Modeling propagation velocity of activity fronts in two-dimensional neuronal networks

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Abstract: This study investigates the propagation of neuronal activity fronts inspired by experiments in one- and two-dimensional neuronal cultures, and by using theoretical and numerical approaches. We derive analytical expressions for the propagation velocity for random geometric networks and exponentially distributed connectivity networks, focusing on the inter-neuronal dynamics and simplifying the intra-neuronal processes. Theoretical results are validated against numerical simulations of such networks using the Izhikevich model of spiking neurons, highlighting the impact of network structure on pulse dynamics. The measured velocities in both 1D and 2D models are constant across space, which is consistent with experimental findings. However, there is a velocity-connectivity dependency that is expected. Additionally, network noise and neuron variability also play a crucial role in initiating or shaping front velocity. Our models and simulations provide insights into how network structure influences the key macroscopic observable that is activity propagation.
Keywords: Biophysics, Modeling, Simulation, Statistics, Symmetry, Waves.
SDGs: This work is related to the sustainable-development goals (ODS) 3, 4 and 17.

I. INTRODUCTION

Modern neuroscience studies the behavior of neuronal circuits by combining different scales, experimental resources and scientific disciplines. Although the ultimate goal is to understand the brain, simpler systems are often used to investigate universal phenomena in neuronal systems, such as the propagation of information or synchronization. One of such simpler systems is neuronal cultures, i.e., dissociated neurons plated on glass, and that can be investigated and manipulated in a laboratory [1]. Additionally, since these cultures are accessible, their study is often combined with numerical simulations that help elucidate the key ingredients of an observed phenomenon. For instance, if one monitors propagation of activity in such neuronal cultures, key questions that simulations help to understand are the dependency of propagation on neuronal density or neuronal connectivity, or the impact of perturbations.

Neural activations, known as pulses, that can be either spontaneous or stimulated, generate traveling waves that can reach the vast majority of the culture as seen experimentally. Those pulses represent the physical transfer of information within the culture. The trajectory and velocity of these pulses is highly linked to the underlying network structure and communication capacity [2, 3]. Thus, it is necessary to understand how the physical structure of the network, as well as the biophysical mechanisms for neuronal activation, interlink one another to shape activity propagation and its velocity.

In this regard, studies on *in vitro* one-dimensional cultures have related the propagation velocity of a pulse to the neural connectivity and, concretely, to the number of connections of the neuron [4]. However, to the best of our knowledge, no analysis of two-dimensional fronts have been investigated beyond a relatively simple experimental description [5, 6]. Inspired by these observations, theoretical developments and numerical simulations of spiking neurons are arising as a useful tool to explore propagation velocity and other traits for different network structures or neuronal dynamics.

The purpose of the present study is to provide, first, a theoretical mathematical framework for the pulse propagation velocity in one- (1D) and two-dimensional (2D) neuronal networks and, second, to compare the theoretical predictions with numerical simulations. To achieve this, we will consider different network structures and study their impact on the connectivity and the neurons' range of interaction, ultimately comparing the outcomes with realistic numerical simulations using the Izhikevich model of spiking neurons [7].

II. THEORETICAL MODEL

In our theoretical approach, we will not consider the detailed processes inside a neuron that bring it to the active state, which have been studied successfully in 1D cortical and thalamic systems [8], but rather the physico-mathematical conditions that allow the propagation of an activity front, understood as a group of neurons placed on a Euclidean space that pass information to another group. Also, it should be noted that the way in which neurons connect to one another shape the interactions between an activated area and the rest of the network, and therefore the topological properties of the neuronal network must be taken into account and explored.

As an example to motivate our work, Fig. 1A provides snapshots of experimental data in which a front of activity (blue dots) propagates across a neuronal culture, and where neurons cover a substrate in a uniform manner [5]. In the neuronal culture, neurons essentially connect to their closest neighbors, as in a random geometric graph, ultimately shaping a wave-like propagation.

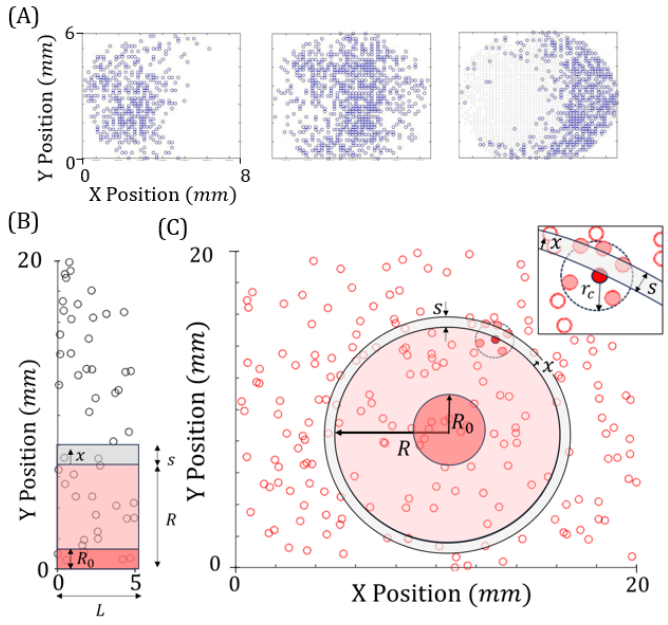

FIG. 1: (A) Pulse propagation in experimental data, from Ref. [5], at different times. From the left to the right: $t_1 = 24.84$ s, $t_2 = 24.90$ s and $t_3 = 25.04$ s. (B) Visual sketch of a 1D culture model. (C) Visual sketch of a 2D culture model. We can observe the parameters considered in this study to model the pulse propagation in a geometric random graph neuronal network. Starting front (red), newly activated areas (orange) and areas of influence for pulse advance (gray) are drawn.

Key concepts of the model.— In our theoretical approach, we will first consider a given number of N_n neurons randomly allocated with density σ within the culture in a homogeneous manner (Fig. 1B). Then, a connectivity blueprint between neurons will be set depending on different connectivity rules. Our first case will consist of a random geometric graph, where neurons connect within a neighborhood of radius r_c (Fig. 1B, Fig. 1C), and that is useful to comprehend restricted connectivity and local interactions. Then, we will consider a distance-dependent exponential distribution in the connectivity probability between neurons, which will be a more realistic sketches since it considers long-range connections in a similar proportion as in the experimental connectivity reconstruction described in Ref. [9].

To obtain analytical solutions, the culture is considered dense enough to involve 'mean field' like properties [10] for the average number of connections each neuron has, $\langle k \rangle$, and the number of pulses a neuron needs to receive to fire, m_0. It is important to mention that we consider that the networks are not directed, i.e., there are just bidirectional connections and not 'input' and 'output' connections.

The number m_0 conceptually captures the integration of inputs in the membrane of a neuron for it to overcome the threshold and activate [11]. We note that the complex 'integrate and fire' nature of neurons, in which sufficiently stimulation has to arrive in a short time window for the neuron to fire, is simplified by a threshold rule in a percolation problem [11]. Also, the signals that a neurons receives or emit are identical in strength.

We also remark that we do not consider inhibitory neurons in the theoretical model, which are present in biological systems, and with a proportion of 80% excitation and 20% inhibition [11]. These inhibitory neurons are essential components in the brain and other living neuronal circuits and play important roles in information transmission and coding [1]. We will, however, discuss their importance when considering numerical simulations.

From a geometrical perspective, one can consider 1D or 2D neural networks. The 1D system (Fig. 1B), will consist of a rectangular culture much longer than wide, and where the synaptic tree of a neuron is of the order of the width of the culture, preventing transverse signal propagation [2]. The synaptic or dendritic tree is the area around a neuron where axons from other neurons establish connections with it. The 2D system will consist of a square area with a lateral dimension much larger than the dendritic tree (Fig. 1C).

Our aim is to compute how far a neuron can be to the propagating front to still receive the m_0 pulses required to be activated, which conceptually provides an area of width s ahead the pulse (Fig. 1B-C). We assume that this area s ignites all at once in a time window Δt if the statistico-geometrical requirements for activation are met. Therefore, front velocity will be given by $v = s/\Delta t$.

Below we elaborate the different geometric scenarios and connectivity blueprints.

1D geometric random graph.— Let us start by considering that a certain pulse is activated at the bottom of the rectangular culture. In a geometrical random graph, neurons will only establish connections with neurons within a certain distance r_c, i.e., dendritic tree. The initial front can only activate those neurons within the r_c distance of the outermost neuron, i.e., it can traverse a distance of r_c units in a single time step. Neurons of the network outside the front and just at its edge will receive almost half of the number of input connections, whereas those neurons just at a distance r_c from the edge will receive no inputs. Thus, the fraction of inputs that a neuron outside the edge of the propagating front may receive changes from $\frac{1}{2}$ to 0.

We can think of infinitesimal sections of area $L\Delta x$ that may activate within the r_c-height section above the initial pulse, where L is the width of the rectangular culture and Δx is an infinitesimal height. This way, we can associate a distance to each infinitesimal section and explore which one does not receive enough pulses to fire.

If we define d as the density of connections (neuronal connections per unit area), then we can define the number of activations or pulses N_A that a certain section $L\Delta x$ receives as:

$$N_A(x) = d\left(\frac{r_c - x}{2r_c}\right)\frac{\pi}{4}L\Delta x, \tag{1}$$

where x denotes the distance of the infinitesimal section to the pulse. The $\frac{\pi}{4}$ factor arises from approximating the activation area to a square $L\Delta x$ while keeping the connectivity within a circular area πr_c^2.

Finally, we compute the maximum distance from the pulse that activates as the section s in which all neurons receive exactly m_0 electrical signals. That is $N_A(s)/N_n = m_0$, where $N_n = L\sigma\Delta x$. This yields:

$$s = r_c \left(1 - \frac{8m_0}{\pi\langle k\rangle}\right), \tag{2}$$

where $\langle k\rangle$ is the average connectivity in the network introduced before.

1D exponential random graph.— We will follow the same construction that brought us to Eq. (2). In this connectivity scenario, neurons can connect all over the culture with a probability $p_c(D) = \exp(-\lambda D)$ where D is the distance between neurons and λ is a parameter of the distribution which we will set as $\lambda = 1/r_c$.

The number of activations in section s will be, then, the half of the connections in the direction of front advance (since the others have been already activated), i.e., at a distance between x and $x+R$, where R is the position of the front from origin (Fig. 1):

$$N_A(x) = d\frac{1}{2}e^{-\lambda x}\left(1 - e^{-\lambda R}\right) L\Delta x. \tag{3}$$

Similarly, we can compute the average number of connections for a sufficiently big system (to avoid considerations regarding border neurons) at a distance between 0 and the culture height C as:

$$\langle k\rangle = \sigma\frac{1}{\lambda}\left(1 - e^{-\lambda C}\right). \tag{4}$$

By replacing λ in Eq. (3) and following Eq. (2), we get:

$$s = r_c \ln\left[\frac{\pi\langle k\rangle\left(1 - e^{-\frac{R}{r_c}}\right)}{8m_0}\right]. \tag{5}$$

2D geometrical random graph.— Here, we assume that a pulse emerges from the center of the culture with a certain initial radius R_0. We can consider again a linear treatment in the computations of the received pulses. However, since there is an increase in the number of neurons in the expanding 2D front, there will be a second decreasing factor in the number of activations received, which will lead to a quadratic proportion of activations. This way, a $\frac{\pi}{4}$ correction is not be applicable. Two factors (marked with [...]) then shape the number of activations N_A: (i) the proportion of the active area that is influential in the infinitesimal section, and (ii) the proportion of area that is active from the total area connected to the section for large values of R. That is:

$$N_A(x) = d\left[\left(\frac{r_c - x}{r_c}\right)\right]\cdot\left[\left(\frac{r_c - x}{2r_c}\right)\right] 2\pi(R+x)\Delta x, \tag{6}$$

which leads to:

$$s = r_c\left(1 - \sqrt{\frac{2m_0}{\langle k\rangle}}\right). \tag{7}$$

2D exponential random graph.— This last case follows the one-dimensional analogue, but here we consider a two-dimensional Gaussian distribution. Our aim is to compute the number of connections that a section at a distance x from the circle receives from it. This non-analytical computation leads us to adopt some considerations to achieve analytical expressions.

If we consider the circle far enough from origin so that the angle variations in a polar coordinates system (describing the position of the pulse and, as a consequence, the probability of activation) are, on average, 0, then:

$$N_A(x) \simeq d\left[e^{-\frac{d^2}{2r_c^2}}\right]\cdot\left[\left(1 - e^{-\frac{R^2}{2r_c^2}}\right)\right](R+x)2\pi\Delta x. \tag{8}$$

Eq. (8) describes a first factor (marked with [...]) in which the amount of connections decreases as the distance of the section to the center of the circle grows, as expected. However, the amount of connections has a second factor in which they decay for a fixed distance section as the size of the pulse increases. In spite of this, we will consider an *effective* average radius $\hat{R}$ in the exponential decreasing term as part of the corrections in our analytical approximations. This way, we find:

$$s \simeq r_c\sqrt{2\ln\left[\frac{\langle k\rangle}{m_0}\left(1 - e^{-\frac{R^2}{2r_c^2}}\right)\right]} - \hat{R}. \tag{9}$$

For the average number of connections, we will take into account that the whole system is $L\times L$ in size, thus:

$$\langle k\rangle = \frac{\sigma\pi r_c^2}{2}\,\mathrm{erf}\left(\frac{L^2}{\sqrt{2}r_c}\right)^2. \tag{10}$$

III. NUMERICAL SIMULATIONS

In order to compare the theoretical models with realistic neuronal networks, numerical simulations of spiking neurons were carried out in equivalent settings of connectivity and culture sizes. We considered in the simulations the Izhikevich model [7], which uses a simplified Hodgkin-Huxley-type dynamics to realize an integrate-and-fire neuron dynamics. This dynamics, intrinsic to neurons, was the one simplified in the theoretical model to consider that a neuron simply required a minimum number of input connections m_0 to activate.

The Izhikevich model considers a two-dimensional system of ordinary differential equations for the evolution of the membrane potential v and a recovery variable u, of the form:

$$\frac{dv}{dt} = 0.04v^2 + 5v + 140 - u + I, \tag{11}$$

$$\frac{du}{dt} = a(bv - u). \tag{12}$$

A neuron activates when $v \geq 30$mV, which is followed by a reset process that brings the neuron back to rest:

$$\text{if } v \geq 30 \text{ mV, then } \begin{cases} v \leftarrow c \\ u \leftarrow u + d \end{cases} . \qquad (13)$$

The parameters a, b, c and d adjust the membrane characteristics, and I is the variable that accounts for the received synaptic currents. This is the term where connections play a role. The parameters a to d describe:

- a: the time scale of u. Large values represent fast recoveries. A typical value is $a = 0.02$.
- b: the sensitivity of the recovery variable u to fluctuations of v. Typically, $b = 0.2$.
- c: the reset value of v. Typically, $c = -65$ mV.
- d: the after-spike reset of u. Typically, $d = 2$.

In all simulations we considered the following values for the parameters: $(a, b, c, d) = (0.02, 0.2, -65, 2)$.

To introduce connectivity in the simulations, we add a connectivity term in the thalamic input. The connectivity matrix $\mathbf{W} = \{w_{ij}\}$ is associated to this term, which is shaped as either 'geometric' or 'exponential' random graphs. The matrix is also undirected (i.e., symmetric) and with uniform weights of value $w_{ij} = 5$ mV $\forall\ i, j$. This way, the voltages of the electric pulses sum up and ultimately provide an average m_0 to the membrane potential.

IV. RESULTS AND DISCUSSION

We present first illustrative results for the numerical simulations since they provide a realistic scenario that serves as a reference for the different theoretical developments. To compare velocities between theory and simulations, we used for the former $\Delta t = 1$ ms.

An example of simulated fronts is provided in Fig. 2 for the 2D random geometric graph case and connectivity $\langle k \rangle \simeq 27.5$ connections/neuron. We can see that an initial pulse propagates as a circular wave, with a neat activity front (red active neurons), comparable to experimental observations [5], e.g., Fig. 1A. From the data, the velocity of the front is extracted and compared, for different connectivity blueprints, with the theoretical model.

Recalling the Izhikevich model, we set $m_0 = 19$ in a similar way as in [11]. Each electric input pulse is 5 mV in strength and the membrane potential starts at -60 mV, activating the neuron when it reaches 30 mV.

Prior to comparing simulations and theoretical models, We observed that the theoretical results showed a constant velocity front the propagating pulse across space in the 1D and 2D geometric random graph, and a constant velocity for large R in the corresponding exponentially-connected networks. This allowed to set simply provide velocity v for a given connectivity $\langle k \rangle$. With this knowledge at hand, Fig. 3 compares simulations and models,

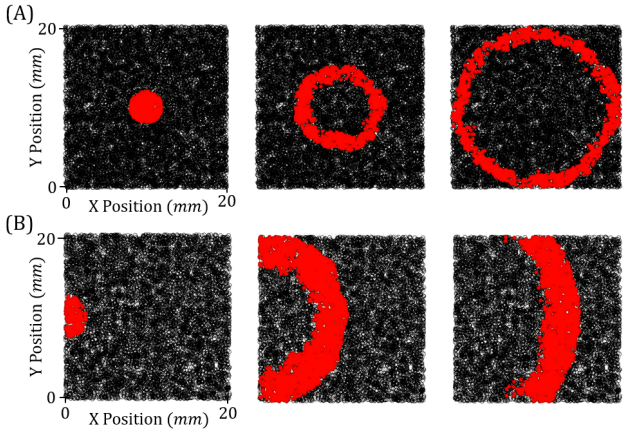

FIG. 2: (A) Numerical simulation of a pulse initiated at the left of a culture 20×20 mm^2 at 3 moments of its trajectory. From left to right: $t_1 = 4$ ms, $t_2 = 40$ ms and $t_3 = 60$ ms. $r_c = 0.5$ mm, $\sigma = 35$ neurons/mm^2. (B) Equivalent simulation of a pulse initiated in the center of the culture at 3 moments of its trajectory. From left to right: $t_1 = 1$ ms, $t_2 = 30$ ms and $t_3 = 70$ ms. $r_c = 0.7$ mm, $\sigma = 25$ neurons/mm^2.

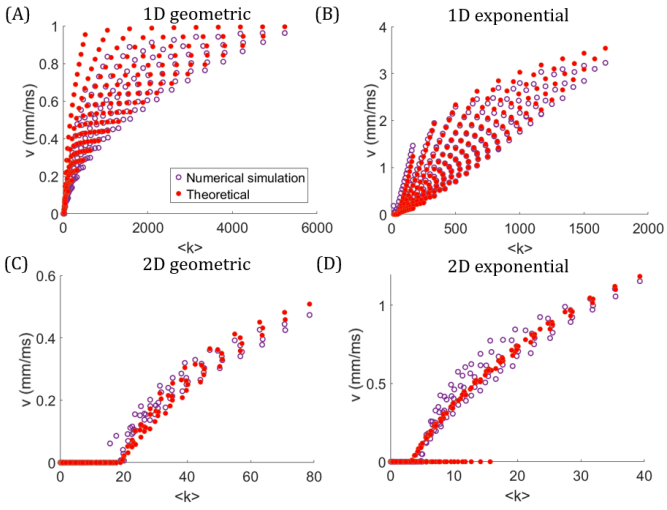

FIG. 3: Theoretical and numerical simulations of the velocity as a function of the connectivity. (A) One-dimensional geometric random graph. (B) One-dimensional exponential random graph. (C) Two-dimensional geometric random graph. (D) Two-dimensional exponential random graph. (C) and (D) are computed within a $r_c \ll R$ regime, low values of $\langle k \rangle$ within the same culture size.

showing that in general there is a good agreement in the velocity-connectivity plots. Indeed, a Pearson correlation coefficient for each panel of Fig. 3 provided $r = 0.98$ (panel A), 0.99 (B), 0.99 (C), and 0.90 (D). Threshold pulse propagation was also coincident.

Since r_c is part of the variables that constitute the $\langle k \rangle$ value in all of the considered cases, its dependency in all velocities does not show a single velocity-connectivity curve, but a variety of them, depending on how the $\langle k \rangle$ value is constructed. Since σ is the other key variable

in the $\langle k \rangle$ computation, we can achieve single curves by considering the variation of one of the variables, fixing the value of the other. An example of the changes in velocity when σ and network construction details (through r_c and L) varied, is shown in Fig. 4A.

On the one hand, considering the theoretical developments, we observed that global elements such as noise η (Fig. 4B) or the presence of inhibitory cells do not qualitatively change the $v(\langle k \rangle)$ behavior, just shifted it. For the noise, it decreases the $\langle k \rangle$ threshold needed for a front to propagate, that is, we observe a displacement in the x-axis of the curve equivalent of a lower m_0 value. For inhibition, its role is to lower the amount of activations in an infinitesimal section by adding 'negative' connections to the total, that is, setting a lower effective $\langle k \rangle$ value.

On the other hand, concerning simulations, changes in the parameters a to d in Sec. III altered the specific velocity values for a given connectivity. Parameter c modified the m_0 value, whereas a, b, and d changed the characteristic integration time for neurons to activate, increasing or decreasing front velocity.

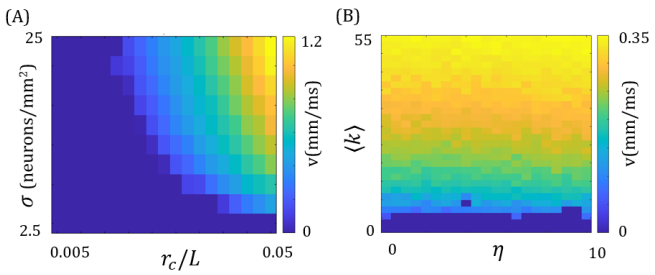

FIG. 4: Heat-maps of the pulse velocity in a 2D exponential random graph. (A) with respect to the density (σ) and the typical axon length in intensive units (r_c/L). We observe the change in the velocity with the components of $\langle k \rangle$. (B) with respect to $\langle k \rangle$ and the maximum noise η, which is added as random electric pulses (mV).

V. CONCLUSIONS

The agreement of the theoretical framework and spiking-neurons realistic numerical simulations supports the elements of a culture that have been chosen to model the pulse propagation in one and two dimensions, and explains the experimental results that link the number of connections of a neuron with the velocity of propagation of the pulse and the threshold values required for it to happen. Pulses in a neuronal culture can be modeled using geometric and statistical arguments regarding the extent of the axons and simple cumulative membrane potentials for the inside processes of a neuron for dense enough networks. Elements such as noise and inhibitory cells do not change the velocity-connectivity behavior but make easier or more difficult the existence of a front itself.

For future research, we intend first, to improve the model to consider directed networks, which are obviously more realistic from a neuroscience perspective. Second, to compare the results of this study with experimental data of spontaneous pulse propagation to investigate the limits of model application in living scenarios. And, third, we also plan on study how non-homogeneous connectivity affects front velocity or its spatiotemporal structure. Nevertheless, this study brings a foundation in the understanding of neuron communities as it explains the homogeneous culture behavior.

Acknowledgments

I would like to express my indebtedness to my advisor Dr. Jordi Soriano for his time and dedication to this study. His guidance throughout the research has been inestimable and has allowed me to go further and take delight in the work. I would also like to thank my family and friends for their support and trust during my whole studies. I am deeply grateful to you all.

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Modelització de la velocitat de propagació de fronts d'activitat en xarxes neuronals bidimensionals

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Resum: Aquest estudi investiga la propagació de polsos d'activació inspirats en cultius neuronals d'una i dues dimensions mitjançant enfocaments teòrics i numèrics. S'obtenen expressions analítiques per a la velocitat de propagació de xarxes aleatòries geomètriques i xarxes que segueixen distribucions exponencials, més realistes, centrant-nos en la dinàmica interneuronal i simplificant els processos intraneuronals. Els resultats teòrics es validen amb simulacions numèriques d'aquestes xarxes mitjançant el model d'Izhikevich de neurones, destacant l'impacte de l'estructura de la xarxa en la dinàmica del pols. Les velocitats mesurades en els models 1D i 2D són constants a través de l'espai, en coherència amb els resultats experimentals. No obstant això, s'observa una dependència esperada entre la velocitat i la connectivitat. A més, el soroll de la xarxa i la variabilitat neuronal també juguen un paper crucial en l'iniciació i configuraci de la velocitat del front. Els nostres models i simulacions aporten informació sobre com l'estructura de la xarxa influeix en l'observable macroscòpic clau que és la propagació de l'activitat
Paraules clau: Biofísica, Modelització, Simulacions, Estadística, Simetries, Ones.
ODSs: Aquest TFG està relacionat amb els Objectius de Desenvolupament Sostenible (SDGs) 3, 4 i 17.

Objectius de Desenvolupament Sostenible (ODSs o SDGs)

1. Fi de la es desigualtats		10. Reducció de les desigualtats	
2. Fam zero		11. Ciutats i comunitats sostenibles	
3. Salut i benestar	X	12. Consum i producció responsables	
4. Educació de qualitat	X	13. Acció climàtica	
5. Igualtat de gènere		14. Vida submarina	
6. Aigua neta i sanejament		15. Vida terrestre	
7. Energia neta i sostenible		16. Pau, justícia i institucions sòlides	
8. Treball digne i creixement econòmic		17. Aliança pels objectius	X
9. Indústria, innovació, infraestructures			

El contingut d'aquest TFG, part d'un grau universitari de Física, es relaciona amb l'ODS 3, i en particular amb la fita 3.D referent a la gestió de malalties, doncs la comprensió dels comportaments neuronals pot ajudar a identificar components patològics. També es relaciona amb l'ODS 4, i en particular amb la fita 4.4, ja que contribueix a l'educació a nivell universitari. Finalment, també es pot relacionar amb l'ODS 17, fita 17.6, perquè fomenta la "triangulació en matèria de ciències", unint conceptes d'àmbits com la física, la matemàtica, biologia i medicina.

GRAPHICAL ABSTRACT