Nitric Oxide Diffusion and Multi-compartmental Systems: Modeling and Implications

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Abstract. The *volume transmission* (VT), a new type of cellular signaling, is based on the diffusion of neuro-active substances such as *Nitric Oxide* (NO) in the *Extracellular Space* (ECS). It is not homogeneous, critically dependent on, and limited by, its structure and physico-chemical properties. We present a different computational model of the NO diffusion based on multi-compartmental systems and transportation phenomena. It allows incorporating these ECS characteristics and the biological features and restrictions of the NO dynamics.

This discrete model will allow to determine the NO dynamics and its capabilities in cellular communication and formation of complex structures in biological and artificial environments.

This paper addresses the design model and its analysis in one-dimensional and three-dimensional environment, over trapezoidal generation and diffusion processes.

Keywords: Multi-compartmental systems · Nitric oxide diffusion · Volume transmission · NO generation/synthesis · Diffusion neighbourhood

1 Introduction

An important mechanism of cellular communication is the *volume transmission* (VT). It coexists with synaptic transmission and it is based on the diffusion of neuro-active substances such as *Nitric Oxide* (NO) in the *Extracellular Space* (ECS), which is not homogeneous, critically dependent on, and limited by, its structure and physico-chemical properties [1]. NO is a free radical gas, highly diffusible in both aqueous and lipid environments. It is considered an *atypical* cellular messenger, since it needs no receptor, does not accumulate in synaptic vesicles and it freely diffuses through membranes affecting neighbouring cells. NO dynamics make up diverse processes: *Generation*, *Diffusion*, *Selfregulation* and *Recombination*, because NO regulates its own production.

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In the absence of determinant experimental data for understanding how NO functions as a neural signalling molecule, we have developed a computational model of NO diffusion based on Multi-Compartmental Systems [2] and transportation phenomena. It is different from the previously proposed models, [3–7], because of it allows to incorporate the biological features and restrictions of the NO dynamics and of the environment where the NO diffusion processes take place. Our proposal can use whatever morphology of NO generation and to consider the diffusion in anisotropic and non-homogeneous environment. The main objective is to define a formal framework for determining the NO dynamics and its capabilities in cellular signalling and formation of complex structures, in biological and artificial environments.

This paper, addresses the model and its analysis in one-dimensional and three-dimensional environment, over generation and diffusion processes.

2 Multi-compartmental Model of NO Diffusion

The multi-compartmental model of NO diffusion appears to be able to consider a plausible biologically morphology of NO generation/synthesis. This feature is not present in the spontaneous generation, which is used in the analytical model [3]. This is because NO diffuse at the same instant of its synthesis. We consider this biological reality and model the NO diffusion at the molecular level where it is mathematically discrete. We define, as a theoretical abstraction, *the compartment*. It is the minimal volume where the NO diffusion is expressed. Its biological counterpart can be found at any neural level, from the molecule to the circuit. We study the NO behavior in complex systems composed of many interconnected compartments. Its formalization is based on multi-compartmental systems [2,8], which are a subclass of linear dynamic systems, given by an equation set like the one given in Eq. (1).

$$\frac{dq_i}{dt} = -(J_{0i} + \sum_{j \neq i} J_{ji})q_i + \sum_{j \neq i} J_{ji} q_i + E_i \tag{1}$$

Where E_i is the input flow. J_{hk}, the transference coefficients, defined as $J_{hk} = f(\mathbf{q}, t)$, the sustance transferences, $t_{ij} = J_{ij}q_j$ and $t_{ji} = J_{ji}q_i$ and the out flow $f_{0i} = J_{0i}q_i$, depending on the substance, $\mathbf{q}$, inside of the compartments.

On the other hand, the transport phenomena takes place when, due to the gradient of a physical magnitude, another is displaced and invades and affects its setting in a structural and/or functional way. Its behavior can be studied from a phenomenological point of view [9].

The proposed model is sustained on these two pillars, where the expressions that define the NO diffusion dynamics are deduced.

Let us consider a set of compartments in a one-dimensional environment, Fig. 1. Any of these compartments allow possibilities of NO generation, diffusion, self-regulation and recombination. The generation process is defined by the F_i function. F_i defines both, the quantity and the morphology of the generated

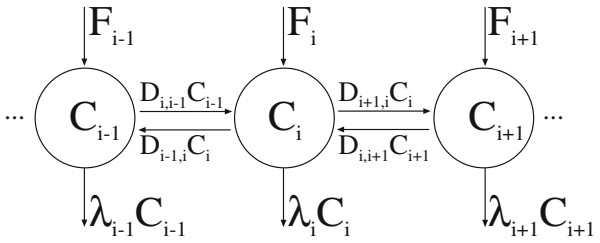

Fig. 1. One-dimensional environment of compartments

NO in the compartment. The transportation phenomena cause the speed of NO flow between two compartments to be proportional to their NO concentration difference. The NO concentration gradient in a compartment takes into account the self-regulation process of NO [9]. This is mathematically expressed by the Eq. (2).

$$\frac{dC_i}{dt} = D_{i,i-1}(C_{i-1} - C_i) + D_{i,i+1}(C_{i+1} - C_i) - \lambda_i C_i + F_i \tag{2}$$

where $D_{i,i-1}$ and $D_{i,i+1}$ are the environmental coefficients of diffusion between the indicated compartments. λ_i is the self-regulation parameter of NO, which is proportional to the quantity of NO concentration.

The model of the NO diffusion dynamics is defined by a system of first order differential equations, as in Eq. (2), where we can consider specific cyclic contour conditions, Eq. (3). It can be extended in direct form to two and three-dimensional environments.

$$\frac{d\mathbf{C}}{dt} = \mathbf{HC} + \mathbf{F} \tag{3}$$

Where $\mathbf{C} = (C_1, C_2, ..., C_N)^T$, $\mathbf{F} = (F_1, F_2, ..., F_N)^T$, and $\mathbf{H}$ (matriz tridiagonal), Eq. (4). Needing to consider the semi-discretization factor $1/(\Delta x)^2$ and multiplying by $\mathbf{H}$.

$$\mathbf{H} = \begin{pmatrix} -(D_{1,N} + D_{1,2} + \lambda_1) & D_{1,2} & \dots \\ D_{2,1} & -(D_{2,1} + D_{2,3} + \lambda_2) & \dots \\ \vdots & \vdots & \ddots \end{pmatrix} \tag{4}$$

The model allows considering the non-homogeneity of the environment, and is also able to cause different forms in the processes of generation of NO in distinct regions of the environment, as well as variations in the self-regulation of NO according to the treated region. This is represented in the model by F_i and λ_i functions. In addition, it allows the anisotropy of the environment to be established by means of the use of specific diffusion coefficients for every inter-compartmental environment, where the NO spreads by. These capabilities provide a model which can be categorized as a generalized formal tool with high power to emulate and to study the NO dynamics very close to the NO behavior in the biological environment.

3 Analysis of the Model

The proposed model is analyzed taking into account those characteristics found in the NO dynamic in addition to the diffusion environment, fitting to the biological reality of the dynamic. We pay specific attention to the analysis of the generation and diffusion processes, of the NO, in a one-dimensional case and in the volumetric case.

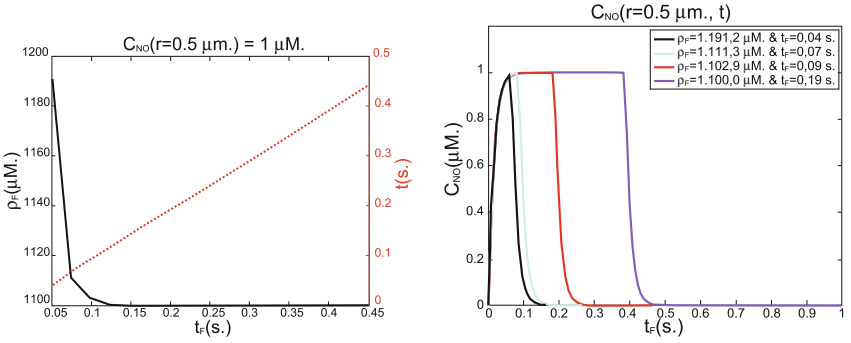

Fig. 2. (a) Behaviour of the multi-compartmental model of NO diffusion for different generation strengths of NO. Single NO generation. (b) Profiles of NO concentration at $r = 0.5\,\mu\text{m}$ as a function of ρ_F and t_F. Single NO generation (Color figure online).

The first part of the study focuses on the generation process of the NO and we call it the F_i Function. It is a trapezoidial function, and has as its source data studies carried out by Aleh Balbatun and other researchers on endothelial cells of rats and rabbits [10].

An analysis of the model behaviour is carried out with respect to strength of the NO generation. We will confirm its consistency, using different values for strength, to those experimentally obtained from Tadeusz Malinski and others [11]. These results determine an induced maximum value of the NO concentration for $1\,\mu\text{m}$ in an endothelial cell membrane of $1\,\mu\text{m}$ in diameter.

We use an environment of 21 linearly arranged compartments, see Fig. 1. Each one represents a space measuring $0.1\,\mu\text{m}$. Given that the NO diffusion is symmetric along the entire sphere which circumscribes the endothelial cell, we analyze the behaviour of the NO concentration which passes through the diameter of this sphere. Given that the endothelial cell is in the center of the environment, the NO generation occurs in compartment 11. We analyze the strength that this generation must have so that the reached value of the NO concentration at $r = 0.5\,\mu\text{m}$ (compartments 6 and 16 of the environment) is $1\,\mu\text{M}$.

Behaviour of the model regarding strength of the NO generation (ρ_F) is shown in Fig. 2(a). We show the relationship between ρ_F and t_F (generation time) (black line), for established biological values [11]. The maximum value is

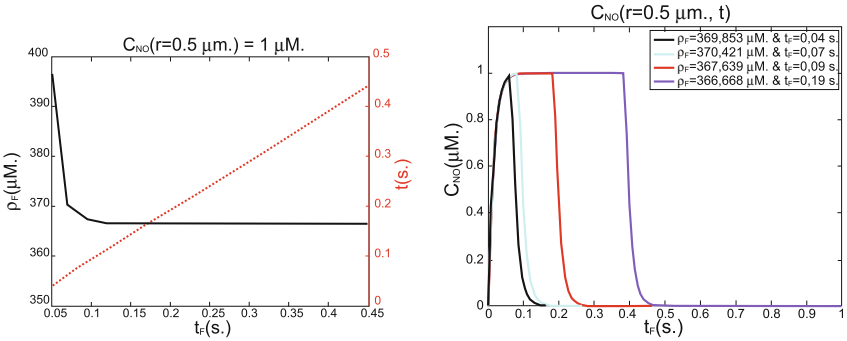

Fig. 3. (a) Behaviour of the multi-compartmental NO diffusion model for different generation strengths of multiple NO generation. (b) NO concentration profiles, for $r = 0.5\,\mu\text{m}$ as a function of ρ_F and t_F. Multiple NO generation.

attained in times very close to the length of the generation process (red line). We observe that there is an exponential increase in the strength of the generation process as the time duration is reduced. In addition, it is noted that the required times for C_6 and C_16 to reach a value of $1\,\mu\text{M}$ is linear with respect to the duration of the generation processes. Similarly, both Figs. 2(b) and 3(b) with NO concentration profiles when $r = 0.5\,\mu\text{m}$ and different values of ρ_F and t_F, reveals that the $1\,\mu\text{m}$ value reached is independent of the duration of the generation process.

When different NO generation processes coexist in the center of the endothelial cell the behaviour of the model is similar to the simple generation, Fig. 3(a). In our study for 3 processes in compartments 10, 11 and 12 values obtained for ρ_F, are approximately one third of the values obtained previously. Presence of self-regulation is not assumed here nor in the single generation, and consequently the relationship of the coexisting sources in the environment and in time is additive.

The second part of our analysis of the model focuses on the NO diffusion, the creation of *diffusion neighborhood* (DNB) and the emergence of complex structures. Data used comes from biological experiments [5]. The diffusion coefficient in an isotropic medium is $D = 3.3 \times 10^3 \mu\text{m}^2\,\text{s}^{-1}$. The quantity of NO at time $t = 0\,\text{s}$, is $0.24\,\text{nmol cm}^{-3}$, which is the time from the generation of the NO until the detection of the diffusion, specifically $400 \pm 20\,\text{ms}$, with a growth ratio of $1.2 \pm 0.05\,\text{nmol cm}^{-3}\text{s}^{-1}$, maximum concentration, $4.30 \pm 0.15\,\text{nmol cm}^{-3}$ at time of $600 \pm 20\,\text{ms}$ and a mean NO lifetime that ranges from $0.5\,\text{s}$ and $5\,\text{s}$. The used three-dimensional isotropic, non-isotropic, homogeneous and non-homogeneous environment, is a $110 \times 110 \times 110\,\mu\text{m}^3$, which includes $11 \times 11 \times 11$ compartments see Fig. 4(e), where $\Delta x = \Delta y = \Delta z = 110\,\mu\text{m}$ and $\delta_i = 10\,\mu\text{m}$.

The generation of NO occurs in centralized compartments of the aforementioned environment and each compartment has a neighborhood made up of the

six nearest compartments, except for those located on the faces, edges and corners of the 3D shape which have five, four and three compartments, respectively, see Fig. 4(a)–(d).

We start by analyzing the NO diffusion model behavior using a trapezoidal morphology of NO generation and different values of average NO lifetime in a homogeneous and isotropic environment. Maximum concentration levels of NO reached, as a function of the distance to the individual compartment, (i, j, k), that generates NO in the medium are shown in Fig. 5(a). The time that is needed

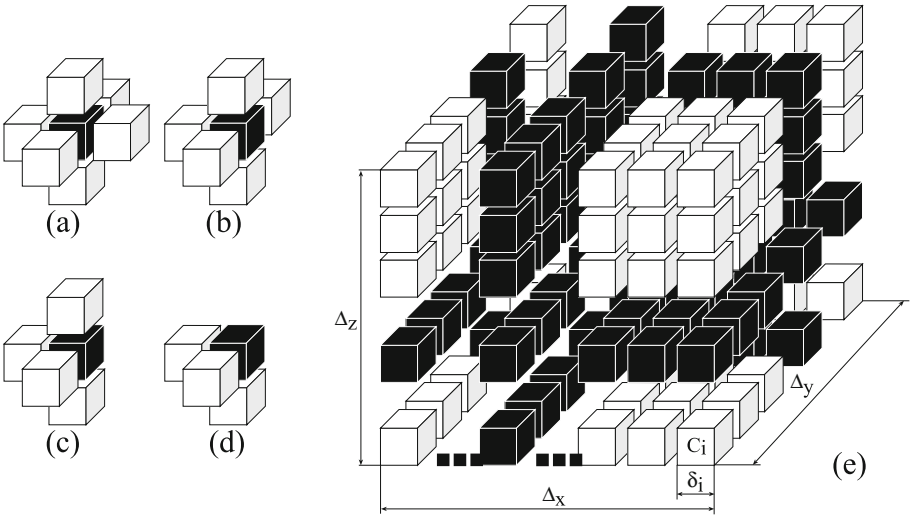

Fig. 4. 3D environment, where the model is analyzed. Black colors represent planes and lines for a visualization of the NO dynamic, (e). Details of neighborhoods for compartment $C_{i,j,k}$ when it is located inside of the 3D shape (a), when it forms part of a face (b), an edge (c), or a corner of the 3D shape (d).

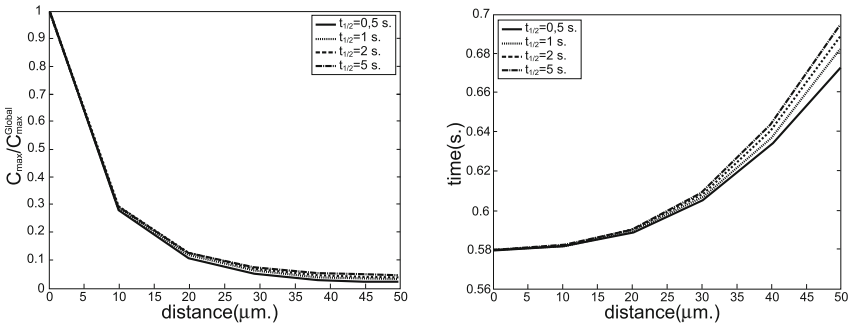

Fig. 5. (a) C_{max}/C_{max}^{global}, as a function of distance. Single generation. (b) Time to reach maximum concentration C_{max} as a function of distance.

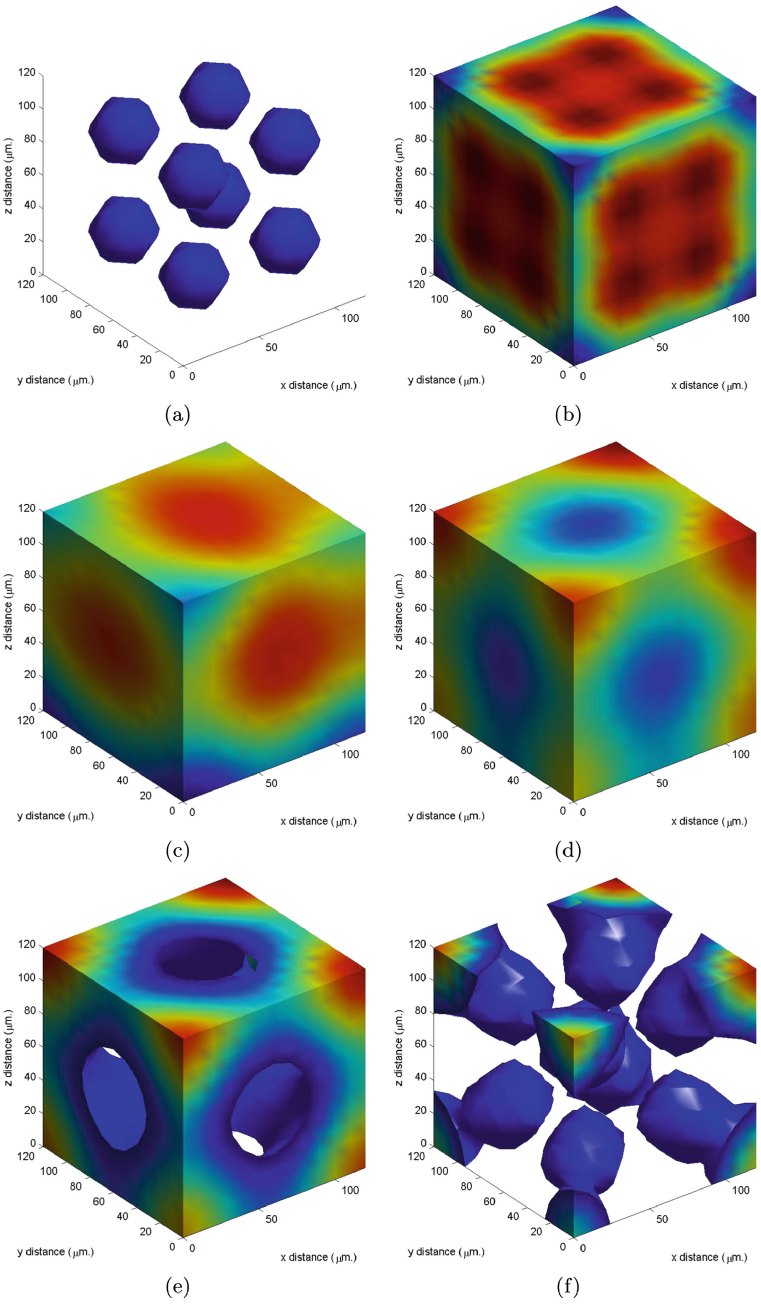

Fig. 6. Emergence of complex structures and DNB in diffusion of NO with 8 coexisting generation processes in an $11 \times 11 \times 11$ compartment environment.

to reach these maxima is represented in Fig. 5(b). This behaviour occur for different values of the self-regulation constant, corresponding to a $t_{1/2} = 0.5$, 1, 2 and 5 s.

In Fig. 5(a) we see that at 30 µm the maximum concentration does not exceed 5 % of the maximum concentration of generated NO. We can also observe the little influence that self-regulation of NO presents for a single generation process and the generated quantity of NO is low. In Fig. 5(b) we show that for a distance of 10 µm there is no delay when reaching the maximum value with respect to the same generation process and as we increase the distance to the generator compartment, the self-regulation becomes more important, creating a delay for reaching such maximum value.

The behaviour of the model shown in these figures allows non symmetric and non local DNB to be obtained and they can be defined as a function of the spread concentration of NO considered as relevant and/or time needed to reach an established maximum concentration level. In our particular study, if the significant NO concentration is only that above 5 % of the generated NO, then the DNB would be made up of only two of the nearest compartments to the generator, one for each direction in space.

We continue our model analysis in a plausible biological situation for NO diffusion, considering the features and restrictions of the environment where the process takes place. We carry out observations for behaviour of volumetric diffusion of NO, including simultaneous NO generation with 8 coexisting processes Fig. 6(a), in an environment of $11 \times 11 \times 11$ compartments with different properties of isotropy and homogeneity. The emergence of complex structures occurs and is shown in Fig. 6. Total symmetry in the formation of DNB and its range in a homogeneous and isotropic environment is presented in Fig. 6(b). This symmetry disappears with the non-isotropy of the medium. This anisotropy produces asymmetric DNB and more complex displacement of NO, Fig. 6(c) and (d). The non-isotropy is established in quadrants, the diffusion coefficients of the first and third quadrants are equal amongst themselves and different from the second and fourth quadrants. The variation of the homogeneity of the environment is also shown, which is related with the self-regulation, and indicates that NO disappears more rapidly in the area where generation processes are produced, see Fig. 6(e) and (f).

4 Conclusions

The description and analysis of the multi-compartmental model of NO diffusion was carried out. It has been introduced a theoretical abstraction of the volume element where the NO dynamics take place, the compartment. The proposed model constitutes a step forward in studying the NO diffusion. It allows any NO generation morphology and it gathers the real features of the ECS such as the no homogeneity and the non-isotropy. This analysis is based on biological data given by Malinski et al. It has been done studying the NO behaviour, with specific attention on the generation and diffusion process, in one-dimensional and three-dimensional environments.

We analysed the NO model with single and multiple generation processes, using trapezoidal morphology. The obtained results fit with biological behaviour of NO. Important aspects regarding generation strength and time have been observed and the no dependency of the time generation for reaching the maximum NO induced concentration. When multiple NO generation processes coexist, DNBs and the formation of complex structures appear. They present high complexity and asymmetries for non-homogenous and asymmetric environments. Therefore, our study shows the possibility of non-local and non-symmetric DNB generation and the influence of the self-regulation process in that dynamic.

Finally, our model is powerful to study and determine the NO dynamics in biological and artificial environments and it represents a generalized formal tool for designing and interpreting biological experiments on NO behaviour.

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