Research Article

A minimalist computational model of slice hippocampal circuitry based on Neuronify™ for teaching neuroscience

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The hippocampal (HP) formation is a vital component of the central nervous system in processing memory, learning, and spatial navigation. Existing methods are obsolete to address new emerging questions as our understanding of HP circuits and its connections advances. Hence, there is a need for new techniques with an accessible approach for visualizing and understanding the inner connections and circuitry.

Research requires a quick update of textbooks and a better integration of new media to facilitate the teaching of these neural structures, which until recently, was an issue due to availability of limited resources. For example, understanding the dynamics of neural circuits' activities is a great challenge in the teaching of neuroscience, because by only using pictures, drawings, and diagrams, it is not possible to express the complete structural and functional effects that each circuit imparts. One solution to this challenge might be the use of computational models adapted to these diverse contexts. The construction of simple computational models can be an excellent alternative in teaching these complex dynamics since they reduce the use of animal models, amplify and simplify structural relationships, promote quick and easy visualization, and uncover possible functional and structural interventions. This interactivity is crucial for a better understanding of the causal relationships between nuclei and neural circuits. Conversely, it is important that computational models aimed at teaching are simple so that any student, regardless of their mathematical background, can understand and manipulate the structures and dynamics of interest.

Further, software packages that do not require programming knowledge for its use are indispensable. However, generally this limitation also restricts the structural and dynamic representations possible for study. Here, we demonstrate the use of Neuronify™ software, which uses simple functional

representations of neurons and circuits. We represent the most important pathways and connections of the HP formation by building a simplified model that shows the main known relations between the subregions [Cornus Ammonis (CA)1, CA2, CA3, and CA4] and afferent nucleus (subiculum and dentate gyrus).

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Summary

The field of computational neuroscience has been fundamental for the increasing knowledge about the brain machinery, its activity, and the relation between these, especially because it enables simulating and visualizing complex brain behavior numerically, without carrying out experiments, which may lead to a better understanding about the system in a shorter time. The present article shows a computational model of hippocampal circuitry modeled using the software Neuronify™ to build a clear representation of this critical structure of the central nervous system (CNS) that can be used for many purposes, the most promising being the study and teaching of neuroscience. By considering this approach, not only can relevant information about the hippocampus be obtained, but it can also help students to better relate concepts covered in class to real applications, ultimately, it endorses neuroscience as an interdisciplinary field.

Introduction

The field of education in neuroscience (RAMIREZ, 2020) faces many specific challenges that differ from other areas of science because of its particularities. Specifically, the requirement of a special set of pedagogic strategies and materials, the limited range of tools available for investigation (e.g., electrophysiological recordings, behavioral index, biochemical markers), and the complex technical language of area of study (WILLINGHAM, 2009). The resources required to teach the different aspects of the brain function are limiting due to various factors, e.g., books show a static view of the brain and fail to show the dynamics in a didactic way, and animal models demand technical skill and thorough dedication as they are difficult to manipulate and need to be used responsibly.

In comparison, computational models are an interesting alternative solution since they bypass many issues (JIRSA et al., 2014), such as forcing students to learn by simple figures and euthanizing animals, thus supporting initiatives like the 3Rs (replace, reuse and refine)
(PRESCOTT and LIDSTER, 2017). Computational models offer a fun, easy and interactive way of studying and understanding the complexity of neural circuits and physiological processes.

However, computational models present a series of limitations. The most common is that they generally require knowledge of programming logic (ROGALSKI and SAMURÇAY, 1990). Additionally, since the mathematical descriptions can be too abstract, researchers investigating biological basis use it minimally.

A few software packages exist that propose simple biological representations with user-
friendly interfaces, thus allowing anyone to manage and construct their own biological system (KIPARISSIDES et al., 2011). Here, we use the free software Neuronify™ (NORTHCUTT, 2021), an intuitive platform with a user-friendly interface that does not require expertise in any programming language. Also, many other applications exist that allow the construction of different types of computational models of biological systems, which are not restricted to neuroscience, such as PhET™, a simulator for physics, chemistry and biology (WIEMANet al., 2008), “portal SESI educação” from Brazil, MERLOT Biology™, and Atomify™. These simulators have a simple interface and are used for education purposes.

Despite the simple biological representations and some functional limitations offered by Neuronify™, we were able to build the complex inner circuitry of hippocampal (HP) formation using only excitatory and inhibitory leaky integrate-and-fire neurons, adjusting them in specific patterns of connectivity to express their real dynamics. For instance, we represented the main pathways of the trisynaptic circuit (JEFFREY and MICHAEL, 2016) and highlighted its subfields. By using the virtual sensors provided by the application, we could show the temporal patterns related to the action potential of specific neurons of each HP subfield.

Considering the HP formation neuroarchitecture (KEINATH et al., 2020), this model preserved the disposition of semicircular-like complementary structures from dentate gyrus (DG), going through the subfields of Cornu Ammonis (CA3, CA2 and CA1) to the subiculum (SUB), yielding a comprehensive view of the circuit connections (SHIMBO et al., 2021). Additionally, we were able to construct a simplified

version of the whole HP circuitry by reducing and emphasizing its main nucleus and path connections. Since this circuitry reduction maintains the same physiological activity outputs, it can be an important educational approach to teach how the brain uses redundancies and 'motifs blocks' to process information (WOMELSDORF et al., 2014).

In summary, we show how computational models might be useful for teaching neuroscience. We propose an easy way to understand brain networks (CLEMENT and LOVAT, 2012) through the construction of a HP network, its main features and connections, using Neuronify™. This work helps the study and understanding of the HP formation, making it easy to observe the response of its parts to stimuli in different conditions determined by the experimenter, simplifying and dynamizing the teaching-learning process.

Methods

The computational model describes the main circuits of the hippocampus and its correlations considering its input-output information. By a motif-based approach (BRAGANZA et al., 2018) of subregions in HP formation, patterns of recursion, inhibition, and propagation of input signals were established, thus setting the connections between these microcircuits. The motif representation uses the minimum number of neurons (excitatory and inhibitory) and synapses, hence emphasizing its main structural connections and functional relationships. This representation makes the model description more intuitive, and morphologically accurate to a HP slice. We used the software Neuronify™ since it is user-friendly with simple features built specifically for educational purposes (ELBEZ et al., 2018). The software's interface is a simple "grab and drop" system, where the users only need to select the components, they want to display on the screen. In the simulator, glutamatergic and cholinergic neurons were labeled as excitatory, and GABAergic as inhibitory. Additionally, the mossy fibers (MF), perforant path (PP) and Schaffer collaterals (SC) were plotted as neurons, and not axons. The information flow crossing these paths were maintained under the same environmental conditions. Therefore, by representing these fibers as neurons, we were able to control the cell parameters needed to hold the concomitant flow of discharge.

Furthermore, the sensors and current sources provided by the software allowed a simultaneous testing process, which made it possible to improve the model during its construction. These sensors offer vast possibilities for analyzing the model, by measuring the activity in any neuron or group of neurons when the input has a specific chosen characteristic (Figure 1).

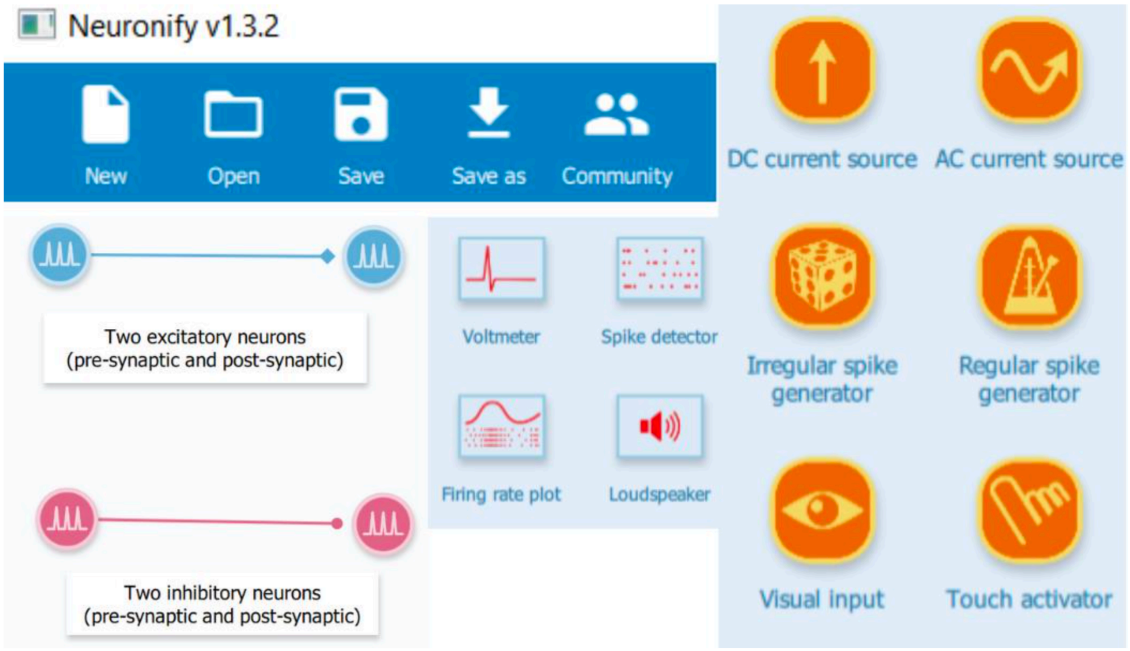

Figure 1: General portrait of Neuronify™ main features. This assembly shows some of the most important components of the software: the option for creating, opening and saving files; the appearance of the neurons, both excitatory and inhibitory, when plotted and connected; the options for sensors that measure the nodes firing by different kinds of plot, such as voltmeter, firing rate plot, spike detector, and a loudspeaker that emits a noise when the selected neuron fires; and the current sources, with a variety of possibilities for stimulating the network by direct or alternating current and generators of spike with regular, irregular or user-defined activation (by using a camera or touching the generator).

The HP circuit has many redundancies and is essentially constructed by links between smaller circuits called motifs (HANGYA et al, 2014). According to Braganza and Beck (BRAGANZA and BECK, 2018), a circuit motif is “a conserved anatomical pattern of connections between specific cell types.” Since motifs are the basic blocks of HP circuitry, understanding these blocks is critical in the implementation of any equivalent computational model.

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To construct the whole HP circuitry, a total number of 226 excitatory and inhibitory neurons were used and displayed in patterns according to reviewed literature (THOMPSON et al., 2008). This construct allowed the analysis of activity of each subfield and component of the HP circuit (Figure 3).

We identified and separated HP formation to determine the specific functionalities of each part (KRAGEL et al., 2021). The five main features of the subfields can be understood as follows: first, sparsity of DG, i.e., less intensity of output compared to the input; second, the recurrence of stimulation of the CA3 with strong and localized inhibition; third, selectivity of excitatory output by inhibitory feedback of CA2; fourth, the information cadenced flow with collateral excitation of CA1; fifth, the relative temporal synchronization of spikes as output through simultaneous excitation coupled to inhibitory feedback of SUB (DE BRIGARD, 2014).

The six motifs were set to match these features. We selected alternative motifs, as follows, that could be incorporated in the network to generate the effects of interest only by using a combination of excitatory and inhibitory neurons:

a) *Simple Feedforward Excitation*: motif relates to the simple and forward propagation of an excitatory signal, causing it to arrive at downstream structures.

b) *Simple Feedback Inhibition*: motif responsible for inhibiting activity on a upstream neuron in a network, preventing it from firing as much as it was previous to excitation of the feedback inhibition network.

c) *Simple Feedforward Inhibition*: similar to 'Simple Feedback Inhibition' where the inhibition occurs on a downstream neuron instead of an upstream neuron.

d) *Recurrent Excitation*: a motif characterized by a postsynaptic excitatory neuron that feeds back to the presynaptic one, therefore reinforcing the signal that it receives.

e) *Simple Feedback Excitation*: similar to 'Recurrent Excitation' where the signal amplified by the recursion between two excitatory interneurons induces a robust representation of a given attribute.

f) *Global Feedback Inhibition*: promotes a selective pattern of activation of the excitatory postsynaptic neurons. An inhibitory neuron selectively chooses which of the neurons are going to fire by varying its synaptic weights while the other neurons remain "silent."

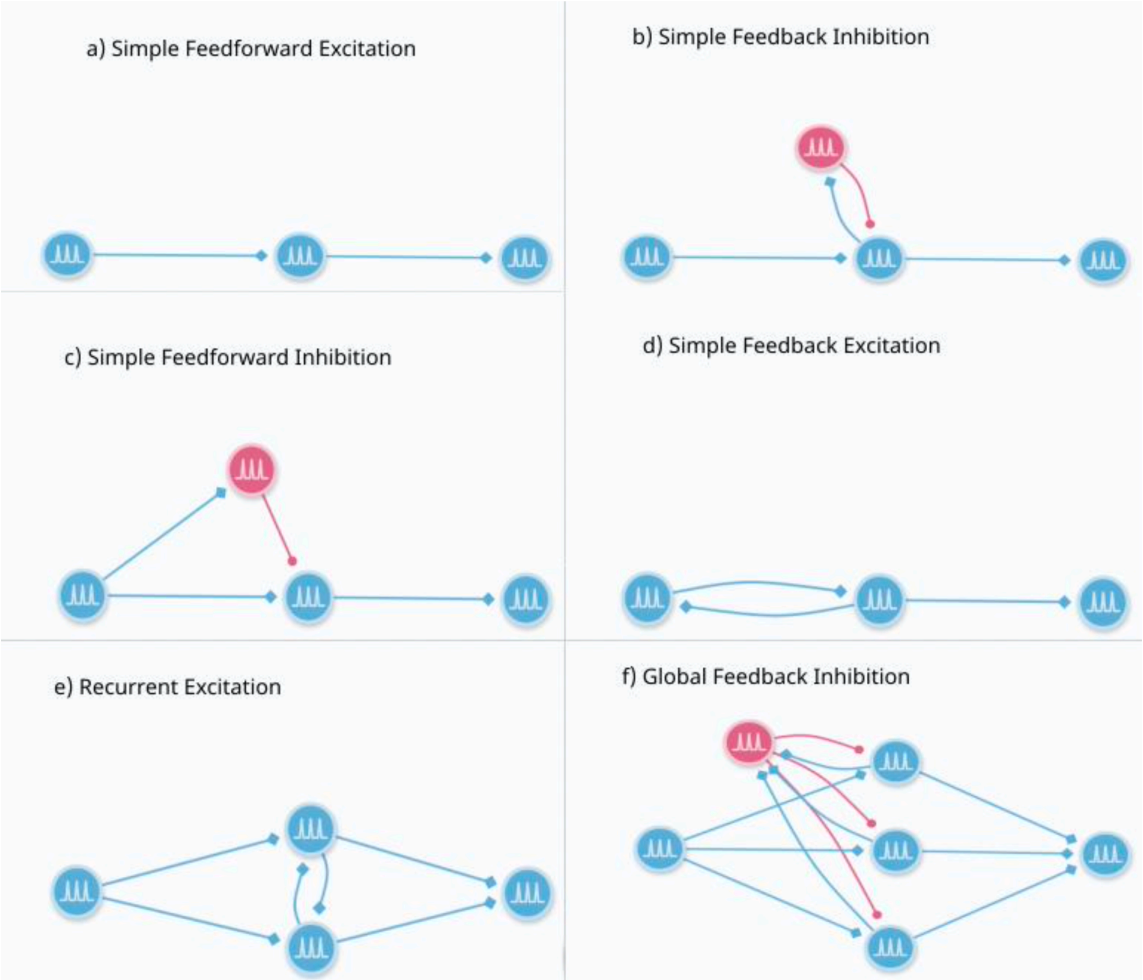

Figure 2: Main circuit-motifs used. This list of constructions shows the motifs needed for building this model. These motifs are useful in computational neuroscience since they simplify complex structures by logical pieces with a not specific anatomic correspondence that is repeated through an area of the nervous system. a) This motif known as “simple feedforward excitation” relates to linear propagation of the signal from one cell to another. Computational mechanism: signal propagation. Computational / behavioral function: linear propagation of information. b) This motif known as “simple feedback inhibition” is characterized by inhibitory feedback that limits the maximum excitation of a neuron and may represent a way to control the output of the structure in network. A variation of this motif was also used, in which the presynaptic neuron was inhibited instead of the neuron that stimulates the inhibitory neuron but resulting in the same effect. Computational mechanism: output normalization. Computational / behavioral function: controlling maximum output / sparsity. c) This motif known as “simple feedforward inhibition” basically plots an inhibitory neuron, which is able to limit the range of activation of another cell by amplifying the possible levels of excitability the next cell will be exposed to. Computational mechanism: input normalization. Computational / behavioral function: increasing the dynamic range. d) This motif known as

"simple feedback excitation" contains a postsynaptic neuron exciting the presynaptic neuron, reinforcing the arriving signal by its repetition between the cells. Computational mechanism: repetition. Computational / behavioral function: reinforcement of the signal. e) This motif known as "recurrent excitation" is made of excitatory neurons stimulating each other in order to amplify the signal, generating a robust representation of a determined feature. Computational mechanism: amplification. Computational / behavioral function: robust feature representation. f) This motif known as "global feedback inhibition" presents a characteristic connectivity between its components, with a row of excitatory neurons establishing synapses with an inhibitory cell that feedbacks them, causing an effect called "k-winners take all." It means that the "k" selected cells that receive a less intense inhibitory feedback will fire while the rest of the neurons will stay inactive, being an effective way to discriminate a pattern of interest to a network. Computational mechanism: k-winners take all. Computational / behavioral function: pattern discrimination.

The above motifs are attributed to every structure of the HP formation. DG has a wide presence of simple feedforward excitation and inhibition as well as feedback inhibition. CA3 has feedforward excitation and inhibition, feedback excitation and inhibition, and recurrent excitation. CA2 has feedforward excitation, and simple and global feedback inhibition. CA1 has feedforward excitation, feedback excitation and inhibition, and recurrent excitation. SUB has feedforward excitation and feedback inhibition. Thus, each constructed region shows the peculiarities in its organization similar to a HP slice.

We emulated the regions on Neuronify™ using only excitatory and inhibitory neurons. The current sources and sensors were tested during and after each region was composed. We maintained default neuron settings (threshold, resting potential, refractory period, membrane resistance and membrane capacitance) for easy manipulation of the network. Alternatively, we implemented a deficiency of a voltage-dependent sodium channel by changing the membrane's threshold potential (HEYNE et al., 2020), while maintaining other properties to equalize every neuron feature. These networks highlighted the spike patterns in relation to the structural connectivity of the cells.

Model building started with characterizing the activity of each portion of HP formation followed by determining the motifs present in in vivo models. Small and enough artificial neurons were connected according to the selected motifs emulating the robust features in a topologically accurate network. To emphasize the educational purpose of the network, we created connections similar to that of a histological HP slice (Figure 3).

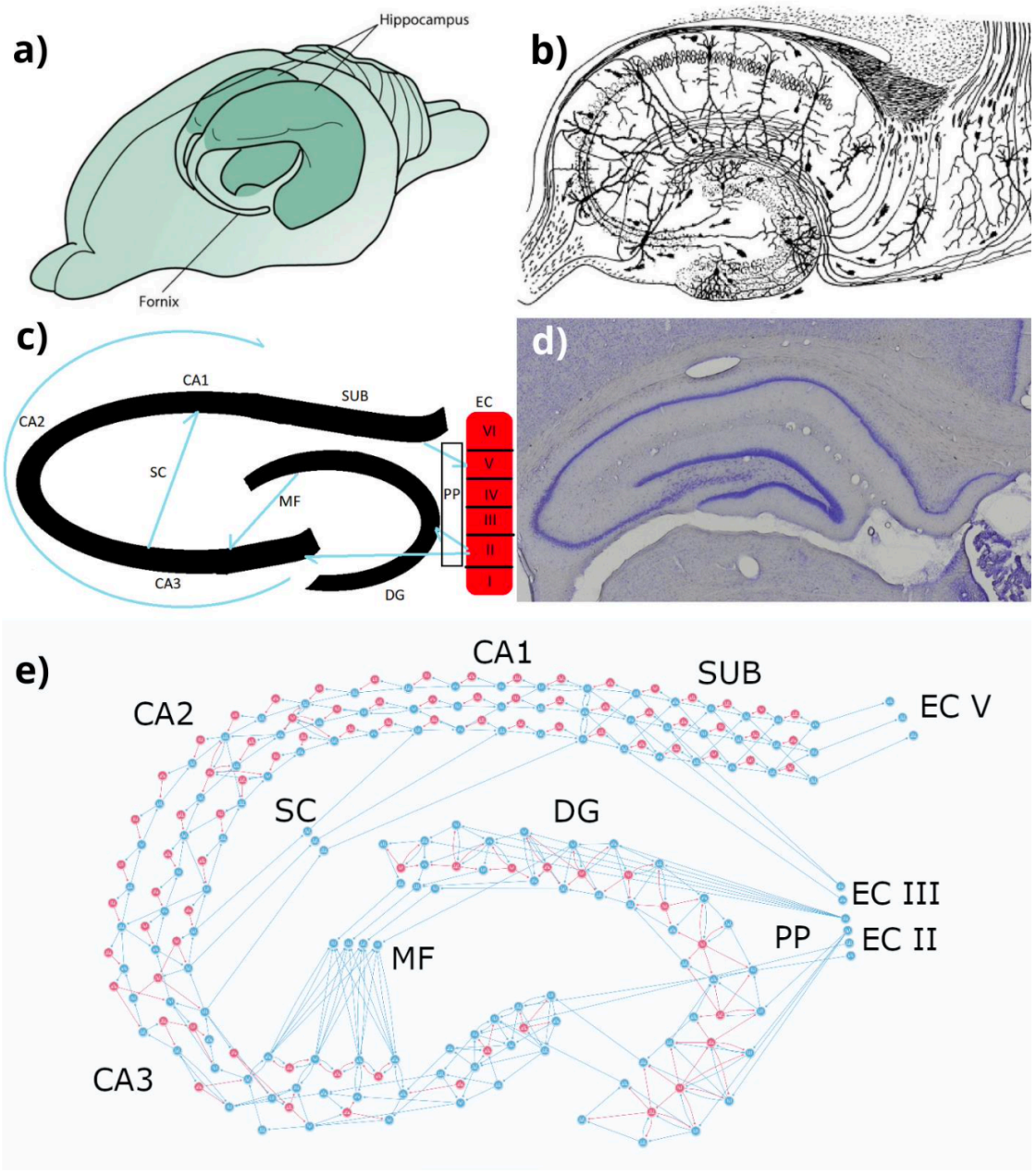

Figure 3: Hippocampus in human brain, mouse hippocampal slice, schematic hippocampal formation, and complete portrait of the computational model of hippocampal formation. a) Schematic representation of the location of the two hippocampi inside a rat brain. *Cellular and Molecular Neurophysiology*, fourth edition. Elsevier, 2015. Copyright™. b) Drawing of a transversal slice of the hippocampus by Ramon y Cajal, 1911. c) The illustration simply represents the main structures of hippocampal formation, with the most relevant efferences indicated by the blue arrows. EC II: entorhinal cortex II; EC III: entorhinal cortex III; PP: perforant path; DG: dentate gyrus; MF: mossy fibers; CA1-3: Cornu Ammonis; SC: Schaffer collaterals; SUB: subiculum; EC V: entorhinal cortex V. d) Hippocampal slice in the brain of a wistar rat in a coronal section stained with cresyl violet. (Own source) e) By plotting 226 neurons with a complex machinery of synapses, the

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neuroarchitecture of hippocampal formation could be preserved whereas its activity could be well demonstrated. Basically, and classically, the information arrives from the EC II and EC III, flows through the "gate," which is the DG by PP up to the CA3 - that receives its afferences mainly by the MF, processes and conducts the information together to the CA2 and CA1 and, in the SUB, shapes the signals directed to neocortex, firstly received in the EC V.

The medial entorhinal cortex (MEC), subregions II (EC II) and III (EC III), was represented by a row of excitatory neurons composed of six sources of input. This row of neurons received connections from current sources chosen by the researcher. These represent the main pathways by which signals arrive at the HP formation in DG (TATU and VUILLIER, 2014). These six excitatory neurons were designed to project efferent to the DG, CA3 and CA1. A feedforward excitation motif allowed the efferents to receive versatile types of input from the current sources provided by Neuronify™.

In DG, the neurons were arranged into a C-shape form with alternating excitatory-inhibitory- excitatory three-layer structure similar to the actual cytoarchitecture of the archicortex (MORAIS et al., 2020). The structure had a total number of 16 excitatory neurons which was the minimum number of cells sufficient to emulate HP functions, while, creating an easy-to- view network. Experimentally, the number of neurons demonstrated the expected performance without compromising the fidelity of the activity. Similar logic was extended to represent other subregions. The second layer strongly inhibits the others, letting only three neurons, adjacent to the superior limit of the DG representing mossy neurons, without inhibitory input, with 12 inhibitory neurons and a large number of synapses. In turn, the excitatory neurons connect with other excitatory neurons positioned laterally or frontally and at least to one inhibitory neuron that feeds back to them. The last layer consists of 16 excitatory neurons including three mossy neurons. Through the layers, feedforward excitation, feedback inhibition and feedforward inhibition can be observed.

In our model, eight excitatory neurons represent the anatomical input from the "mossy neurons" from the DG to the CA3 subfield, such that four neurons each represent the fibers and the receivers of the input. Additionally, we used two neurons in the inferior part of the DG representing input from the SC. For the connections from EC II, we used two neurons directly connected from the PP, which are the main pathway of fibers from the neocortex to HP formation (AMANI et al., 2021).

Further, the subfields' inner connections were randomly plotted, with 12 excitatory neurons and 3 inhibitory ones showing SC stimulation to each other with a strong aspect of inhibition. However, they

were organized in a way that allowed any amount of input signals to be filtered by the inhibitory neurons, strategically connected to afferent neurons and excitatory interneurons. This characteristic is better observed in its portion adjacent to DG, almost located in its hilus, where CA4 can be found (EZAMA et al., 2021).

Another important feature of this part of the hippocampus is the recursion observed between the MF from the DG and the first afferent pyramidal cells in CA3. This recursion corresponds to the reinforcement of arriving information that will be only processed into the hippocampus by the action of biochemical and electrophysiological mechanisms, thus enhancing the learning (BARTSCH and WULFF, 2015). To represent this recursion, we used the motifs feedforward excitation and feedback excitation coupled to inhibitory feedback in CA3 to limit the excitability of the signal-receiver cells.

Next, we represent the connections between CA2 and CA3 (DING, L. et al., 2020). We used four afferent cells from CA3 connecting to the surrounding neurons in a pattern characterized by inhibitory feedback that limits the excitability of these cells and the other ones connected to them. Therefore, one of these pyramidal neurons' synapses onto one inhibitory cell and the other three pyramidal neurons synapse onto two inhibitory neurons each. Also, these afferents establish connections to one excitatory neuron to keep the information flowing to the CA2. Computationally, a greater number of connections between both excitatory and inhibitory neurons were required to generate the huge activation attached to a high level of inhibitory feedback in CA2. This structure required a total number of 11 excitatory and 4 inhibitory neurons.

Furthermore, we must consider that CA3's border with CA2 is not precise since these subfields are not anatomically well established (MAHZER and HASSAN, 2021). However, a "transition area" that is still a part of CA3 shows a gradual regularization of motifs more related to CA2. This area also has efferents directly to CA1. Assuming the role of SC, we placed three neurons between the area and CA1 to mediate these connections. Hence, the way out CA3 leads information to CA2 by three layers of neurons connected in a pattern of feedforward excitation coupled to feedback inhibition, maintaining the pseudo-unidirectional propagation of information (SUN et al., 2021). The boundary of the transition area is immediately after the last (upper) excitatory cell, where the SC is present. Here, SC was modeled by ten excitatory and six inhibitory neurons disposed in connectivity patterns that mix the partially randomly plotted CA3 neurons with great recursion and limitation of excitability paired to the continuous propagation and inhibitory feedback typically seen in CA2.

Furthermore, CA2 has a feature of global feedback inhibition (MCHUGH et al, 2021), by which it selectively enhances synapses according to the stimulus provided (NAVAKKODE et al, 2022). In our model, this feature was represented by a feedback system of three neurons, one from each layer to the same inhibitory neurons where synapses might have their weights changed to strengthen few connections over others, thus composing the global feedback inhibition motif.

In CA1, 23 neurons were used to maintain proportional numbers in the subfields of the three- layer structure. This configuration was sufficiently large to conduct experiments even in a non- scientific computer, while also including the pattern of linear propagation feedforward excitation and inhibitory feedback mechanisms.

In our model, CA1 also received input directly from EC III by PP, showing a different pattern of organization. This pattern was represented as a row of excitatory neurons that stimulate itself located before the SUB layer (BÖHM et al., 2018). The configuration was adopted to maximize the stimulation of the network since beyond the SUB layer the information will flow from the HP formation to the neocortex.

In summary, a total number of 15 excitatory and 15 inhibitory neurons were plotted, where 27 of them were designed to keep the feedforward excitation coupled to feedback inhibitions. The last three excitatory neurons denote recurrent connections, thus stimulating each other to enhance the activation of the organized region and start the relative temporal synchronization of the signal.

The SUB structure was designed to be a continuation of the three-layer architecture, but the layers are less independent. Here, the propagation of the signal takes collateral direction and is not linear as seen in CA2 and CA1. Each neuron is configured to stimulate two other neurons in the following row until the end of the SUB, projecting its efferents to the three terminal neurons labeled as entorhinal cortex V (EC V) which is a part of the lateral entorhinal cortex (LEC) (NILSSEN et al., 2019). The LEC receives three to five spikes from SUB sequentially and spreads the information to the adjacent neocortex (YU et al., 2021). Considering the configuration of this area, 18 excitatory and 18 inhibitory neurons were plotted maintaining this connectivity pattern of inhibitory feedback and forward and collateral excitation (using the motifs of feedback inhibition and feedforward excitation).

Results

Using this computational model, we propose a simple platform that allows the study of the structural configuration and functional activities of each subfield of the HP formation, and their relationships. By placing the virtual sensors on each subregion, it was possible to observe the interdependence and the type of information processing that each region performs with respect to the other, and relative to the whole HP circuit.

HP subfield formations and their dynamics

The signal first arrives at the DG of the HP formation. The pattern of eliciting action potentials is sparse and wide-distributed around the structure, because the granular cells (excitatory neurons) are exposed to intense inhibition. Information gets to DG through PP from EC II and EC III and its activity clearly shows fewer spikes in comparison to that of its neighborhood (PIATTI et al., 2013; Figure 5).

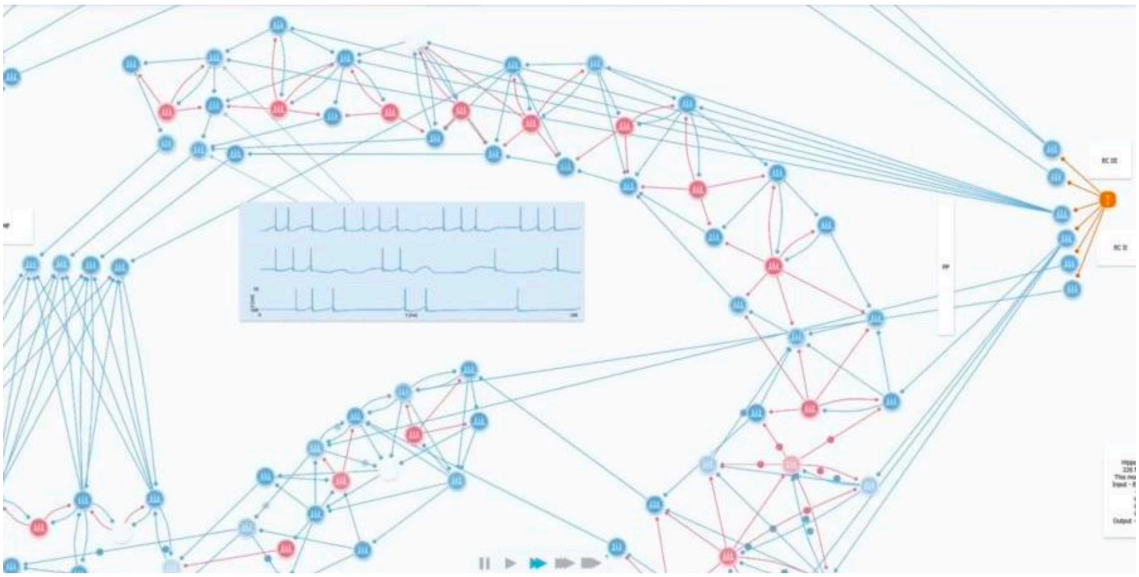

Figure 4: Activity of dentate gyrus. The signal coming from the medial entorhinal cortex (EC) II is processed in a way that sparsity (less spikes in the output when compared with the input) is widely observed, not because of a greater number of inhibitory neurons, but by the number of synapses they establish with the granular (excitatory) ones.

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From DG, information flows to CA3 through the axons of mossy glutamatergic neurons in MF. Since Neuronify™ cannot build an autapse, MF were plotted as excitatory neurons receiving feedforward input from DG and feedback input from pyramidal neurons of CA3 to simulate an autapse of CA3 pyramidal neuron. This motif is based on a learning rule (BECKER, 2005) according to the synchronization of spikes of postsynaptic and presynaptic neurons as a regulator for strengthening an associative memory.

It is possible to observe recurrent excitation and feedback inhibition (with feedforward excitation, feedback excitation, recurrent excitation, feedforward inhibition and feedback inhibition motifs) between the pyramidal and basket cells in CA3, which is part of the hippocampus proper and located on the fornix (BENEAR et al., 2020). They can be found all over the hippocampus in circuits of feedback inhibition, and hilar interneurons, propagating signals in convergent and divergence patterns (Figure 3). Besides these main components, CA3 receives information directly from EC II and shows two main outputs: CA2, continuing from the fornix, and CA1, through SC (CACUCCI et al., 2017), composing the well-studied trisynaptic circuit (DG, CA3, CA1, SUB).

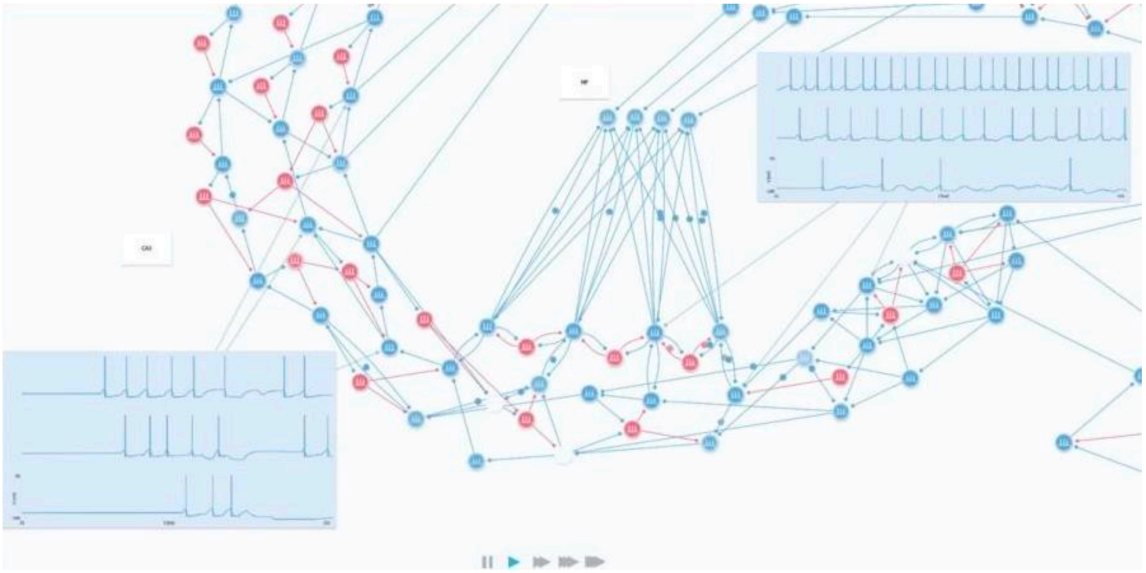

Figure 5: Activity of Cornus Ammonis (CA) 3. A considerable variety of patterns of spikes are observed as a result of the different kinds of connections, inputs, and types of cells in this field. The portion next to dentate gyrus (DG) shows randomized patterns of connectivity that respect the purpose of softening the signal since the following part receives the main and stronger input. Thereafter, a region in the “curve” mixes these characteristics with the features of CA2, with a simpler propagation of the information attached to a simple inhibitory feedback system.

CA2 connections followed a basic pattern with three layers of inner pathways representing linear propagation and feedback inhibition (Figure 4; HIRASE et al, 2003). Its pathways have been well characterized recently and data suggests that this structure is important for social memory (TZAKIS et al., 2019).

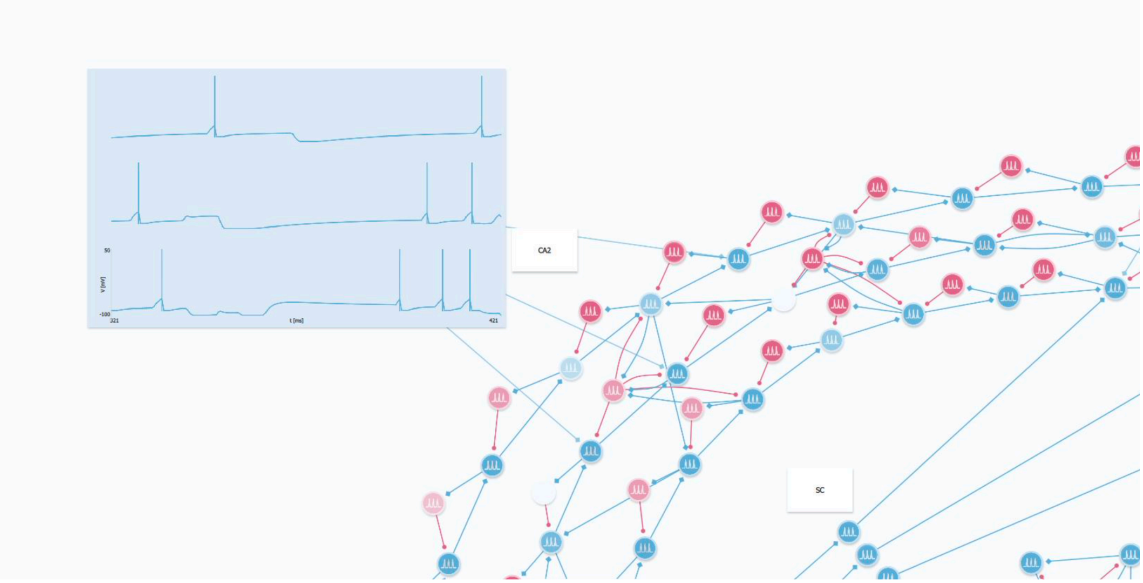

Figure 6: Activity of Cornus Ammonis (CA)2. The linear propagation of information is easily observed by the voltage sensor as the spikes occur almost simultaneously between the layers and with a relatively huge temporal separation provided by the individual inhibitory feedback (that is given by the inhibitory neurons). Besides these, the feature of global inhibitory feedback practiced by two inhibitory neurons that plays the role of "gates," functioning as nodes that decide which neurons will fire by the weights of their efferent synapses are notable.

The last part of hippocampus proper is CA1, whose circuitry was designed partly in continuity with CA2 and partly mixed with the components of SUB in a more complex configuration of afferents and efferent. The subfields CA1 receives input directly from EC III by PP (Figure 5). It works as an information integrator, being a fundamental part of hippocampus in processing memory, learning, and spatial navigation. Spatial navigation is especially relevant due to the molecular particularities of some of its cells (grid cells and place cells) responsible for mapping the world around us (SOLTESZ and LOSONCZY, 2018).

Despite the widely accepted notion that CA3 connects to CA1, recent studies (SHI et al., 2013) indicate a

bidirectional propagation between CA3 and CA1, where the path from CA3 to CA1 is much more developed. Hence, we plotted only a portion of partial random synapses, so that the signals from CA1 could flow to CA3. Since the literature is unclear whether the recurrent excitation between some neurons of CA1 exists, we plotted it only once.

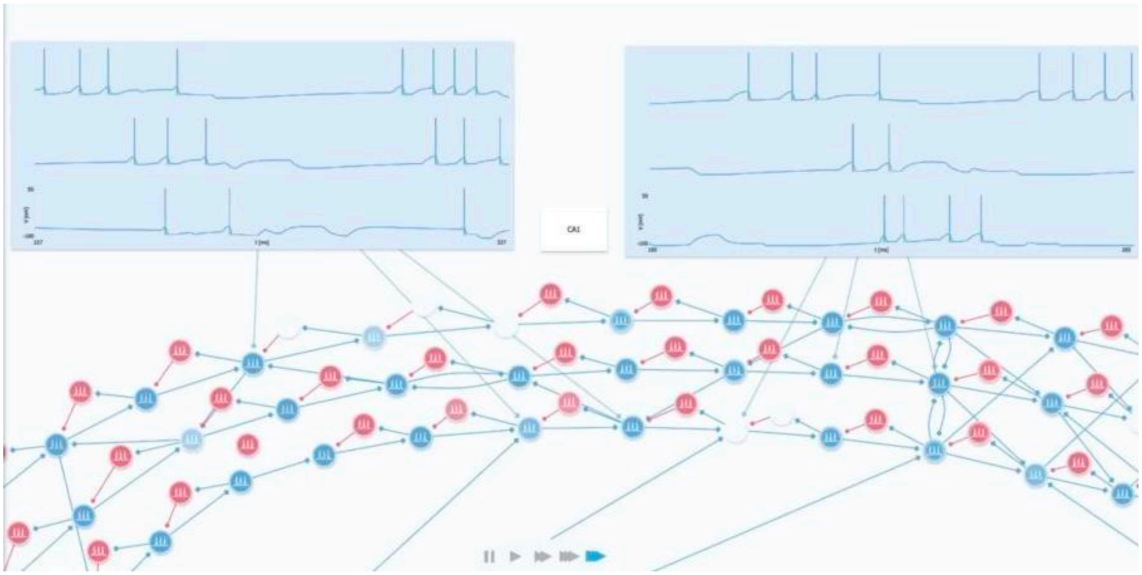

Figure 7: Activity of CA1. Features of feedforward propagation are combined with feedback inhibition between the three neuronal layers, besides a bidirectional spreading of the signal in singular and random excitatory neurons (one every layer), which coupled with recursion between three neurons next to the subiculum (SUB), gives this region the main role in the processing of information by a spectacular variety of connections

The output coming from HP formation is forwarded to SUB, whose connections look less random than CA3 but is equally complex, with feedforward propagation applied to excitatory convergence and feedback inhibitory (STAFSTROM, 2005). The normalized output reaches LEC in EC V, spreading itself to the neocortex around (Figure 6).

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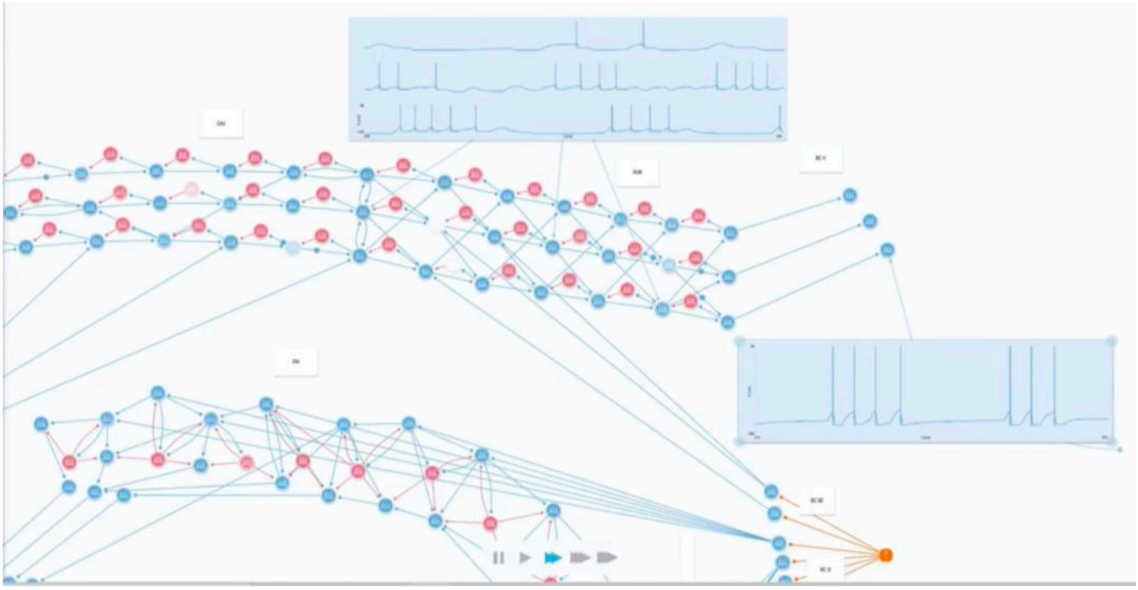

Figure 8: Activity of SUB and the output. Beyond a linear propagation of the signal (restricted to feedforward neurons of only its own layer a divergent pattern by which the spikes gradually and partially synchronize up to the final portion of subiculum (SUB) is observed, leading the information to medial entrohinal cortex (EC) V with clustered spikes, in series of three to five shoots every stimulus.

Not all features of inputs and outputs of hippocampus could be modeled. Yet, the spike activity in each of the subfields by sensors provided by the software match well when compared with biological HP slices (REYES-GARCIA et al., 2018). Thus, his simple model aids in the discussion and understanding of structural connections and its associated activities. The difference seen between the model and biological sample is a good opportunity to discuss the universality and redundancies of the neural circuits. Therefore, throughout the process of building the simple model, it is even possible to formulate predictions and hypotheses using solely the structural and functional modifications (Figure 9) of the circuit.

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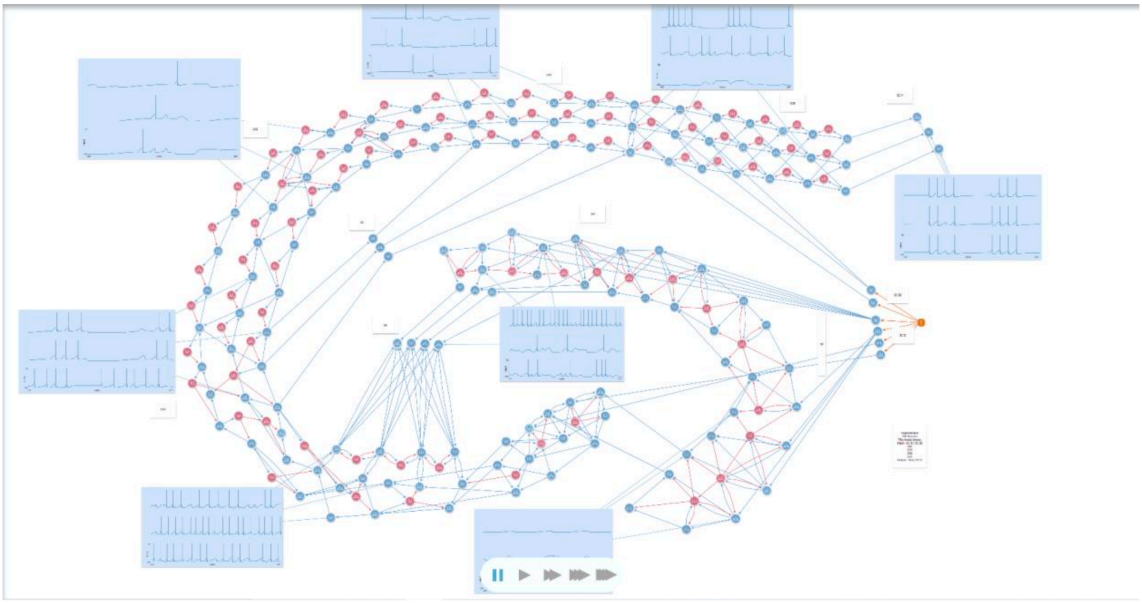
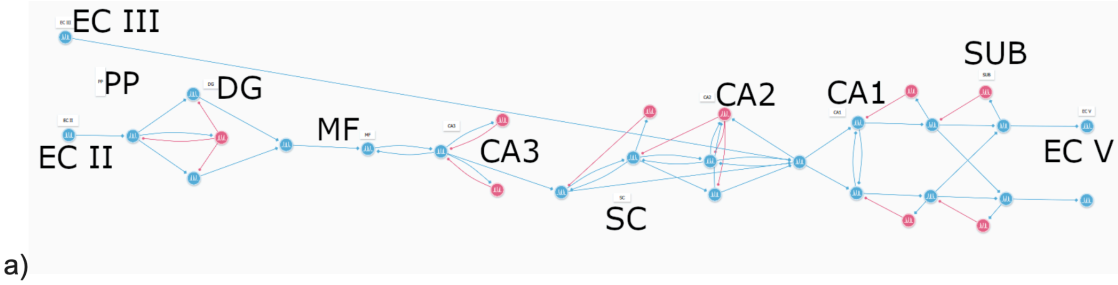


Figure 9: Portrait of full hippocampal activity. Wide view of the complete model working, with the behaviors of each field of hippocampal formation being shown smaller than in Figures 2-7. It is possible to visualize the "entire pathway" of the main circuit: information coming from the medial entrohinal cortex (EC) II and EC III and passing through the whole hippocampal formation until it arrives again at the neocortex by EC V.

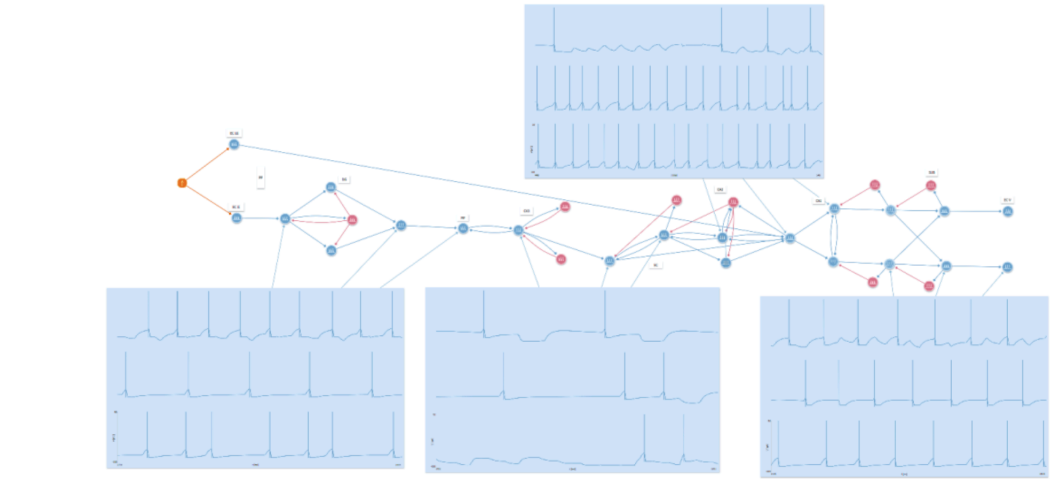
Computational simplification of HP circuitry

The establishment of circuit motifs allowed a subsequent construction of a simpler version of the HP circuitry. We observed a broader view of the flow of information in the structure, thus making it easier to visualize the HP activities (WOMELSDORF and EVERLING, 2015). Here, we were able to reproduce most of the complex HP activities and preserve its main recurrent connections, motifs configurations, while using only 31 cells, 21 excitatory and 10 inhibitory (Figure 10).

By turning the complex network into a simpler one, we asked whether it is possible that the brain uses redundancies between neural connections, perhaps for code protection? Reducing the structures and connection rules of HP circuitry can be an interesting educational strategy since it can simplify the understanding of its functional aspects.



a)



b)

Figure 10: Simplification of the model of hippocampal circuitry a) With 31 neurons, it was possible to emulate the main activity of each subregion of hippocampal formation by this motif-driven model (by comparing these recordings with the ones in Figures 5-9 it is possible to find a good compatibility level). b) The activity of each subregion and the reason for these specific firing patterns are described in the article.

This model's simplification shows how effective the motif-approach is. Specially in context of limited computational power, simplified models like this can be of great applicability depending on the purpose of the experimenter. Additionally, they indicate the effectiveness of neural redundancies since they tend to appear in structures according to their functionalities (INGALLS et al., 2015; GOOGLE QUANTUM IA, 2021).

Discussion

Despite the simplification of the proposed model, it demonstrates high accuracy related to the neuroarchitecture and functional correspondence with real HP circuitry (Figure 11). We believe this type

of model and modeling practice can be very useful for teaching and learning neuroscience, such as studying the HP formation, connectivity between neural networks, and electrophysiological properties of neuronal cells.

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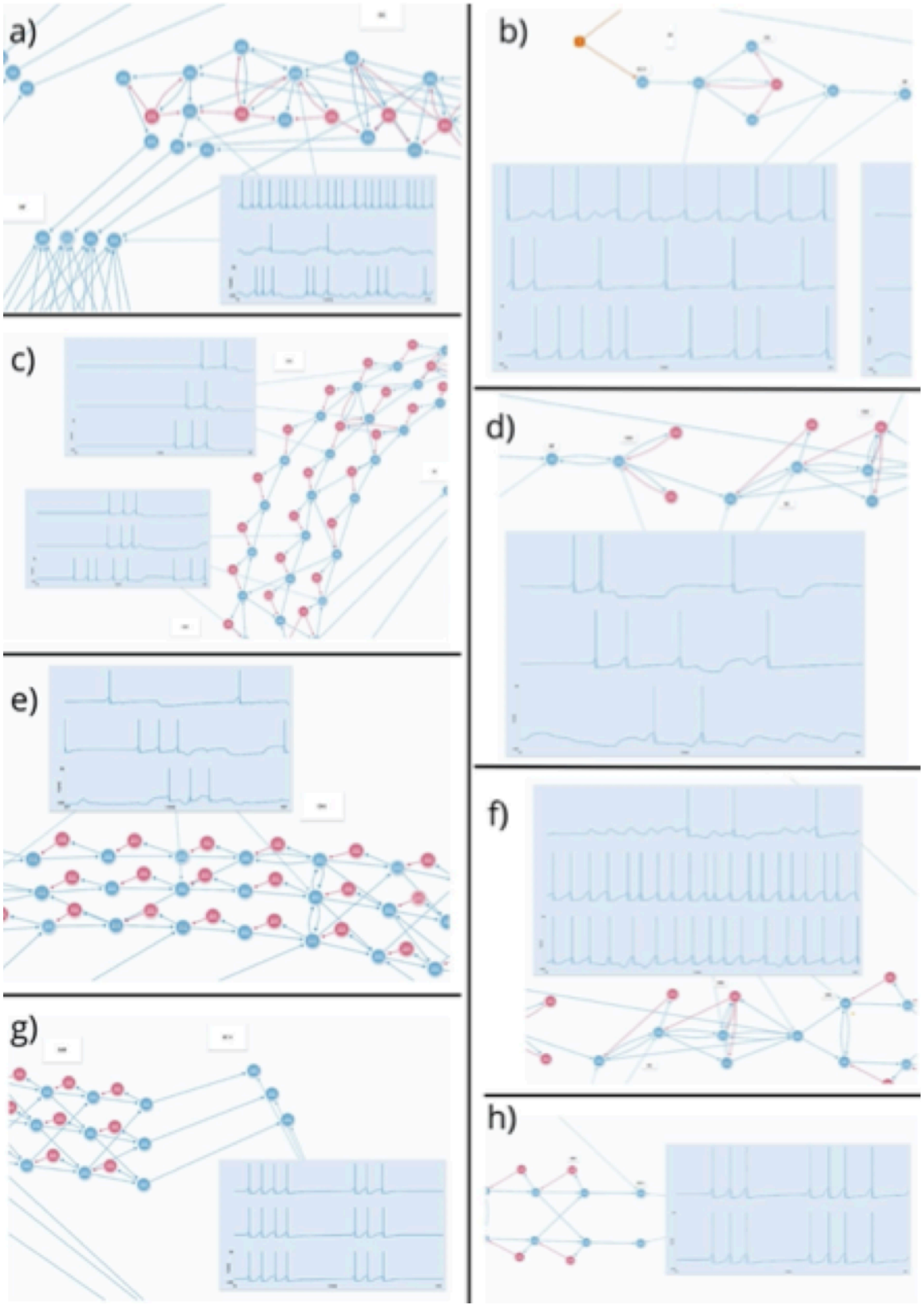

Figure 11: Comparison between activity of the general model and its simplification. a) Activity of dentate gyrus of the general model. b) Activity of dentate gyrus of the simplified model. c) Activity of **Cornus**

Ammonis (CA) 3-CA2 of the general model. d) Activity of CA3-CA2 of the simplified model. e) Activity of CA1 of the general model. f) Activity of CA1 of the simplified model. g) Output of subiculum of the general model. h) Output of subiculum of the simplified model.

The simplicity of the platform and biological structures provides anyone a highly accessible way to study this model using basic computers, tablets or even cell phones. Also, it overcomes the limitation of books that fail to demonstrate the cell dynamics.

Computational models like the one proposed here are an interesting alternative for teachers and students interested in understanding the function and structure of the hippocampus or any other brain region. The teaching and learning dynamics open many possibilities not offered by traditional lessons. The model allows for interacting with each structure, manipulating it with different input sources, measuring sensors, changing electrical properties of cells or even varying the position and connectivity of neurons in any region of interest, all through a simple screen and easy mechanism without harming any animals.

While computational models are useful for education in neuroscience, they have some key limitations. For example, we need to determine how to faithfully represent a realistic and complex HP formation in Neuronify™. Despite it being a user-friendly and stable platform, there are limited options to modify the biophysical aspects of cells. To solve this problem, we cluster a variety of cell types into only two categories: (1) every neuron related to a neurotransmitter capable of inducing a depolarization in the cell membrane of a postsynaptic neuron was plotted as excitatory, and (2) every neuron with the opposite effect on postsynaptic membrane potential were designed as inhibitory. Moreover, other neuronal biophysics features including resting potential, membrane capacitance, resistive current were standardized such that discharge patterns were generated via circuit motifs.

Thus, modeling using the circuit motifs approach successfully represent the HP circuitry. The approach allowed the simultaneous prediction of computation effects and construction by only organizing the structure. The choice of the right motifs was crucial, since they determine the functional aspects of each region represented individually and together.

In case of DG, we implemented the sparsity described in this region. Instead of only minimizing the relative firing rate between the output and the input, we also needed to limit the number of inhibitory cells without creating many synapses between an inhibitory and excitatory neuron. To fix this problem, a proportion of 8:3 was set between the excitatory and inhibitory cells to balance the number of cells and the required properties.

Similarly, in CA3, the challenges included representing the afferent pathways from MF with the strong recurrent connections and coupling these afferent neurons to its inhibitory mechanism. Furthermore, the first signal of action potentials is propagated, processed, and directed to CA2, precisely through the excitatory-inhibitory neural process. To implement this, we defined motifs to properly fit to the dynamics and partially randomize the cell positions.

Thus, they could keep their effects even without being restricted to a single and particular organization, but also be able to work in alternative scenarios, e.g., –conditions where the environmental variables could not be fully captured by a simplified model.

The representation of the CA2 subfield addressed selective activation mechanism using the global feedback inhibition motif, which enabled an acceptable level of selectivity that can be virtually modulated by the user. The implementation of this mechanism emphasized the importance of motifs as modular units for building neural circuits.

The CA1 subregion was one of the hardest to implement since it represents different features and specific connections that must be well described. The first portion of CA1 in this model was characterized by the cadence of the signal while the second portion was characterized by a recursion mechanism through which the signal is amplified before arriving at SUB. These characteristics could be implemented because we conjugated the motifs of feedforward excitation and recurrent excitation with feedback inhibition.

Lastly, the SUB region's biggest challenge was to implement the related synchronization of action potentials, so they could represent constructive interference patterns. The solution was to couple the simple feedforward excitation linearly and collaterally to the simple feedback inhibition motif. Thus, the neurons could start firing simultaneously, triggering three to five action potentials per stimuli as

described by the literature (AGGLETON et al., 2015; XU et al., 2016).

Considering all these points, one of the main limitations of this model is its physiological simplicity. Physiological details such as cell types and specific potentials of each neuron could not be fully addressed mainly due to the features of Neuronify™. Nevertheless, this simplicity can be seen as an interesting feature, since the model is more intuitive and easier to manipulate during the learning process. Another limitation to consider is the output measurements. The sensors only allow individual neuron measures, not neuronal populations. Particularly it measures only extracellular spike-train activities and does not allow local field potential measurements (VINCK et al., 2012). Additionally, the stimulation of the network is limited to six options provided by the software that act directly on a selected neuron, without being able to cause an extracellular-like stimulation that simultaneously excites a group of neurons next to an electrode.

Despite these restrictions, the platform and the model itself present many possibilities for analyzing the signals in each node of the network. We believe this model can be a good object for teaching hippocampus circuitry and its correspondent dynamics. It can even work as an initial step for research on HP disorders based on modifying the connections of the subregions and balancing the functions of each region.

One of the most interesting achievements through this computational model was the demonstration of circuit redundancy, where we were able to reproduce the main aspects of HP circuitry using a motif approach. It provides a good opportunity for students to discuss the arrangement of complex brain networks and how to improve the efficacy of information processing while maintaining energy consumption.

Conclusions

Using the Neuronify™ computational platform we were able to implement a model of the hippocampus circuit. The model primarily satisfied the structural architecture encompassing the pathways between the main subregions. Despite the limitations of the platform, such as the use of only excitatory and inhibitory neurons and the restricted biophysical modulation of the cells, we reproduced the main mechanisms of activity modulation using specific circuit blocks. This implementation by block, known as motifs, was fundamental to better understand the structural relations between each subregion and to

reproduce their activities.

The model proved to be very robust and at the same time malleable for virtual interventions such as synaptic interruption, short circuit construction, and stimulation. The simplicity of the computation model, along with the user-friendly interface of the platform, makes it important in interactive teaching and learning of neuroscience concepts. This model can potentially contribute to studying other similar dynamics, thus is capable of enriching and assisting the teaching process inside and outside the experimental laboratories.

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Declarations

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