Nitric Oxide Diffusion Attributes in Biological and Artificial Environments: A Computational Study

C.P. Suárez Araujo[1], P. Fernández López[1] and P. García Báez[2]
1- Institute for Cybernetics, University of Las Palmas de Gran Canaria, Spain.
Email: cpsuarez@dis.ulpgc.es (Corresponding author), pfernandez@dis.ulpgc.es
2- Dept. of Statistics, Operations Research and Computation, University of La Laguna, Spain.
Email: pgarcia@ull.es

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ABSTRACT:
This paper presents a computational study on the dynamic of nitric oxide (NO) in both the biological and artificial environments, by the analysis of important nitric oxide diffusion attributes. We apply the compartmental model of NO diffusion as a formal tool, using a computational neuroscience point of view. The main objective is the analyses of the emergence and dynamic of complex structures, essentially diffusion neighbourhood (DNB), in environments with volume transmission (VT). The study is performed by the observation of the NO diffusion attributes, the NO directionality (NOD), the average influence (AI) and the center of DNB (CDNB). We present a study of the influences and dependences with respect to associated features to the NO synthesis-diffusion process, and to the different environments where it spreads (non-isotropy and non-homogeneity). The paper is structured into three sets of experiences which cover the aforementioned aspects: influence of the NO synthesis process, isolated and multiple processes, influence of distance to the element where NO is synthesized, and influence of features of the diffusion environment. The developments have been performed in mono bi-and three-dimensional environments, with endothelial cell features. The study contributes the needed formalism to management the dynamic of NO in artificial and biological environments also to quantify the information representation capacity that a type of NO diffusion-based signaling presents and their implications in many other underlying neural mechanisms, such as neural recruitment, synchronization of computations between neurons and in the brain activity in general.

KEYWORDS: Nitric Oxide, Artificial Neural Networks, Cellular Signalling, Volume Transmission, and Diffusion Neighbourhood.

1. INTRODUCTION

The understanding of brain structure and function and its computational style is one of the biggest challenges both in Neuroscience and Neural Computation. Knowledge of the underlying mechanisms of brain activity are essencial if we are going to reach this aim.

Biological Neural Network (BNN) is the principal agent responsible for brain activity, affecting cellular communication and learning. Neural recruitment, or synchronization of computations between neurons, the existence of an information indexing schema at the BNN, or the LTP expression, are aspects that can directly depend on an neural underlying signaling schema. We understand that such aspects will play a crucial role in the information representation capacity, and consequently, in the BNN and ANN computation potential.

Volume Transmission (VT) is located among all sets of cellular signals that globally affect brain activity. The underlying mechanism of VT is the diffusion of neuroactive substances and diffusible signals, such as Nitric Oxide (NO). NO is one of the liposoluble molecules generated by cells from its own tissue which permit a volumetric transmission. A key property of NO is its extreme diffusibility in both aqueous and lipid environments, which allows a rapid three-dimensional spread of the signal irrespective of the presence of membranes [1]. Because of this, it freely diffuses through membranes affecting all neighbouring cells [2], [3], [4] and [5].

The presence of a molecule in the brain such as NO, opens new perspectives in the study of brain functioning. NO can help as an control element for several systems. It can act as a retrograde neurotransmitter; it can be involved in learning and memory, and it can play a role in the LTP process. NO is capable of producing a hybrid neuromodulation: Diffusive Hybrid Neuromodulation (DHN) [1]. NO has also opened a new dimension in our concept of neural communication, one overlaying the classical synaptic neurotransmission, where information is passed between neuronal elements at discrete loci (synapses).

An intrinsic feature of the NO diffusion is the formation of not-wired neighbourhoods, diffuse neighbourhoods (DNB), which supports the emerging of complex structures. The formation of these structures has been studied by several authors [6], but has not been considered as a possible underlying communication schema in BNN and ANN. Our studies consider this capacity.

In this paper we present a computational study on the dynamic of nitric oxide (NO) in both the biological and artificial environments, by means the analysis of important nitric oxide diffusion attributes. We focus on the analysis of the DNB dynamic and its possible influence in mechanisms and processes at the neural circuit and/or higher level. An important aim is to infer from the analysis a possible implication of VT in the increase of the information representation capacity in both BNN and ANN, in their architectures and in the functional complexity of its main computation element, the neuron.

The computational analysis of DNB and its dynamic performed in this study is based on our compartmental model of diffusion of NO [1]. This work also defines and analyzes new nitric oxide diffusion attributes which are defined in the paper: Directionality of NO dynamics (NOD), Average Influence (AI), DNB by directionality, Diffusion Centre of the DNB (CDNB) and DNB Limit (DNBL).

The importance of this study is providing the needed formalism to quantify the information representation capacity that a type of NO diffusion-based signaling can present.

2. METHOD

Diffusion is the main axis in the study of the NO dynamics [7], as well as the responsible agent of the NO influence to different brain zones from a functional and structural point of view. This influence is materialized, essentially, by means of Diffuse Neighbourhoods (DNB). This concept allows to analyze the dynamic of NO influences through the diffusion environment, and which is their dependence with non-isotropy and non-homogeneity. The establishment and analysis of DNB, which we will perform using the compartmental model of NO diffusion, are required to formalize intrinsic aspects of the diffusion phenomena and to NO dynamics. On one hand, we have the directionality measure of the NO dynamics, which provokes different spatial-temporal influences in the diffusion environment and a new concept of DNB, the DNB by directionability. This makes us towards the concept of Average NO Influence, key variable in the DNB definition and the. On the other hand, adaptive a no local character of the DNB dynamic justifies the need of variables which formalize that dynamism and its effect as diffusion centre of the DNB and DNB limit.

2.1. Compartmental Model of NO Diffusion and Diffusive Concepts

The compartmental model of NO diffusion [1] is a discrete computational model that allows us to study the dynamic of NO, generation, diffusion, self-regulation and recombination, in biological and artificial environments. Its main features are its simplicity, and it can be considered as a general formal tool with biological plausibility. It gathers the real features of the diffusion environment such as non-homogeneity and the non-isotropy and possible morphology of the NO synthesis.

The model represents an important tool for the design and interpretation of biological experiments on NO behaviour and its effect on brain structure and function.

The model is based on compartmental systems [8] and is defined by a system of first order differential equations, like those seen in Eq. 1, where we can consider specific cyclic contour conditions.

$$\frac{dC_i}{dt} = D_{i,i-1}(C_{i-1} - C_i) + D_{i,i+1}(C_{i+1} - C_i) - \lambda_i C_i + F_i \quad (1)$$

where $D_{i,i-1}$ and $D_{i,i+1}$ are the coefficients of diffusion between the compartments i and $i-1$ and between i and $i+1$, respectively. λ_i is the self-regulation parameter of NO. It is being considered, for this case, for the self-regulation of NO dynamics proportional to the quantity of concentration, and F_i is the function of generation of NO.

The computational analysis of DNB and its dynamic, using this model, is performed by means the analysis of important nitric oxide diffusion attributes, which will be mathematically defined and formalized in this paper, that are: Directionality of NO dynamics (NOD), Average Influence (AI), DNB by directionality, Diffusion Centre of the DNB (CDNB) and DNB Limit (DNBL) [9].

NO Directionality (NOD)

What we shall call Directionality of NO dynamics (DNO) first needs to be formalized before entering into the concept of quantifying the influence that a compartment has on another, specifically in a VT environment. This definition will later be used when introducing the formalization of DNB dynamics.

NOD is a magnitude that is defined for each compartment h and dimension, and its value is given as a function of the concentration dynamics of the NO that are associated with the h compartments that are adjacent to each dimension. The compartments that are adjacent to a given h are determined by the defined propagation scheme. The propagation scheme is determined by the connection topology among the compartments in order to create the compartmental medium where the NO diffusion occurs. Our study uses a *von Neumann* type propagation scheme [10].

The NOD allows us to assign to each compartment *h* the value of an associated movement or displacement that the NO is carrying out in a specific spatial dimension, and then calculate the probability that this compartment is in such a state.

The expressions that formalize the probability that a compartment *h* of the neighborhood, is found in states 0, 1 or 2, are given by the functions $\psi_0(h, t)$, $\psi_1(h, t)$ and $\psi_2(h, t)$, Eq. 2. These functions allow the said compartment to be quantified so that the compartment remains indifferent, that is, either being allowed or prohibited, respectively, to the influence among compartments, based on it, in a specified dimension.

$$\Psi_0^{d_i}(h,t) = 1 - (\Psi_1^{d_i}(h,t) + \Psi_2^{d_i}(h,t))$$

$$\Psi_1^{d_i}(h,t) = \frac{\int_0^t H\left(C_{h-1}^{d_i}(\tau) - C_{h+1}^{d_i}(\tau)\right) d\tau}{\int_0^t \left|sgn\left(C_{h-1}^{d_i}(\tau) - C_{h+1}^{d_i}(\tau)\right)\right| d\tau} \qquad (1)$$

$$\Psi_2^{d_i}(h,t) = \frac{\int_0^t H\left(C_{h+1}^{d_i}(\tau) - C_{h-1}^{d_i}(\tau)\right) d\tau}{\int_0^t \left|sgn\left(C_{h-1}^{d_i}(\tau) - C_{h+1}^{d_i}(\tau)\right)\right| d\tau}$$

where d_i specifies the dimension along which functions $\psi_0(h, t)$, $\psi_1(h, t)$ and $\psi_2(h, t)$ are calculated and $H(x)$ is the step-wise function according to the following definition: $H(x)=0$ for all $x \le 0$ and $H(x)=1$ for all values of $x > 0$.

By using the defined probability functions for each state, we obtain the mathematical expression for the directionality of NO, namely **NOD***(h, t),* Eq. 3, which is a function of time and of compartment *h* where NOD is calculated

$$\mathbf{NOD}(h,t) = \begin{pmatrix} \Psi_0^{d_0}(h,t) & \Psi_0^{d_1}(h,t) & \ldots \\ \Psi_1^{d_0}(h,t) & \Psi_1^{d_1}(h,t) & \ldots \\ \Psi_2^{d_0}(h,t) & \Psi_2^{d_1}(h,t) & \ldots \end{pmatrix} \qquad (2)$$

NOD is a matrix with dimension 3×n, where *n* corresponds to the dimension of the environment. Thus, in real environments we will have a **NOD** matrix with a 3×3 dimension.

NOD provides an additional degree of information which reveals other intrinsic aspects of diffusion and commonly used considerations for the study of the dynamics of NO, such as the diffused substance level, NO, or its gradient. It provides information on how the displacement of NO has progressed in the environment with the passing of time, leaving a trace. An important characteristic of this newly defined aspect of the NO dynamic is that it can only consider the directionality criteria of the displacement, Eqs. 2 and 3, topic that is being developed in this paper, and can also be analyzed by taking into account the NO concentration level in the area under study. These considerations lead us to the concept of a Diffusion Neighbourhood (DNB) by directionality.

The shapes of these curves, associated with the compartment *h* in a specified dimension, are a function of the difference of the concentration levels of NO among the adjacent compartments of said compartment *h*, according to the dimension under study.

Figure 1 shows the associated curves of $\psi_0(h, t)$, $\psi_1(h, t)$ and $\psi_2(h, t)$. In this figure we can observe that in the initial stage of the process, the value of $\psi_0(h, t)$ are greater and consequently indicate that there is a step when NO (changes) through a compartment *h*, which is very low or almost zero. Once 0.*2* seconds have passed, the values of $\psi_1(h, t)$ are the greatest of the three and is attributable to the passing through a process region where the NO behaviour is carried out in favor of dimension d_i.

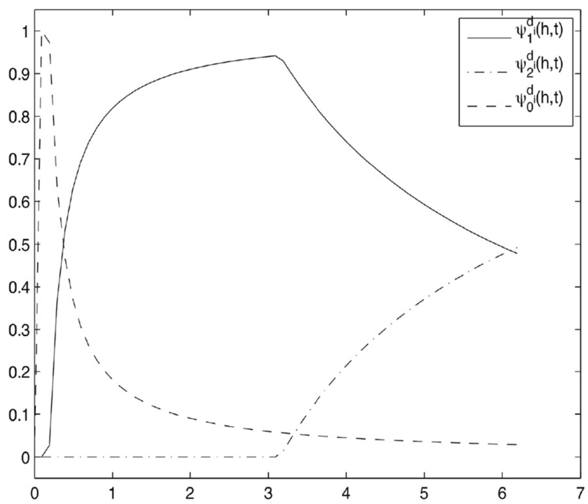


Fig. 1. Profile of time evolution of the $\psi_0(h, t)$, $\psi_1(h, t)$ and $\psi_2(h, t)$ in an environment where the calculation of NOD is carried out without considering NO level.

In the final stage, understood to be the time period between *3.1* and *6.2* seconds, the value of the functions $\psi_1(h, t)$ and $\psi_2(h, t)$ present notable change and at time equal to *6.2* seconds, the values of the functions $\psi_1(h, t)$ and $\psi_2(h, t)$ are both near *0.5* (see figure 2), indicating that the proportion of time in compartment *h* observing the transition of NO in favor of dimension d_i is similar to the time that it has been observing the opposite case.

Average Influence (AI)

Average Influence between compartments by the NO dynamics (AI) is a magnitude that quantifies the influence *k* compartment is performing into *r* compartment. AI depends on the directionality of NO and is calculated using the maximum value of the successive multiplication of the directionalities that allow us to arrive from compartment *k,* to compartment *r,* throughout all of the possible trajectories *T(k, p, r, T(p, q, r, T(...)))*, Eq. 4.

$$AI(k,r,t) = \max\left(\prod_{h\in T(k,p,r,T(p,q,r,T(\dots)))} \Psi_i^{d_j}(h,t)\right) \quad (4)$$

where *h* is every compartment which is located in *T(k, p, r, T(p, q, r, T(...)))*, path, of recursive definition, which goes from *k* compartment to *r* compartment, passing by intermediate compartment *p* and using path *T(p, q, r, T(...))*. The function $0 < \psi_i(h,t) < 1$ for dimension d_j, defines calculated NO directionality in favor of the direction that marks the followed T trajectory. This last situation is defined on the set of dimensions *j* that can exist and imply the choice of a value *i=1 or 2* in function of whether or not the trajectory is in favor or against the dimension d_j, respectively.

Note that AI is a value that is calculated for a specific time *t*, and can exist for the cases where there are NO synthesis/generation processes in some of the compartments *k* or *r*, for which it is calculated, or in the case when this/these NO synthesis/generation process(es) are present in themselves, where both compartments are simply receptors of NO.

Diffusion Neighbourhood (DNB)

Neighbourhood Diffusion (DNB) of an *i* compartment, Eq. 5, is constituted by a set of compartments which fulfill certain criteria with relation to the AI *i* compartment is performing in them.

$$DNB_i(t) = \{j: Q(AI(i,j,t),t)\} \quad (5)$$

where *Q(AI(i, j, t))* is the *Q* criteria over the AI that *i* compartment performs in the *j* one, and *j* represents every compartment that fulfills *Q*. *Q* can be the exceed of a threshold value θ by the AI. This way, $j \in DNB_i(t) \Leftrightarrow Q(AI(i,\ j,\ t))$ is fulfilled, where *Q* is defined according to the logical expression $AI(i,\ j,\ t) > \theta$. Another criteria could be that AI is located between two values, θ_1 y θ_2. So the criteria *Q* would be defined by the logical expression $\theta_1 < AI(i,\ j,\ t) < \theta_2$. The way in which *Q* criteria is defined causes different types of neighbourhoods, and the DNB of a compartment can change throughout time. This way, the DNB is dynamic and adaptive that generates complex structures. These aspects of the DNB can be featured by tracing the diffusion centres of every instance of the DNB throughout time. This diffusion centre of the DNB (CDNB) determines a position, which corresponds to the averaged position of all the influences that the compartments belonging to the neighbourhood perform between them

$$CDNB_i(t) = \frac{\sum_{j\in DNB_i} AI(i,j,t) r_j}{\sum_{j\in DNB_i} AI(i,j,t)} \quad (6)$$

where $\mathbf{r}_j$ corresponds to the position *j* compartment has in the diffusion media.

We define Diffusion Neighbourhood Limit (DNBL) of an *i* compartment as the $max(|\mathbf{r}_j-\mathbf{r}_i|)$, where $\mathbf{r}_i$ is the position vector of the *i* compartment, $\mathbf{r}_j$ is the position vector associated to the *j* compartment, and such compartment corresponds to any of the compartments belonging to the DNB of the *i* compartment $i,j \in DNB_i(t)$.

3. RESULTS AND DISCUSSION

We have performed a computational study of NO dynamic, based on mechanisms defined and using the compartmental model of NO diffusion. This study was carried out in one - two and three dimensional diffusion environments.

We have focused our efforts in the analysis of one of the great potentialities of NO as diffusive signaling, the emergency of DNB defined according to the directionality criteria, and hence, complex structures. We have established influences and dependences with respect to associated features to the NO synthesis-diffusion process, and to the environment where it spreads (non-isotropy and no-homogeneity). We have structured the study into three sets of experiences which cover the quoted aspects: influence of the NO synthesis process, isolated and multiple processes, influence of distance to the element where NO is synthesized, influence of features of the diffusion environment, isotropy and homogeneity, presenting our obtained results in this section.

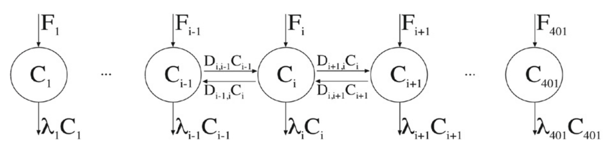


Fig. 2. Environment of 401 compartments. The synthesis processes are in the compartment 201 for synthesis alone, and at 101, 201 and 301 for multiple synthesis.

The first two studies are focused on the analysis of the AI, which is defined on a basis of NO directionality and takes values among compartments. AI is the magnitude that allows defining which compartments the DNB is made of. These studies have been performed in a mono-dimensional environment, Figure 2, with endothelial cell features. It is presented the profiles of AI among several compartments, Figures 3 and 4, showing its evolution through time, and being analyzed the DNB formation. We will observe that temporal evolution of AI depends on the global morphology of the NO synthesis existing in the environment, being able to arise situations where AI converge into null values. This indicates the existence of isolating zones among different DNB, Figure 4. The values of the diffusion and auto-regulation constants are, respectively, $D=3,3\cdot10^3\ \mu m^2 s^{-1}$and $\lambda=1,3863\ s^{-1}$ and average life $t_{½}$=0.5s. [11] and [12].

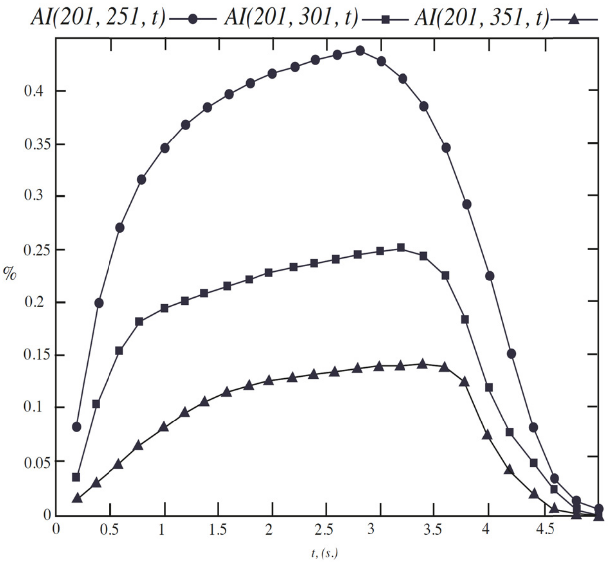


Fig. 3. AI(201, 251, t), AI(201, 301, t), AI(201, 351, t) AI Profiles that compartment 201 exerts into compartments 251, 301 and 251 and where 1 ≡ 100% and 0 ≡ 0%.

Figure 3 shows the AI which exerts the compartment 201 into compartments placed at different distances from it. It is observed the AI dependence with the distance to the NO-generator compartment and time. The synthesis process at compartment 201 starts at *t=0 s.*, takes *0.2 s.* and presents trapezoidal morphology [1]. We have observed that *AI(201, 251, t)* gets its maximum, $AI_{max}(201,251,t) \cong$ 45%, at $t \cong 2.75$ *s.* Initially, compartments exert influence into other compartments, in a fast way, the more the less distance. This is fundamental to propitiate neural recruitment processes, computations synchronizations, adaptations to changes of environment. Thus, when synthesis is over, there already exists an AI greater than 15% of $AI_{max}(201, 251, t)$. After reaching its maximum, *AI(201, 251, t)* decays at a faster speed, getting at *t=5 s.,* negligible values. *AI(201, 301, t)* takes a 25% more than *AI(201, 251, t)* in reaching the maximum, and *AI(201, 351, t)* a 30% more, being the max influences much lower in these compartments. When increasing the distance in 50µm, the max AI value falls in a 50%, and when increasing it in 50 µm. more, AI_{max} decreases a 75%, Figure 3. This analysis takes us to another concept as "the importance of neighbourhood" is threshold value of *I* which compartments have to reach to consider them as belonging to a DNB. Thus, DNB are dynamic and adaptive, being formed gradually in time by means of the incorporation of compartments and, at the same time, modifying their order at the neighbourhood. Importance will be an indicator of the generated DNB stability; the more stable the DNB, the lower its importance. This changing character of DNB handles working in non-stationary environments, real environments. It can help the formation of cortical maps [6], hybrid complex structures, DNB + wired neighbourhoods, as well as the incorporation of volume learning into BNN and ANN.

All these computation and/or information representation potentialities will be more justified with the emergence of complexity in DNB when we increase complexity in NO generation processes.

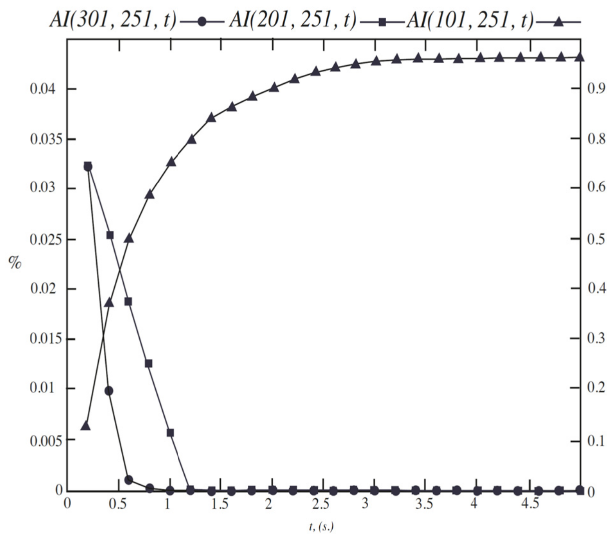


Fig. 4. AI(201, 251, t), AI(301, 251, t), AI(101, 251, t) AI Profiles that compartments 201 and 301 exert into compartment 251, and compartment 101 into compartment 251, when there exist two, and three, simultaneous synthesis processes, respectively and where 1 ≡ 100% and 0 ≡ 0%.

We have studied the dynamics in an environment where there coexist several simultaneous synthesis processes. We analyzed the AI in compartment 251, when synthesis process exists in two symmetrical positions to 251 at both sides. We have observed a dynamics where compartments with minimum influence exist. *AI(201, 251, t)* as well as *AI(301, 251, t)* are lower than 3,5%, Figure 4. Thus, a value of importance higher than this 3,5% implies this compartment does not belong to both neighbourhoods, even though it is at short distance from the NO generation. It can be understood that compartment 251 plays an isolator role of the several complex structures that are formed. This feature can indicate the existence of isolation zones in the biological level, which can cause computational segmentation and information indexing.

It has been performed the study of the AI-NOD profiles throughout time, when 3 simultaneous NO synthesis processes exist, separated by 100 μm. one another (compartments 101, 201 and 301). Analyzing the AI-NOD compartment 101 exerts into compartment 251, it is observed the additive character that multiple and aligned generation causes, Figure 4. To thwart this effect, it becomes necessary the variability of the average NO lifetime in the neural tissue. This is one of the biological phenomena which can justify the environment non-homogeneity.

By considering the observed behaviour in prior research, we extend our study to the analysis of diffusion neighborhoods, using directionality, generation of complex structures and their dynamics.

Figure 6, 7 and 8 show, using gray scaling, the AI that a compartment exerts on the compartments belonging to its DNB. The AI in different time instances can be observed, Figures 6(a, b, c, d) and 7(a, b, c, d), as well as its dependence regarding isotropy and environment homogeneity features. Figure 6, isotropic and homogeneous environment; Figure 7, non-isotropic and non-homogeneous environment. Figure 8 shows DNB formation when 8 synthesizing NO sources in an isotropic and homogeneous environment exist.

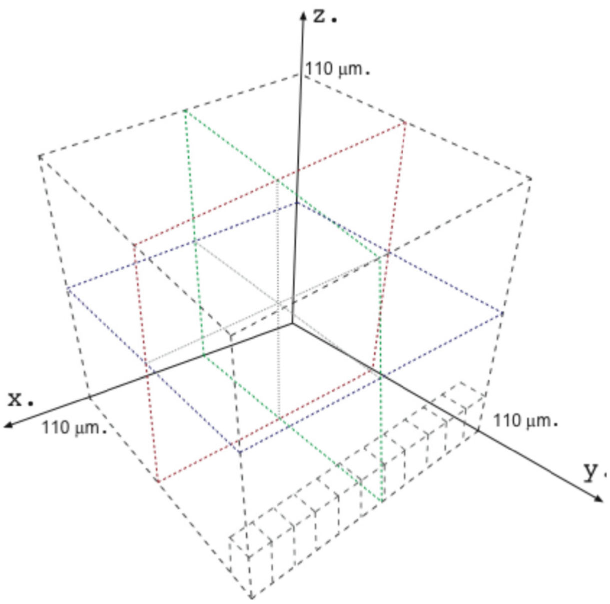
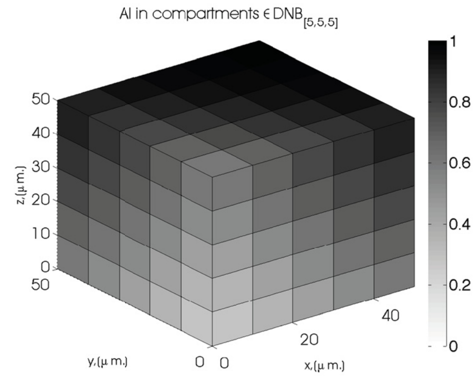
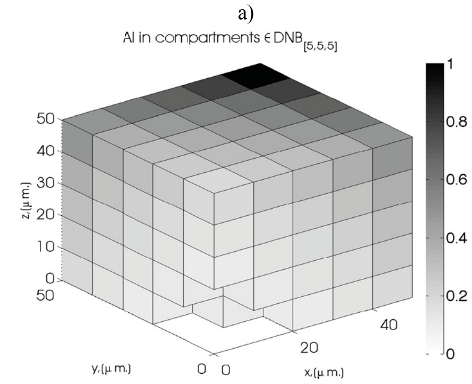


Fig. 5. Three dimensional environment formed by 11×11×11 compartments with 10 μm edges.

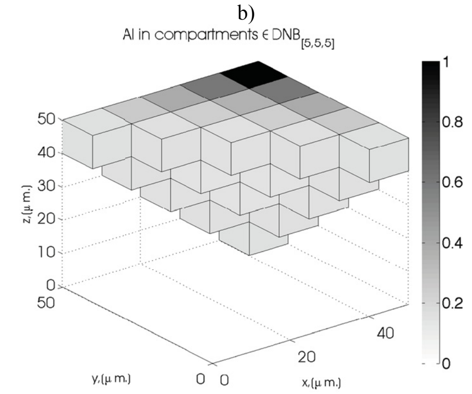
We carry out the same in a three dimensional environment, Figure 5, using 11×11×11 compartments that cover a volume in the shape of a cube with edge length of 110 μm.



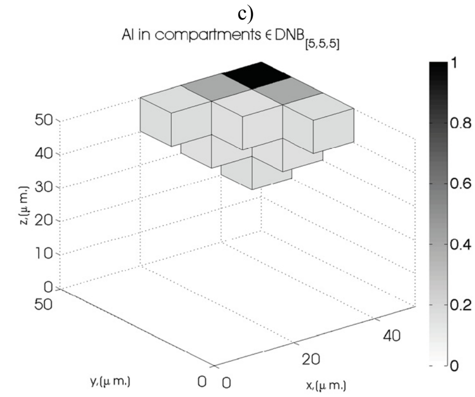
a)



b)



c)



d)

Fig. 6. Temporal dynamic of the formation of the DNB associated with compartment [5 5 5] for a value I=10% where 1≡100% and 0≡0%.
a) $DNB_{[5\ 5\ 5]}$(t=0.5s.), b) $DNB_{[5\ 5\ 5]}$(t=0.75s.),
c) $DNB_{[5\ 5\ 5]}$(t=1.0s.) and d) $DNB_{[5\ 5\ 5]}$(t=1.5s.).

The synthesis process reveals the same shape as in the monodimensional studies, with a trapezoidal morphology that begins at time t=0s. and ends at t=0.2s. The location of the compartments where the processes are carried out vary, depending on the analyses that are carried out and the mechanisms that are studied. The first study observes the generation of DNB and its dynamics throughout time. We present a unique synthesis process in the central compartment of the environment (position [6 6 6]). The second study is oriented towards showing the generation of isolated areas, on which the segmentation can be computed and an index of the information in biological and/or artificial contexts, and we generate eight symmetrical synthesis processes in the central compartments of each sub-cube of a 15×15×15 environment (positions [4 4 4], [4 4 12], [4 12 4], [4 12 12], [12 4 4], [12 4 12], [12 12 4] and [12 12 12]).

Figure 6 shows the dynamics of the shape from the DNB by directionality of the compartment located in position [5 5 5] in an isotropic and homogeneous environment. Investigation of the DNB at times t=0.5s.,0.75s.,1s. and 1.5s. clearly reveals the dynamic character of this complex structure, where the change is present, not only in the distribution of AI, but also in the size of the neighborhood. This reduction is gradual and almost symmetric throughout time, showing the characteristic that in specific moments close to the synthesis process (t=0.5s. and 0.75s.), creating reductions even greater than the distribution of the AI, maintaining the size without significant variations. As time goes by (t=1s. and 1.5s.), and the distance from the instant when the synthesis process taking place increases, a reduction in volume in the DNB begins, always satisfying that $DNB_{[5\ 5\ 5]}(t_a) \in DNB_{[5\ 5\ 5]}(t_b)$ for values of $t_a > t_b$ and where t_a and t_b are follow-up times to the final synthesis process time.

Similarly, in this figure we can see the distribution of AI within the DNB. As stated previously, the synthesis process in this particular case is located in the compartment of position [6 6 6] of the environment, where there is evidence its isotropic and homogeneous character relative to diffusion, self-regulation of NO and the recombination of NO with other substances, respectively.

Figure 7, shows the time evolution profile of $DNB_{[5\ 5\ 5]}$ in a non-isotropic and non-homogeneous environment at coordinate X. Note how the symmetry of the neighbourhood breaks up and displays a tendency towards shapes with greater structural complexity.

This fact allows us to infer that the no-isotropy and non-homogeneity of the environment imply non symmetric DNB, not only in the shape but also in the distribution of the AI in the compartments that belong to this DNB.Similarly, in these computational studies

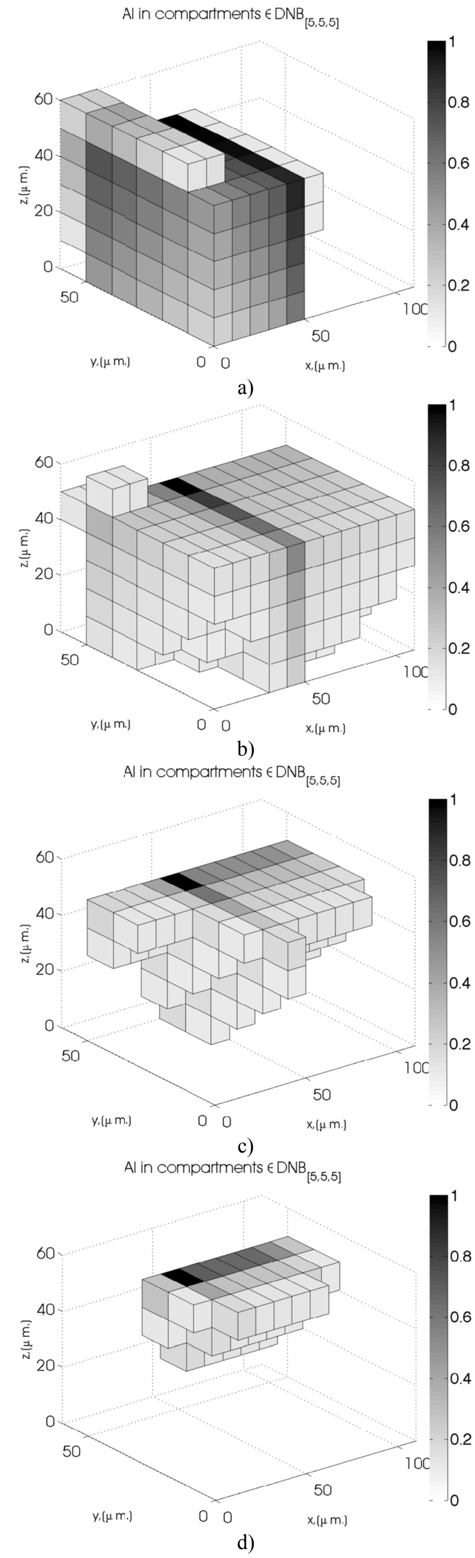
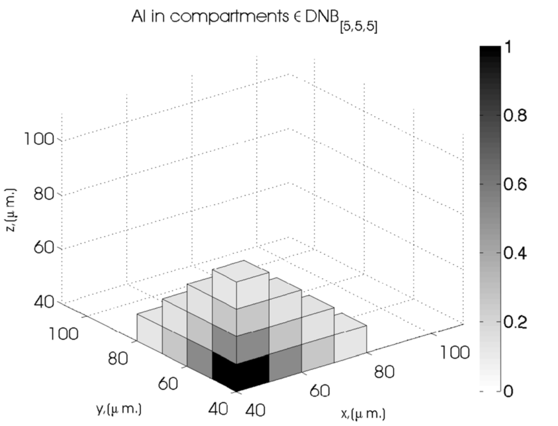


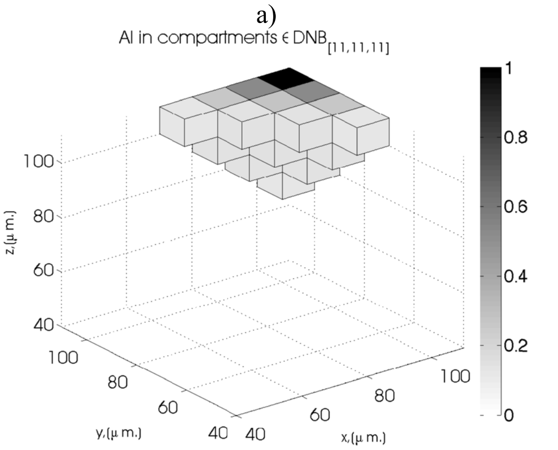
Fig. 7. Temporal dynamic of the DNB associated with compartment [5 5 5] in a non-isotropic and non-homogeneous environment for a value I=10% and where 1≡100% and 0≡0%.
a) $DNB_{[5\ 5\ 5]}$(t=0.5 s.), b) $DNB_{[5\ 5\ 5]}$(t=0.75 s.),
c) $DNB_{[5\ 5\ 5]}$(t=1.0 s.) and d) $DNB_{[5\ 5\ 5]}$(t=1.5 s.).

the asymmetry of the neighborhoods are observed and show a greater dependence of the non-isotropy of the environment, not the non-homogeneity.

On the other hand, we have a situation where, even though the limit of the dynamics of the DNB, when $t \rightarrow \infty$, it approaches a shape where the shape has fallen with respect to the shapes in earlier times, and the dynamic until convergence is not homogeneous. It shows transitory movements which can be observed in the isotropic and homogeneous environment. Situations can occur where $DNB_{[5\ 5\ 5]}(t_a) \not\in DNB_{[5\ 5\ 5]}(t_b)$ for $t_a > t_b$ and where t_a and t_b are time references after the end of the synthesis process. This can be seen in Figure 7, a) and b), where t_a=0.5 s. and t_b=0.75 s. Note that $DNB_{[5\ 5\ 5]}(t_a)$ displays a greater size than $DNB_{[5\ 5\ 5]}(t_b)$, having generated a clear increase in the $DNB_{[5\ 5\ 5]}$.



a)

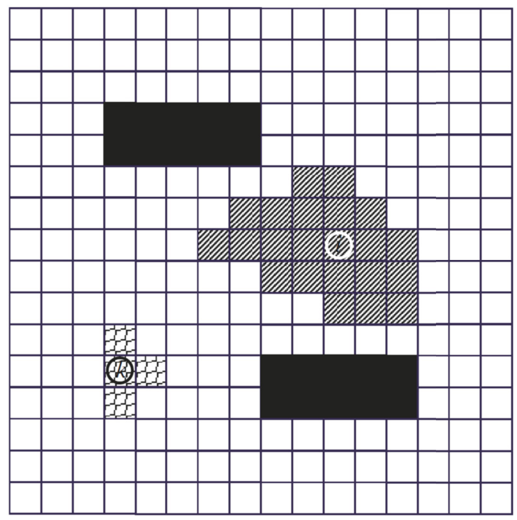


b)

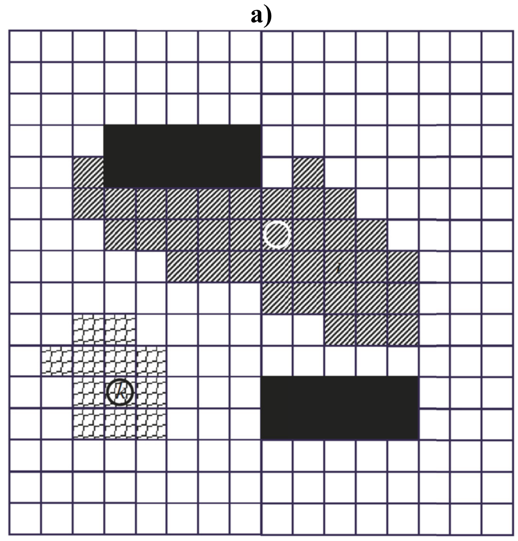
Fig. 8. DNB associated with the compartments located in positions a) [5 5 5] and b) [11 11 11], when 8 generation processes located in positions coexist [4 4 4], [4 4 12], [4 12 4], [4 12 12], [12 4 4], [12 4 12], [12 12 4] and [12 12 12], and in an isotropic and homogeneous environment, for a value I=10% and where 1≡100% and 0≡0%.

The next result analyzed in our three dimensional environment is the generation of isolated areas relative to AI, and their influence on the shapes of the DNB by directionality. Figure 8 shows the DNB associated with the compartments located in positions [5 5 5] and [11 11 12], where 8 generation processes coexist, as explained previously.

The shapes of $DNB_{[5\ 5\ 5]}(t)$ and $DNB_{[11\ 11\ 11]}(t)$, reveal structures that do not share any compartment throughout the time period. The explanation is found in the existence of an area between the two compartments, beyond both, specifically compartment [5 5 5] which never has an impact on the compartments, nor the opposite case. Consequently this situation produces the generation of the limits that divide the environment based on the simultaneous synthesis processes that are present and the so-called isolation areas.



a)



b)

Fig. 9. Snapshot of the generation of two DNB and the dynamic of its CDNB (indicated by a circle). Non-isotropic environment of 16x16 compartments, where black zone indicates not null NO dynamic. a) t=0,6s., b) t=1,3s.

These isolation areas are not static if they are not displaced with time as a function of the generation and diffusion of the dynamics of the NO in the environment. The displacement allows us to highlight an important result in the dynamics of the NO, directing in the end of the time period a dynamic and self-adjusting tessellation of the environment that could lead to the segmentation of computations and indexing of the information in this biological and/or artificial setting.

Two important attributes of these complex structures that are also found in DNB, are CDNB and DNBL. We conclude the computational study with an analysis of CDNB dynamics. The dependence that DNB dynamics and CDNB have with respect to non-isotropic and non-homogeneous environments has already been discussed. We have worked in a bi-dimensional environment with very low diffusion constant values in two areas/zones, which makes the NO dynamics to be almost null.

The diffusion constant is in the range $3.3\times10^3\pm0.2\times10^3\ \mu m^2 s^{-1}$ in the rest of the environment. Two NO synthesis processes are induced in two compartments *i, k*. A formation of non-symmetrical and non-local DNB_i and DNB_k at times $t=0,6$ *s*. and $t=1,3$ *s*. are observed (see Figures 9a and 9b). Thus a changing trajectory in CDNB is apparent in addition to a possible dependence on the shape of DNB. For t=0,6 s., in both neighbourhoods, CDNB matches with the compartment where synthesis was caused; however for t=1,3 s. in DNB_i the position of CDNB has changed, moving in agreement to that neighbourhood shape, Figure 9.

4. CONCLUSIONS

We present a work developed from a computational neuroscience point of view which provides a step forward in the understanding of the VT and their implications in the biological and artificial environments.

We have performed a computational analysis of one of the great potentialities of NO as diffusive signaling, the DNB. We have used the compartmental model of NO diffusion, showing its high capacity to study the dynamic of NO.

We have proposed, defined and analyzed attributes associated to the diffusion phenomena which present significant capabilities to characterize the NO dynamic. These attributes are Directionality of NO dynamic, Average Influence, Diffusion Neighborhood by directionality, Diffusion Centre of the DNB and DNB Limit.

We have established that the generation and dynamical behavior of the DNB depend on associated characteristics to the NO synthesis-diffusion processes, and to the environment where it spreads (non-isotropy and non-homogeneity). The complexity in DNB emerges when the complexity in NO generation processes has increased, and when the NO spreads in complex environments, with non-isotropy and non-homogeneity. These environment characteristics are also responsible for a non uniform dynamic of DNB. The non symmetry in DNB presents a greater dependence of the non isotropy of the environment, not the non-homogeneity.

This paper also shows that the dynamic of NO leads a dynamic and self-adjusting tessellation of the environment that could guide the segmentation of computations and indexing of the information in this biological and/or artificial setting. This phenomenon relies on the existence of non static isolation zones. With this study it is possible to explain some important environment characteristics such as non-homogeneity. Finally all these results allow us to detect the implications of VT, by means of DNB, in the increase of information representation capacity, in the neural recruitment, in the synchronization of computations between neurons, and in the neural modulation, in both scenarios, biological and artificial. These implications will also permit to confirm the possible role of the NO on several neural circuits as the sleep-wake cycle control.

Future research will include an analysis of the behavior of DNB by developing complementary studies such as complex systems using bifurcation theory and analysis

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