.1 Synaptic configurations

Synapses allow the information flux from a general neuron to another. In particular, tripartite synapses allow a directed information flux from the pre-synaptic neuron to the post-synaptic neuron, from the pre-synaptic neuron to an astrocyte, and from the astrocyte to the post-synaptic neuron. We can represent this synaptic configuration as a binary relation, where each ordered pair represents a direction of information flux.

Definition 3. A tripartite configuration is represented by $s_t$ that is a binary relation on a set $\{n_i, n_j, a_i\}$ such that $n_i, n_j \in N$ and $a_i \in A$, where $n_i$ is the presynaptic neuron, $n_j$ is the postsynaptic neuron, and $a_i$ is an astrocyte. $s_t$ is defined as

$$s_t := \{(n_i, n_j), (n_i, a_i), (a_i, n_j)\}.$$ 

Since not all directed synapses between neurons are associated with astrocytes, we have a kind of configuration that is called one-one-directed configuration and are defined as follows.
Definition 4. A one-one-directed configuration is represented by $s_d$ that is a binary relation on a set $\{n_i, n_j\}$ such that $n_i, n_j \in N$. $s_d$ is defined as

$$s_d := \{(n_i, n_j)\}.$$ 

Finally, gap junctions can connect both neurons and astrocytes [10, 20, 26]. In neurons, gap junctions mainly allow the diffusion of ions, and, in astrocytes, IP3 and calcium ions [10, 20, 26]. Gap junctions bidirectionally connect neural-like cells, so we will call these connections symmetric synapses and represent their information flow as symmetric binary relations by definition.

Definition 5. A symmetric configuration is represented by $s_s$ that is a binary relation on a set $\{x_i, x_j\}$ such that $x_i, x_j \in N$ or $x_i, x_j \in A$. $s_s$ is defined as

$$s_s := \{(x_i, x_j), (x_j, x_i)\}.$$ 

Figure 1: a) Schematic representation of a neuron-glia network. $N_1$ and $N_2$ are two neurons, and $A_1$ and $A_2$ are two astrocytes. 1 is a tripartite synapse, 2 is a symmetric synapse between neurons, 3 is an one-one-directed synapse, and 4 is a symmetric synapse between astrocytes. b) Graphical representation of the directions of information flux inside synapses (synaptic configuration) (numbers refer to synapses showed in a))

3.2 $\Upsilon$-graph representation

Here, we create two representations of the collection of synapses of a neuron-glia network: $\Upsilon$-family and $\Upsilon$-multiset. But first, we will define $S_X$ which is a set of synaptic configurations of the NL-set $X$.

Definition 6. An $S_X$ is a finite set of binary relations on subsets of an NL-set $X$, satisfying the following condition.

A1. $\forall U \in S_X$, $U$ is a binary relation $s_d$, $s_s$ or $s_t$.

A2. $\forall x \in X$, $x \in \text{dom } U \lor x \in \text{ran } U : U \in S_X$

Elements of an $S_X$ represent the directions of information flow inside a synapse, however, in a network, more than one synapse can share a synaptic configuration. To represent this fact, we create the definition of $\Upsilon$-family.

Definition 7. An $\Upsilon$-family $F$ is a finite indexed family $F : I \to S_X$ ($I \neq \emptyset$), satisfying the following condition.

B1. $\exists U \in S_X$ such that $U$ is $s_t$.

Note 2. B1 defines the minimal composition of the range of an $\Upsilon$-family. This is necessary because there are ever at least one tripartite synapses in a neuron-glia network.

$\Upsilon$-families relate synaptic configurations with indexes. In this context, $F : i \mapsto s$, where $F$ is an $\Upsilon$-family, represents a single synapse. Consequently, two single synapses with synaptic configuration $s$ can be represented by equations $F(i) = s$ and $F(j) = s$. $\Upsilon$-families are very detailed. However, we need to simplify them to facilitate the comparison between networks. We have done this simplification by using multiset theory in the definition of $\Upsilon$-multiset.

Definition 8. An $\Upsilon$-multiset $A$ is a mset represented by the function $\text{Count} : S_X \to \mathbb{N}$, satisfying the following condition. Given an $\Upsilon$-family $F : I \to S_X$, for all sets $x = \{i : i \in I, F(i) = U\}$, $\text{Count}_A(U) = |x|$.
Given this definition, we can represent a neuron-glia network by the tuple \((X, A_X)\) where \(X\) is a NL-set and \(A_X\) is a \(\Upsilon\)-multiset. We will call this tuple the \(\Upsilon\)-graph of a neuron-glia network.

A connected \(\Upsilon\)-graph \((X, A_X)\) is a \(\Upsilon\)-graph in which \(\forall x, y \in X, \exists (a_n)_0^k : P_0, P_1(x, y), P_2, P_3(x, y), P_4\), where

\[
\begin{align*}
P_0 &\equiv [0, k] \subset \mathbb{N} \\
P_1(x, y) &\equiv x \neq y \\
P_2 &\equiv \forall n \in [0, k], a_n \in X \\
P_3(x, y) &\equiv a_0 = x \land a_k = y \\
P_4 &\equiv \forall n \in [0, k - 1], \forall r \in A_X, (a_n, a_{n+1}) \in r \lor (a_n, a_{n+1}) \in r^{-1}
\end{align*}
\]

### 3.3 \(\Upsilon\)-graph isomorphism

Similarly to multidigraph homomorphism, we define homomorphism for \(\Upsilon\)-graphs as follows.

**Definition 9.** Given two \(\Upsilon\)-graphs \(\alpha = (X_a, A)\) and \(\beta = (X_b, B)\), an homomorphism is a bijective function \(f : X_a \to X_b\) such that for any element \(\{(u, v)\}, \{(u, v), (v, u)\}, \{(u, v), (v, w), (u, w)\}\) of \(A^*\), the following conditions are true, respectively.

\[
\begin{align*}
\text{Count}_A(\{(u, v)\}) &= \text{Count}_B(\{(f(u), f(v))\}) \\
\text{Count}_A(\{(u, v), (v, u)\}) &= \text{Count}_B(\{(f(u), f(v)), (f(v), f(u))\}) \\
\text{Count}_A(\{(u, v), (v, w), (u, w)\}) &= \text{Count}_B(\{(f(u), f(v)), (f(v), f(w)), (f(u), f(w))\})
\end{align*}
\]

As before, if \(\alpha\) is homomorphic to \(\beta\), and \(\beta\) is homomorphic to \(\alpha\), \(\alpha\) and \(\beta\) are isomorphic (\(\alpha \cong \beta\)). For the sake of clarity, we introduce the following notation, being \(f\) an homomorphism between \(\Upsilon\)-graphs and \(s\) an element of the set of relations of the domain of \(f\), if \(s = \{(a, b), \{(a, b), (b, c), (c, a)\}\}_{\alpha,\beta}\), \(s_f\) will be \(\{(f(a), f(b)), (f(b), f(c)), (f(c), f(a))\}\), respectively.

In order to add functional relevance to the isomorphism concept, we use the term \(\alpha\)-isomorphic (represented as \(\cong_{\alpha}\)) which means that the homeomorphisms are functions that relates neurons to neurons and astrocytes to astrocytes. This concept can be applied to both multidigraph and \(\Upsilon\)-graph isomorphisms; in either case, this implies that, being \(x\) and \(y\) \(\alpha\)-isomorphic, \(V(x)_A\) the subset of astrocytes of \(V(x)_A\), \(V(x)_N\) the subset of neurons of \(V(x)_A\), \(V(y)_A\) the subset of astrocytes of \(V(y)_A\), and \(V(y)_N\) the subset of neurons of \(V(y)_N\); then \(|V(x)_A| = |V(y)_A|\) and \(|V(x)_N| = |V(y)_N|\).

### 3.4 Unnesting an \(\Upsilon\)-graphs

Let \(A\) be the set of finite multisets and \(A^m\) a set of sets. For any \(A \in A\) and \(B \in A^m\), we say \(A \sim B\) if and only if the following holds.

\[
\begin{align*}
1. \forall a \in B, a \in A \times N.
2. \forall b \in A^*, \exists a \in B : \{b\} \in a.
3. \forall a \in B, \{c\} \in a \implies \{c, \text{Count}_A(c)\} \in a.
\end{align*}
\]

Being \(c\) any element, i.e., a free variable of the statement, the relation \(\sim\) defines a function from \(A\) to \(A^m\). Since \(\forall A, B \in A, C \in A^m, (A \sim B \land A \sim C \implies B = C)\) and domain and range are sets, then \(\sim\) defines a function. We denote this function as \(\pi\). It is clear that \(\pi\) is injective.

Being \(\pi(A)\) the range of \(\pi\) in \(A^m\), we define a function \(\delta\) from \(\pi(A)\) to \(\varphi(\pi(A))\) by the following proposition:

\[
a \in \pi(A) \iff \alpha := (s, n) \implies ((\forall \alpha \in s, (\alpha, n) \in b) \land (\forall (\alpha, m) \in b, \beta \in s \land m = n))
\]

The next step is to define a function \(\cup^+\) as

\[
\cup^+ : \varphi(\pi(A)) \times \varphi(\pi(A)) \to \varphi(\pi(A))
\]

\[
(\delta(a), \delta(b)) \to B
\]

In this fashion, \(B\) is defined as the set \(\{(\alpha, n) \in \pi(A) : P_1 \land P_2\}\), where \(P_1\) and \(P_2\) are the following

\[
\begin{align*}
P_1 &\equiv \forall (\alpha, n) \in B, \exists m \in N : (\alpha, m) \in \delta(a) \lor (\alpha, m) \in \delta(b). \\
P_2 &\equiv \forall (\alpha, n) \in B, n = \text{Count}_a(\alpha) + \text{Count}_b(\alpha).
\end{align*}
\]
From $\cup^+$, we define $\cup^+\Omega$ as the successive application of $\cup^+$ among the elements of $\Omega$. Needless to say, $\cup^+$ is a function with no inverse. Formally, $\cup^+$ maps elements of $\phi(\phi(\pi(A)))$ to $\phi(\pi(A))$.

As a final step, we define another function $\pi^-$ from $\pi(A)$ to $A$ from the relation $\sim$. Since $\pi$ is injective, $\pi^-$ is also injective. Furthermore, $\pi^-$ is also surjective since its range is the whole codomain $A$.

For any $\Upsilon$-graph $(X, A_x)$, we can apply the defined functions in and inside $A_x$ as follows. First, we apply the composition $\delta \circ \pi$ restricted to $A_x$. The range of $\delta \circ \pi_{|A_x}$, labeled as $\delta \circ \pi(A_x)$, will be taken as an element of the domain of $\cup^+$. In this way, since $\cup^+ \delta \circ \pi(A_x)$ is a subset of the domain of $\pi^-$, we restrict $\pi^-$ to $\cup^+ \delta \circ \pi(A_x)$. Finally, the range of $\pi^-_{|\cup^+ \delta \circ \pi(A_x)}$ is written as $pre - \phi(A_x)$. Bear in mind that $pre - \phi$ is not the composition $\pi^- \circ \cup^+ \circ \delta \circ \pi$, but $pre - \phi$ is a function from a subset of $\phi(A)$ to $\phi(A)$.

In the context of connected $\Upsilon$-graphs, $\Upsilon$-multisets are associated with only one NL-set since there exists at least an ordered pair $(x, y)$ as an element of some element of the $\Upsilon$-multiset for any element $x$ of the NL-set where $y$ is some other element of the NL-set. If $X$ is an NL-set, this, in turn, implies that $X \cup \{x\}$ ($x \notin X$) has at least a new element in its $\Upsilon$-multiset, and $X - \{x\}$ ($x \in X$) has at least a different element in its $\Upsilon$-multiset. Summarizing, if $(X, A_x)$ and $(Y, A_y)$ are connected $\Upsilon$-graphs, then $X = Y$. Phrased in another way, for a given connected $\Upsilon$-mset $A_x$, there exists one and only one associated $\Upsilon$-graph $(X, A_x)$; in the same way, for a given mset $pre - \phi(A_x)$, there exists one and only one associated multidigraph $(V(x), pre - \phi(A_x))$. Therefore, it is possible to construct another function called $\phi$ that relates $\Upsilon$-graph and multidigraph from $pre - \phi$ as described. This new function would represent the “unnested relation”, being the images the unnested form of the arguments. Let $P$ be a collection of connected $\Upsilon$-graphs $P = (a, b, ...)$ and $Q$, a collection of their associated multidigraphs $Q = (\phi(a), \phi(b), ...)$. Fig. 2 graphically explains the domain and range of $pre - \phi$ and $\phi$ functions. We will prove some propositions using these functions, but first we need to define the matrix equation of an $\Upsilon$-graph.

3.5 Matrix equation of an $\Upsilon$-graphs

It is necessary to bear in mind that the series of repetitions of all the synapses that includes a certain ordered pair is equal to the repetition of that ordered pair. Formally, being those synapses denoted as $s_1, s_2, ..., s_k$ and the ordered pair $(a, b)$, then $Count(a, b) = Count(s_1) + Count(s_2) + ... + Count(s_k)$. We denote the set of all synapses that include $(a, b)$ as $S_{(a,b)}$ and the series as $\sum(S_{(a,b)})$. Given a system of equations that comprehends all the elements of a certain neuron-glia network. If $(V(x), E(x))$ is the multidigraph of this network and $(X_x, A_x)$, its $\Upsilon$-graph, then the following system of equations is the bridge between these representations.
Mathematical representation of the structure of neuron-glia networks

\[
\begin{align*}
\text{Count}_{E(x)}(a, b) &= \sum (S_{a,b}) \\
\vdots \quad \text{Count}_{E(x)}(u, v) &= \sum (S_{u,v})
\end{align*}
\]

However, provided there are \(n\) synapses in the network and \(m\) ordered pairs, the above system is also

\[
\begin{align*}
\text{Count}_{E(x)}(a, b) &= c_{11}\text{Count}_{A_x}(s_1) + \ldots + c_{1n}\text{Count}_{A_x}(s_n) \\
\vdots \\
\text{Count}_{E(x)}(u, v) &= c_{m1}\text{Count}_{A_x}(s_1) + \ldots + c_{mn}\text{Count}_{A_x}(s_n)
\end{align*}
\]

Where each \(c_{ij}\) represents the presence or absence of the \(s_j\) synapse in the \(i\)-th ordered pair. We represent this later system of equations in the following matrix equation

\[
P = Ax.
\]

The vector \(P\) is a \(m\) by 1 matrix. Each element represent the \(\text{Count}_{E(x)}\) of an ordered pair in \((V(x), E(x))\). The coefficient matrix \(A\) is a \(m\) by \(n\) matrix with 1 and 0 as elements. 1 implies the existence of the ordered pair represented by the row in the synapse represented by the column. In other words, 1 at the position \((i, 1)\) implies that the ordered pair at the position \((i, 1)\) of \(P\) is included in the synapse \((j, 1)\) of \(x\). In addition, the vector \(x\) is a \(n\) by 1 matrix; each element represents the \(\text{Count}_{A_x}\) of a synapse in \((X_x, A_x)\). Finally, given two matrix equations \(Ax = P\) and \(By = Q\), if \(A = B\) and \(P = Q\), then both equations are associated with the same \(Y\)-graph.

Using matrix equations, in the following, we prove that the isomorphisms between unnested forms does not guarantee the isomorphism between their \(Y\)-graphs even deleting some types of synapses.

**Proposition 1.** \(\exists a, b \in P : \phi(a) \equiv_{\alpha} \phi(b) \land \neg(a \equiv b)\)

This proposition holds true in each of the following scenarios of synaptic configurations in neuron-glia networks.

1. There are only tripartite synapses and symmetric synapses between astrocytes.
2. There only tripartite synapses, symmetric synapses between astrocytes, and one-one-directed synapses.
3. There only tripartite synapses, symmetric synapses between astrocytes, and symmetric synapses between neurons.
4. All types of synaptic configuration are present.

**Proof.** Let \(a := (X_x, A_x), b := (X_y, A_y)\), \(\phi(a) := (V(x), E(x))\), and \(\phi(b) := (V(y), E(y))\). The second part of the proposition \((\neg(a \equiv b))\) can be translated as

\[
\exists s \in A_x : \text{Count}_{A_x}(s) = n \land \text{Count}_{A_x}(s_\neg) = m \land n \neq m
\]

Using the matrix equation (3), this means that the system has multiple solutions, each solution corresponding to a different \(Y\)-graph that are not isomorphic among each other. Let \(A\) be the coefficient matrix of the matrix equation of \(a\) and \(B\) the coefficient matrix of the matrix equation of \(b\). The method that we will be using is to show cases in which the null space of \(A\) has more elements than the zero vector. An exception is the last case where we found an instance in which \(P = Ax = By\), being \(A \neq B\).

Since the existence of symmetric synapses between astrocytes is of no interest to this proof, it is the only way in which astrocytes are related, symmetric synapses between astrocytes will not be shown in the following cases.

1. **There are only tripartite synapses and symmetric synapses between astrocytes.**

   Every neuron-glial network that includes the following sub-network (coefficient matrix) satisfies the proposition

   \[
   A = \begin{bmatrix}
   1 & 1 & 1 & 1 & 0 & 0 & 0 & 0 & 0 \\
   1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
   1 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
   0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
   0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
   0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\
   0 & 0 & 1 & 1 & 0 & 0 & 0 & 1 & 0 \\
   0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\
   0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
   0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\
   0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1
   \end{bmatrix}
   \]
Mathematical representation of the structure of neuron-glia networks

That is because $Ax = 0$ has non-zero solutions such as $s = [1, -1, -1, 1, 1, 1, -1]^T$ and every vector $ks$ where $k$ is a positive integer. This implies that $P = Ax$ has either 0 or infinite solutions, since there is at least one solution, then there are countable many others. This, as a whole, implies that there are neuron-glia networks that share the same Count of ordered pairs while holding different Counts of synapses.

2. **There only tripartite synapses, symmetric synapses between astrocytes, and one-one-directed synapses.**

Likewise the above case, any neuron-glial network that includes the following sub-network satisfies the proposition.

$$A = \begin{bmatrix}
1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
\end{bmatrix}$$

Here, the solutions of $Ax = 0$ are of the form $ks$, where $s = [1, -1, -1, -1, 1, 1, 1, -1]^T$ and $k$ is a positive integer.

3. **There only tripartite synapses, symmetric synapses between astrocytes, and symmetric synapses between neurons.**

In this scenario,

$$A = \begin{bmatrix}
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
1 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
0 & 0 & 1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
\end{bmatrix}$$

satisfies the proposition with $[-1, 1, 1, -1, -1, 1, 1, -1, -1, 1, 1, 1, 1, -1, 1, 1, 1, -1, 1, 1, -1, 1, 1, -1]^{T}$ as a solution for $Ax = 0$. 

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4. All types of synaptic configuration are present.
In this scenario, any pair of \( T \)-graphs with the following sub-network

\[
A = \begin{bmatrix}
1 & 0 \\
1 & 0 \\
0 & 1 \\
0 & 1 \\
\end{bmatrix}
\quad \text{and} \quad
B = \begin{bmatrix}
1 & 0 \\
1 & 0 \\
0 & 1 \\
0 & 1 \\
\end{bmatrix}
\]

satisfy the proposition. The proposition is true since even though \( x \neq y \), \( Ax = P \) and \( By = P \) can be easily achieved provided \( x = [a, b]^T \) and \( y = [a, b, b]^T \). The reason why \( x \neq y \) negates \( a \equiv b \) is this case is the following: let \( s \) be the synapse represented by the second row of \( x \), \( \text{Count}_{A_s}(s) \neq \text{Count}_{A_s}(s_f) \) since \( s_f \notin A_y \).

\[Q \]

After exploring the proposition 1, it is reasonable to ask when \( \phi(a) \equiv_a \phi(b) \implies a \equiv b \). The answer of this question will be given in the form of a proposition.

**Proposition 2.** \( \forall a, b \in \mathbf{P}, (\phi(a) \equiv_a \phi(b) \land Q_1(a, b) \land Q_2(a, b)) \implies a \equiv b \)

\( Q_1 \) and \( Q_2 \) are conditions applied over \( a \) and \( b \). Being \( Ax = P \) and \( By = Q \), the matrix equations of \( a \) and \( b \), respectively. Let \( A_n \) be the \( T \)-multiset of \( a \) and \( A_s \), the \( T \)-multiset of \( b \). If \( \text{rank}(A) \) and \( \text{rank}(B) \) are the ranks of \( A \) and \( B \), respectively, then \( Q_1 \equiv \text{rank}(A) = |A_n^0| \land \text{rank}(B) = |A_s^0| \). This implies that all the columns of \( A \) and \( B \) should be linearly independent in their matrices.

\( Q_2 \) is more flexible depending on the relation between the matrix equations of \( a \) and \( b \); if \( Ax = P \) is the matrix equation of \( a \) and \( By = P \) is the matrix equation of \( b \), then \( Q_2 \equiv A = B \). However, if \( Ax = P \) and \( By = RP \), being \( R \) a row exchange matrix, then \( Q_2 \equiv B = RC \land A = C \). Finally, if \( Ax = P \) and \( BRy = P \), then \( Q_2 \equiv A = BR \lor A = B \). The last part implies that \( x = y \) is not a necessary condition in order to \( a \equiv b \) be true.

\[Q \]

**Proof.** \( Q_1 \) guarantees that the equations have either 1 or 0 solutions since all coefficient matrices have more rows than columns or are square matrices. Provided our matrix equations are well written, \( Q_1 \) implies that the equations have only 1 solution. \( Q_2 \), in turn, implies that the space of solutions of the two equations is equal or equivalent. With equivalent is meant that all the elements of one solution space is a transformation of the second one. Particularly, the transformation is row exchange by the matrix \( R \). After applying the transformation to all the elements of the second solution space, both solution spaces are equal. Finally, since our matrix equations have only 1 solution, the solution spaces have only one element. \( a \equiv b \) is satisfied since \( x = y \) or \( x = Ry \) for all pair of matrix equations that hold \( Q_1 \), \( Q_2 \), and are \( \alpha \)-isomorphic.

3.6 Network shape

Nowadays, a huge amount of information about neural shape and network connectivity is available in open databases \([7][33][36]\). However, the mathematical tools to study neuronal shape are still under development \([16][19]\). Natural structure theory could contribute to this research field by providing a theoretical framework to study the shape of neurons, astrocytes or even networks \([3][4]\).

A connected neuron-glia network is evidently a natural structure, where its elements are neural-like cells and synapses are NE-connections \([3][4]\). In general, a single synapse is composed of a perisynaptic matrix (if it is chemical), a presynaptic membrane, an astrocyte membrane (if it is tripartite) and a postsynaptic membrane. The Synaptic cleft is a region of the space filled of perisynaptic matrix which is composed of proteoglycans and proteins \([21][14][23]\). This matrix mediates trans-synaptic adhesion (NE-connection role) and regulates the synaptic transmission (communication role) \([14][35]\). Thus, in our model, a single synapse is spatially distributed. In the following, we roughly model a neuron-glia network, applying part of the mathematical definition of natural structures from Cabrera-Febola, 2021-in preparation for publication.

**Definition 10.** (Cabrera-Febola, 2021-in preparation for publication) A natural structure (NE) is a triple \((X, D, C)\), where \(X\) is a collection of the elements of NE which \(\not\emptyset \not\subseteq X\), \(C\) is a family of collections of NE-connections, and \(D\) is a distribution of the elements, being a pair \((S, \{m_x \mapsto S : m \in X, s = 1, 2, ..., v, v \in \mathbb{N}\})\), where \(S\) is the “known” natural space and \(m_x \mapsto S\) stands for \(m_x\) exists along \(S\).
In our case, the natural structure model of a connected neuron-glia network (connected Υ-graph) whose synapses collection is represented by a Υ-family $F : I \mapsto S_X$ is $(X,D,C)$, where $X$ is a NL-set and $C = \{(h,i) : i \in I, F(i) = h\}$. We can model the “known” natural space by using $\mathbb{R}^3$. We can also define a distribution function $g : X \cup C \mapsto P$, where $P$ is a family of subsets of $\mathbb{R}^3$. An element $x$ of the domain of $g$ is distributed in all the points of $g(x)$ and nowhere else. Hence, we can represent $D$ by $(\mathbb{R}^3,g)$ to model the spatial distribution of the network.

Neural-like cells has not cavities, so we can assume that $g(x)$ with $x \in X$ is homeomorphic to a solid ball. On the other hand, $g(s)$ with $s \in C$ is the volume where neurotransmission occurs, thus it is also homeomorphic to a solid ball. Additionally, we can state that synapses are partially composed of membranes from all implied general neurons, so $g(s) \cap g(x_j) \cap g(x_j) \cap \ldots \cap g(x_z) \neq \emptyset$ if and only if $s \in C$ and $s$ is a relation on $\{x_i, x_j, \ldots, x_z\}$. As the Υ-graph is connected, it is possible to conjecture that the $\bigcup g(e) : e \in X \cup C$ is a solid. There are more topological and geometrical properties of neuron-glial networks, however, this topic is out of the scope of our article.

4 Discussion

Neurons has been the focus of two hundreds of years of neuroscience research [28]. However, experimental evidence suggests that astrocytes play an important role in neuronal dynamics, making it necessary to deepen our understanding of how astrocytes network influences neural phenomena [6, 9, 18]. Although there were some attempts to model neuron-glia network dynamics, they lack of an accurate network representation [5, 29, 34]. Here we present a representations of a neuron-glia network by defining Υ-graph.

In our framework, synaptic configurations which are represented by binary relations are the elements of Υ-families and Υ-multisets. Neurons can establish many synapses with the same information flux, i.e. the same synaptic configuration. This fact is represented in two different ways in these representations.

On one hand, an Υ-family represents each single synapse as a distinguishable element. In this representation, a synaptic configuration that appears more than once is represented by a codomain element related with more than one index. Therefore, all synapses are different by definition even if they share synaptic configuration. In a further development stage, this representation will allows researchers to attach descriptors (shape, volume, strength, etc) to each single synapse.

On the other hand, an Υ-multiset contains repeated synaptic configuration as identical elements. A counting function allow us to know the number of occurrence of a synaptic configurations in the multiset. Then, the network (Υ-graph) is defined as a tuple $(X, S_X)$ where $X$ is a set of neural-like cells and $S_X$ is its Υ-multiset. Υ-multisets allows us to easily define Υ-graph isomorphism by generalizing the concept of multidigraph isomorphism (section 2).

Our work presents a new mathematical object, Υ-graph, that represent neuron-glia networks, considering each single synapses as an element of the network. Previous works on neural networks had not considered each synapse as an individual element but the collection of synapses as the edge of the digraph or graph [22, 24, 30]. In fact, digraph representation can lead to misrepresentation if the network has electrical synapses, because this bidirectional connection, in a digraph, is equivalent to two chemical synapses with inverse directions. However, functionally, two chemical synapses are not equivalent to an electrical synapses. This misrepresentation can not happen in Υ-graphs.

In section 2, we have defined multidigraphs as a generalization of digraphs, using multiset theory. In subsection 3.4, we show that this concepts is relevant because if we unnest an Υ-graph, we have a multidigraph. We can also connected both objects by a matrix equation (subsection 3.5). Using matrix equations, we proved that, in general, the isomorphism between unnested forms does not entail isomorphism between their Υ-graphs, considering all types of synapses nor deleting some types e.g. electrical synapses (proposition 1). Therefore, multidigraph representations can also lead to misrepresentation in neuron-glia networks even with out electrical synapses. However, we also found that if the matrix equations of two connected Υ-graphs are equal after interchanging row and columns and have only linearly independent columns, the isomorphic between unnested forms guarantees the isomorphism between Υ-graphs. Therefore, under this specific conditions, we can use definition 2 which is simpler than definition 9.

In this work, we also sketch a novel approach to model the network shape. As Υ-family represents each synapses as distinguishable elements, we use this object to create a natural structure model. This natural structure is a tuple $(X, D, C)$ where $X$ is a set of neural-like cells, $C$ is a set of single synapses, and $D$ is a tuple $(\mathbb{R}^3, g)$ ($g$ is the distribution function). In our model, single synapses and neuron-like cells are homeomorphic to solid balls. We conjecture that the portion of space where neuron-like cells and synapses are distributed is also a solid. This hypothetical solid could be studied applying differential geometry or algebraic topology which open new ways for studying structural connectomes.
Mathematical representation of the structure of neuron-glia networks

In conclusion, we have developed a mathematical framework for working with the spatial and connectivity structure of neuron-glia networks. For working with the connectivity structure, we have \( \Upsilon \)-graphs and related concepts (connectedness, isomorphism, matrix equation, etc.) We have also connected the concept of \( \Upsilon \)-graphs with a graph-like object, multidigraph. On the other hand, we have the natural structure model to study the spatial structure of neuron-glia networks.

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