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Simulating reaction-diffusion with state-dependent diffusion coefficients

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Abstract

The present models and simulation algorithms of intracellular kinetics are usually based on the premise that diffusion is so fast that the concentrations of all the involved species are homogeneous in space. However, recents experimental measurements of intracellular diffusion constants indicate that the assumption of a homogeneous well-stirred cytosol is not necessarily valid even for small prokaryotic cells. In this work we first present a mathematical description of the diffusion induced by concentration gradient. In our model the diffusion coefficients and mechanical quantities as frictional forces are dependent on the local values of solutes concentration. We then present an algorithm implementing our model and simulating a reaction-diffusion system. The algorithm is an efficient modification of the well known Gillespie algorithm, adapted for systems that are both reactive and diffusive.

1 Introduction

As their names indicates, reaction-diffusion models consist of two components. The first is a set of biochemical reactions which produce, transforms or removes chemical species. The second component is a mathematical description of the diffusion process. At molecular level, diffusion is due to random motion of molecules in a medium. The great majority of mesoscopic reaction-diffusion models in intracellular kinetics is usually performed on the premise that diffusion is so fast that all concentrations are homogeneous in space. However, recent experimental data on intracellular diffusion constants, indicate that this supposition is not necessarily valid even for small prokaryotic cells. If two mutually accessible regions of space contain substantially different numbers of molecules, in absence of other effects and forces, this random motion will result in a net flow of molecules from the region of high concentration to the region of lower concentration. The diffusion, as a result of Brownian motion, is a simple statistical effect that does not depend on the detailed mechanism by which molecules transit from a region to the other. If the system is composed by a sufficiently large number of molecules, the concentration, i. e. the number of molecules per unit volume, becomes a continuum and differentiable variable of space and time. In this limit a reaction diffusion system can be modelled by using differential equations. In an unstructured solvent, ideally behaving solute (i. e. ones for which solute-solute interaction are negligible) obey the Fick's law of diffusion. However in biological system even for purely diffusive transport phenomena the classical Fickian diffusion is at best a first approximation [1, 2]. Spatial effect are present in many biological systems, so that the spatially homogeneous assumption will not always hold. Examples of spatial effects include mRNA movement within the cytoplasm [3], Ash 1 mRNA localization in budding yeast [4], morphogen gradients across egg-polarity genes in Drosophyla oocyet [4], and the synapse-specificity of long-term facilitation in Aplysia [5]. Since intracellular medium can be hardly described as unstructured, The chief effect is this fact is to make the diffusion coefficient of a species dependent on the concentration of that species and on the other species of solutes eventually present in the medium.

Before proceeding further, it is useful to review the concepts of diffusive flux and Fick's law. The key concepts in the mathematical description of diffusion are summarised in the definition of flux of solute moving from one region to the other of the space. Consider a small surface S of are dA oriented perpendicular to one of the coordinate axes, say the y-axis. The flux of solute in the y direction, J, is defined as the number of molecules which pass through the surface per unit area per unit time. Therefore, the number of solute molecules crossing the surface in time dt is $JdAdt$. The net flux depends on the number of molecules in small regions to either side of the surface: if there are more molecules on the left, then we expect a left-to-

right flux which grows in size as the difference of concentration to either side of the surface increases. Moving the surface S from one point in space to another, we may find that this local difference changes. Therefore the flux is a vectorial quantity depending on the position in space, i. e. $J = J(x, y, z)$. The simplest description of the concentration dependence of the flux is the Fick's first law, namely the flux is proportional to the local derivative of the concentration c of solute with respect to the spatial variables: $J = -D\partial c/\partial x$ in one dimension, or $\vec{J} = -D\nabla c$ in three dimensions. The quantity D in the Fick's law is known as diffusion coefficient. If the medium is isotropic, D is a constant scalar independent of the concentration of the solute.

In this paper we present a new model of the concentration dependence of the diffusion coefficients for a reaction-diffusion system and we calculate the rates of diffusion of the biochemical species in terms of these concentration-dependent diffusion coefficients. For simplicity we treat here purely diffusive transport phenomena of non-charged particles, and, in particular, the case in which the diffusion is driven by a chemical potential gradient in x direction only (the generalisation to the three-dimensional case poses no problems). The method of our derivation consists of the following five main steps: 1. calculation of the *local* virtual force F per molecules as the spatial derivative of the chemical potential 2. calculation of the particles mean drift velocity in terms of F and local frictional f; 3. estimation of the flux J as the product of the mean drift velocity and the local concentration; 4. definition of diffusion coefficients as function of local activity and frictional coefficients and concentration, and 5. calculation of diffusion rates as the negative first spatial derivative of the flux J. The determination of the activity coefficients has required the estimation of the second virial coefficient, that in our model is calculated from its mechanical statistical definition and using a Lennard-Jones potential to describe the molecular interactions. The frictional coefficient is here modeled as linearly dependent on the local concentration.

In our model the system spatial domain is divided into a number of reaction chambers, which we call *cells* or *meshes*; the reaction chambers can exchange molecules in a way to simulate diffusion and they can also host chemical reactions between internal molecules. The reaction-diffusion system is then solved by the Gillespie algorithm.

2 Diffusion of non-charged molecules

If solutions of different concentrations are brought into contact with each other, the solute molecules tend to flow from regions of higher concentration to regions of lower concentration, and there is ultimately an equalisation of concentration. The driving force of the diffusion is the Gibbs energy difference between regions of different concentration, i. e. the gradient of

chemical potential μ. Consider a solution containing N different solutes. The chemical potential μ_i of any particular chemical species i is defined as the partial derivative of the Gibbs energy G with respect to the concentration of the species i, with temperature and pressure held constant. Species are in equilibrium if their chemical potentials are equal.

$$\mu_i \equiv \frac{\partial G}{\partial c_i} = \mu_i^0 + RT \ln a_i \tag{1}$$

where c_i is the concentration of the species i, μ_i^0 is the standard chemical potential of the species i (i .e. the Gibbs energy of 1 mol of i at a pressure of 1 bar), $R = 8.314$ J $\cdot$ K^{-1} $\cdot$ mol^{-1} is the ideal gas constant, and T the absolute temperature. The quantity a_i is called *chemical activity* of component i. The activity is decomposed into

$$a_i = \frac{\gamma_i c_i}{c^0} \tag{2}$$

where γ_i is the *activity coefficient*, c^0 being a reference concentration. The activity coefficients express a deviation of a solution from the ideal thermodynamic behavior and in general they may depend on the concentration of all the solutes in the system. For ideal solution, a limit which is recovered experimentally at high dilutions, $\gamma_i = 1$. If the concentrations of species i varies from point to point in space, then so does the chemical potential. For simplicity, we treat here the case in which there is only a chemical potential gradient in the x direction only. Chemical potential is the free energy per mole of substance i, free energy is the negative of the work W which a system can perform, and work is connected to force F by $dW = Fdx$. Therefore an inhomogeneous chemical potential is related to a virtual force per molecule of

$$F_i = -\frac{1}{N_A}\frac{d\mu_i}{dx} = -\frac{k_B T c^0}{\gamma_i c_i}\sum_j \frac{\partial a_i}{\partial c_j}\frac{\partial c_j}{\partial x} \tag{3}$$

where $N_A = 6.022 \times 10^{23}$ mol^{-1} is the Avogadro's number, $k_B = 1.381 \times 10^{-23}$ J $\cdot$ K^{-1} is the Boltzmann's constant, and the sum is taken over all species in the system other than the solvent. This force is balanced by the drag force experienced by the solute ($F_{drag,i}$) as it moves through the solvent. Drag forces are proportional to the speed. If the speed of the solute is not too high in such a way the solvent does not exhibit turbulence, we can assume that the drag force is

$$F_{drag,i} = f_i v_i \tag{4}$$

where $f_i \propto c_i$ is the frictional coefficient, and v_i is the mean drift speed.

Again, if the solvent is not turbulent, we can assume that the *flux*, defined as the number of moles of solute which pass through a small surface per unit time per unit area, is

$$J_i = c_i v_i \tag{5}$$

i. e. the number of molecules per unit volume multiplied by the linear distance travelled per unit time.

Since the virtual force on the solute is balanced by the drag force (i. e. $F_{drag,i} = -F_i$), we obtain the following expression for the mean drift velocity

$$v_i = \frac{F_i}{f_i}$$

so that Eq. (5) becomes

$$J_i = -\frac{k_B T}{\gamma_i f_i} \sum_j \frac{\partial a_i}{\partial c_j} \frac{\partial c_j}{\partial x} \equiv -\sum_j D_{ij} \frac{\partial c_j}{\partial x} \tag{6}$$

where

$$D_{ij} = \frac{k_B T c^0}{\gamma_i f_i} \frac{\partial a_i}{\partial c_j} \tag{7}$$

are the diffusion coefficients. The Eq. (7) states that, in general, the flux of one species depends on the gradients of all the others, and not only on its own gradient. However, here we will suppose that the chemical activity a_i depends only weakly on the concentrations of the other solutes, i. e. we assume that $D_{ij} \approx 0$ for $i \neq j$ and the Fick's laws still holds. Let D_i denote D_{ii}. It is still generally the case that D_i depends on c_i in sufficiently concentrated solutions since γ_i (and thus a_i) has a non trivial dependence on c_i. In order to find an analytic expression of the diffusion coefficients D_i in terms of the concentration c_i, let us consider that the rate of change of concentration of the substance i due to diffusion is given by

$$\mathscr{D}_i = -\frac{\partial J_i}{\partial x} \tag{8}$$

Substituting Eq. (7) into Eq. (6), and then substituting the obtained expression for J_i into Eq. (8), gives

$$\mathscr{D}_i = -\frac{\partial}{\partial x}\left(- D_i(c_i) \frac{\partial c_i}{\partial x} \right) \tag{9}$$

so that

$$\begin{aligned}\mathscr{D}_i &= \left(\frac{\partial D_i(c_i)}{\partial x}\right)\frac{\partial c_i}{\partial x} + D_i(c_i)\frac{\partial^2 c_i}{\partial x^2} \\ &= \frac{\partial D_i(c_i)}{\partial c_j}\frac{\partial c_j}{\partial x}\frac{\partial c_i}{\partial x} + D_i(c_i)\frac{\partial^2 c_i}{\partial x^2}\end{aligned} \tag{10}$$

Let $c_{i,k}$ denote the concentration of a substance i st coordinate x_k, and $l = x_k - x_{k-1}$ the distance between adjacent mesh points. The derivative of c_i with respect to x calculate in $x_{k-\frac{1}{2}}$ is

$$\frac{\partial c_i}{\partial x}\Big|_{x_{k-\frac{1}{2}}} \approx \frac{c_{i,k} - c_{i,k-1}}{l} \tag{11}$$

By using Eq. (11) into Eq. (6) the diffusive flux of species i midway between the mesh points $J_{i,k-\frac{1}{2}}$ is obtained

$$J_{i,k-\frac{1}{2}} = -D_{i,k-\frac{1}{2}}\frac{c_{i,k} - c_{i,k-1}}{l} \tag{12}$$

where $D_{i,k-\frac{1}{2}}$ is the estimate of the diffusion coefficient midway between the mesh points.

The rate of diffusion of substance i at the mesh point k is

$$\mathscr{D}_{ik} = -\frac{J_{i,k+\frac{1}{2}} - J_{i,k-\frac{1}{2}}}{l}$$

and thence

$$\mathscr{D}_{ik} = \frac{D_{i,k-\frac{1}{2}}}{l^2}(c_{i,k-1} - c_{i,k}) - \frac{D_{i,k+\frac{1}{2}}}{l^2}(c_{i,k+1} - c_{i,k}) \tag{13}$$

To determine completely the right-hand side of Eq. (13) is now necessary to find an expression for the activity coefficient γ_i and the frictional coefficient f_i, contained in the formula (7) for the diffusion coefficient. In fact, by substituting Eq. (2) into Eq. (7) we obtain an expression of the diffusion coefficient in terms of activity coefficients γ_i

$$D_{ii} = \frac{k_B T}{f_i}\Big(1 + \frac{c_i}{\gamma_i}\frac{\partial \gamma_i}{\partial c_i}\Big) \tag{14}$$

Let focus now on the calculation of the activity coefficients, while a way to estimate the frictional coefficients will be present in Section 2.1. By using the subscript '1' to denote the solvent and '2' to denote the solute, we have

$$\mu_2 = \mu_2^0 + RT\ln\left(\frac{\gamma_2 c_2}{c^0}\right) \tag{15}$$

where γ_2 is the activity coefficient of the solute and c_2 is the concentration of the solute. By differentiating with respect to c_2 we obtain

$$\frac{\partial \mu_2}{\partial c_2} = RT\Big(\frac{1}{c_2} + \frac{1}{\gamma}\frac{\partial \gamma_2}{\partial c_2}\Big) \tag{16}$$

The chemical potential of the solvent is related to the osmotic pressure (Π) by

$$\mu_1 = \mu_1^0 - \Pi V_1 \tag{17}$$

where V_1 is the partial molar volume of the solvent and μ_1^0 its standard chemical potential. Assuming V_1 to be constant and differentiating μ_1 with respect to c_2 we obtain

$$\frac{\partial \mu_1}{\partial c_2} = -V_1\frac{\partial \Pi}{\partial c_2} \tag{18}$$

Now, from the Gibbs-Duhen relation, the derivative of the chemical potential of the solute with respect to the solute concentration is

$$\frac{\partial \mu_2}{\partial c_2} = -\frac{M(1-c_2\overline{v})}{V_1 c_2}\frac{\partial \mu_1}{\partial c_2} = \frac{M(1-c_2\overline{v})}{c_2}\frac{\partial \Pi}{\partial c_2} \tag{19}$$

where M is molecular weight of the solute and $\overline{v}$ is the partial molar volume of the solute divided by its molecular weight. The concentration dependence of osmotic pressure is usually written as

$$\frac{\Pi}{c_2} = \frac{RT}{M}\Big[1 + BMc_2 + O(c_2^2)\Big] \tag{20}$$

where B is the second virial coefficient (see Section 2.2), and thence the derivative with respect to the solute concentration is

$$\frac{\partial \Pi}{\partial c_2} = \frac{RT}{M} + 2RTBc_2 + O(c_2^2) \tag{21}$$

Introducing Eq. (21) into Eq. (19) gives

$$\frac{\partial \mu_2}{\partial c_2} = RT(1-c_2\overline{v})\Big(\frac{1}{c_2} + 2BM\Big) \tag{22}$$

From Eq. (16)and Eq. (22) we have

$$\frac{1}{\gamma_2}\frac{\partial \gamma_2}{\partial c_2} = \frac{1}{c_2}\Big[RT(1-c_2\overline{v})(1+2BMc_2) - 1\Big]$$

so that

$$\int_1^{\gamma_2'}\frac{d\gamma_2}{\gamma_2} = \int_{c^0}^{c_2'}\frac{1}{c_2}\Big[RT(1-c_2\overline{v})(1+2BMc_2) - 1\Big]dc_2$$

On the grounds that $c_2\overline{v} \ll 1$ [6], by solving the integrals we obtain

$$\gamma_2' = \exp[2BM(c_2' - c^0)] \tag{23}$$

The molecular weight $M_{i,k}$ of the species i in the mesh k can be expressed as the ratio between the mass $m_{i,k}$ of the species i in that mesh and the Avogadro's number $M_{i,k} = m_{i,k}/N_A$. If p_i is the mass of a molecule of species i and $c_{i,k}l$ is the number of molecules of species i in the mesh k, then the molecular weight of the solute of species i in the mesh k is given by

$$M_{i,k} = \frac{p_i \;\; l}{N_A} c_{i,k} \tag{24}$$

Substituting this expression in Eq. (23) we obtain for the activity coefficient of the solute of species i in the mesh k ($\gamma_{i,k}$), the following equation

$$\gamma_{i,k} = \exp\left(2B \; \frac{p_i \; l}{N_A} \; c_{i,k}^2\right) \tag{25}$$

2.1 Intrinsic viscosity and frictional coefficient

The diffusion coefficient depends on the ease with which the solute molecules can move. The diffusion coefficient of a solute is a measure of how readily a solute molecule can push aside its neighboring molecules of solvent. An important aspect of the theory of diffusion is how the magnitudes of the frictional coefficient f_i of a solute of species i and, hence, of the diffusion coefficient D_i, depend on the properties of the solute and solvent molecules. Examination of well-established experimental data shows that diffusion coefficients tend to decrease as the molecular size of the solute increases. The reason is that a larger solute molecule has to push aside more solvent molecules during its progress and will therefore move slowly than a smaller molecule. A precise theory of the frictional coefficients for the diffusion phenomena in biological context cannot be simply derived from the elementary assumption and model of the kinetic theory of gases and liquids. The Stokes's theory considers a simple situation in which the solute molecules are so much larger than the solvent molecules that the latter can be regarded as a continuum (i. e. not having molecular character). For such a system Stokes deduced that the frictional coefficient of the solute molecules is $f_i = 6\pi r_i^H \eta$, where r_i^H is the hydrodynamical radius of the molecule and η is the viscosity of the solvent. For proteins diffusing in the cytosol, the estimate of frictional coefficient through the Stokes's law is hard, for several reasons. First of all, the assumption of very large spherical molecules in a continuous solvent is not a realistic approximation for a protein moving through the cytosol: the protein may be not spherical and the solvent is not a continuum. Furthermore, in the protein-protein interaction in the cytosol water molecules should be included explicitly, thus complicating the estimation of the hydrodynamical radius. Finally, the viscosity of the solvent η

within the cellular environment cannot be approximated either as the viscosity of liquid or the viscosity of gas. In both cases, the theory predict a strong dependence on the temperature of the system, that has not been found in the cell system, where the most significant factor in determining the behavior of frictional coefficient is the concentration of solute molecules. To model the effects of non-ideally on the friction coefficient we assume that its dependence on the concentration of the solute is governed by expression similar to the one used to model friction coefficient in sedimentation processes [7]

$$f_{i,k} = k_f c_{i,k} \tag{26}$$

where k_f is an empirical constant, whose value can be derived from the knowledge of the ratio $R = k_f/[\eta]$. Accordingly to the Mark-Houwink equation, $[\eta] = kM^{\alpha}$ is the intrinsic viscosity coefficient, α is related to the shape of the molecules of the solvent, and M is still the molecular weight of the solute. If the molecules are spherical, the intrinsic viscosity is independent of the size of the molecules, so that $\alpha = 0$. All globular proteins, regardless of their size, have essentially the same $[\eta]$. If a protein is elongated, its molecules are more effective in increasing the viscosity and $[\eta]$ is larger. Values of 1.3 or higher are frequently obtained for molecules that exist in solution as extended chains. Long-chain molecules that are coiled in solution give intermediate values of α, frequently in the range from 0.6 to 0.75 [8]. For globular macromolecule, R has a value in the range of 1.4 - 1.7, with lower values for more asymmetric particles [9].

2.2 Calculated second virial coefficient

The mechanical statistical definition of the second virial coefficient is given by the following

$$B = -2\pi N_A \int_0^{\infty} r^2 \exp\Big[-\frac{u(r)}{k_B T}\Big] dr \tag{27}$$

where $u(r)$ is the interaction free energy between two molecules and r is the intermolecular center-center distance. In this work we assume for $u(r)$ the Lennard-Jones pair (12,6)-potential (Eq. 28), that captures the attractive nature of the Van der Waals interactions and the very short-range Born repulsion due to the overlap of the electron clouds.

$$u(r) = 4\Big[\Big(\frac{1}{r}\Big)^{12} - \Big(\frac{1}{r}\Big)^{6}\Big] \tag{28}$$

and expanding the term $\exp\left(\frac{4}{k_B T}\frac{1}{r^6}\right)$ into an infinite series, the Eq. (27) becomes

$$B = -2\pi N_A \sum_{j=0}^{\infty} \frac{1}{j!} (T^*)^j \int_0^{\infty} r^{2-6j} \exp\Big[- T^* \frac{1}{r^2} \Big] dr$$

where $T^* \equiv 4/(k_B T)$ and thus

$$B = -\frac{\pi N_A}{6} \sum_{j=0}^{\infty} \frac{1}{!j} 4^j (k_B T)^{-\frac{1}{4}+\frac{1}{2}j} \, \Gamma\Big(- \frac{1}{4} + \frac{1}{2} j \Big) \tag{29}$$

In our model the estimate of B is given by truncating the infite series of Γ functions to $j = 4$, since taking into account the additional terms, obtained for $j > 4$, does not significatively influence the simulation results.

3 Algorithm and data structures

We developed an algorithm that computes the diffusion rates as described in the previous sections. The algorithm first subdivides the volume into cells of fixed dimension. The dimension of each cell in the mesh is chosen to be not too fine-grained, in order to reduce simulation time, but within the constraints described in [10] to preserve accuracy. Both the method and the algorithm and data structures trivially generalises to meshes in any dimension; however, to make the analysis as simple as possible, we focused our attention to meshes in one dimension. The algorithm is a refinement of those proposed by Bernstein [10] and by Elf et al. [11]. The *Next subvolume method* proposed by Elf et al. is a two level system in which every cell computes individually the next event, a chemical reaction or a diffusion, using the Gillespie direct method [12]. The cell where the next event will occur is determined using a global priority queue that holds the times of the quickest event for each cell. This event is consumed and only the one or two cells affected by the event are updated, adjusting their position in the priority queue accordingly. This algorithm is therefore efficient but centralised and sequential in nature, and can have problems in scaling to very large systems. Moreover, it can not easyly to adapt to take advantage of parallel or distributed systems. Since the number of reactions in the master system can easily be in the millions for even a modest mesh and a small set of chemical reactions, scalability is required to make large simulations feasible. Our algorithm overcomes these limitations by eliminating the use of a global priority queue.

Assume that every cell knows its own concentrations, diffusion and reaction rates, along with the next event (reactive or diffusive) and the time at which it will occur, as well as its neighbour cells. Moreover, in order that the original Gillespie algorithm be applicable to the chemical reaction occuring in each reaction chamber, we require that the concentration there be considered uniform. Each cell has *dependency relations* on a set of neighbour cells;

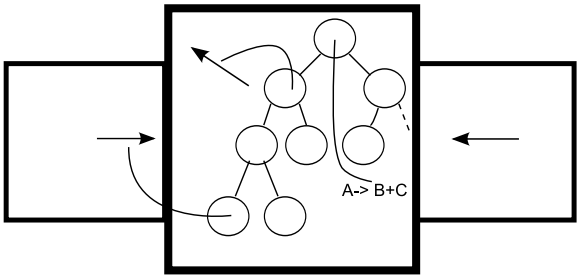

Figure 1: The *dependency relations* of a cell.

the cell can perform its next event only if it is quicker than the diffusion events of the neighbour cells, because diffusion events can change reactant concentrations, and therefore the time and order of the events (Figure 1).

The algorithm makes use of this property: as each cell can *evolve* independently from other cells if it does not violate the restrictions imposed by its dependencies, at every step all the cells that can evolve are allowed to consume one event and advance one simulation step. Note that, as we executed reactions quicker than our neighbours, we do not have to worry about them altering our concentrations meanwhile.

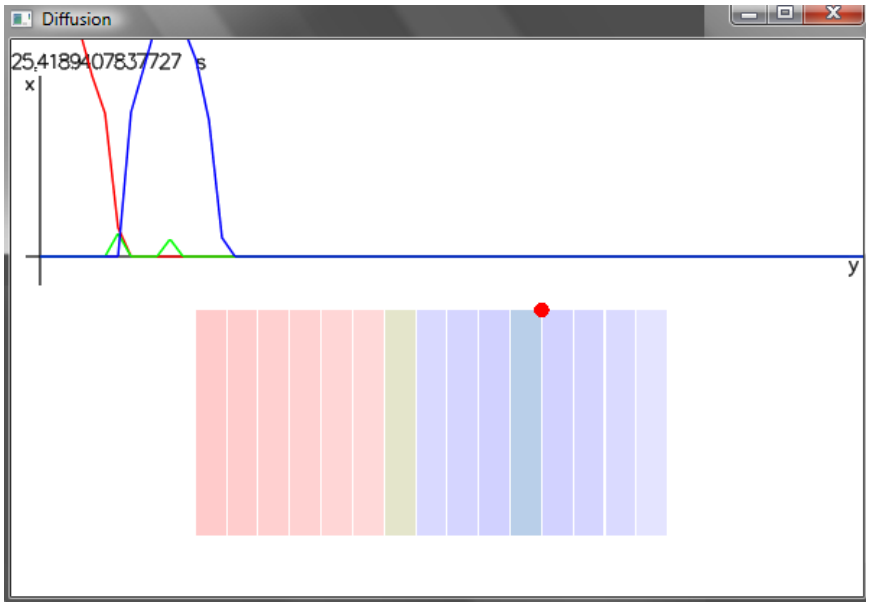

Figure 2: The OpenGL viewer.

The algorithm has still the same average computational complexity; however, removing the global priority queue allows it to scale gracefully with the number of reactions and processors.

A tool that implements the algorithm described here was developed in

C# for the .NET and Mono Frameworks; the tools also has an interactive OpenGL viewer that shows the progress of the simulation in realtime (Figure 2). The viewer window is divided into two zones: in the upper zone, a plot shows the variation of concentration in space; in the lower zone, cells in the mesh are drawn as rectangles. The rectangles are filled with an amount of color that is proportional to the concentration of each specie so that it is possible to immediately view the variation in space of the gradient. The small red dot indicates the cell in which the reaction-diffusion is taking place.

3.1 Simulations

To test our approach, we simulated two simple systems: one with only diffusion events, the other with a mixture of reactive and diffusive actions. For both the systems we simulated also the case in which the D_{ii} of Eq. (14) are fixed, reducing the simulation to a case similar to the one in [10].

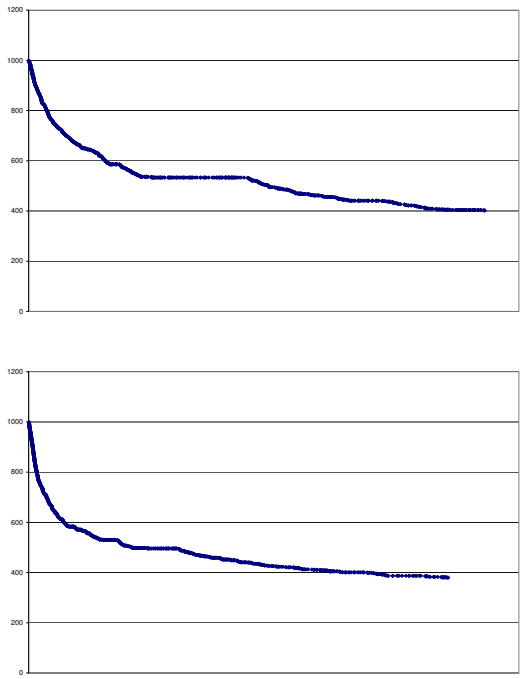

Figure 3: Concentration of a single species in the first cell. On the x-axis, the number of molecules, on the y-axis the step in the simulation.

It can be noted from Figures 3 and 4 - showing the simulation of a pure diffusion system - that the two approaches led to similar results. In both figures, the upper plot is for fixed values of D, the lower one with D computed as in Eq. (14). The upper plot of Figure 4 shows a linear dependence

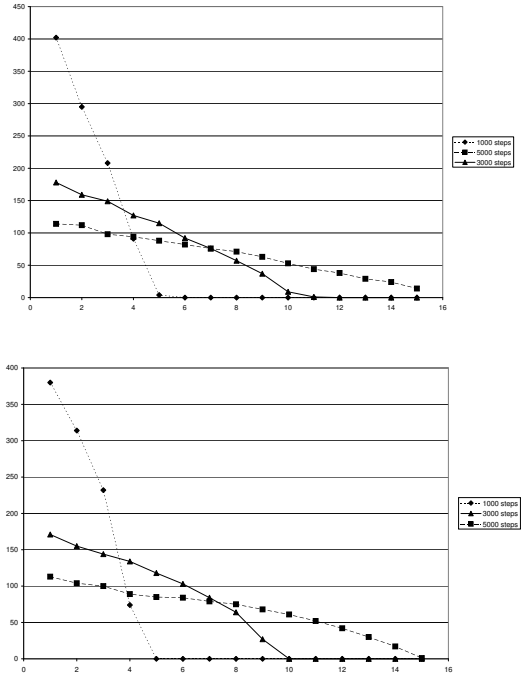

Figure 4: On the x-axis, the number of molecules, on the y-axis the variation in space.

of the spatial coordinate of the solute molecules on their concentration, whereas the lower plot shows significant deviations from the linearity due to the dependence of the diffusion coefficients D, and consequently of the rate of diffusion, on an inhomogeneous concentration. Furthermore, focusing on the a given mesh, the upper plot of Figure 3 shows a decrease of the solute concentration slower than the decrease of the one simulated with concetration-dependent D. In fact, in this case, the algorithm needs a less number of steps to reach the final stable configuration, in which there is no further movement of the solute molecules. With D depending on the concentration as in Eq. (14), the rate of diffusion of the solute, calculated with Eq. (13), is directly proportional to the square of the concentration, that increments the speed of the diffusion reactions.

4 Conclusions and future directions

We have presented a model for the diffusion of non-charged molecules, in which the diffusion coefficient are not constant. In particular we have developed a model of a diffusion mechanism where the diffusion coefficients are concentration-dependent. Our work is motivated because constant dif-

fusion coefficients are rather more the exception than the rule in biological cells and, more generally in biological tissues. With respect to previous works as [13, 10, 14], our model provides a theoretical derivation of the molecular origins of the parameters, that determine the time-behavior of the diffusive phenomena. Future work will consist of a calculation of the second virial coefficient for biomolecules, especially for proteins. The use of the Lennard-Jones potential is a good approximation of the molecular interaction, but it is a drawback in describing protein-protein interaction is that water molecules must be included explicitly [15], complicating the computational task. The condition of solvated molecules is reflected also to the expression of the concentration-dependence of frictional coefficient, that will need to be accordingly modified. The algorithm which simulates this diffusion model produces more accurate results with respect to the algorithm simulating classical Fickian diffusion and can be used to calculate and predict the time-behavior of proteins and biomolecules diffusing in a highly structured and inhomogeneous medium.

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