Open Science Repository Mathematics

MATHEMATICAL MODELING OF REACTION-DIFFUSION PROCESS IN CELL MEMBRANES

SAHEED AKINDEINDE *

Abstract. In this paper, we discuss the mathematical modeling and numerical implementation of reaction-diffusion processes inside a cell nucleus where the diffusion of nuclear materials is restricted by its membrane. Viewing the two-specie interaction between the chemical composition of the cell and its membrane as an enzyme-substrate process we modeled the reaction-diffusion in the cell membrane under quasi-steady state equilibrium assumption. The pure diffusion process inside the three-dimensional cell depends on the solution of a two-dimensional reaction-diffusion process on the interface on its cell membrane. Through adaptive finite element discretization, we solve the three-dimensional pure diffusion problem using the solution of the two-dimensional problem on the membrane as a Dirichlet data. The paper is complemented with numerical results.

Key words. Mathematical modeling, reaction, diffusion, finite element, discretization, cell membrane

1. Background and problem statement. This work has evolved through the need to understand the various biological processes continually taking place in living organisms as well as problems in various field of science involving transport of materials and interactions of chemical compounds. The underlying physical processes involved are reaction and diffusion. A reaction process involves inter-conversion of chemical substances as a result of random motion of molecules and the forming and breaking of chemical bonds resulting into formation of one or more new products. In some cases, the intermediate product formed simultaneously breaks down into new chemical compounds and are transported within the cell by the process of diffusion. This is the case of the first enzymatic reactions proposed by Michaelis and Menten [12] in 1913 involving the conversion of substrate via reaction with enzyme to form a product. Diffusion process on the other hand results in mixing of chemical substances as it moves materials from one point to another within regions of different concentration gradients. Aside been vital biological processes, reaction-diffusion process have also found applications, to mention but a few, in the production of semiconductors, catalyst design in chemical industry, transportation of air and ground water pollutant e.t.c. In living cells, the exchange of chemical materials and subsequent formation of complex are carried out through the cell membranes. In this work, we are concerned with the modeling of reaction-diffusion processes in cell membrane as well as finding a numerical solution to the resulting model problem in the stationary case.

Our motivation for this work lies in the various works of several authors ranging from the study of protein-protein interaction in cells [15], through analysis of reaction-diffusion of compounds in cells. Notable among these works are [14] which focused on the numerical simulations of reaction-diffusion systems in cells. [3] specifically studied the reaction-diffusion of carcinogenic compounds in cells, and model for determining the concentrations of these chemical substances in cells was obtained. Analysis of reaction-diffusion processes in cell tissues is extensively discussed in [6]. It is worth mentioning that the works cited above have either considered reaction-diffusion processes solely within cells or have tailored their models to special problems which makes extension to different problems like the one considered in this article impossible. In this article, we develop a general model that describes reaction-diffusion in an arbitrary living cell. Our reaction-diffusion model comprises a coupled model of three-dimensional diffusion process within the cell and a two-dimensional reaction-diffusion model on the cell membrane. Through adaptive discretization of the coupled model, we obtain numerical solution of the model problem.

We shall denote the cell by a bounded domain $\Omega \subseteq \mathbb{R}^3$. Let us assume that the cell is made up of a chemical specie B with concentration u_B. This chemical specie B reacts with an external chemical species at some parts Γ of its membrane denoted by $\partial\Omega$, which results in the formation of chemical complexes on Γ. The formed complexes are continually formed and accumulated on Γ but do not diffuse into the cell by assumption. Within the cell, we assume a pure diffusion process. Let α, D, n denote respectively the permeability constant of the cell, the diffusion coefficient of the cell and an outward pointing unit normal on the domain Ω. Thus, in this case of pure diffusion in the cell, the three dimensional model describing the pure diffusion process in Ω is given by

$$\begin{aligned} -\nabla \cdot (D\nabla u_B) &= 0 \quad \text{in } \Omega, \\ u_B &= g \quad \text{on } \Gamma, \\ -D\frac{\partial u_B}{\partial n} &= \alpha u_B \quad \text{on } \partial\Omega\backslash\Gamma. \end{aligned} \tag{1.1}$$

*IBM Research Africa, Nairobi, Kenya akinsahe@ke.ibm.com, saheed.akindeinde@gmail.com

Here the Dirichlet data g has to be computed as a solution of a two-dimensional problem on the interface Γ, see (2.26).

Let us comment briefly on the creation of geometries describing the cell. A living cell is a tiny structure with the size of about $3 \times 10^{-6} m$. Hence for the purpose of modeling and computation, scaling and non-dimensionalization have to be carried out. The non-dimensionalization analysis is treated in Section 2.2 of this paper. The representation of the cell on a computer is shown in Figure 1.1 below. The

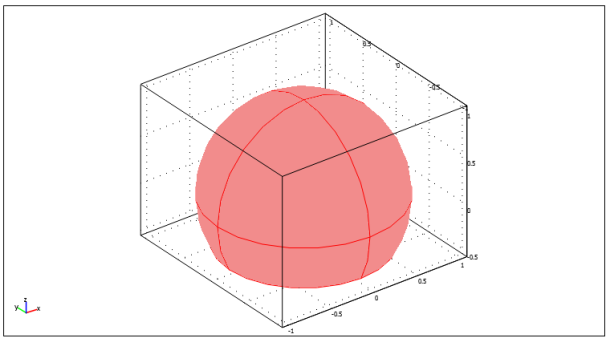


FIG. 1.1. *The geometry for the cell.*

interface Γ, a part of the cell membrane is a modeled as an intersection of a ball with a rectangular plane.

We emphasize that the Dirichlet data g obtained from solving the two-dimensional model on Γ cannot be used directly in (1.1), we shall therefore employ the multi-physics capability of Comsol[1] to couple the $3D$ pure diffusion model (1.1) within the cell and the $2D$ reaction-diffusion model on the interface Γ.

The paper is organized as follows; we describe in detail the mathematical modeling of reaction-diffusion equation in Section 2 where the model problems are derived. In Section 3, we discuss numerical discretization of the model problem. In the fourth section, numerical implementation of the reaction-diffusion problem is discussed. There, the computation of the numerical solutions to the two-dimensional problem, the three-dimensional problem as well as the coupled model is carried out in detail. The paper concludes with discussion of our numerical results.

2. Model description of reaction and diffusion processes. In this section, the set of equations governing the reaction and diffusion processes in the cell and its membrane will be established. We will start by considering reaction process between different chemical species interacting at the contact point Γ on the cell membrane, and then give a description of the diffusion process within the cell under consideration. Finally we derive the reaction-diffusion model that remains the backbone for the rest of the analysis in this paper.

2.1. Reaction Process. Let us consider a two-specie reaction between two chemical species A and B represented by a reversible reaction equation given by

$$A + B \underset{k_2}{\overset{k_1}{\rightleftharpoons}} AB. \tag{2.1}$$

Here, A denotes an external chemical specie and B the chemical composition of the cell under consideration (Figure 2.1) respectively. The above interaction between A and B results in the formation of a chemical complex AB on the interface Γ. We assume that the chemical specie A and the complex AB do not diffuse into the cell after the reaction, but however have great influence on the concentration of B in the cell through further possible decomposition.

To be consistent with previously introduced notation, let us denote concentrations of chemical species A, B and the complex AB by u_A, u_B, and u_{AB} respectively. Now applying the law of mass action (the

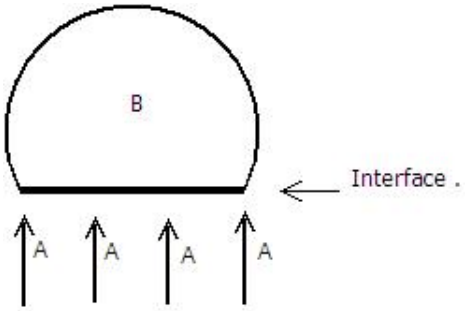


FIG. 2.1. *Illustration of the reaction between chemical specie A and the composition of the cell.*

rate of a reaction is proportional to the product of the concentrations of the reactants) to (2.1) gives

$$\frac{du_A}{dt} = -k_1 u_A u_B + k_2 u_{AB}, \tag{2.2}$$

$$\frac{du_B}{dt} = -k_1 u_A u_B + k_2 u_{AB}, \tag{2.3}$$

$$\frac{du_{AB}}{dt} = k_1 u_A u_B - k_2 u_{AB} \tag{2.4}$$

where k_1, k_2 are constants of proportionality. If we impose initial conditions $u_A(0) = u_{A_0}, u_B(0) = u_{B_0}, u_{AB}(0) = 0$, solving the above equations gives evolution of the concentrations of the reactants u_A, u_B and the product u_{AB}.

2.2. Multi-reaction processes on Γ. Here we will extend the model derived in Section 2.1 to include a more common cases of multiple chemical species interactions on cell membrane. We follow the previous notation and Γ remains a part of the cell membrane. Suppose that the interface Γ comprises two sub-domains Γ_R and Γ_S and are arranged alternately as in the Table 2.1 below. Now let us consider

Γ_R	Γ_S	Γ_R	Γ_S
Γ_S	Γ_R	Γ_S	Γ_R
Γ_R	Γ_S	Γ_R	Γ_S
Γ_S	Γ_R	Γ_S	Γ_R

TABLE 2.1
Distribution of the two sub-domains on Γ.

two chemical species R and S interacting with chemical specie B according as the following reversible reaction equations

$$R + B \underset{k_3}{\overset{k_2}{\rightleftharpoons}} RB \quad \text{on } \Gamma_R, \tag{2.5}$$

$$S + B \underset{k_5}{\overset{k_4}{\rightleftharpoons}} SB \quad \text{on } \Gamma_S \tag{2.6}$$

where Γ_R, Γ_S are subsets of Γ.

Applying the law of mass action as in Section 2.1 gives

$$\frac{du_B}{dt} = -k_2 u_R u_B + k_3 u_{RB} \quad \text{on } \Gamma_R \tag{2.7}$$

and

$$\frac{du_B}{dt} = -k_4 u_S u_B + k_5 u_{SB} \quad \text{on } \Gamma_S \tag{2.8}$$

which with initial condition $u_B(0) = u_{B_0}$ gives the evolution of the chemical specie B on Γ_R, Γ_S respectively.

2.3. Reaction-diffusion process. In this part of the paper, we will derive the reaction-diffusion equation describing the entire process happening within the cell as well as on its membrane.

Let us start by deriving a general reaction-diffusion model before applying the model to the present problem. Since the volume of diffusing materials usually depends on the concentration gradients across the medium, it is quite reasonable to assume that the diffusion of materials within the cell follows the classical diffusion process so that the Fick's law of diffusion applies. Fick's law describes the relationship between the concentration of the material u_B and the flux J. The Fick's law states that the steady state diffusion flux J is proportional to the concentration gradient expressed mathematically as $J = -D\dfrac{\partial}{\partial x}u_B(x,t)$, where D is the diffusion coefficient which measures how efficiently chemical specie B moves from a region of higher concentration of the chemical material to regions of lower concentrations. The value of D depends on the size of u_B, as well as the medium in which it is diffusing. In three dimensions, the flux is of the form

$$J = -D\nabla u_B \tag{2.9}$$

with ∇ denoting the vector differential operator.

Now we will use the conservation equation to derive the general reaction-diffusion equation. Let τ be a small time period and denote the cell as an open, bounded and smooth domain $\Omega \subseteq \mathbb{R}^3$ and regard $\partial\Omega$ as the cell membrane. In general, let S be an arbitrary surface enclosing a volume $V \subset \Omega$. The general conservation equation holds i.e.

$$\int_V [u_B(x,t+\tau) - u_B(x,t)]\,\mathrm{d}V = \int_t^{t+\tau} \left[-\int_S J \cdot n \mathrm{d}S + \int_V f(u_B,x,t')\mathrm{d}V \right] \mathrm{d}t', \tag{2.10}$$

where J is the flux of material (e.g. equation (2.9) above) and f represents the source of material which may be functions of u_B, x and t. Dividing through (2.10) by τ and subsequently taking the limit as $\tau \to 0$, we obtain

$$\lim_{\tau\to 0}\int_V \left[\frac{u_B(x,t+\tau) - u_B(x,t)}{\tau}\right] \mathrm{d}V = \lim_{\tau\to 0}\frac{1}{\tau}\int_t^{t+\tau} \left[-\int_S J \cdot n \mathrm{d}S + \int_V f(u_B,x,t')\mathrm{d}V \right] \mathrm{d}t'.$$

This gives

$$\int_V \frac{\partial u_B(x,t)}{\partial t}\mathrm{d}V = -\int_S J \cdot n \mathrm{d}S + \int_V f(u_B,x,t)\mathrm{d}V. \tag{2.11}$$

Applying divergence theorem

$$\int_\Omega \nabla \cdot u \mathrm{d}x = \int_S u \cdot n \mathrm{d}S \tag{2.12}$$

to the flux integral in (2.11) we have

$$\int_S J \cdot n \mathrm{d}S = \int_V \nabla \cdot J \mathrm{d}V. \tag{2.13}$$

Altogether from (2.11) we arrive at

$$\int_V \left[\frac{\partial u_B}{dt} + \nabla \cdot J - f(u_B,x,t)\right] \mathrm{d}V = 0. \tag{2.14}$$

As the volume V is arbitrary, the integrand must be zero and we have

$$\frac{\partial u_B}{dt} + \nabla \cdot J - f(u_B,x,t) = 0. \tag{2.15}$$

Here, $\nabla \cdot J$ is the diffusion term which describes the movement of the chemical specie B within the cell, and $f(u_B,x,t)$ is the reaction term which describes the reaction occurring on the cell membrane. Now, inserting the flux J given by (2.9) into (2.15) we obtain the reaction-diffusion equation

$$\frac{\partial u_B}{\partial t} = \nabla \cdot (D\nabla u_B) + f(u_B,x,t). \tag{2.16}$$

Equation (2.16) holds for a general flux transport J, irrespective of a diffusion process or other transport processes. For the problem described in Section 1, the reaction term f will be determined from the reactions on the cell membrane and this is discussed below.

Our model will be based on the quasi steady state equilibrium assumption [5] (a reasonable assumption as (2.1) is viewed as an enzyme-substrate reaction, a very common form of reaction processes in living cell) where we assume that the concentration of the enzyme catalyst $u_R, u_S << u_B$ and therefore the concentration u_B effectively remains constant (see [13]) and (2.16) becomes

$$\nabla \cdot (D\nabla u_B) + f(u_B, x) = 0. \tag{2.17}$$

To apply (2.17) to our problem, let us distinguish different choices of the source term $f(u_B, x)$ based on the problem description in Section 1.

1. If there is no reaction as in the case inside the cell, $f := f(u_B, x) = 0$ and we obtain the pure diffusion equation

$$-\nabla \cdot (D\nabla u_B) = 0 \tag{2.18}$$

   inside Ω.
2. On the interface $\Gamma \subset \partial\Omega$; the point of contact between the chemical species R, S and B, the reaction term is given by (2.7) and (2.8) i.e.

$$f = -\alpha u_B + \beta \tag{2.19}$$

   where

$$\gamma = \begin{cases} k_2 u_R & \text{on} \quad \Gamma_R \\ k_4 u_S & \text{on} \quad \Gamma_S \end{cases}, \tag{2.20}$$

   and

$$\beta = \begin{cases} k_3 u_{RB} & \text{on} \quad \Gamma_R \\ k_5 u_{SB} & \text{on} \quad \Gamma_S \end{cases}. \tag{2.21}$$

Finally, substituting (2.19) in the reaction-diffusion equation (2.17) gives

$$-\nabla \cdot (D\nabla u_B) + \gamma u_B = \beta, \tag{2.22}$$

the reaction-diffusion equation on Γ.

Choice of boundary conditions. The pure diffusion equation (2.18) and the reaction-diffusion equation (2.22) only make sense, in terms of solvability, if appropriate boundary conditions are specified. These conditions are specified by the appropriate balance equations at each of the boundary surfaces. Let the boundary of the cell be divided into two non-intersecting partial surfaces: Γ and $\partial\Omega\backslash\Gamma$. We can fix the concentration of the cell component B at the interface Γ. That is, we specify a Dirichlet boundary condition

$$u_B = g \quad \text{on } \Gamma. \tag{2.23}$$

Furthermore, cell membranes are considered a barrier (but permeable), so Robin boundary condition can also be specified at the other part of the cell membrane i.e.

$$-D\frac{\partial u_B}{\partial n} = \alpha u_B \quad \text{on } \partial\Omega\backslash\Gamma, \tag{2.24}$$

where $\dfrac{\partial u_B}{\partial n} = \nabla \cdot n$ is the co-variant normal derivative, α the permeability constant of the cell membrane and n is the outward normal at the boundary.

With the boundary conditions specified, we now have all the necessary ingredients for a complete description of the model problem.

2.4. The model problem. Our model problem is given by the pure diffusion equation (2.18) in the cell with appropriate boundary conditions described above:

$$\begin{aligned} -\nabla \cdot (D\nabla u_B) &= 0 \ \text{ in } \Omega, \\ u_B &= g \ \text{ on } \Gamma, \\ -D\frac{\partial u_B}{\partial n} &= \alpha u_B \ \text{ on } \partial\Omega\backslash\Gamma, \end{aligned} \tag{2.25}$$

where the Dirichlet data g has to be computed by solving the reaction-diffusion process on Γ given by

$$\begin{aligned} -\nabla \cdot (D\nabla g) + \gamma g &= \beta \ \text{ in } \Gamma, \\ g &= 0 \ \text{ on } \partial\Gamma \end{aligned} \tag{2.26}$$

with γ, β given by (2.20) and (2.21) respectively. Note that the model parameters γ, β and α are non-negative due to the fact that concentrations as well as rates of reaction are non-negative.

Unless specified otherwise, the partial differential equations (2.25)-(2.26) shall be the model problem for the rest of this article. Numerical solution of this problem is sought in Section 4.

3. Discretization of the reaction-diffusion equation. In general it is not possible to solve (2.25) or (2.26) analytically. The closest we can get to the analytical solution is an approximate solution which is obtained by discretizing the original problem. One of the most efficient method for finding the approximate solution of (3.1) is the finite element method, see [2, 4, 9, 7]. Therefore in this part of the paper, we will discuss the finite element discretization of the model problem (2.25) and (2.26). For completeness, let us illustrate the finite-element discretization method with a general problem (3.1)

$$\begin{aligned} -\nabla \cdot (D\nabla u_B) + \gamma u_B &= \beta \ \text{ in } \Omega, \\ u_B &= g \ \text{ on } \Gamma, \\ -D\frac{\partial u_B}{\partial n} &= \alpha u_B \ \text{ on } \partial\Omega\backslash\Gamma, \end{aligned} \tag{3.1}$$

that covers both (2.25) and (2.26).

One would normally approach finite element approximation of (3.1) by first obtaining a computable form of the problem, the so called weak form. For example, the weak form of the general problem (3.1) reads: find u in the space $H^1_\Gamma(\Omega) = \{v \in H^1(\Omega) \mid v = g \text{ on } \Gamma\}$ such that

$$a(u_B, v) = f(v), \tag{3.2}$$

for all $v \in H^1_0(\Omega)$ where

$$a(u_B, v) = \int_\Omega D\nabla u_B \cdot \nabla v \ \mathrm{d}x + \alpha \int_{\partial\Omega\backslash\Gamma} u_B v \ \mathrm{d}x + \int_\Omega \gamma u_B v \ \mathrm{d}x, \quad \gamma \geq 0, \tag{3.3}$$

and

$$f(v) = \int_\Omega \beta v \ \mathrm{d}x, \quad \beta \geq 0.$$

The space $H^1_\Gamma(\Omega)$ above is a closed subspace of the space of $H^1_0(\Omega)$, the space of square integrable functions whose trace vanishes on the boundary Γ, defined by

$$H^1_0(\Omega) = \{v \in H^1(\Omega) \mid v = 0 \text{ on } \Gamma\}.$$

The functional $a(\cdot, \cdot)$ is called a bi-linear form on the space $V := H^1_\Gamma(\Omega)$.

In the next step of finite element approximation of (3.1) we will construct a finite dimensional space V_h which approximates the infinite dimensional space V. To do this, the computation domain Ω has to be discretized. Let the conforming triangulation $\mathcal{T}_h$ of the computational domain Ω consist of tetrahedral elements $T \in \mathcal{T}_h$ for the three dimensional problem (2.25), and triangular elements for the two dimensional problem (2.26). Here h is called the diameter of $\mathcal{T}_h$ and is defined by $h = \max_{T \in \mathcal{T}_h}(\text{diameter}(T))$. The space V_h is then chosen to be the space of functions consisting of continuous piecewise-polynomials i.e. for each $T \in \mathcal{T}_h$ the space V_h is defined for $k \geq 1$ as

$$V_h = V_{h,k}(\Omega) := \left\{u \in C^0(\Omega) \text{ such that } u_{|T} \in P_k(T), \ T \in \mathcal{T}_h\right\}$$

where C^0 denotes the space of continuous functions, $u_{|T}$ the restriction of function u to element T and the space P_k consisting of algebraic polynomials of total degree at most k.

Now let $\phi_j, j = 1, 2, ..., N$ be the set of basis for the finite-dimensional space V_h. The typical choice for ϕ_j are the shape functions defined by

$$\phi_j(a_i) = \delta_{ij} \equiv \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j \end{cases} \tag{3.4}$$

where $a_i, i = 1, 2, ..., N$ denotes the global set of nodes in $\mathcal{T}_h$. Then for a fixed polynomial degree k, any function $u \in V_h$ has a unique representation

$$u(x) = \sum_{j=1}^{N} c_j \phi_j(x), x \in \Omega. \tag{3.5}$$

Now using the above representation and setting $v = \phi_i$ in the weak form (3.2), an easy computation shows that (3.2) can be written as a linear system

$$A\ c = b$$

where matrix A is large and sparse, and the non-zero entries have a regular pattern. This favors the use of iterative methods (e.g. Gauss-Seidel, Jacobi) for solving the resulting linear system. However, since the spectral radius of matrix A, $\rho(A) \approx \mathcal{O}(h^{-2})$, many iterative procedures will exhibit a slow rate of convergence. In the next section, Comsol Multiphysics solves the resulting linear system using multi-grid methods (see e.g. [10]) whose convergence speed is independent of the discretization mesh size h.

4. Numerical implementation of the reaction-diffusion model problem. Here we will report on numerical solution of the model problem (2.25)-(2.26) obtained with Comsol Multiphysics 3.5a [1]. Recall that in finding the numerical solution to model problem re-stated here for convenience

$$\begin{aligned} -\nabla \cdot (D \nabla u_B) &= 0 \ \text{ in } \Omega, \\ u_B &= g \ \text{ on } \Gamma, \\ -D \frac{\partial u_B}{\partial n} &= \alpha u_B \ \text{ on } \partial\Omega \backslash \Gamma, \end{aligned}$$

we will need to compute the Dirichlet data g as a solution of the $2D$ problem (2.26)

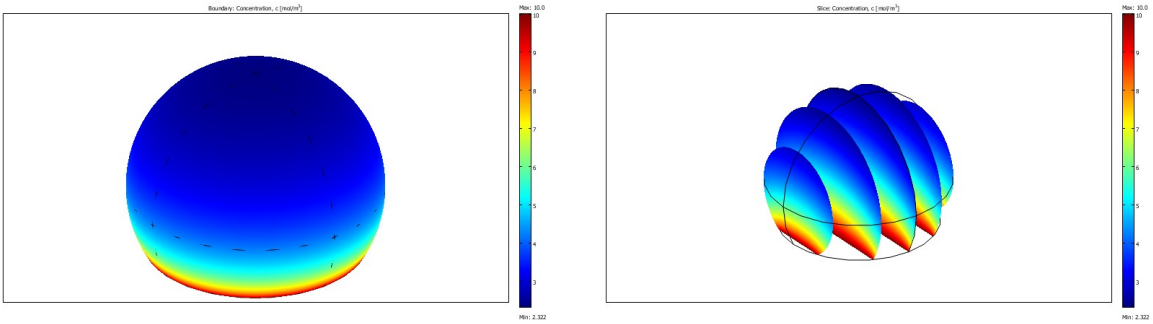
$$\begin{aligned} -\nabla \cdot (D \nabla g) + \gamma g &= \beta \ \text{ in } \Gamma, \\ g &= 0 \ \text{ on } \partial\Gamma \end{aligned}$$

on the interface Γ, with piece-wise constant coefficients γ, β given by (2.20), (2.21) respectively. In what follows, for the purpose of comparison, we will build up the solution to the problem accordingly by first solving the pure diffusion problem with a constant-valued Dirichlet data chosen as $g = 10$, and then solve the $2D$ reaction-diffusion problem on the part Γ of the cell membrane to obtain the non-constant and the desired Dirichlet data g. Ultimately, we couple the two models using the non-constant data g as a Dirichlet data for the pure diffusion model (2.25).

A few comments is in order here about the linear system solver in Comsol Multiphysics. The linear system solver is a $V-$cycle multi-grid method. It used the Successive Over-relaxation method (SOR) as a pre-smoother with relaxation factor $\omega = 1.0$. As a post-smoother, it used SORU (the version of SOR which uses the upper triangle of the matrix [1]) with relaxation factor 1.0.

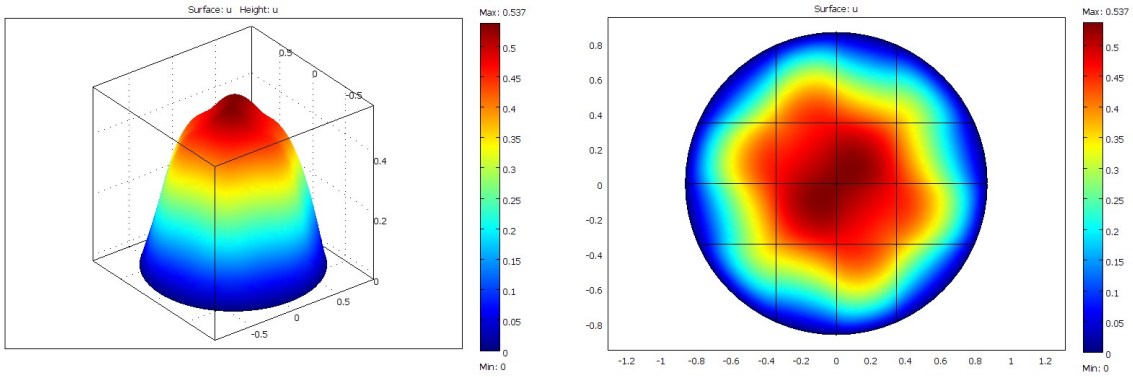
4.1. Solution of the $3D$ model in the cell with constant Dirichlet data g. The $3D$ diffusion problem in the cell is a very simple elliptic problem, but the Comsol Multiphysics provides all the major ingredients needed to solve not only problem of this type but a general stationary problems. Figures 4.1 show the solution to the pure diffusion problem (2.25) with Dirichlet data $g = 10\ mol/m^2, D = 0.5 \times 10^{-13} m^2/s, \alpha = 4 \times 10^{-5} m/s$. The plot shows the diffusion pattern of the chemical specie B from the cell interface Γ into the cell.

4.2. Numerical solution of the $2D$ model on the cell membrane. Imposing homogeneous Dirichlet boundary condition, we solve the reaction-diffusion model (2.26) with Comsol Multiphysics using tetrahedral elements for discretizing the computation domain and solving the resulting linear system with



(a) (b)

FIG. 4.1. *Numerical solution of the pure diffusion model with a constant Dirichlet data* $g = 10\ mol/m^2$



(a) (b)

FIG. 4.2. *Numerical solution of the* $2D$ *reaction-diffusion on the interface* Γ.

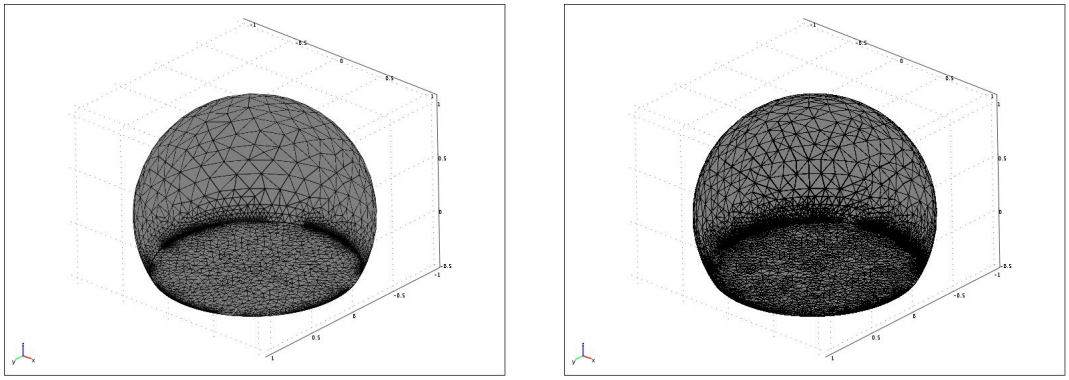
multi-grid method. The model parameters were chosen as $D = 0.5 \times 10^{-13}\ m^2/s, \alpha = 4 \times 10^{-5}\ m/s, k_2 = 2\pi\ m^2/(s \cdot mol), k_3 = 1\ s^{-1}, k_4 = k_5 = 0$. The numerical solution obtained is shown in Figure 4.2

The plot shows the concentration distribution of the chemical specie B on the interface Γ. The concentration on the sub-domains sharing the homogeneous Dirichlet boundary are greatly influenced by the boundary condition; the obtained results are roughly the average of the concentrations in such sub-domains. Therefore, it is expected that the concentration of chemical specie B be concentrated or have a maximum value at the center of the domain. This is exactly depicted with the two peaks in Figure 4.2.

4.3. Numerical solution of the coupled model. So far, we have obtained numerical solutions of two different models describing the pure diffusion process within the cell and the reaction-diffusion process on the part of the cell membrane. In this section, we will find numerical solution of the coupled model.

Due to the structure of the model for the cell, there are some singularities at the sharp edges between the plane interface Γ and the cell geometry. Hence, there is a need for adaptive procedure to cater for this observation in our numerical implementation. The coupled model is therefore solved using an adaptive finite element method with a rough global minimum as an element selection method. Due to a high degree of freedom of the mesh, we restrict the refinement levels to two, since more levels of refinement makes the mesh too complicated to handle. Comsol returned 6 as the maximum number of levels for the multi-grid method. Figures 4.3 show the initial mesh and the level-two refined mesh.

Let us now comment on the numerical solution of the coupled model. Figure 4.4 shows the result of our Comsol implementation of the coupled model. The plots show the diffusion pattern of the chemical

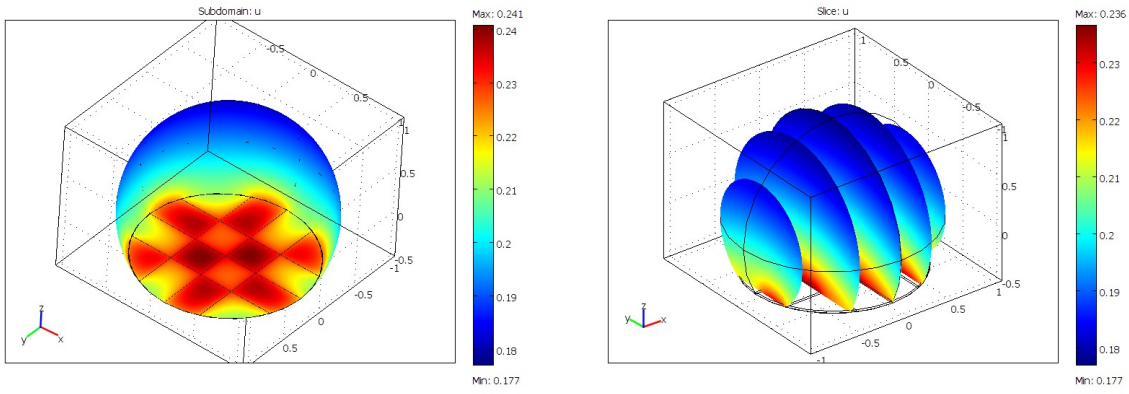


(a) The initial mesh for the coupled model consisting of 71,540 elements.

(b) The level-two refined mesh consisting of 304,053 elements.

FIG. 4.3. *The mesh structure of the coupled model.*

specie B within the cell as influenced by the reaction-diffusion processes on the cell membrane interface Γ. In contrast with the result obtained in Section 4.1 where we have used a constant Dirichlet data $g = 10$, here the symmetry pattern shown by the solution in Figure 4.1 is no longer visible here. This is a direct consequence of the non-constant Dirichlet value g.



(a) (b)

FIG. 4.4. *Numerical solution of the coupled reaction-diffusion model.*

Acknowledgment. The author gratefully acknowledges the support of this work by the European Erasmus Mundus Scholarship Program through its Master's Program in Industrial Mathematics.

REFERENCES

[1] Comsol multiphysics. `http://www.comsol.com/`.
[2] Robert A. Adams. *Sobolev Spaces*. Academic Press, 1975.
[3] Donald O. Besong. Mathematical modelling and numerical solution of chemical reactions and diffusion of carcinogenic compounds in cells. Master's thesis, KTH Royal Institute of Technology, Stockholm, Sweden, 2004. `http://www.nada.kth.se/utbildning/grukth/exjobb/rapportlistor/2004/rapporter04/besong_donald_04152.pdf`.
[4] Dietrich Braess. *Finite Elements*. Cambridge University Press, 3rd edition, 2007.
[5] Haldane JBS Briggs GE. A note on the kinetics of enzyme action. *Biochem*, 19(338339), 1925.
[6] Alexandre N. Carvalho and Jose A. Cuminato. Reaction-diffusion problems in cell tissues. *Journal of Dynamics and Differential Equations*, 9(1):93–131, 1997.
[7] Philippe G. Ciarlet. *The Finite Element Methods for Elliptic Problems*. North-Holland Publishing Company, Amsterdam, New York, Oxford, Tokyo, first edition, 1987.
[8] Christof Eck, Harald Garcke, and Peter Knabner. *Mathematische Modellierung*. Springer Press, 2008.
[9] Jacob Fish and Ted Belytschko. *A First Course in Finite Elements*. John Wiley and Sons, 2007.
[10] Wolfgang Hackbush. *Multi-Grid methods and applications*, volume 4 of *Springer series in Computational Mathematics*. Springer-Verlag Berlin Heidelberg, 1985.

[11] Michael Hanke. Short introduction to comsol multiphysics. 2006.
[12] Menten M Michaelis L. Die kinetik der invertinwirkung. *Biochem. Z.*, 49(333369), 1913.
[13] James D. Murray. *Mathematical Biology*, volume 17. Springer Press, 2002.
[14] Chamakuri Nagaiah. *Adaptive Numerical Simulation of Reaction-Diffusion Systems*. PhD thesis, Otto-von-Guericke University, Magdeburg, Germany, 2007.
[15] Michaela Schwarzenbacher et al. Micropatterning for quantitative analysis of protein-protein interactions in living cells. *Nature Methods*, 5(12), December 2008-09.