Biological neural networks: an application to odor information processing

Author: Raquel Pruna Morales
*Facultat de Física, Universitat de Barcelona, Diagonal 645, 08028 Barcelona, Spain.**

Abstract: Traditionally, there has been a lot of research on how the brain manages visual and auditory inputs, but not that much attention has been devoted to the olfactory sensory system due, in part, to the complex nature of volatile organic compounds (VOCs). The aim of this project is to understand and build a computational neural model of the first stage of the olfactory pathway: the glomerular layer. Some experts in the field, supported by experimental evidence, point at this first stage as the neural location where an important aspect of odor information processing takes place: odor segregation. Our working hypothesis states that this input layer performs normalization and contrast and concentration enhancement over odorants before the odorant information is conveyed to deeper olfactory structures for detection. By performing an experiment on the computed neural network, we will be able to determine whether and how this odor segregation occurs. This is achieved by statistical analysis of the structure of the high-dimensional output space, understood as the spiking frequency and synchronization of glomerular neurons firing patterns.

I. A BIOLOGICAL APPROACH

How the brain works is one of the greatest mysteries of Humanity, due to the complexity of the study that it supposes. Since Santiago Ramón y Cajal discovered the neuron in the late 19^{th} century, numerous advances have been done in Neurosciences.

The present project attempts to understand and model a part of the brain's neural circuitry, taking neurons as elementary units. These cells have a particular morphology: they are composed of a main body (called *soma*), which contains the genetic material, that is sourrounded by thin ramifications known as dendrites, and one thick ramification: the axon. Connection between cells takes place in a process called *synapse* (presynaptic neuron's axon connecting to postsynaptic neuron's dendrites), which supposes an information exchange between neurons.

Part of our study focuses on what in physiology is called an *action potential*. Due to an uneven distribution of ions between the internal and external cell environment, the cell membrane finds itself submitted to a resting potential. The cell membrane has voltage-gated ion channels embedded in it, which are shut when the membrane potential is close to the cell's resting potential value. An external stimulus can cause the membrane potential to reach a threshold value. The cell membrane is said to be depolarizing, which causes the sodium (Na^+) channels to gradually open, producing at the same time a greater inward electric current across the membrane. After reaching a maximum value for the membrane potential, the membrane polarity reverses, causing the sodium channels to inactivate while opening the potassium ones (which causes an outward K^+ current) and repolarizing the cell membrane. The fact that the external stimulus is more or less intense has an influence in that the membrane voltage reaches or not the threshold value, from which it will trigger an action potential. The firing frequency also depends on the stimulus intensity, and this will be the basis of our study.

The olfactory bulb is the brain region in charge of regulating the olfactory system. As a first stage, there are the so-called *glomeruli*, which are espherical regions containing four neurons each: mitral, external tufted, periglomerular and superficial short-axon cells. These units find themselves connected one to another, giving rise to the glomerular network, a primary olfactory bulb microcircuit, on which the study of the present work focuses.

In biological terms, the nasal cavity contains the olfactory sensory neurons (OSNs), which turn to be the primary elements in interaction with inhaled odorant molecules. Each OSN expresses a single type of protein called odorant receptor (OR) with a particular olfactory receptive field. As a consequence of this, each odor elicits a characteristic activation pattern across OSNs, depending on which molecular features it is composed of. This translates into the fact that each glomerulus is excited by an external current, causing its cells to start firing at a frequency determined by the intensity of the aforementioned current.

The purpose of the present project is to study how a network of these characteristics manages to classify different kinds of odorants, yet at the same time detecting the concentration at which the samples are presented to the OSNs. To this end, a network of sixteen glomeruli was computed. After a set of four different odors at six different concen-

*Electronic address: rprunam@gmail.com

Neuron/Parameter	C [pF]	k [GΩ^{-1}mV^{-1}]	v_r [mV]	v_t [mV]	a [ms^{-1}]	b [GΩ^{-1}]	v_{peak} [mV]	c [mV]	d [mV]
Mitral cell	40	1.000	-55.0	-50	0.4000	2.60	35	-50	200
Periglomerular cell	59	0.049	-53.1	-20	0.0167	-0.94	35	-20	50
Tufted cell	40	1.000	-55.0	-50	0.4000	2.60	35	-50	200
Short axon cell	58	0.061	-67.0	-30	0.0490	-0.68	35	-30	150

Table I: Values for the different parameters of the four known types of cells used in the model.

trations (which we took as our input space) was built, it was sequentiallty presented to the network, leading to the study of the network's response by means of a statistical analysis of the mitral and tufted cells firing rate (considered as output spaces).
The statistical comparison between the input and output spaces gives account for the validity of the modelled and computed network, in terms of odor identity and intensity inference.

II. NEURON MODEL

The mathematical model that reproduces the spiking behaviour of the neurons composing our simulated glomerular layer is based on the results of E.M. Izhikevich [3]. This neural model achieves a good biological accuracy with limited computational complexity. On the countrary, the Hodgkin-Huxley model [7], notwithstanding its computational load, stands for the fidelity of the model's biological counterpart, which is required in other scientific fields.
Our model of neuron consists in a system of two coupled ordinary differential equations for variables v and u, which give account for the membrane potential and the membrane recovery variable, respectively. By solving both potentials over time, this approximation of the membrane's electrical characteristics leads to a mathematical description of how action potentials initiate and propagate along the cell membrane (Figure 1).
The mentioned mathematical description is shaped as follows:

$$\begin{aligned} C \cdot \dot{v} &= k\,(v - v_r) \cdot (v - v_t) - u + I(t) \\ \dot{u} &= a \cdot [b\,(v - v_r) - u] \end{aligned} \tag{1}$$

$$\text{if } v \geq v_{peak} \Longrightarrow \begin{cases} v \to c \\ u \to u + d, \end{cases} \tag{2}$$

where (2) is the boundary condition that resets the membrane potential after a spike takes place.
The goal is to have the cell membrane represented by a set of electrical elements, attending to its biophysical characteristics. For instance, the lipid bilayer takes the form of a capacitance C in the computational model, whereas voltage-gated and leaky ion channels are represented by conductances. In equation (1), v_r is a value for the resting membrane potential, at which the membrane current is null; v_t represents an instantaneous threshold potential and v_{peak} indicates the spike peak voltage maximum value. Parameter a represents the recovery time constant, and b takes the role of the recovery variable depending on the sub-threshold fluctuations of the membrane potential. Parameters c and d are voltage-dimensioned and stand for the after-spike reset value of the membrane potential and the recovery variable, respectively. $I(t)$ is considered as an external current, doing its part for the odor being detected by the ORN as well as the injected current (which is a consequence of neuronal synapses). Computationally, $I(t)$ has been modelled as a step function over time. Table I summarizes the parameter values chosen to compute the neurons conforming our model [5]. All cells were initially set at the resting potential value (v_r).
It should be noted the fact that parameter values for mitral and tufted cells are identical. It will not be until the time to connect all the cells in the network that the role these two types of neurons take at odor processing will differ, given the fact that the more different the connectivities are, the more unsimmilar the elicited firing patterns will result.
The ordinary differential equations system in (1) was solved implementing a fourth-order Runge-Kutta integration and a time step of 0.1 ms, which

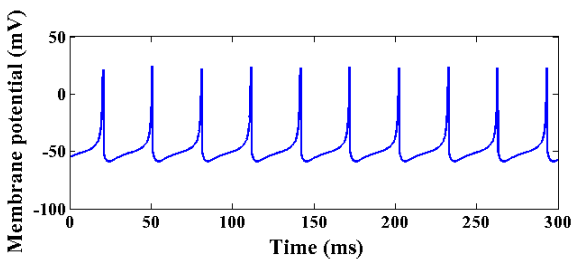

Figure 1: Tufted cell firing pattern during a time window of 300 ms.

is enough resolution to represent a spike that takes place in a time window of approximately 3 ms.

III. NEURAL NETWORK STATICITY AND PLASTICITY

A. Architecture of the glomerular network

Following the known architecture of the glomerular layer and based on [1], we built our computational model of the glomerular network layer.
Each glomerulus receives inputs from a specific class of OSNs. Inside each glomerulus, it takes place the synapse between the OSNs' axonal arbors and the olfactory bulb principal neurons' (mitral -MI- and external tufted -ET- cells) and interneurons' (periglomerular cells -PG-) dendrites. These cells are connected between them inside the glomerulus to which they belong: the PG cell is inhibiting the MI cell, while in turn, the last one is exciting the PG cell, altogether forming a negative feedback loop. The ET cell has also an excitatory effect on the PG cell, hence delivering further inhibition onto MI cell dendrites. In its way, the ET cell in a specific glomerulus excites the superficial short axon in the same glomerulus. Superficial short axons (sSA) have the specific function of interconnecting glomeruli between them in a lateral excitatory network, in a way that the sSA of a glomerulus synapses to all ET and PG cells belonging to the rest of glomeruli in the network (this is known as *a full-connectivity model*). These last connections can be regarded as a broadly laterally distributed inhibitory network (due to the fact that the sSA, by exciting PG cells, are making them inhibit MI cells in their turn), which is regulated by a network of excitatory connections. This set of intra- and inter-glomerular connections is schematically shown in Figure 2. MC, PG and ET cells of two glomeruli receive inputs from each glomerulus' OSNs. The sSA cell in the first glomerulus is excited by the same glomerulus' ET cell, and it is exciting ET and PG cells in the second glomerulus.
Bearing all this in mind, the next step is to *simulate* electrical connections between neurons. These, technically known as *synaptic weights*, are summarized in a *connectivity matrix*, which contains values that represent the strength of all the possible connections between all neurons in the network. Excitatory synapses were initially set at a positive value, whereas inhibitory connections were defined negative. The final static synaptic weights were probed *a posteriori*, at the time of performing the "odor identity/intensity" experiment.

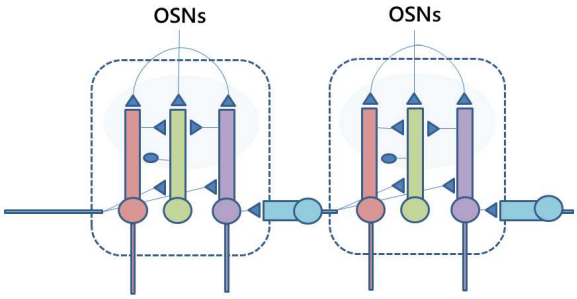

Figure 2: Schematic representation of connections in a two-glomeruli network. Trianglular connections represent excitatory synapses, whereas round connections play the role of inhibitory synapses. Red, green, purple and blue units simulate MI, PG, ET and sSA cells, respectively.

B. Making a way through learning: STDP

Hitherto, neurons have been treated as statically inter-connected units. Nevertheless, there exists experimental evidence that synaptic connections strengthen and weaken along time, in a process which is mediated by activity-dependent modifications in the neural circuitry. These processes constitute the cellular basis both for learning and memory. A first approach to the subject was made by neuropsychologist Donald Hebb in 1949, who made the following statement [6]:
"Let us assume that the persistence or repetition of a reverberatory activity (or *trace*) tends to induce lasting cellular changes that add to its stability (...) When an axon of cell A is near enough to excite a cell B and repeatedly or persistently take part in firing it, some growth process or metabolic change takes place in one or both cells such that A's efficiency as one of the cells firing B is increased".
Back to our computational network model, it is the connectivity matrix the one who plays a crucial role here, as it is the one who determines the magnitude of all the synapses in the network.
The Spike-Timing Dependent Plasticity (STDP) algorithm is based on Hebb's postulate, in a sense of giving account for the importance of causality at the time of determining the direction of the synaptic modification [4]. Basically, the STDP algorithm consists on strengthening the synapse between neurons whose firing-activity pattern reflects plausibility for them being connected, while at the same time weakening the connection weight between neurons whose activity pattern does not give account for them being connected. An intuitive interpretation of Hebb's original postulate is that the presynaptic neuron should spike before the postsynaptic neuron does in time. The closer

both spikes are in time, the greater importance the role of causality gets in this phenomenon, hence the weight of this synapse ought to be strengthen. Analogously, if the postsynaptic neuron fires before the presynaptic one, then it is clear that it cannot be a consequence of a presynaptic neuron firing. Thereby, the weight of this connection finds itself weakened.
The point of computing the STDP algorithm is no other but to test if, starting from some random parameters in the connectivity matrix, the system is capable of converging to values simmilar to the statically probed ones.

IV. STATISTICAL METHODS

In this section we briefly describe the statistical methods that were used after performing the "odor identity/intensity" experiment, in order to analyze the experimental results. As it is going to be explained in the section below, two output spaces from one input space were obtained.
A statistical procedure known as Principal Component Analysis (PCA) was useful to analyze both output spaces as well as the input space. Let us suppose we have a set of possibly correlated experimental data distributed in a multidimensional space. PCA consists in performing an orthogonal transformation to this space, transferring the initial set of experimental points to this new space conformed of linearly uncorrelated variables: the principal components.
To endorse these qualitative results, two additional statistical methods were computed: Fisher's Discriminant Ratio (FDR), for the quantification of odor identity discrimination, and Pearson's Correlation Coefficient (PCC), doing its part for odor intensity detection.
PCC states for the correlation level between two variables, x accounting for the concentrations (being μ_x the mean value of all the samples of variable x, i.e. concentrations), and y, the odors coordinates in the tufted cells output space (μ_y, as before, the mean value of all samples in y):

$$\mathrm{PCC} = \frac{\sum_i (x_i - \mu_x)(y_i - \mu_y)}{\sqrt{\sum_i (x_i - \mu_x)^2 \sum_i (y_i - \mu_y)^2}} \tag{3}$$

To analyze and compare both input and mitral cells output spaces, FDR, which is defined as the proportion of the variance between classes and the variance within classes (being the classes the groups of different odors, each one of them sheltering six samples, accounting for different concentrations), was performed:

$$\mathrm{FDR} = \frac{\mathrm{tr}\,(S_\mathrm{B})}{\mathrm{tr}\,(S_\mathrm{W})} \tag{4}$$

S_B and S_W are the *between scatter* and *within scatter* matrices respectively, defined as follows:

$$S_\mathrm{B} = \sum_{i=1}^{N} (\mu_i - \mu)(\mu_i - \mu)^\mathrm{T} \tag{5}$$

$$S_{\mathrm{W}_i} = \sum_{x \,\in\, \text{Odor } i} (x - \mu_i)(x - \mu_i)^\mathrm{T} \tag{6}$$

$$S_\mathrm{W} = \sum_{i=1}^{N} S_{\mathrm{W}_i} \tag{7}$$

N is the total number of odor types (four in our experiment), and given one of them, Odor i, x accounts for the six experimental points, attending to odor concentration. μ_i denotes the mean value of samples in odor i, whilst μ stands for the mean value of all data samples.

V. IDENTITY/INTENSITY EXPERIMENT: CONCLUSIONS

Once the neural network was designed and built (in computational terms), the next step was to test it. The network was subjected to an experiment that guided us to accept or discard the initial hypothesis that odor identification and concentration analysis (at least part of it) is facilitated at an early olfactory bulb stage (i.e. the glomerular layer).
To this end, a set of four odor stimuli at six different concentrations was created. It was computed as a combinatorial code, meaning this that each odor stimulus was represented by an n-tuple (being n the number of glomeruli, sixteen in the present case) of random numbers obbeying a normal distribution, and saturating them at a value of 60 pA. Once the four odorants were created, each one of them was re-scaled at six different concentrations, thus obtaining a set of twenty-four input items that were sequentially presented to the network, as part of the intensity $I(t)$ value in equation (1). Thus, a particular odorant produced a concrete spiking frequency pattern in each neuron. Starting from a point in the 16-dimension input space (the coordinates of which were determined by the aforementioned combinatorial code) and after a 300 ms time of network training, the spike-timing frequencies analysis gave rise to two n-dimensional output spaces: the mitral cells' and the external tufted cells'.

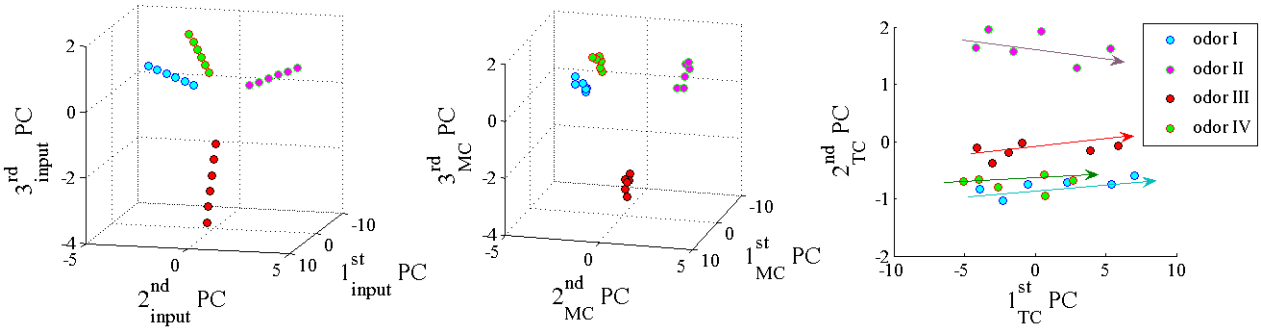

Figure 3: Results obtained after performing the "Odor identity/intensity" experiment. (a) Principal Components 3-dimensional representation of input space. $\mathbf{1^{st}_{input}PC = 51.8}$ %, $\mathbf{2^{nd}_{input}PC = 23.5}$ %, $\mathbf{3^{rd}_{input}PC = 16.7}$ %. (b) Principal Components 3-dimensional representation of MC space. $\mathbf{1^{st}_{MC}PC = 41.4}$ %, $\mathbf{2^{nd}_{MC}PC = 28.1}$ %, $\mathbf{3^{rd}_{MC}PC = 18.7}$ %. (c) Principal Components 2-dimensional representation of TC space. $\mathbf{1^{st}_{TC}PC = 84.2}$ %, $\mathbf{2^{nd}_{TC}PC = 6.6}$ %, $\mathbf{3^{rd}_{TC}PC = 5.0}$ %.

Mitral cells are expected to perform normalization and contrast enhancement over samples. Normalization means that, regardless of odor concentration, all samples of a specific odorant tend to cluster. Contrast enhancement takes place when different clusters (representing different odorants) tend to sparse over the mitral cells output space more than they do in the input space. This translates into a loss of correlation between variables, hence the first principal component in the output space (Figure 3b) captures around a 10% less of variance than the first principal component of the input space (Figure 3a). Moreover, the FDR calculated with input data (0.3) is smaller than the FDR worked out with mitral cell output data (0.6), meaning this that different odorants tend to cluster, and clusters tend to flounce away from one another in mitral cells output space, in contrast with what is represented in the input space.

On the other hand, external tufted cells are expected to give account for odor concentration, regardless of its identity. In order to get this, the first principal component in the tufted cells output space should capture quite enough variance to say that concentration can be estimated over this one single dimension. This indeed happens, as seen in Figure 3c, as for the output space, $1^{st}_{TC}PC = 84.2$ %, while in the input space, $1^{st}_{input}PC = 51.8$ %. PCC was computed to extract the correlation between concentrations and tufted cells output, getting a value of 0.94. Quite a big correlation.

What inmediately strikes about the results presented in Figure 3 is the clear normalization and contrast enhancement MCs perform, as well as the fact that TCs information is contained along one single direction in its Principal Components space. We consider this a first approach to understand how the brain codifies the information collected by the olfactory sensory system.

Acknowledgments

I would like to express my special gratitude to my project advisor, Dr. Agustí Gutiérrez, for his patience and confidence. Thanks to Javi, who turned everything upside down since I met him, for smart advices on the code. To the ladies and Bosch, for being always there listening to me... or not. To my family, for their support and faith in everything I do.

[1] Linster, C. *et al.* "Glomerular microcircuits in the olfactory bulb." Neural Networks 22.8 (2009): 1169-1173.

[2] Cleland, T. *et al.* "Computation in the olfactory system". Chemical senses 30.9 (2005): 801-813.

[3] Izhikevich, E.M. "Simple model of spiking neurons". IEEE Transactions on neural networks 14.6 (2003): 1569-1572.

[4] Caporale, N. *et al.* "Spike timing-dependent plasticity: a Hebbian learning rule". Annu. Rev. Neurosci. 31 (2008): 25-46.

[5] Polese, D. *et al.* "Understanding odor information segregation in the olfactory bulb by means of Mitral and Tufted cells". Submitted to PLoS One (2014)

[6] Hebb, D. O. "The organization of behavior: a neuropsychological theory". Psychology Press, 2005.

[7] Hodgkin, A., and A. F. Huxley. "A quantitative description of membrane current and its application to conduction and excitation in nerve". The Journal of physiology 117.4 (1952): 500.