Relating PDEs in Cylindrical Coordinates and CTMCs with Levels of Concentration

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Abstract

We present the derivation of a CTMC with levels model of diffusion in cylindrical coordinates from the partial differential equation for Fick's law. The resulting model abstracts both molar concentration, by discrete levels, *and* spatial location, by discrete compartments. We apply the results to the diffusion of nitric oxide in human vessels and illustrate with simulations in the PRISM tool.

Keywords: geometrical space, reaction-diffusion equations, cylindrical coordinates, partial differential equations, CTMC with levels

1 Introduction

Formalisms such as process algebras and other calculi [15,19,11,6], rewriting rules [12,5] or languages [8,18], can be used to improve modelling and analysis of systems of biochemical reactions. Usually a model defined with these approaches uses mathematical techniques such as *ordinary differential equations* (ODEs), *continuous time Markov chains* (CTMCs), *CTMC with levels* [9] or *monte carlo simulations* as the underlying concrete semantics. In some cases, more than one mathematical semantics can be derived from the same formalism, e.g. Bio-PEPA [11], and they can be related to one another for a more robust interpretation of the result [9].

Recently, increasing interest has been given to the integration of location and movement in space within such formalisms. Spatial location and the

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This paper is electronically published in
Electronic Notes in Theoretical Computer Science
URL: www.elsevier.nl/locate/entcs

diffusion of biochemical species can be represented in many ways. For example, space can be topological, i.e. hierarchical locations, or geometrical, i.e. a coordinate system of spatial positions [13]. The diffusion of molecules can be described at a microscopic level by random walks, or at a macroscopic level by Fick's law of diffusion [16,4].

In such scenarios, mathematical models are usually highly specific, incorporating assumptions that simplify the set of equations used. An example of this is the variety of mathematical models of nitric oxide (NO) transport and availability in blood vessels (see [20] for a complete review). These models all use sets of *partial differential equations* (PDEs), representing diffusion with Fick's law in one dimensional cylindrical coordinates.

Our goal is to derive models of NO transport and availability in blood vessels in terms of CTMC with levels, from a set of PDEs. CTMC with levels are CTMCs whose states are characterised by the concentration of each species expressed in discrete levels. The motivation for this is the additional analysis available, e.g. testing of robustness under different degrees of stochasticity. An approximation of PDEs in terms of such semantics ensures that we can use state-based tools, such as the PRISM [3] model checker, to simulate and analyse this scenario. Before we can do so, the missing piece of the puzzle is a derivation of diffusion in one dimensional cylindrical coordinates in terms of CTMC with levels. In this paper we present such a derivation, whose main novelties are:

- the rates of the resulting CTMC with levels are derived directly from the diffusion constant of the diffusing biochemical species. This derivation, trivial in case of Cartesian coordinates, requires additional assumptions in the case of cylindrical coordinates;
- the rates of the CTMC with levels depend not only on the concentration of the species and the volumes of the compartments, but also on the spatial position.

The paper is organised as follows. In Section 2 we present the derivation of the PDEs to CTMC with levels. In Section 3 we present an example. In Section 4 we mention related work, while conclusions and future work are in Section 5.

2 Diffusion in a one-dimensional cylindrical vessel: relating PDEs, ODEs and CTMC models

The derivations in this section refer to a one-dimensional model in cylindrical coordinates. Although the only dimension considered is the radius, it is essential to note that the concentration at each point distant r from the centre represents the concentration at each point along the circumference of the circle

with radius r. The length of the cylinder can be neglected, as it is an invariant for our derivations. For this reason we use the terms *area* and *volume* as synonymous.

Before we give the details of the derivation, we give a brief overview. First we introduce the PDE and we derive a numerical approximation in terms of ODEs. This is obtained by dividing the space in segments and computing numerical approximations of first and second derivatives with respect to radial position. Second, we describe the diffusion in terms of ODEs with compartments, where the velocities of the transport reactions are in terms of mass action kinetic law. Third, we demonstrate that if we choose appropriately the kinetic constants for the mass action equations, the resulting equations are identical to the approximation of the PDE. Fourth, we derive the CTMC with levels from the ODEs with compartments. We know from [10] that this is possible.

2.1 Partial Differential Equations

Modelling diffusions of species S is defined at a macroscopic level by Fick's equation, a Partial Differential Equation (PDE) of the form:

$$\frac{\delta[\mathrm{S}]}{\delta t} = D_{\mathrm{S}} \nabla^2 [\mathrm{S}] \tag{1}$$

where D_{S} is the diffusion coefficient of species S, [S] is the concentration of S (in molar, M) and ∇^2 is the Laplacian operator, which can be interpreted in different ways, depending on the coordinate system. Since we consider diffusion along with local biochemical interactions, we use the following reaction-diffusion equation [16,4]:

$$\frac{\delta[\mathrm{S}]}{\delta t} = D_{\mathrm{S}} \nabla^2 [\mathrm{S}] \pm \mathrm{React} \tag{2}$$

where React represents other reactions involving species S.

We assume cylindrical coordinates and that the concentration changes only with respect to radial position and only because of diffusion or biochemical reactions. As a consequence Equation (2) can be simplified to a one dimensional form in cylindrical coordinates, where the only dimension considered is the radius:

$$\frac{\delta[\mathrm{S}](r)}{\delta t} = D_{\mathrm{S}} \cdot \left(\frac{\delta^2 [\mathrm{S}]}{\delta r^2} + \frac{1}{r} \cdot \frac{\delta[\mathrm{S}]}{\delta r} \right) \pm \mathrm{React} \tag{3}$$

Boundary conditions are:

$$\left.\frac{\delta[\mathrm{S}]}{\delta r}\right|_{r=0} = 0 \qquad\qquad \left.\frac{\delta[\mathrm{S}]}{\delta r}\right|_{r=R} = 0 \tag{4}$$

where $r = 0$ represents the centre of the coordinate system while R is the radius of the circular region considered. At each moment t in time we can

compute the concentration of S at any point r along the radius, starting from an initial concentration profile $f(r)$.

Consider now how to solve Equation (3) numerically. First, we divide the radius in K segments of length $\Delta r = R/K$. Each segment i is related to a variable $[\mathrm{S}_i]$, $i = 1, ..., K$, that represents the average concentration in that segment. Second, we compute approximations of first and second order derivatives of [S] at radial positions using the $[\mathrm{S}_i]$. These approximations represent derivatives at the middle point of the ith segment, at a distance $r = \Delta r(2i-1)/2$ from the centre of the coordinate system. Derivatives are computed using the central *finite difference method*:

$$\frac{\delta[\mathrm{S}](r)}{\delta r} \approx \frac{\delta[\mathrm{S}_i]}{\delta r} = \frac{[\mathrm{S}_{i+1}] - [\mathrm{S}_{i-1}]}{2\Delta r} \qquad \frac{\delta^2[\mathrm{S}](r)}{\delta r^2} \approx \frac{\delta^2[\mathrm{S}_i]}{\delta r^2} = \frac{[\mathrm{S}_{i+1}] - 2[\mathrm{S}_i] + [\mathrm{S}_{i-1}]}{(\Delta r)^2} \tag{5}$$

We can now rewrite Equation (3) using the approximations in Equation (5):

$$\begin{aligned}\frac{\delta[\mathrm{S}](r)}{\delta t} \approx \frac{\delta[\mathrm{S}_i]}{\delta t} &= D_{\mathrm{S}} \cdot \Big(\frac{[\mathrm{S}_{i+1}] - 2[\mathrm{S}_i] + [\mathrm{S}_{i-1}]}{(\Delta r)^2} + \frac{1}{\Delta r(2i-1)/2} \\ &\qquad \cdot \frac{[\mathrm{S}_{i+1}] - [\mathrm{S}_{i-1}]}{2\Delta r} \Big) \pm \mathrm{React} \\ = \frac{D_{\mathrm{S}}}{(\Delta r)^2} \cdot \Big(\big(1 + \frac{1}{(2i-1)}\big)[\mathrm{S}_{i+1}] &- 2[\mathrm{S}_i] + \big(1 - \frac{1}{(2i-1)}\big)[\mathrm{S}_{i-1}] \Big) \pm \mathrm{React}\end{aligned}$$

And rewriting the last equation we obtain the final numerical approximation:

$$\begin{aligned}\frac{\delta[\mathrm{S}_i]}{\delta t} = \frac{D_{\mathrm{S}}}{(\Delta r)^2} \cdot \Big(\frac{2i}{(2i-1)}[\mathrm{S}_{i+1}] - 2[\mathrm{S}_i] + \frac{(2i-2)}{(2i-1)}[\mathrm{S}_{i-1}] \Big) \pm \mathrm{React} \\ i = 2, ..., (K-1)\end{aligned} \tag{6}$$

In order to write Equation (6) also for $i = 1$ and $i = K$ we need to employ the boundary conditions (Equation (4)), from which we obtain:

$$\frac{[\mathrm{S}_1] - [\mathrm{S}_0]}{\Delta r} = 0 \qquad \frac{[\mathrm{S}_{K+1}] - [\mathrm{S}_K]}{\Delta r} = 0$$

As a consequence, approximations in Equation (5) become:

$$\begin{aligned}\frac{\delta[\mathrm{S}_1]}{\delta r} &= \frac{[\mathrm{S}_2] - [\mathrm{S}_1]}{2\Delta r} & \frac{\delta^2[\mathrm{S}_1]}{\delta r^2} &= \frac{[\mathrm{S}_2] - [\mathrm{S}_1]}{(\Delta r)^2} \\ \frac{\delta[\mathrm{S}_K]}{\delta r} &= \frac{[\mathrm{S}_K] - [\mathrm{S}_{K-1}]}{2\Delta r} & \frac{\delta^2[\mathrm{S}_K]}{\delta r^2} &= \frac{[\mathrm{S}_{K-1}] - [\mathrm{S}_K]}{(\Delta r)^2}\end{aligned} \tag{7}$$

Employing Equation (7) we derive the two additional equations:

$$\begin{aligned} \frac{\delta[\mathrm{S}_1]}{\delta t} &= \frac{2D_\mathrm{S}}{(\Delta r)^2} \cdot \Big([\mathrm{S}_2] - [\mathrm{S}_1]\Big) \pm \mathrm{React} \\ \frac{\delta[\mathrm{S}_K]}{\delta t} &= \frac{2K-2}{2K-1} \cdot \frac{D_\mathrm{S}}{(\Delta r)^2} \cdot \Big([\mathrm{S}_{K-1}] - [\mathrm{S}_K]\Big) \pm \mathrm{React} \end{aligned} \tag{8}$$

As a final step, we derive the value of the $[\mathrm{S}_i]$ at time $t = 0$, using the initial condition $f(r)$, $r \in [0, R]$. Notice that every point of the circumference with radius r has concentration $f(r)$. This means that each point in the ith segment has a different weight when we compute $[\mathrm{S}_i]$, the average concentration of the segment. Since $V_i{=}\pi(\Delta r)^2(2i-1)$ is the area of the ring whose average concentration is represented by $[\mathrm{S}_i]$, such average concentration at time $t = 0$ is given by:

$$[\mathrm{S}_i](t=0) = \frac{1}{V_i} \int_{\Delta r(i-1)}^{\Delta r(i)} 2\pi r \cdot f(r) dr \tag{9}$$

We have just derived an approximation of PDEs in terms of ODEs. We now demonstrate that, if the kinetic constant used for the mass action law of the transport is chosen appropriately, the set of equations for the PDEs approximation is identical to the set of equations for the same system described with ODEs and compartments.

2.2 Ordinary Differential Equations

In this section we derive an approximation of Equation (3) in terms of ODEs, where we discretise the space into K compartments C_i with volume V_i $(i = 1, ..., K)$. In order to represent a species S in the presence of compartments we need a variable S_i for each compartment C_i. We identify the average concentration of the species S in a compartment C_i by $[\mathrm{S}_i]$. Concentration $[\mathrm{S}_i]$ can migrate from a compartment C_i to an adjacent compartment, i.e. either C_{i-1} or C_{i+1}, and the migration happens at a velocity given by the Mass Action law with kinetic constant $k_{i,i-1}$ $(i = 2, ..., K)$ or $k_{i,i+1}$ $(i = 1, ..., (K-1))$ respectively (see Figure 1). In particular, we show that **the kinetic constants can be derived from the diffusion constant** D_S and the numerical solutions for the PDEs and ODEs are equivalent for a given K.

The ODE system described above is composed of the following equations:

$$V_1 \cdot \frac{\delta[\mathrm{S}_1]}{\delta t} = k_{2,1}[\mathrm{S}_2] - k_{1,2}[\mathrm{S}_1] \pm V_1 \cdot \mathrm{React}$$

$$V_i \cdot \frac{\delta[\mathrm{S}_i]}{\delta t} = k_{i+1,i}[\mathrm{S}_{i+1}] - k_{i,i+1}[\mathrm{S}_i] - k_{i,i-1}[\mathrm{S}_i] + k_{i-1,i}[\mathrm{S}_{i-1}] \pm V_i \cdot \mathrm{React}$$
$$i = 2, ..., (K-1)$$

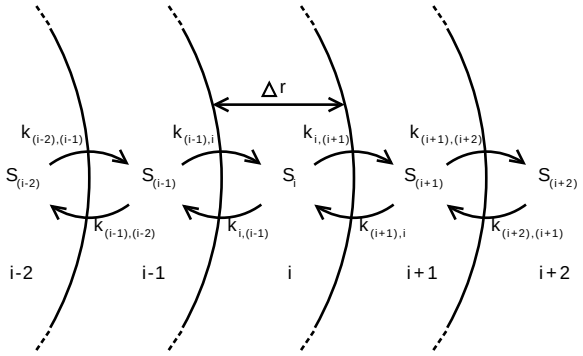

Fig. 1. Division of space in compartments.

$$V_K \cdot \frac{\delta[\mathrm{S}_K]}{\delta t} = k_{K-1,K}[\mathrm{S}_{K-1}] - k_{K,K-1}[\mathrm{S}_K] \pm V_K \cdot \mathrm{React}$$

where volume $V_i{=}\pi(\Delta r)^2(2i-1)$. We can then rearrange the above equations:

$$\frac{\delta[\mathrm{S}_1]}{\delta t} = \frac{k_{2,1}}{V_1}[\mathrm{S}_2] - \frac{k_{1,2}}{V_1}[\mathrm{S}_1] \pm \mathrm{React} \tag{10}$$

$$\frac{\delta[\mathrm{S}_i]}{\delta t} = \frac{k_{i+1,i}}{V_i}[\mathrm{S}_{i+1}] - \frac{k_{i,i+1}}{V_i}[\mathrm{S}_i] - \frac{k_{i,i-1}}{V_i}[\mathrm{S}_i] + \frac{k_{i-1,i}}{V_i}[\mathrm{S}_{i-1}] \pm \mathrm{React} \qquad i = 2, ..., (K-1) \tag{11}$$

$$\frac{\delta[\mathrm{S}_K]}{\delta t} = \frac{k_{K-1,K}}{V_K}[\mathrm{S}_{K-1}] - \frac{k_{K,K-1}}{V_K}[\mathrm{S}_K] \pm \mathrm{React} \tag{12}$$

At this point, we choose the kinetic constants, parametric in D_S, that substituted in Equations (10), (11) and (12) yield Equations (6) and (8). We derive these constants from inspection of Equation (6):

$$k_{i,i+1} = V_i \frac{D_\mathrm{S}}{(\Delta r)^2}\frac{2i}{(2i-1)} = 2i\pi D_\mathrm{S} \qquad i = 1, ..., (K-1) \tag{13}$$

$$k_{i,i-1} = V_i \frac{D_\mathrm{S}}{(\Delta r)^2}\frac{(2i-2)}{(2i-1)} = (2i-2)\pi D_\mathrm{S} \qquad i = 2, ..., K \tag{14}$$

Note that $k_{i,i+1} = k_{i+1,i}$. We can then substitute Equations (13) and (14) in Equation (11):

$$\frac{\delta[\mathrm{S}_i]}{\delta t} = \frac{(2(i+1)-2)\pi D_\mathrm{S}}{\pi(\Delta r)^2(2i-1)}[\mathrm{S}_{i+1}] - \frac{2i\pi D_\mathrm{S}}{\pi(\Delta r)^2(2i-1)}[\mathrm{S}_i]$$
$$-\frac{(2i-2)\pi D_\mathrm{S}}{\pi(\Delta r)^2(2i-1)}[\mathrm{S}_i] + \frac{(2(i-1))\pi D_\mathrm{S}}{\pi(\Delta r)^2(2i-1)}[\mathrm{S}_{i-1}] \pm \mathrm{React}$$

$$= \frac{D_\mathrm{S}}{(\Delta r)^2} \cdot \left(\frac{2i}{(2i-1)}[\mathrm{S}_{i+1}] - \frac{(2i+2i-2)}{(2i-1)}[\mathrm{S}_i] + \frac{(2i-2)}{(2i-1)}[\mathrm{S}_{i-1}]\right) \pm \mathrm{React}$$

And with a final rearrangement:

$$\frac{\delta[\mathrm{S}_i]}{\delta t} = \frac{D_\mathrm{S}}{(\Delta r)^2} \cdot \left(\frac{2i}{(2i-1)}[\mathrm{S}_{i+1}] - 2[\mathrm{S}_i] + \frac{(2i-2)}{(2i-1)}[\mathrm{S}_{i-1}] \right) \pm \mathrm{React}$$
$$i = 2, ..., (K-1)$$

which is identical to Equation (6). In a similar way we can derive the two additional equations, starting from Equations (10) and (12):

$$\frac{\delta[\mathrm{S}_1]}{\delta t} = \frac{2D_\mathrm{S}}{(\Delta r)^2} \cdot \Big([\mathrm{S}_2] - [\mathrm{S}_1] \Big) \pm \mathrm{React}$$
$$\frac{\delta[\mathrm{S}_K]}{\delta t} = \frac{2K-2}{2K-1} \cdot \frac{D_\mathrm{S}}{(\Delta r)^2} \cdot \Big([\mathrm{S}_{K-1}] - [\mathrm{S}_K] \Big) \pm \mathrm{React}$$

which are identical to Equation (8). Initial conditions are derived exactly as showed for the PDEs.

Thus we have shown that we can derive ODEs with compartments from PDEs in cylindrical coordinates. This is possible because of the correspondence we have found between the diffusion constant D_S in the PDE and the kinetic constants $k_{i,j}$ of mass action transport reactions in the ODEs.

2.3 Continuous Time Markov Chains with Levels of Concentration

In the previous two sections we related a continuous space PDEs model with a discrete space ODE model. Now we consider further discretisation: we relate the continuous concentration of the latter to the discrete concentration of a CTMC with levels model [9,10].

The organisation of the model is similar to the one just presented: space is divided in compartments C_i, with volumes $V_i{=}\pi(\Delta r)^2(2i-1)$, each of which represents a ring where the average concentration of a species S is given by $[\mathrm{S}_i]$ $(i = 1, ..., K)$. However, this concentration is not expressed in a continuous form like in the ODE model, but by a discrete level $\langle \mathrm{S}_i \rangle = 0, ..., \mathrm{N}_i$, with N_i the maximum level. The amount of concentration can be evaluated at any time using the relationship $[\mathrm{S}_i]{=}\ \langle \mathrm{S}_i \rangle \cdot h_i$, where h_i is called *step size* and is the amount of concentration represented by one level.

We shall now define states and transitions of a CTMC with levels derived from the models presented in the previous sections. A state of a CTMC with levels is defined by a vector of levels $\sigma = (\langle \mathrm{S}_1 \rangle, ..., \langle \mathrm{S}_K \rangle)$.

In order for the state space of the CTMC to be finite, a maximum concentration M_i is fixed for each variable S_i, to be divided in N_i intervals representing h_i molar of concentration, with $h_i = \mathrm{M}_i/\mathrm{N}_i$ and $i = 1, ..., K$.

Transitions of the CTMC with levels and their activation in time are derived from the ODE model, using biochemical reactions and their velocities.

We use the following additional notation:

$$R_{i,i+1} : S_i \rightarrow \mathrm{S}_{i+1} \qquad v_{i,i+1} = k_{i,i+1}[\mathrm{S}_i] \qquad i = 1, ..., (K-1)$$
$$R_{i,i-1} : S_i \rightarrow \mathrm{S}_{i-1} \qquad v_{i,i-1} = k_{i,i-1}[\mathrm{S}_i] \qquad i = 2, ..., K$$

where the reaction $R_{i,j}$ represents the transformation of S_i into S_j (i.e. the migration of S from C_i to C_j), while $v_{i,j}$ is the velocity of the reaction $R_{i,j}$ expressed in $molar/s$, $j \in \{i+1, i-1\}$. Moreover, we assume that when a reaction $R_{i,i+1}$ or $R_{i,i-1}$ takes place, the CTMC will transit from a state $\sigma = (\langle \mathrm{S}_1 \rangle, ..., \langle \mathrm{S}_{i-1} \rangle, \langle \mathrm{S}_i \rangle, \langle \mathrm{S}_{i+1} \rangle, ..., \langle \mathrm{S}_K \rangle)$ to a state $\sigma' = (\langle \mathrm{S}_1 \rangle, ..., \langle \mathrm{S}_i \rangle - 1, \langle \mathrm{S}_{i+1} \rangle + 1, ..., \langle \mathrm{S}_K \rangle)$ or $\sigma'' = (\langle \mathrm{S}_1 \rangle, ..., \langle \mathrm{S}_{i-1} \rangle + 1, \langle \mathrm{S}_i \rangle - 1, ..., \langle \mathrm{S}_K \rangle)$ respectively. Reaction $R_{i,j}$ cannot take place if $\langle \mathrm{S}_i \rangle = 0$ or if $\langle \mathrm{S}_j \rangle = \mathrm{N}_j$.

Now consider the ODE of a single reaction $R_{i,i+1}$. It is composed by two complementary equations:

$$V_i \cdot \frac{\delta[\mathrm{S}_i]}{\delta t} = -k_{i,i+1}[\mathrm{S}_i] \qquad V_{i+1} \cdot \frac{\delta[\mathrm{S}_{i+1}]}{\delta t} = k_{i,i+1}[\mathrm{S}_i] \qquad i = 1, ..., (K-1) \tag{15}$$

Furthermore, Equation (15) can be written in the following difference form:

$$\begin{aligned} V_i \cdot \frac{\delta[\mathrm{S}_i]}{\delta t} &\approx V_i \cdot \frac{\Delta\langle \mathrm{S}_i \rangle \cdot h_i}{\Delta t} = -k_{i,i+1} \cdot \langle \mathrm{S}_i \rangle \cdot h_i \\ V_{i+1} \cdot \frac{\delta[\mathrm{S}_{i+1}]}{\delta t} &\approx V_{i+1} \cdot \frac{\Delta\langle \mathrm{S}_{i+1} \rangle \cdot h_{i+1}}{\Delta t} = k_{i,i+1} \cdot \langle \mathrm{S}_i \rangle \cdot h_i \end{aligned} \tag{16}$$

Our assumptions about the transitions on the CTMC state are that when reaction $R_{i,i+1}$ takes place, one level of S_i is consumed and one level of S_{i+1} is produced. This implies that in Equation (16) $\Delta\langle \mathrm{S}_i \rangle = -1$ and $\Delta\langle \mathrm{S}_{i+1} \rangle = 1$. Notice now that the only unknown term in Equation (16) is Δt, which can be regarded as the average time required to convert a level of S_i into a level of S_{i+1}. So we have:

$$\Delta t = \frac{V_i \cdot h_i}{k_{i,i+1} \cdot \langle \mathrm{S}_i \rangle \cdot h_i} = \frac{V_{i+1} \cdot h_{i+1}}{k_{i,i+1} \cdot \langle \mathrm{S}_i \rangle \cdot h_i} \qquad i = 1, ..., (K-1) \tag{17}$$

Rearranging Equation (17) we obtain the following equality:

$$h_i = \frac{h_{i+1} \cdot V_{i+1}}{V_i} = h_{i+1} \cdot \frac{(2i+1)}{(2i-1)} \qquad i = 1, ..., (K-1)$$

As a main consequence, we have that once a step size h_i is chosen, the other step sizes are derived automatically. We suggest to compute h_1 first, though it is possible to begin from other compartments. In particular, beginning from C_1 will ensure that all the other h_i $(i = 2, ..., K)$ will be smaller than h_1.

We can then use $r_{i,i+1} = 1/\Delta t$ as the parameter of the exponential distribution of the time required for reaction $R_{i,i+1}$. Through manipulation of Equation (17) we have:

$$\begin{aligned} r_{i,i+1} &= \frac{k_{i,i+1}\langle \mathrm{S}_i \rangle}{V_i} & i &= 1, ..., (K-1) \\ r_{i,i-1} &= \frac{k_{i,i-1}\langle \mathrm{S}_i \rangle}{V_i} & i &= 2, ..., K \end{aligned} \tag{18}$$

2.4 Additional Notes

Although we have shown that the numerical solution for the PDE and the ODE model of diffusion are equivalent, a few further considerations are necessary. In the case of the PDEs, K will be hidden to the modeller and in general is quite large, in order to obtain an output that is as close as possible to the analytical solution. When translating to ODEs, a lower K is advisable, as the modeller has to deal with compartments directly and a large amount of them would be difficult to manage.

Passing from the ODEs to the CTMC with levels, we notice that the state space of the CTMC depends on K and, additionally, on the maximum number of levels N_i. Intuitively, larger K and N_i yield Markov chains whose output tends more and more to the output of the original PDEs.

Finally we note the tension between complexity, ability of the CTMC to reproduce PDE output, and stochastic effects due to concentration discretisation. Managing this tension is the job of the modeller.

3 Example

We now turn our attention to an example, inspired by a series of publications about Nitric Oxide (NO) diffusion in human blood vessels. In particular, in [17] a vessel with a radius R of 138 μm is defined; we consider NO having a diffusion constant $D_{\mathrm{NO}} = 3300\ \mu m^2 s^{-1}$.

As the initial concentration function $f(x)$ at $t = 0$ we choose:

$$f(r, \alpha, \beta) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)\cdot\Gamma(\beta)} \cdot \left(\frac{r}{R}\right)^{\alpha-1} \cdot \left(\frac{R-r}{R}\right)^{\beta-1} \cdot 10$$

with $\alpha = 1$ and $\beta = 3$, defined in $[0, R]$, with unit measure $\mu molar$. This choice is based on our experience of the concentration of NO in literature, as a result of measurements or as observed in other mathematical models. It is parametric in α and β, to allow the generation of a full range of initial conditions starting from the same function.

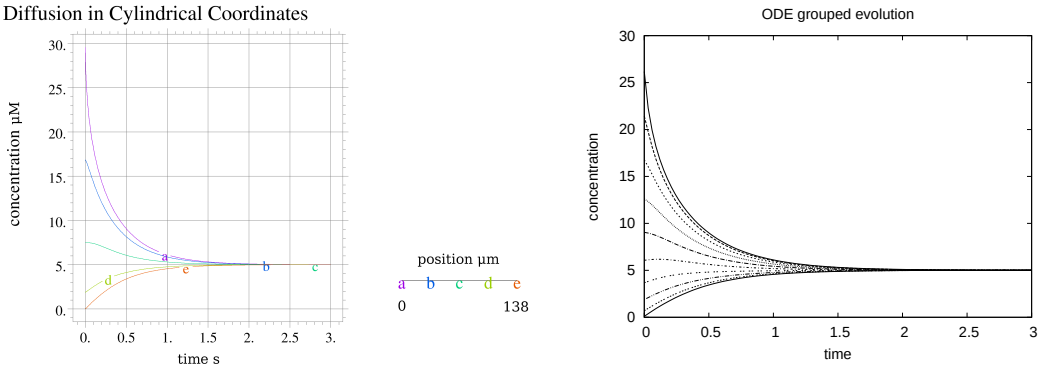

Fig. 2. PDE output (left) and ODE output (right) for the first 3 seconds of diffusion. Lines are the concentration at sample points along the radius (left) and the average concentration of compartments C_i $(i = 1, ..., 10)$ (right).

Notice that the information so far is enough to solve Equation (1) in one dimensional cylindrical coordinates. We used the simulator FlexPDE [2] (Figure 2 on the left). By defining the number of compartments to be $K = 10$, we can compute the ODE solution as well. For this task we used the simulator Copasi [1] (Figure 2 on the right, where a line is drawn for the average concentration of each compartment).

The implementation of the CTMC model requires little additional information as well. We define a maximum number of levels N_1=10 and a maximum concentration M_i=40 $\mu molar$, $i = 1, ..., K$. Here we used the PRISM model checker [3]. The result was a CTMC with $1.4 \cdot 10^{13}$ states and $2.4 \cdot 10^{14}$ transitions.

As a first exploration of the properties of the chain, we used stochastic simulations, taking average and standard deviation of model output from 100 runs. Some simulation results are shown in Figure 3.

4 Related Work

Translation from ODEs to CTMC with levels of concentration finds its roots in [7]. This has been then investigated further in [9], where a more solid theoretical link between the two approaches is introduced. Transport between compartments is considered in [10], where rates for transitions in the CTMC with levels between compartments with different volumes are derived.

Our starting point for the translation of diffusion equations from PDEs to ODEs with compartments has been [14], which considers stochastic simulations of reaction-diffusion processes. However, only Cartesian coordinates are considered.

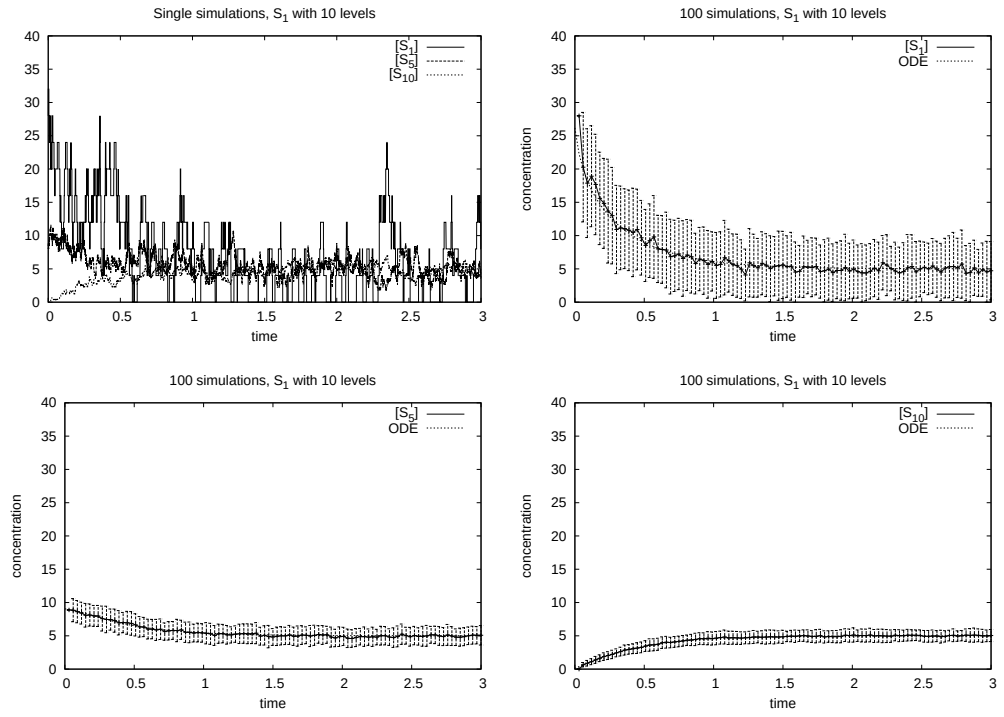

Fig. 3. CTMC stochastic simulations, average and standard deviation over 100 runs. S_1, S_5 and S_{10} are the average concentrations of compartments C_1, C_5 and C_{10}. Standard deviation over the 100 runs is shown.

5 Conclusions and Future Work

We presented a derivation of Fick's law of diffusion in one-dimensional cylindrical coordinates from partial differential equations to CTMC with levels. As an intermediate step, we converted the PDEs to ordinary differential equations with compartments, where transport velocities are implemented with mass action kinetic law. The novelties of this derivation are the kinetic constants derived directly from the diffusion constant and their dependency on the radial position. We then illustrated the result with an example, where we showed the consistency between simulations of PDEs, ODEs and CTMC.

In the future, we plan to develop a CTMC with levels model of NO transport and bioavailability in blood vessels, where diffusion is implemented using the derivation presented here.

6 Acknowledgements

Andrea Degasperi is supported by a Lord Kelvin / Adam Smith Scholarship of the University of Glasgow and by the EPSRC funded SIGNAL project.

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