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Reaction-Diffusion in Cell Membranes

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Abstract

In this study we developed a mathematical model that describes the diffusion process inside a cell. The cell is considered to be a three dimensional bounded domain which restricts the diffusion of the contained chemical species out of the boundary according as some permeability value that characterized the cell. We solved the resulting three dimensional model using an adaptive finite element procedure.

The 3D model is coupled with a two-dimensional reaction-diffusion process along a plane interface. The resulting two dimensional problem on the boundary was solved with adaptive finite element methods and the result obtained was combined with the original three dimensional problem. Finite element methods is no trivial task in three dimensional situation, so Comsol was used for the 3D mesh generation and for the solution.

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Chapter 1

Introduction

1.1 Reaction-Diffusion Processes

The present work has evolved through a multitude of problems in various field of science involving transport of materials, and interactions of chemical compounds. The underlying physical processes involved are chemical reactions and diffusion which can be found in all facets of science most especially in physical and engineering problems. A reaction process involves interconversion of chemical substances which arises from the random motion of the molecules and the forming and breaking of chemical bonds resulting into the formation of one or more new products. In most cases, the intermediate product(s) formed simultaneously breaks down into new chemical compounds and are transported within the cell by the process of diffusion. Diffusion process is of great importance in physics, chemistry and biology and it results in mixing of chemical substances as it moves materials from one point to another within a cell as a result of different concentration gradients. These phenomenon are found in many applications which includes production of semiconductors, catalyst design in chemical industry, transportation of air and ground water pollutant e.t.c.

The exchange of chemical materials in living cells, and subsequent formation of complex are carried out through the cell membranes. In this work, we consider the modeling of reactiondiffusion processes in cell membrane as well as finding a numerical solution to the resulting model problem in the stationary case. We start with modeling of each processes separately, and then study process involving both reaction and diffusion.

Our motivation for this work lies in the various works of several authors ranging from the study of protein-protein interaction in cells, [22], through detailed analysis of reactiondiffusion of compounds in cells. Notable among these works are [20] which focused on the numerical simulations of reaction-diffusion systems in cells. The paper [7] specifically studied the reaction-diffusion of carcinogenic compounds in cells, and model for determining the concentrations of these chemical substances in cells was obtained. A detailed analysis of reaction-diffusion processes are extensively considered in cell tissues by [11].

It is worth mentioning that the works cited above have either considered reaction-diffusion

processes solely within cells or have tailored their models to specific problems. We therefore present in this work, model that encompasses both reaction-diffusion withing cells as well as on cell membranes.

More specifically, in a general situation, we consider a cell (Ω) that is made up of a chemical specie B. It reacts with an external chemical species R and S at some parts of its membrane denoted by Γ , which results in the formation of a chemical complexes RB and RS on Γ . RB and RS are continually formed and accumulated on Γ but do not diffuse into the cell. Within the cell, we assume a pure diffusion process. Thus, in the absence of a reaction term, we obtain a three dimensional model describing the pure diffusion process in Ω given by

$$-\nabla \cdot (D\nabla u_B) = 0 \quad \text{in } \Omega, \tag{1.1}$$
$$u_B = g \quad \text{on } \Gamma,$$
$$-D\frac{\partial u_B}{\partial n} = \alpha (u_B - u_1) \quad \text{on } \partial \Omega \backslash \Gamma, \ u_1 \approx 0,$$

where α , D and u_B denote respectively, the permeability constant of the cell, the diffusion coefficient of the cell and the concentration of the chemical specie B. One of the major task in this thesis is the computation of the Dirichlet data g which has to be computed from the two-dimensional reaction-diffusion model on Γ . We start with the creation of the geometries.

The cell is a tiny structure with the size of about $3 \times 10^{-6}m$. Therefore, to be able to represent the cell on computer for the sake of modeling, some scaling and non-dimensionalization has to be done. The non-dimensional analysis is treated in details in Chapter 4 of this thesis. The three dimensional cell is modeled by the intersection of a sphere of a unit radius centered at the origin (0, 0), and a block of side length two metres as shown in Figure 1.1.



Figure 1.1: The geometry for the cell.

Therefore, the interface Γ , a part of the cell membrane is a result of the intersection of a ball with a plane. Precisely in our model, Γ is a circle of radius 0.8641 (about 2.59 × $10^{-6}m$ in actual size) and is centered at the origin (0,0). Assuming that Γ is subdivided into two subdomains Γ_R and Γ_S (represented in Figure 1.2 by the red tiles and white tiles respectively), then Figure 1.2 describes the geometry for Γ . Γ_R and Γ_S correspond to the part of Γ where chemical specie *B* reacts with the species *R* and *S* respectively.



Figure 1.2: The geometry for the interface Γ .

However, the g obtained from solving the two-dimensional model on Γ cannot be used directly in (1.1), we will therefore employ the multiphysics capability of Comsol to couple the 3D pure diffusion model (1.1) within the cell and the 2D reaction-diffusion model on the interface Γ .

1.2 Thesis Organization

This thesis is organized as follows: Chapter 2 introduces the mathematical modeling of reaction, diffusion and reaction-diffusion processes, from which the three dimensional model problem was formulated. In Chapter 3 we consider discretization of the reaction-diffusion model. We begin by providing basic background theories in finite element methods, and then introduce the multi-grids methods as the mathematical basis of our solver. We also introduce Comsol Multiphysics in Chapter 3. As a simplification of the problem, we implement our model with Comsol Multiphysics using a constant Dirichlet boundary data, and the results of the 3D implementation presented. Chapter 4 is devoted entirely to the modeling and implementation of reaction-diffusion process on the cell membrane. The 2D model is implemented both with Matlab and Comsol on different grid structures, and the results obtained presented. Finally in Chapter 5, we will consider coupling of the non-constant solution of the 2D problem on the cell membrane with the 3D model, and we conclude in Chapter 6 by synthesizing our arguments, and citing a possible direction for future work.

Chapter 2

Mathematical Modeling of Reaction-Diffusion Process

In this chapter, we give the formulation of the equations governing the reaction diffusion process in cell membranes. We will start by considering the reaction between the different chemical species interacting at the contact point on the cell membranes, and then give a description of the diffusion process within the cell under consideration.

2.1 Reaction Process

We consider a reaction between two different chemical species A and B described by a reversible reaction equation given by

$$A + B \stackrel{k_1}{\underset{k_2}{\longleftarrow}} AB, \tag{2.1}$$

where A and B denote the chemical specie A and the chemical composition of the cell under consideration (Figure 2.1) respectively. This reaction results in the formation of a chemical complex AB. We assume that the chemical specie A and the complex AB do not diffuse into the cell after the reaction, but however have a great influence on the concentration of B in the cell. This is depicted in Figure 2.1.

Denoting the concentrations by

$$u_a = [A], u_b = [B], u_c = [AB],$$

the concentration of the complex formed can be obtained by the application of the law of mass action which states that the rate of a reaction is proportional to the product of the concentrations of the reactants. Applying this law to (2.1) gives

$$\frac{du_a}{dt} = -k_1 u_a u_b + k_2 u_c, \tag{2.2}$$



Figure 2.1: Illustration of the reaction between chemical specie A and the composition of the cell.

$$\frac{du_b}{dt} = -k_1 u_a u_b + k_2 u_c, \tag{2.3}$$

$$\frac{du_c}{dt} = k_1 u_a u_b - k_2 u_c. \tag{2.4}$$

Furthermore, under quasi steady state assumption that the concentration of the intermediate complex formed remain constant we have

$$\frac{du_c}{dt} = k_1 u_a u_b - k_2 u_c = 0, (2.5)$$

and from this we immediately obtain

$$u_b = \frac{k_2}{k_1} \frac{u_c}{u_a}.$$
 (2.6)

(2.6) models the concentration of the chemical specie B in the cell without diffusion, for a given k_1 and k_2 .

2.2 Diffusion Process

In this part we derive the governing equation describing the diffusion process within the cell.

We assume that the diffusion of materials within the cell follows the classical diffusion process so that the Fick's law of diffusion applies.

2.2.1 Fick's Law of Diffusion

It is often important to find the relation between the concentration of the material u_b and the flux J. An equation describing this relation is termed constitutive equation, and is usually determined empirically.

An applicable constitutive law here is the Fick's law which states that the steady state diffusion flux J is proportional to the concentration gradient i.e.(in one dimension)

$$J \propto \frac{\partial}{\partial x} u_b(x,t) \Longrightarrow J = -D \frac{\partial}{\partial x} u_b(x,t),$$
 (2.7)

D is the diffusion coefficient which measures how efficiently u_b moves from a region of high concentration to regions of low concentrations. The value of D depends on the size of u_b , as well as the medium in which it is diffusing. It has dimensions $(length)^2/time$. In three dimensions, the flux is of the form

$$J = -D\nabla u_b. \tag{2.8}$$

The diffusion equation is generally written as

$$\frac{\partial u_b}{\partial t} = -\nabla \cdot (D\nabla u_b) \tag{2.9}$$

[19].

2.3 Reaction-Diffusion

Equations (2.3) and (2.9) describe respectively the reaction and diffusion rates of the chemical specie B in the cell. We now consider a general situation involving both reaction and diffusion processes, and it is derived from balance law as follows. 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 $V \subset \Omega$ and n, the outward normal at the boundary. The general conservation equation holds i.e.

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

where J is the flux of material and f represents the source of material which may be functions of u_b , x and t. Dividing through by τ and then taking the limit as $\tau \to 0$, we have

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

This gives

$$\int_{V} \frac{\partial u_b(x,t)}{\partial t} dV = -\int_{S} J \cdot n dS + \int_{V} f(x,t) dV.$$
(2.11)

Applying the divergence theorem

$$\int_{\Omega} \nabla \cdot u \mathrm{d}x = \int_{\partial \Omega} u \cdot n \mathrm{d}a(x) \tag{2.12}$$

to the flux integral in (2.11) we have

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

If the function $u_b(x,t)$ is smooth enough, then integration and differentiation can be interchanged, and (2.11) becomes

$$\int_{V} \left[\frac{\partial u_b}{\partial t} + \nabla \cdot J - f(u_b, x, t) \right] dV = 0.$$
(2.14)

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

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

The equation (2.15) is called a reaction-diffusion equation and it holds for a general flux transport J, whether diffusion or some other processes. Here, $\nabla \cdot J$ is the diffusion term which describes the movement of the chemical specie within the cell, and $f(u_b, x, t)$ is the reaction term which describes the reaction occurring inside the cell.

Inserting (2.8) into (2.15) gives

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

In our case, the reaction term f will be determined from the reactions on the cell membrane and this is discussed in Chapter 4.

Our model will be based on the quasi steady state equilibrium assumption that the concentration of the cell remains constant, and thus we consider a time-independent reaction-diffusion equation

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

We distinguish between different choices of the reaction term in the following remark.

Remark:

1. If there is no reaction, f = 0, and we obtain the pure diffusion equation

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

inside $\Omega.$



Figure 2.2: Boundary conditions on the cell membrane.

2. On the interface $\Gamma \subset \partial \Omega$; the point of contact between the chemical species A and B, the reaction term is given by (2.3) i.e.

$$f = -k_1 u_a u_b + k_2 u_c.$$

Substituting this in (2.17) gives the equation

$$-\nabla \cdot (D\nabla u_b) + k_1 u_a u_b = k_2 u_c, \tag{2.19}$$

describing the reaction-diffusion process on $\Gamma.$

2.4 Choice of Boundary Conditions

A complete reaction-diffusion problem is usually specified by the differential equation (2.15) and some boundary conditions. The boundary conditions are specified by the appropriate balance equations at each of the boundary surface.

Let the boundary of the cell be divided into two partial surfaces: Γ and $\partial \Omega \setminus \Gamma$ and let the concentration of the cell at the interface Γ be fixed i.e. we specify a Dirichlet boundary condition

$$u_b = g \quad \text{on } \Gamma. \tag{2.20}$$

Furthermore, cell membranes are considered a barrier (but permeable), so we specify a Robin boundary condition at the other part of the membrane (as shown in Figure 2.2) i.e.

$$-D\frac{\partial u_b}{\partial n} = \alpha(u_b - u_1) \quad \text{on } \partial\Omega \backslash \Gamma, \quad u_1 \approx 0,$$
(2.21)

where $\frac{\partial u_b}{\partial n} = \nabla \cdot n$ is the covariant normal derivative, α denotes the permeability constant of the cell membrane and n is the outward normal at the boundary.

2.5 The Model Problem

The pure diffusion equation (2.18) is complete with appropriate boundary conditions (2.20) and (2.21) respectively, and consequently our model problem is

$$-\nabla \cdot (D\nabla u_b) = 0 \text{ in } \Omega, \qquad (2.22)$$
$$u_b = g \text{ on } \Gamma,$$
$$-D\frac{\partial u_b}{\partial n} = \alpha(u_b - u_1) \text{ on } \partial\Omega \backslash \Gamma,$$

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

$$-\nabla \cdot (D\nabla g) + k_1 u_a g = k_2 u_c \text{ in } \Gamma, \qquad (2.23)$$
$$g = 0 \text{ on } \partial \Gamma,$$

In the above, ∇ is the two-dimensional nabla operator and the computation of the Dirichlet data g is done in Chapter 4.

Chapter 3

Discretization of the Reaction-Diffusion Equation

Since it is not possible to solve (2.22) analytically for a general g, we need some discretization method. One of the most efficient method for the approximation of the solution of (2.22) is the finite element method. We therefore devout this chapter to the discretization of the model problem (2.22) with finite element methods. The approach is based on discrete representation of the weak form of (2.22). First, we provide some basic idea of the method.

3.1 Basic Introduction to Finite Element Methods

To introduce finite element method, brief definition of certain spaces and norms are imperative. We are only introducing the important notions as needed in the present work, we refer the readers to [9, 15, 13] for a comprehensive introduction to finite element methods.

3.1.1 Function Spaces

We start with the definitions of some function spaces [2].

Definition 3.1. Let the domain $\Omega \subset \mathbb{R}^d$ be Lebesgue measurable with non-empty interior. The class of all measurable functions u is defined as

$$L^{p}(\Omega) = \left\{ u: \Omega \longmapsto \mathbb{R} | \int_{\Omega} |u|^{p} dx < \infty \right\}, \quad 1 \le p < \infty.$$

These spaces are equipped with the norms

$$||u||_{L^p(\Omega)} := \left(\int_{\Omega} |u|^p dx\right)^{1/p}, \quad 1 \le p < \infty.$$

Also important are vector subspaces of $L^p(\Omega)$, the Sobolev spaces.

Definition 3.2. For a nonnegative integer k, the **Sobolev space** $H^k(\Omega)$ is defined as

$$H^{k}(\Omega) = \left\{ u \in L^{2}(\Omega) | D^{\alpha}u \in L^{2}(\Omega) \quad \forall \ |\alpha| \leq k \right\},\$$

where the weak derivative D^{α} for $\alpha = (\alpha_1, \cdots, \alpha_d) \in \mathbb{N}_0^d$ with $|\alpha| = \sum_{j=1}^d \alpha_j$ is given by

$$D^{\alpha}u = \partial_{x_1}^{\alpha_1} \cdots \partial_{x_d}^{\alpha_d} := \frac{\partial^{|\alpha|}u}{\partial^{\alpha_1}x_1 \cdots \partial^{\alpha_d}x_d}$$

The Sobolev space $H^k(\Omega)$ is equipped with the norm

$$||u||_k := \left(\int_{\Omega} \sum_{|\alpha| \le k} |D^{\alpha} u|^2 dx \right)^{1/2}.$$
(3.1)

Correspondingly, a semi-norm on this space is defined as

$$|u|_k := \left(\int_{\Omega} \sum_{|\alpha|=k} |D^{\alpha} u|^2 dx \right)^{1/2}.$$
(3.2)

Of great use will be $H^1_{\Gamma}(\Omega)$, a closed subspace of $H^1(\Omega)$ defined as

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

It consists of square integrable functions whose trace vanishes on the boundary Γ , [2].

Next, we obtain the weak formulation of the model problem (2.22).

3.1.2 Variational Formulation

In order to apply the finite element method, we must develop a computable form of our problem, the so called weak form. We do the variational formulation for the general form of the model problem

$$-\nabla \cdot (D\nabla u_b) + k_1 u_a u_b = k_2 u_c \text{ in } \Omega, \qquad (3.3)$$
$$u_b = g \text{ on } \Gamma,$$
$$-D \frac{\partial u_b}{\partial n} = \alpha (u_b - u_1) \text{ on } \partial \Omega \backslash \Gamma,$$

which covers (2.22). As before, *n* here denotes the outward normal at the boundary.

The weak form is obtained as follows. First we multiply the problem with a test function $v \in H^1_{\Gamma}(\Omega)$ and integrate over Ω

$$-\int_{\Omega} \nabla \cdot (D\nabla u_b) v \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x = \int_{\Omega} k_2 u_c v \, \mathrm{d}x.$$

Applying Gauss' theorem gives

$$\int_{\Omega} D\nabla u_b \cdot \nabla v \, \mathrm{d}x + \int_{\partial \Omega} D\nabla u_b \cdot nv \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x = \int_{\Omega} k_2 u_c v \, \mathrm{d}x$$

and because of the structure of the boundary, we have

$$\int_{\Omega} D\nabla u_b \cdot \nabla v \, \mathrm{d}x + \int_{\Gamma} D\nabla u_b \cdot nv \, \mathrm{d}x + \int_{\partial\Omega\setminus\Gamma} D\nabla u_b \cdot nv \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x = \int_{\Omega} k_2 u_c v \, \mathrm{d}x$$

Since $v \in H^1_{\Gamma}(\Omega)$ and $-D\frac{\partial u_b}{\partial n} = \alpha(u_b - u_1)$, we obtain

$$\int_{\Omega} D\nabla u_b \cdot \nabla v \, \mathrm{d}x + \int_{\partial\Omega\setminus\Gamma} \alpha u_b v \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x = \int_{\Omega} k_2 u_c v \, \mathrm{d}x + \int_{\partial\Omega\setminus\Gamma} \alpha u_1 v \, \mathrm{d}x.$$

The weak form of (3.3) is thus: find $u_b - g \in H^1_{\Gamma}(\Omega)$ such that

$$a(u_b, v) = f(v) \tag{3.4}$$

for all $v \in H^1_{\Gamma}(\Omega)$ with

$$a(u_b, v) = \int_{\Omega} D\nabla u_b \cdot \nabla v \, \mathrm{d}x + \int_{\partial\Omega\setminus\Gamma} \alpha u_b v \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x, \quad k_1 \ge 0, u_a \ge 0,$$

and

$$f(v) = \int_{\Omega} k_2 u_c v \, \mathrm{d}x + \int_{\partial \Omega \setminus \Gamma} \alpha u_1 v \, \mathrm{d}x, \quad k_2 \ge 0, u_c \ge 0.$$

 $a(\cdot, \cdot)$ is called a bilinear form on $H^1_{\Gamma}(\Omega)$. We will see that this is an H^1 - elliptic problem.

Fundamental to the theory of elliptic problems is the famous Lax-Milgram Lemma. We introduce this lemma by first giving some appropriate definition and proposition.

Definition 3.3. A bilinear form $a(\cdot, \cdot)$ on a normed linear space H is said to be **bounded** (or **continuous**) if there exists $C < \infty$ such that

$$|a(v,w)| \le C||v||_{H}||w||_{H} \quad \forall v, w \in H,$$
(3.5)

and coercive on $V \subset H$ if there exists $\alpha > 0$ such that

$$a(v,v) \ge \alpha ||v||_H^2 \ \forall \ v \in V.$$

$$(3.6)$$

Proposition 3.4. Let H be a Hilbert space, and suppose $a(\cdot, \cdot)$ is a symmetric bilinear form that is continuous on H and coercive on a closed subspace V of H. Then $(V, a(\cdot, \cdot))$ is a Hilbert space.

Proof. see [10].

Now, we present the Lax-Milgram Lemma [10].

Lemma 3.5. (*Lax-Milgram's Lemma*) Given a Hilbert space $(V, a(\cdot, \cdot))$, a continuous, coercive bilinear form $a(\cdot, \cdot)$ and a continuous linear functional $f \in V'$ (the dual space of V), there exists a unique $u \in V$ such that

$$a(u,v) = f(v) \ \forall \ v \in V.$$

$$(3.7)$$

In order to apply the Lax-Milgram lemma to our present problem, we have to establish that the conditions of the lemma are indeed fulfilled by (3.4). An important tool in establishing the coercivity of $a(\cdot, \cdot)$ on the space $H_0^1(\Omega)$ is the Poincare-Friedrich's Inequality, and it simply states that the semi-norm (3.2) is equivalent to the norm (3.1) on $H_0^1(\Omega)$.

Lemma 3.6. (*Poincare-Friedrich's Inequality*) Let $\Gamma \subseteq \partial \Omega$ have a non-vanishing (n - 1)-dimensional measure. Then, there exists constants, depending only on Ω and Γ , such that, for $u \in H^1(\Omega)$,

$$||u||_{L^{2}(\Omega)}^{2} \leq C_{1}|u|_{H^{1}(\Omega)}^{2} + C_{2}||u||_{L^{2}(\Gamma)}^{2}.$$
(3.8)

In particular, if u vanishes on Γ ,

$$||u||_{L^{2}(\Omega)}^{2} \leq C_{1}|u|_{H^{1}(\Omega)}^{2}, \qquad (3.9)$$

and thus

$$|u|_{H^{1}(\Omega)}^{2} \leq ||u||_{H^{1}(\Omega)}^{2} \leq (C_{1}+1)|u|_{H^{1}(\Omega)}^{2}.$$
(3.10)

Proof. We refer the reader to [24] for the proof.

The bilinear form in (3.4) is clearly symmetric, so we only need to establish its continuity and coercivity as well as showing that the right hand side f(v) is a linear functional on the dual space V' (which is $(H^1_{\Gamma})^*$ in our case).

Continuity

Proof.

$$\begin{aligned} |a(u_b, v)| &\leq \int_{\Omega} |D| |\nabla u_b| |\nabla v| + \int_{\Omega} |k_1| |u_a| |u_b v| + \int_{\partial \Omega \setminus \Gamma} |\alpha| |u_b v| \\ &\leq \alpha_0 \int_{\Omega} (|\nabla u_b| |\nabla v| + |u_b v|) + \int_{\partial \Omega \setminus \Gamma} |\alpha| |u_b v| \\ &\leq \alpha_0 \left(\int_{\Omega} |\nabla u_b|^2 + |u_b|^2 \right)^{1/2} \left(\int_{\Omega} |\nabla v|^2 + |v|^2 \right)^{1/2} + \alpha \left(\int_{\partial \Omega \setminus \Gamma} |u_b|^2 \right)^{1/2} \left(\int_{\partial \Omega \setminus \Gamma} |v|^2 \right)^{1/2} \\ &= \alpha_0 ||u_b||_{H^1(\Omega)} ||v||_{H^1(\Omega)} + \alpha ||u_b||_{L^2(\partial \Omega \setminus \Gamma)} ||v||_{L^2(\partial \Omega \setminus \Gamma)} \\ &\leq C ||u_b||_{H^1(\Omega)} ||v||_{H^1(\Omega)} \quad \text{(Trace mapping theorem cf.[24]),} \end{aligned}$$

where $(C = \alpha_0 + \alpha)$.

We have used the Cauchy-Schwarz Inequality in the third line of the proof, and α_0 is some bounds for |D| and $|k_1||u_a|$.

Coercivity

Proof. We distinguish two cases based on whether there is a Dirichlet boundary condition or not.

1. There is a Dirichlet boundary condition on a part of $\partial \Omega$. We can thus estimate α with 0 and using the fact that the coefficient D is positive, u_a and k_1 are nonnegative, we can write

$$\begin{aligned} a(v,v) &= \int_{\Omega} D\nabla v \nabla v + \int_{\partial \Omega \setminus \Gamma} \alpha v^2 + k_1 \int_{\Omega} u_a v^2 \\ &\geq \int_{\Omega} D\nabla v \nabla v = D \int_{\Omega} |\nabla v|^2 \\ &= D|v|^2_{H^1(\Omega)} \geq \frac{D}{(C_1+1)} ||v||^2_{H^1(\Omega)}. \end{aligned}$$

where the constant $(C_1 + 1)$ comes from the Friedrich's Inequality lemma 3.6.

2. There is no Dirichlet boundary condition. Then, we have a Robin boundary condition

on $\partial \Omega$ with $\alpha > 0$. This implies

$$\begin{aligned} a(v,v) &= \int_{\Omega} D\nabla v \nabla v + \int_{\partial\Omega\backslash\Gamma} \alpha v^2 + k_1 \int_{\Omega} u_a v^2 \\ &\geq \int_{\Omega} D\nabla v \nabla v + \int_{\partial\Omega\backslash\Gamma} \alpha v^2 \\ &= D \int_{\Omega} |\nabla v|^2 + \alpha \int_{\partial\Omega\backslash\Gamma} |v|^2 \\ &= D|v|_{H^1(\Omega)}^2 + \alpha ||v||_{L^2(\partial\Omega\backslash\Gamma)}^2 \\ &\geq ||v||_{H^1(\Omega)}^2. \quad \text{(Lemma 3.6, (3.8))} \end{aligned}$$

Finally, the application of Cauchy-Schwarz inequality on the linear form f(v) gives

$$|f(v)| \le ||f||_{(H^{1}_{\Sigma})^{*}} ||v||_{H^{1}}, \qquad (3.11)$$

and this implies that f(v) is a bounded linear functional on $(H_{\Gamma}^{1})^{*}$. Therefore, we are assured of a numerical solution to our problem by the Lax-Milgram's lemma.

Next, we describe the steps involved in applying a finite element procedure to a weak form.

3.1.3 Finite Element Method (Approximating the weak form)

The finite element method is a process of constructing finite dimensional subspaces V_h of spaces $V = H_{\Gamma}^1$, called finite element spaces which approximate the original solution u. The discretization of the weak formulation (3.4) will then involve finding approximations $u_h \in V_h$, the so-called Ritz projection of u in the finite dimensional subspace. More specifically, with any finite dimensional subspace V_h of V, we associate the discrete problem: Find $u_h \in V_h$ such that

$$\forall v_h \in V_h \ a(u_h, v_h) = f(v_h) \tag{3.12}$$

[13].

This construction is characterized by three basic aspects:

- the existence of the triangulation of the polygonal set Ω ,
- the construction of a finite dimensional subspace consisting of piecewise-polynomials and
- the existence of a basis of functions having small support

[9].

The well-posedness of problem (3.12) is ensured by the Lax-Milgram Lemma 3.5. This implies that (3.12) has a unique solution which shall be referred to as a discrete solution.

Triangulation

Let $\Omega \subset \mathbb{R}^d$ be a bounded polygonal or polyhedral domain with a Lipschitz continuous boundary. A triangulation (or equivalently, mesh) is a non-overlapping partition of Ω into elements. Here we shall consider meshes consisting of triangles in the 2D problem on the cell membrane, and of tetrahedral elements in the 3D problem in the cell. A family of triangulations \mathcal{T}_h , h > 0 is formally defined below [13].

Definition 3.7. Let $\Omega \subset \mathbb{R}^d$ be a bounded domain. A partition \mathcal{T}_h of Ω into subsets $T \in \mathcal{T}_h$ is called a triangulation if the following properties are satisfied

- 1. $\bar{\Omega} = \bigcup_{T \in \mathcal{T}_h} T.$
- 2. For each $T \in \mathcal{T}_h$, the set is closed and its interior int(T) is non-empty and connected.
- 3. For each distinct $T_1, T_2 \in \mathcal{T}_h$, one has $int(T)_1 \cap int(T)_2 = \emptyset$.
- 4. If $F = T_1 \cap T_2 \neq \emptyset$, T_1 and T_2 distinct elements of \mathcal{T}_h , then F is a common edge, face or vertex of T_1 and T_2 .
- 5. $diam(T) \leq h$ for each $T \in \mathcal{T}_h$.

Then \mathcal{T}_h is called a triangulation of $\overline{\Omega}$, [20]. h is called the diameter of \mathcal{T}_h , and the family \mathcal{T}_h satisfying the above properties is said to be geometrically conforming. Other required properties of triangulations are given in the following definitions.

Definition 3.8. [24] A family of triangulations \mathcal{T}_h is called shape-regular if there exists a constant independent of h, such that

$$h_T < C_{\rho_T}, \ T \in \mathcal{T}_h,$$

where ρ_T is the radius of the largest circle or sphere contained in T. The ratio h_T/ρ_T is called the aspect ratio of T.

Definition 3.9. [24] A family of triangulations \mathcal{T}_h is called quasi-uniform if it is shaperegular and if there exists a constant independent of h, such that

$$h_T > Ch, \ T \in \mathcal{T}_h.$$

Finite Element Spaces

The second aspect of finite element involves the construction of the space V_h which approximates the infinite dimensional space V. V_h is chosen to be the space of functions consisting of piecewise-polynomials i.e. for each $T \in \mathcal{T}_h$ the space

$$P_{k,T}(V_h) := \{ v_{h|T} | v_h \in V_h, k \ge 0 \}$$

consisting of algebraic polynomials of total degree at most k defined on V_h . In this work, the triangulation of Ω shall consist of tetrahedral elements for the three dimensional problem (diffusion within the cell), and triangles for the two dimensional problem on Γ .

Let \mathcal{T}_h be a conforming triangulation. We have the following result [24]:

Lemma 3.10. A function $u : \Omega \longrightarrow \mathbb{R}$ belongs to $H^1(\Omega)$ if and only if the restriction of u to every $T \in \mathcal{T}_h$ belongs to $H^1(T)$, and, for each common face (or edge in two dimensions) $\bar{f} = \bar{T}_1 \cap \bar{T}_2$, we have

$$u_{|T_1} = u_{|T_2}, on f.$$

Consequently, finite element spaces, chosen as a space of continuous piecewise polynomial functions are contained in $H^1(\Omega)$. Furthermore, if \mathcal{T}_h consists of triangles or tetrahedral as we have in our case (2D and 3D respectively), we define the finite element space for $k \geq 1$

$$V^{h} = V^{h}_{k}(\Omega) := \left\{ u \in C^{0}(\Omega) | u_{|T} \in P_{k}(T), \ T \in \mathcal{T}_{h} \right\},$$
(3.13)

$$V_0^h = V_{k:0}^h(\Omega) := V_k^h(\Omega) \cap H_0^1(\Omega).$$
(3.14)

Remark: Throughout this work, our implementation with Matlab will involve finite element spaces consisting of only linear elements. Higher order elements in P_k , $k \ge 2$ will be considered only when using Comsol Multiphysics for the implementation (cf. Section 3.3). Although the use of linear elements is also possible in Comsol, we will nevertheless use quadratic elements in our implementation.

Choice of Basis Elements

After a successful construction of the finite dimensional space, the next hurdle is to find a set of basis elements for the subspace V_h . One basic requirement is that the basis have a small support with little overlap of neighboring basis functions. This ensures that the resulting system is sparse. The usual basis function for V_h is the shape functions $\phi_j \in V_h$ chosen in such a way that

$$\phi_j(a_i) = \delta_{ij} \equiv \begin{cases} 1 & \text{if } i = j \\ 0 & \text{if } i \neq j. \end{cases}$$
(3.15)

where $a_i, i = 1, ..., N$ denotes the global set of nodes in \mathcal{T}_h .

For a fixed polynomial of degree k, and the set of basis function $\{\phi_i^h\}$ associated to a set of nodes $\{a_i\}$ of the triangulation, the degree of freedom are the values of a function at these nodes. Then

$$u(x) = \sum_{i} u(a_i)\phi_i^h(x), \ u \in V_h,$$
(3.16)

for a defined system of basis function ϕ_i^h 's.

We finally give the formal definition of finite element method.

Definition 3.11. A finite element in \mathbb{R}^d is a triple (T, P_T, Σ) where

- T is a closed subset of \mathbb{R}^d with a non empty interior and a Lipschitz continuous boundary.
- P_T is a finite dimensional linear space of functions defined on T,
- Σ is a set of degrees of freedom,

such that a function $v \in P_T$ is determined by the degrees of freedom Σ

[13].

Since $\{\phi_j\}_1^N$ is a set of test functions v that form a basis for V_h , any function $u \in V_h$ (and consequently the finite element approximation u_h of u) has a unique representation

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

Applying this and setting $v = \phi_i$ for each *i* in the weak form (3.4), we obtain a system of N linear algebraic equations for the unknowns c_i 's

$$\sum_{j=1}^{N} \left(\int_{\Omega} D\nabla \phi_j \cdot \nabla \phi_i + \int_{\partial \Omega \setminus \Gamma} \alpha \phi_j \cdot \phi_i + \int_{\Omega} k_1 u_a \phi_j \cdot \phi_i \right) c_j = \int_{\Omega} k_2 u_c \phi_i + \int_{\partial \Omega \setminus \Gamma} \alpha \phi_i \tilde{u}_1,$$

$$i = 1, 2, ..., N.$$

Introducing the following notations

$$K = (K_{ij}) = \left(\int_{\Omega} D\nabla \phi_j \cdot \nabla \phi_i \right)_{ij}, \qquad (3.17)$$

$$R = (R_{ij}) = \left(\int_{\partial \Omega} k_1 u_a \phi_j \cdot \phi_i + \int_{\partial \Omega \setminus \Gamma} \alpha \phi_j \cdot \phi_i \right)_{ij}, \qquad (3.18)$$

$$b = (b_i) = \left(\int_{\Omega} k_2 u_c \phi_i + \int_{\partial \Omega \setminus \Gamma} \alpha \phi_i \tilde{u_1} \right)_i, \qquad (3.19)$$

i, j = 1, 2, ..., N. We finally have, in matrix form, a linear system

$$Ac = b, (3.20)$$

where A = K + R.

3.1.4 Error Estimates

It should be recalled that the application of the Lax-Milgram Lemma to the weak form of our problem ensures the existence (and the uniqueness) of a numerical solution. However, it is important to able to ascertain the quality of the approximate solution. We therefore investigate the quality of the approximation of the solution by the elements in the corresponding finite element space $V_h = V_h(\mathcal{T}_h)$. The error bounds for the finite element approximations can be determined with the Cea's Lemma. And according to the lemma, the accuracy of a numerical solution essentially depends on choosing function spaces which approximates well the exact solution u [9].

Lemma 3.12. (*Cea's Lemma*) Suppose the bilinear form is coercive and continuous with $H_0^k(\Omega) \subset V \subset H^k(\Omega)$. In addition, suppose u and u_h are the solutions of the variational problem in V and $V_h \subset V$, respectively. Then

$$||u - u_h||_k \le \frac{C}{\alpha} \inf_{v_h \in V_h} ||u - v_h||_k.$$
(3.21)

Proof. By the definition, u and u_h are the solutions of the variational problem, then

$$a(u,v) = f(v) \quad \forall v \in V, \tag{3.22}$$

$$a(u_h, v) = f(v) \quad \forall v \in V.$$
(3.23)

Since $V_h \subset V$, subtracting (3.23) from (3.22) results in

$$a(u-u_h,v) = 0 \quad \forall v \in V_h,$$

which is termed the *Galerkin Orthogonality*.

Let $v_h \in V_h$ and setting $v = u - v_h \in V_h$, it follows from the Galerkin orthogonality that

$$a(u - u_h, u - u_h) = a(u - u_h, u - v_h) \quad \forall v \in V_h.$$

Now, using the bi-linearity, the coercivity and the continuity of $a(\cdot, \cdot)$, we have

$$\begin{aligned} \alpha ||u - u_h||_k^2 &\leq a(u - u_h, u - u_h) \\ &= a(u - u_h, u - v_h) \\ &\leq C ||u - u_h||_k ||u - v_h||_k \quad \forall v \in V_h. \end{aligned}$$
(3.24)

This implies that

$$|u - u_h||_k \le \frac{C}{\alpha} ||u - v_h||_k \le \frac{C}{\alpha} \inf_{v_h \in V_h} ||u - v_h||_k.$$
(3.25)

In the next step, we have to construct a suitable element $v_h \in V_h$. Taking the interpolant $I_h v$ of the exact solution, we are able to prove the following error estimate as obtained in [10].

Theorem 3.13. (*Error Estimate*) Let a(u, v) be a symmetric, coercive and continuous bilinear form, and let u and u_h be the solutions of the variational problems

$$a(u,v) = f(v) \quad \forall v \in V,$$

$$a(u_h, v_h) = f(v_h) \quad \forall v_h \in V_h, \text{ with } f \in L^2(\Omega).$$

If $u \in H^2(\Omega)$, then

$$|u - u_h||_{H^s(\Omega)} \le Ch^{2-s} ||u||_{H^2(\Omega)}, \ s = 0, 1,$$
(3.26)

where C is a constant independent of h.

3.1.5 Adaptive Finite Element Methods

Adaptivity is an important aspect of finite element method. In general, the more elements we have in a mesh, the more precise is the solution due to the availability of more nodes for calculating responses [9]. Furthermore, more elements implies smaller elements and this tends to minimize the discretization error of the approximation. However, constraints on computational space and costs do not allow too fine discretization. Therefore, an adaptive procedure is imperative as a trade-off between the discretization error minimization and the computational costs.

A typical adaptive finite element procedure follows this sequence:

$$SOLVE \implies ESTIMATE \implies MARK \implies COARSEN/REFINE.$$

- 1. Solve: This involves computation of a trial solution of the finite element discretized problems on a coarse mesh with a lower dimensional finite element space.
- 2. Estimate: Given a tolerance Tol > 0, the global discretization error denoted as ||E|| is estimated using the local discretization error $||E||_T$ as an enrichment indicator, i.e

$$\frac{||u - u_h||^2}{\text{global error}} = \sum_{T \in \mathcal{T}_h} \frac{||u - u_h||^2}{|\text{local error}}.$$
(3.27)

We require that

$$||E||_T = ||u - u_h||_T \le \text{Tol.}$$
 (3.28)

- 3. Mark: Here all elements that needs to be refined are marked using (3.28) as indicator. The assumption is that large errors come from regions where the local error estimate $||E||_T$ is large.
- 4. **Refine**: The marked elements will be refined by subdividing the elements ensuring quasi-uniformity requirement among others.

This procedure will be repeated until an optimal solution is obtained or the error tolerance level is reached by every elements of the discretized domain. Standard literatures on error estimators and adaptive procedures include [25, 8, 5].

3.2 The Solver

The matrix A in (3.20) is large and sparse, and the non-zero entries has a regular pattern. This favors the use of iterative methods for solving it. Since the spectral radius $\rho(A) \approx \mathcal{O}(h^{-2})$, many iterative procedures (Gauss-Seidel, Jacobi etc.) have a slow rate of convergence. The software that will be used finds its solution by the use of multigrid methods.

3.2.1 Multigrid Methods

Multigrid is an iterative linear solver and an optimal order algorithm for solving a discrete elliptic boundary value problem. They are essentially used to improve the rate of convergence of basic iterative methods. One important feature of multigrid is that its convergence speed is independent of the discretization mesh size h. Also, the amount of computational work involved is proportional only to the number of unknowns in the discretized equations.

The multigrid method has two main features; smoothing on the current grid and error correction on a coarser grid. The smoothing step has the effect of damping out the oscillatory part of the error. The smooth part of the error can then be accurately corrected on the coarser grid [10]. So, the multigrid iterative formula can be interpreted as an error averaging process. This phenomenon is always recognized after a few iteration steps, where the error of the approximation becomes smooth (but not necessarily become small).

We recall our model problem in the variational form

$$a(u_b, v) = f(v),$$
 (3.29)

for all $v \in H^1_{\Gamma}(\Omega)$ with

$$a(u_b, v) = \int_{\Omega} D\nabla u_b \cdot \nabla v \, \mathrm{d}x + \int_{\partial\Omega\backslash\Gamma} \alpha u_b v \, \mathrm{d}x + \int_{\Omega} k_1 u_a u_b v \, \mathrm{d}x, \quad k_1 \ge 0, u_a \ge 0, \quad (3.30)$$

$$f(v) = \int_{\Omega} k_2 u_c v \, \mathrm{d}x + \int_{\partial \Omega \setminus \Gamma} \alpha u_1 v \, \mathrm{d}x, \quad k_2 \ge 0, u_c \ge 0, \tag{3.31}$$

and we seek a solution $u_b - g \in V := H^1_{\Gamma}(\Omega)$.

By elliptic regularity we know that $u_b \in H^2(\Omega) \cap H^1_{\Gamma}(\Omega)$. From the triangulation \mathcal{T}_h of the physical domain Ω , u_b is approximated as follows. Following [10], suppose \mathcal{T}_1 is given and let $\mathcal{T}_k \ k \geq 2$, be obtained from \mathcal{T}_{k-1} via a *regular* subdivision; edge midpoints in \mathcal{T}_{k-1} are connected by new edges to form \mathcal{T}_k . Denoting by V_k the \mathcal{C}^0 piecewise linear functions with respect to \mathcal{T}_k that vanish on $\partial\Omega$, then we have

$$\mathcal{T}_k \supset \mathcal{T}_{k-1} \Longrightarrow V_{k-1} \subset V_k,$$

for all $k \ge 1$. The discretized model problem in the weak form thus reads: find $u_k \in V_k$ such that

$$a(u_k, v) = (f, v) \ \forall v \in V_k.$$

$$(3.32)$$

Suppose that for any $T \in \mathcal{T}_{k-1}$, the elements of \mathcal{T}_k are all similar to T and have half the size of T, then

$$h_k = \frac{1}{2}h_{k-1},$$

where $h_k = \max_{T \in \mathcal{T}_k} \text{diam } T$. The multigrid methods aim to calculate $u_k \in V_k$ in $\mathcal{O}(n_k)$ operations such that (3.21) holds where n_k denotes the dimension of the space V_k .

3.2.2 Multigrid Scheme

We introduce the multigrid scheme by making the following definitions. First, we define the operator $A_k: V_k \longrightarrow V_k$ by

$$(A_k v, w)_k = a(v, w) \ \forall v, w \in V_k.$$

$$(3.33)$$

Then the discretized equation (3.32) can be written as

$$A_k u_k = f_k \tag{3.34}$$

where $f_k \in V_k$ satisfies

$$(f_k, v)_k = (f, v) \ \forall v \in V_k.$$

$$(3.35)$$

The implementation of the multigrid scheme involves transferring of estimates between grids (in 2-cycle multigrid method: between coarse and fine grid), so we describe the inter-grid transfer operators as follows. We take the Galerkin interpolation as the coarse-to-fine grid transfer operator

$$I_{k-1}^k: V_{k-1} \longrightarrow V_k \tag{3.36}$$

and it is illustrated in Figure 3.1. The values at points on the coarse grid map unchanged



Figure 3.1: Illustration of the coarse-to-fine grid Galerkin interpolation (prolongation).

to the fine grid while the values on the fine grid points which are not on the coarse grid are the average of their coarse-grid neighbors. Correspondingly, the fine-to-coarse grid transfer (restriction) operator is defined as the transpose of the prolongation operator i.e.,

$$I_k^{k-1} = (I_{k-1}^k)^T. ag{3.37}$$

Also important is the following lemma about the estimate of the spectral radius, $\rho(A_k)$, of A_k .

Lemma 3.14.

$$\rho(A_k) \approx C h_k^{-2}. \tag{3.38}$$

Proof. see [10].

We now describe the multigrid scheme. The scheme that we present here will require that the discretized domains be nested. This means that the nodes of the coarse grid matches the nodes of the fine grid. For a non-nested domain, we refer interested readers to [9].



Figure 3.2: Example of nested domains.

Let k represents the level of iteration, and l, the number of iterations. Now, denote the k^{th} level iteration of the multigrid scheme by $MG(k, u_0, f)$ for initial guess u_0 . The case k = 1 represents the direct solution of the equation $A_1 u = f$ i.e,

$$MG(1, u_0, f) = A_1^{-1}f (3.39)$$

The MG iterates for the case $k \ge 2$ is obtained recursively in the following steps:

1. Presmoothing step:

• Perform m_1 smoothing operations by a chosen iterative scheme (e.g damped Jacobi method) i.e., for $1 \le l \le m_1$, let

$$u_{l} = u_{l-1} + \frac{1}{\rho(A_k)} (f_k - A_k u_{l-1})$$
(3.40)

where $\rho(A_k)$ denotes some upper bound for the spectral radius of A_k satisfying Lemma 3.14.

- Compute the defect $d_k = f_k A_k u_{m_1}$.
- 2. Error correction (or Coarse-Grid Correction): This is done in the following steps:
 - Project the defect to the coarse grid and solve the coarse problem:
 - Let $\bar{f} = I_k^{k-1} d_k$ and $q_0 = 0$.
 - For $1 \leq i \leq p$, let

$$q_i = MG(k-1, q_{i-1}, \overline{f}).$$

- Project back to the fine grid and do correction: $u_{m_1+1} := u_{m_1} + I_{k-1}^k q_p$.
- 3. Postsmoothing step: Carry out m_2 smoothing steps, i.e., for $m_1 + 2 \le l \le m_1 + m_2 + 1$, let

$$u_{l} = u_{l-1} + \frac{1}{\rho(A_{k})} (f_{k} - A_{k} u_{l-1}).$$
(3.41)

Then the output of the k^{th} level iteration is

$$MG(k, u_0, f) := u_{m_1 + m_2 + 1}, \tag{3.42}$$

for positive integers m_1, m_2 . The parameter p in the error correction step is called the *cycle index* and it denotes the number of times the multigrid scheme is applied to the coarse level problem. Typical values for p are 1, 2 and represents respectively the V-cycle and W-cycle multigrid method.

3.2.3 Convergence of Multigrid Method

One of the major concern on the use of the basic iterative scheme for solving a big linear system is their slow rate of convergence. Some of these methods require an appropriate choice of the parameters for convergence to be ensured. The damped Jacobi methods for instance converges if only the damp factor $\omega \in (0, 2)$. Constructing a linear system solver that converges independently of the discretization parameter h is the motivation for developing the multigrid methods.

Naturally for convergence of a multigrid method, it is required that the approximate solutions $u_l^{(k)} \longrightarrow A_l^{-1} f_l$ for $k \to \infty$. The convergence proof is given in [17] where the convergence of the V-cycle multigrid method for a general symmetric problems was proved based on sufficient regularity of the problems.

Before we formulate this important theorem, we introduce some notations. Let A be a symmetric positive definite matrix. Then, we define the matrix norm

$$|||u|||_{1,A}^2 = (Au, u). \tag{3.43}$$

We now present the multigrid convergence theorem [16].

Theorem 3.15. Let V be a Hilbert space, $a(\cdot, \cdot) : V \times V \longrightarrow \mathbb{R}$ a coercive, bounded and symmetric bilinear form of the finite element discretization (3.32) on V, and f(v) a linear functional on the dual space V'. Let Au = b be the resulting linear system according as (3.33).

Suppose that u_l^{k+1} and u_l are the l^{th} iterate and the exact solution of a multigrid method applied to the linear system, respectively. Furthermore, if $f \in L^2(\Omega)$, and u_h is H^2 -regular, then a multigrid method applied to the linear system Au = b converges in the norm $||| \cdot |||_{1,A}$ and

$$|||u_l - u_l^{k+1}|||_{1,A} \le \gamma |||u_l - u_l^k|||_{1,A}$$
(3.44)

with $0 < \gamma_l \leq \gamma < 1$.

In order to apply this theorem to our problem, we have to verify the assumptions of the theorem. First, we have already shown in Subsection 3.1.2 that the bilinear form (3.30) is coercive, continuous and symmetric. Furthermore, our present problem is a standard elliptic problem which enjoys the H^2 -regularity. Therefore, applying the multi-grid scheme described in Subsection 3.2.2, all the assumptions of the theorem are undoubtedly satisfied. Hence, a multigrid method applied to our problem converges based on Theorem 3.15.

Remark: Extension to local refinements (i.e. adaptivity) is also possible.

3.3 Model Implementation with Comsol

In finding the numerical solution to our model problem (2.22), we need to compute the Dirichlet data g by the reaction on the interface Γ . As a simplification, we discuss in this part the implementation of our problem with Comsol Multiphysics using a constant value g. The extension to the case of a non-constant g will be treated in the next chapter. First, we briefly introduce Comsol.

3.3.1 Comsol Multiphysics

Comsol Multiphysics [1] (formally known as FEMLAB) is an integrated environment for solving systems of time dependent or stationary second order in space partial differential equations in one, two, and three dimensions [18]. It performs equation-based multiphysics modeling which implies that the equations in Comsol can be manipulated to suit our problem.

There are many application modes in Comsol Multiphysics which serves as template for various scientific problems. The underlying mathematical structure for the solver is a system of partial differential equation, and there are two forms of the PDEs available; the coefficient form and the general form. We select the coefficient form. This allows us to choose the coefficients freely and by so doing, so many problems could be handled.

Comsol Multiphysics also provides sophisticated tools for geometric modeling of the physical domain. A complex geometry can easily be drawn by appropriate combinations of the set of standard geometries (rectangles, circles etc. in 2D and block, sphere etc. in 3D). The details behind the creation of the geometry in Figure 3.3(a) is provided in Chapter 5.

3.3.2 Model Implementation

The Comsol Multiphysics solves the following boundary value problem (in the coefficient form)

$$e_a \frac{\partial^2 u}{\partial t^2} + d_a \frac{\partial u}{\partial t} + \nabla \cdot (-c\nabla u - \delta u + \gamma) + \beta \cdot \nabla u + au = f$$
(3.45)

with boundary conditions

$$hu = r \quad \text{on } \partial\Omega, \tag{3.46}$$

$$n \cdot (c\nabla u + \delta u - \gamma) + qu = g - h^T \mu \quad \text{on } \partial\Omega.$$
(3.47)

n is the unit normal and $e_a, d_a, c, \delta, \gamma, \beta, a, f, g, h$ are scalar functions. Our model problem is easily realizable by setting $e_a = d_a = \beta = \delta = \gamma = 0$.

Comsol implements a finite element method thats is based on tetrahedral element and piecewise linear functions. The linear system arising from the discretization is solved with multigrid method.

3.3.3 Geometry

A complex geometry is drawn in Comsol using the sophisticated set of tools and the set of standard geometric objects available. Through several combinations of these basic objects, our physical domain was created.

3.3.4 Numerical Solution

In this part of the work, we present the result of the 3D model implementation of (2.22) by the use of Comsol. This is a very simple elliptic problem, but the program used provides all the major ingredients needed to solve not only problem of this type but a general stationary problems. The Figures 3.3 show the solution to the pure diffusion problem (2.22), and the corresponding refined mesh of the physical domain is as shown in Figure 3.4.

The plot shows the diffusion pattern of the chemical specie B within the cell. A symmetry pattern behavior is observable in the result and this implies that our 3D problem is easily reducible to a 2D problem.



(a) Numerical solution of the pure diffusion problem with constant $g. \label{eq:general}$



(b) The numerical solution of the pure diffusion problem with constant g in slice form.

Figure 3.3: Numerical solution of the pure diffusion model with a constant Dirichlet data g.



Figure 3.4: The corresponding meshed domain for the solution to the diffusion model.

Chapter 4

Reaction-diffusion on Cell Membrane

Usually there are more than one chemical species interacting within a cell. In this chapter, we will consider a situation where there are two different species R and S interacting with B on a part of the cell membrane Γ as shown below.

RB	SB	RB	SB
SB	RB	SB	RB
RB	SB	RB	SB
SB	RB	SB	RB

Table 4.1: Multi-species Interaction.

We will derive the model problem in this case and implement it with Matlab and Comsol Multiphysics.

4.1 Formulation of the 2D Problem on the Cell Membrane

The geometry for the interface Γ is modeled from the intersection of a ball with a plane. This gives a circle. However, first we consider the problem on a simple rectangular geometry. Suppose the interface Γ composes of two sub domains Γ_R and Γ_S arranged alternately as in the table 4.1.

And suppose the two chemical species react according to these equations

$$R + B \stackrel{k_2}{\underset{k_3}{\longleftarrow}} RB \quad \text{on } \Gamma_R, \tag{4.1}$$

$$S + B \stackrel{k_4}{\underset{k_5}{\rightleftharpoons}} SB \text{ on } \Gamma_S.$$
 (4.2)

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 4.2: Distribution of the two sub domains on the membrane.

Applying the law of mass action (cf. Section 2.1) on (4.1), (4.2) gives the reaction terms

$$f(u_B, u_R, u_{BR}) = -k_2 u_B u_R + k_3 u_{BR} \quad \text{on } \Gamma_R, \tag{4.3}$$

and

$$f(u_B, u_S, u_{BS}) = -k_4 u_B u_S + k_5 u_{BS}$$
 on Γ_S . (4.4)

We obtain the reaction-diffusion equation governing this process on Γ by substituting (4.3) and (4.4) into the reaction-diffusion equation (2.15). Under our assumption of quasi steady state equilibrium, we have the following equations

$$-\nabla \cdot (D\nabla u_B) + k_2 u_B u_R = k_3 u_{BR} \quad \text{on } \Gamma_R, \tag{4.5}$$

and

$$-\nabla \cdot (D\nabla u_B) + k_4 u_B u_S = k_5 u_{BS} \quad \text{on } \Gamma_S. \tag{4.6}$$

These equations describe the reaction-diffusion processes on Γ_R and Γ_S respectively. We assume that the reaction rates k_4 and k_5 are zero so that we have a pure diffusion process in the subdomain Γ_S , i.e.

$$-\nabla \cdot (D\nabla u_B) = 0 \quad \text{on } \Gamma_S. \tag{4.7}$$

It is important to ascertain whether the reaction or the diffusion process dominates the reaction-diffusion equation. To achieve this, and to be able to choose the parameters freely so as to ease numerical programming, we have to non-dimensionalize the above equations [14]. First, we introduce the characteristic length L (chosen here to be the size of the cell) and the characteristic concentration u^* . Next, we introduce the dimensionless quantities

$$u = \frac{u_B}{u^*}, \quad \epsilon = \frac{x}{L}.$$
(4.8)

We obtain the dimensionless form of (4.5) by substituting (4.8) into (4.5) as follows (the process for (4.7) is trivial).

$$\epsilon = \frac{x}{L} \tag{4.9}$$

implies that

$$\nabla_{\epsilon} = L \nabla_x$$
 and $\Delta_{\epsilon} = L^2 \Delta_x$

This gives

$$k_{3}u_{BR} = -\nabla_{x} \cdot (D\nabla_{x}u_{B}) + k_{2}u_{B}u_{R}$$

$$= -D\Delta_{x}u_{B} + k_{2}u_{B}u_{R}$$

$$= -\left(\frac{Du^{*}}{L^{2}}\right)\Delta_{\epsilon}u + (k_{2}u^{*}u_{R})u_{R}$$

Multiplying through by $\left(\frac{L^2}{Du^*}\right)$, we obtain

$$-\Delta_{\epsilon}u + \left(\frac{k_2 L^2 u_R}{D}\right)u = \left(\frac{k_3 L^2 u_{RB}}{D u^*}\right).$$
(4.10)

Introducing the dimensionless quantities

$$p = \left(\frac{k_2 L^2 u_R}{D}\right), \quad q = \left(\frac{k_3 L^2 u_{RB}}{D u^*}\right), \tag{4.11}$$

we finally obtain the dimensionless equations

$$-\Delta_{\epsilon} u + pu = q \quad \text{on } \Gamma_R, \tag{4.12}$$

and

$$-\Delta_{\epsilon} u = 0 \quad \text{on } \Gamma_S. \tag{4.13}$$

In a compact form, the dimensionless problem reads:

$$-\Delta u + au = f,\tag{4.14}$$

with piecewise constant coefficients

$$a = \left\{ \begin{array}{ll} p & \mathrm{on} & \Gamma_R \\ 0 & \mathrm{on} & \Gamma_S \end{array} \right\},$$

and

$$f = \begin{cases} q & \text{on} & \Gamma_R \\ 0 & \text{on} & \Gamma_S \end{cases}$$

Equation (4.14) comprises a reaction term as well as a diffusion term. So, to be able to efficiently write an appropriate programming code for numerical solution of the problem, it is important to have a feeling of the magnitudes of the quantities p and q.

Symbol	Meaning	Type	Values	Units
u	mass concentration	unknown	-	$\frac{mol}{m^2}$
t	time	variable	-	s
x	space	variable	-	m
D	diffusion coefficient	parameter	0.5E-13	$\frac{m^2}{s}$
k_2	forward reaction rate	parameter	2π	$\frac{m^2}{s}$
k_3	reverse reaction rate	parameter	10E-1	s^{-1}
R	size of the cell	parameter	3E-6	\overline{m}
r	size of the planar interface	parameter	2.59E-6	m

Table 4.3: Table of values and units of the variables and parameters describing the model.

The table 4.3 shows the chosen values of the variables and the parameters that describe our model.

With the values of the parameters in table 4.3, we obtain $p \approx 18$ and $q \approx 18$. This implies that our problem is not highly reaction dominated, and thus the standard finite element method could be applied.

4.2 Numerical Solution of the 2D Problem on the Cell Membrane.

In our quest for the non-constant Dirichlet boundary value data g, the two dimensional problem on the membrane (Γ) is solved in this section.

4.2.1 Matlab Implementation on a Rectangular Domain.

Here, we consider the structure of the solution of (4.14) on a more simple geometry. Therefore, in this part of the work we implement (4.14) on a rectangular domain shown in Figure 4.1.

First we obtain the variational formulation of the problem. Following the usual process of multiplying by a test function $v \in H_0^1(\Gamma)$ and integrating over the domain using the Green's formula (cf. Section 3), we obtain (after applying homogeneous Dirichlet boundary condition on $\partial\Gamma$): find $u \in H_0^1(\Gamma)$ such that

$$\int_{\Gamma} \nabla u \cdot \nabla v + \int_{\Gamma} auv = \int_{\Gamma} fv.$$
(4.15)

Following the finite element procedure described in Section 3, we obtain the linear system

$$(K+N)c = b$$



Figure 4.1: Discretized rectangular domain.

with

$$K_{ij} = \int_{\Gamma} \nabla \phi_i \cdot \nabla \phi_j, \qquad (4.16)$$

$$N_{ij} = \int_{\Gamma} a\phi_i \cdot \phi_j, \qquad (4.17)$$

$$b_i = \int_{\Gamma} f\phi_i, \tag{4.18}$$

 $i, j = 1, 2, \dots, n.$

The most important step in Matlab implementation is the assemblies of the global stiffness matrix K, the mass matrix N and the right hand side b. These matrices can be written as a sum over all the elements of the triangulation \mathcal{T}_h (of Γ)

$$K_{ij} = \sum_{T \in \mathcal{T}_h} \underbrace{\int_T \nabla \phi_i \cdot \nabla \phi_j}_{K_{\text{loc}}^{(T)}}, \tag{4.19}$$

$$N_{ij} = \sum_{T \in \mathcal{T}_h} \underbrace{\int_T a\phi_i \cdot \phi_j}_{N_{\text{loc}}^{(T)}}, \tag{4.20}$$

$$b_i = \sum_{T \in \mathcal{T}_h} \int_T f \phi_i. \tag{4.21}$$

The matrices $K_{loc}^{(T)}, N_{loc}^{(T)} \in \mathbb{R}^{3 \times 3}$ are called the local stiffness matrix and mass matrices respectively.

We approximate the local stiffness matrix as follows. Consider an element with three vertices $(x_1, y_1), (x_2, y_2)$ and (x_3, y_3) , and let ϕ_1, ϕ_2, ϕ_3 be the associated basis elements. If |A| denotes the area of the element, then

$$2|A| = \begin{vmatrix} 1 & 1 & 1 \\ x_1 & x_2 & y_3 \\ y_1 & y_2 & y_3 \end{vmatrix}.$$

Following [23], the basis function can be chosen in terms of the barycentric coordinates for the linear triangular element. This is because the barycentric coordinates for the linear



Figure 4.2: Length ratios of a triangle element.

triangular elements are identical to the shape function, and the two set of quantities can be interchanged. The length ratios (barycentric coordinates) for a triangular element shown in Figure 4.2 are defined as

$$L_1 = \frac{1}{2|A|} [(x_2y_3 - x_3y_2) + (y_2 - y_3)x + (x_3 - x_2)y], \qquad (4.22)$$

$$L_2 = \frac{1}{2|A|} [(x_3y_1 - x_1y_3) + (y_3 - y_1)x + (x_1 - x_3)y], \qquad (4.23)$$

$$L_3 = \frac{1}{2|A|} [(x_1y_2 - x_2y_1) + (y_1 - y_2)x + (x_2 - x_1)y].$$
(4.24)

Consequently the basis functions associated with the vertices of the element can be written as

$$\begin{pmatrix} \phi_1(x,y)\\ \phi_2(x,y)\\ \phi_3(x,y) \end{pmatrix} = \begin{pmatrix} L_1(x,y)\\ L_2(x,y)\\ L_3(x,y) \end{pmatrix} = \begin{pmatrix} 1 & 1 & 1\\ x_1 & x_2 & x_3\\ y_1 & y_2 & y_3 \end{pmatrix}^{-1} \begin{pmatrix} 1\\ x\\ y \end{pmatrix}.$$
 (4.25)

There is a big advantage of this choice of the basis functions. We immediately see that the derivatives of the basis functions are constants and the evaluation of area integrals is simplified as follows

$$\int_{A} L_{1}^{a} L_{2}^{b} L_{3}^{c} \, \mathrm{d}A = \frac{a! b! c!}{(a+b+c+2)!} 2|A|. \tag{4.26}$$

For instance,

$$\int_{A} \phi_{1}\phi_{2} \, \mathrm{d}A = \int_{A} L_{1}^{1} L_{2}^{1} L_{3}^{0} \mathrm{d}A = \frac{1!1!0!}{(1+1+0+2)!} 2|A| = \frac{|A|}{12}$$

[23, 9].

Thus, the local mass matrix can be written as

$$N_{\rm loc}^{(T)} = \frac{|A|}{12} \begin{pmatrix} 2 & 1 & 1\\ 1 & 2 & 1\\ 1 & 1 & 2 \end{pmatrix}.$$

Using (4.22 - 4.24), it can also easily be computed that

$$\nabla \phi_i(x,y) = \frac{1}{2} \left(\begin{array}{c} y_{i+1} - y_{i+2} \\ x_{i+2} - x_{i+1} \end{array} \right),$$

and consequently, the local stiffness matrix is

$$\int_{T} \nabla \phi_{i} \cdot \nabla \phi_{j} \, \mathrm{d}x = \frac{1}{4|A|} (y_{i+1} - y_{i+2} \ x_{i+2} - x_{i+1}) \begin{pmatrix} y_{i+1} - y_{i+2} \\ x_{i+2} - x_{i+1} \end{pmatrix},$$

where all indices are taken modulo 3. This can further be written in a more compact form for all indices as

$$K_{\rm loc}^{(T)} = \frac{|A|}{2} \cdot G \cdot G^T,$$

where

$$G = \left(\begin{array}{rrrr} 1 & 1 & 1 \\ x_1 & x_2 & x_3 \\ y_1 & y_2 & y_3 \end{array}\right)^{-1} \left(\begin{array}{rrrr} 0 & 0 \\ 1 & 0 \\ 0 & 1 \end{array}\right).$$

In our case, all elements of the finite element mesh are congruent, isosceles, right angled triangles. This implies (after proper permutation of the nodes) that (see Figure 4.3)

$$G = \left(\begin{array}{rrr} -1 & -1\\ 1 & 0\\ 0 & 1 \end{array}\right),$$

and therefore

$$K_{\rm loc}^{(T)} = \frac{1}{2} \begin{pmatrix} 2 & -1 & -1 \\ -1 & 1 & 0 \\ -1 & 0 & 1 \end{pmatrix}.$$

Finally, we assemble the right hand side (4.18) making use of (4.26) and the fact that f is a constant function

$$b_{\rm loc}^{(T)} = \int_T f\phi_j = \frac{|A|}{3}f.$$
 (4.27)

In general, the right hand side is evaluated using the one-point quadrature

$$b_{\rm loc}^{(T)} = \int_T f\phi_j = \frac{|A|}{3} f(x_s, y_s), \qquad (4.28)$$



Figure 4.3: A unit element.

where (x_s, y_s) represents the centroid of the element T. This clearly coincides with (4.27) for a constant function f.

It is important to comment that the choice of numbering of the elements in the discretized domain (counter-clockwise numbering) assures that the area |A| is always positive.

The global stiffness matrix, the mass matrix, and the right hand side is then obtained by summing over all elements of the triangulation according to (4.19), (4.20) and (4.21). Figure 4.4 shows the result obtained.

4.2.2 Numerical Solution on a Disc-shaped Domain with Comsol.

As mentioned earlier, the interface Γ is not rectangular in shape, we have only demonstrated our understanding of the finite element implementation performed by the solver software, via the matlab program in Subsection 4.2.1. The interface Γ is in form of a circular disc shown in Figure 4.5. In oder to have a much more improved numerical solution, the problem is implemented with Comsol. This affords finite element implementation with more number of elements.

We solve (4.12), (4.13) imposing homogeneous Dirichlet boundary condition. Figure 4.6 shows the result of this implementation.

The plot shows the concentration distribution of the chemical specie B on the cell membrane. The concentration on the sub-domains sharing the homogeneous Dirichlet boundary are greatly influenced by the boundary condition; the results are roughly the average of the concentrations in such subdomain. Therefore, it is expected that the concentration be concentrated or have a maximum value at the centre of the domain. This is exactly depicted with the two peaks in Figure 4.6 and Figure 4.4.



(a) 3D plot of the numerical solution obtained with Matlab.



(b) 2D color view of the numerical solution obtained with Matlab.

Figure 4.4: Numerical solution of the 2D reaction-diffusion on the cell membrane.



Figure 4.5: A more realistic interface Γ with sub-domains alternately arranged.



(a) 3D plot of the numerical solution of the 2D problem on the cell membrane.



(b) 2D view of the numerical solution.

Figure 4.6: Numerical solution of the 2D reaction-diffusion on the cell membrane.

Chapter 5

Coupling of the 2D and the 3D Models

So far, we have obtained two different models describing the pure diffusion process within the cell and the reaction-diffusion process on the part of the cell membrane Γ . The next task is now to integrate the results of the two models into a single one. This chapter is therefore devoted to the coupling of the 3D model described in Chapter 2, and the 2D model on the cell membrane discussed in Chapter 4.

5.1 Coupling by Interpolation

We solved in Chapter 3, the model problem with a constant Dirichlet boundary condition. Now, we will attempt to use the result from the 2D model of the membrane's reactiondiffusion problem as the Dirichlet value. The basic and the simplest way to achieve this is to approximate the trial solution on each elements of the discretized domain.

Consider a triangulation consisting of triangle elements as shown in Figure 5.1.



Figure 5.1: A triangular element.

We first define the local degree of freedom (on each element) as the number of nodes per element (which is equal to three in this case). Let g_i , i = 1, 2, 3 be the approximations of the solution at each of the three nodes of an element. Then, for a given element, the

approximation to the solution g(x, y) on each element is defined as follows:

$$g(x,y)|_{T} = \sum_{i=1}^{3} \phi_{i}(x,y)g_{i}.$$
(5.1)

 $\phi_i(x, y)$ in (5.1) represents the shape function at node *i*. So, there is a need to choose appropriate shape functions. One way of doing this it to define them on a reference element. In the 2D case, the reference element is

$$\hat{T} = \{(\xi, \eta) | \xi, \eta \ge 0, 0 \le \xi, \eta \le 1\},\$$

i.e. the triangle \hat{T} is spanned by $\hat{v}_1 = (1,0)$, $\hat{v}_2 = (0,1)$ and $\hat{v}_3 = (0,0)$. Therefore, we treat any triangle $T \in \mathcal{T}_h$ as an image of \hat{T} under an affine map $F : \hat{T} \longrightarrow T$ [12]. Given a triangle T with corner points $(x_0, y_0)^t$, $(x_1, y_1)^t$, $(x_3, y_3)^t$ we consider the following affine linear mapping

$$F_T: \hat{T} \longrightarrow T, \ \begin{pmatrix} \xi \\ \eta \end{pmatrix} \longrightarrow F_T \left(\begin{array}{c} \xi \\ \eta \end{array} \right),$$

$$F_T\left(\begin{array}{c}\xi\\\eta\end{array}\right) = B\left(\begin{array}{c}\xi\\\eta\end{array}\right) + \left(\begin{array}{c}x_0\\y_0\end{array}\right), \ B = \left(\begin{array}{c}x_1 - x_0 & x_2 - x_0\\y_1 - y_0 & y_2 - y_0\end{array}\right),$$

which maps the corner points of \hat{T} to the corner points of T:

$$F_T \begin{pmatrix} 0 \\ 0 \end{pmatrix} = \begin{pmatrix} x_0 \\ y_0 \end{pmatrix}, F_T \begin{pmatrix} 1 \\ 0 \end{pmatrix} = \begin{pmatrix} x_1 \\ y_1 \end{pmatrix}, F_T \begin{pmatrix} 0 \\ 1 \end{pmatrix} = \begin{pmatrix} x_2 \\ y_2 \end{pmatrix}$$

Consequently, a linear ansatz functions on the reference triangle \hat{T} will have the following form

$$\phi_1(\xi,\eta) = (1-\xi-\eta), \phi_2(\xi,\eta) = \eta, \phi_3(\xi,\eta) = \xi.$$
(5.2)

One obvious observation is that an inverse transformation has to performed in order to use and to specify (5.2) in Comsol. However, to avoid this, we can make use of our choice of the basis functions described in Subsection 4.2.1, and the trial solutions can then be specified at the appropriate part of the membrane in the 3D model.

Although, this is a very good idea to specifying the result of the 2D model as a boundary data for the 3D model. Nevertheless, since we are solving the 3D model with Comsol Multiphysics and do not have control over the mesh generation, we are faced with the tedious task of specifying trial solutions on thousands of elements! Consequently, we consider coupling of the two models using multi-physics tool in Comsol.

5.2 Coupling by Comsol Multiphysics

Solving a finite element problem in Comsol generally involves these steps:

- 1. Choice of the representative physics (i.e. we choose the PDE),
- 2. Create the geometry on which to solve the problem,
- 3. Set the *material properties* i.e. setting all the constants that appear in the PDE,
- 4. Set the boundary conditions and initial conditions,
- 5. Choose an element type and mesh the geometry,
- 6. Choose a solver and solve for the unknowns, and
- 7. Post-process the results to find the information that is required

[27].

Following these basic steps, we now present the coupling and the implementation of the two models in Comsol Multiphysics.

5.2.1 The Choice of PDE

We select the physics model in its coefficient form:

$$e_a \frac{\partial^2 u}{\partial t^2} + d_a \frac{\partial u}{\partial t} + \nabla \cdot (-c\nabla u - \delta u + \gamma) + \beta \cdot \nabla u + au = f, \qquad (5.3)$$

with boundary conditions

$$hu = r, (5.4)$$

$$n \cdot (c\nabla u + \delta u - \gamma) + qu = g - h^T \mu.$$
(5.5)

Setting $e_a = d_a = \beta = \delta = \gamma = 0$, we realize our model problem.

5.2.2 The Geometry

We model the 3D geometry by performing the following steps in the drawing mode of Comsol:

- 1. Draw a unit sphere by selecting a sphere from the drawing mode,
- 2. Draw a box of dimensions (2,2,2),
- 3. Cut the box,
- 4. Paste the box and move it to engulf the sphere by setting displacement to (-1,-1,-0.5),
- 5. In creating composite object tab, select intersection of the two objects,



Figure 5.2: The geometry for the 3D reaction-diffusion model.

6. Confirm selection by clicking the key symbol.

The resulting geometry consisting of nine sub-domains is shown in Figure 5.2.

In a similar manner, through a series of intersections of rectangles and circles, the geometry for the cell membrane is created. This is depicted in Figure 5.3.

5.2.3 Subdomain Properties, and Equation Parameters

We make use of the coefficient form of the PDE model in Comsol, and by selecting the subdomain settings dialog box under the physics menu, the appropriate choices of the parameters are entered. Comsol allows us to specify the values for the PDE coefficients on each sub-domains, hence the piecewise constants coefficients of our problem is easily entered.

5.2.4 Boundary Conditions

The boundary conditions are specified through the Physics \longrightarrow Boundary settings menu of Comsol. We apply the Robin boundary condition on the external boundaries of the domain;



Figure 5.3: The meshed geometry for the 2D reaction-diffusion model on the cell membrane.



Figure 5.4: The extruded geometry for the 2D reaction-diffusion model on the cell membrane.

this is equivalent to setting $c = 1, q = \alpha$, the permeability constant, h = 0 and g = 0 in (5.5).

5.2.5 Choice of Element's type and Meshing

We used the pre-defined quadratic Lagrange elements for the stationary analysis of the chosen PDE module in its coefficient form. The mesh is created with a click on mesh button.

5.2.6 Solver's Setting

The solver used the V-cycle multigrid method as the linear system solver. The relaxation factor (ω) for the Successive Overrelaxation method (SOR, as a presmoother) was 1.0 and the number of iterations returned as 2. Comsol also returned 2 and 6 for the number of iterations and the maximum number of levels respectively, for the multigrid method. As a postsmoother, it used SORU (the version of SOR using the upper triangle of the matrix [1]) with relaxation factor 1.0 and the number of iterations was also returned as 2.

Remark: 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 these corners.

The coupled model is therefore solved using an adaptive finite element method with a rough global minimum as an element selection method. Here, we restrict the refinement levels to two, since more levels of refinement makes the mesh too complicated to handle. Figures 5.5 show the initial mesh and the level-two refined mesh.



(a) The initial mesh for the coupled model consist- (b) The level-two refined mesh consisting of 304,053 ing of 71,540 elements.

Figure 5.5: The mesh structure of the coupled model.

5.2.7 Results

Figure 5.6 shows the result of our Comsol implementation of the coupled model. The plots show the diffusion pattern of the chemical specie B within the cell. In contrast with the result obtained in Section 3 where we have used a constant value g = 10 for the Dirichlet data, the symmetry pattern shown by the solution in Figure 3.3(a) is no longer visible here. This is a direct consequence of the non-constant Dirichlet value g.



(a) Numerical solution of the coupled reaction-diffusion model (slice form).



(b) Numerical solution of the coupled reaction-diffusion model.

Figure 5.6: Numerical solution of the coupled reaction-diffusion model.

Chapter 6

Conclusion and Outlook

The thesis has systematically described the modeling of the reaction-diffusion on cell membrane and the subsequent implementation of the model. We started in Chapter 2 with the modeling aspect where the reaction-diffusion model was derived from a general conservation law and the application of the Fick's law of diffusion.

In Chapter 3, where we have considered the discretization of the reaction diffusion equation, we showed the V-ellipticity and elliptic regularity of our model problem. This allowed us to apply the famous Lax-Milgram lemma for the existence of a numerical solution of our model problem. We obtained the numerical solution by implementing the general model, first its simplification with a constant boundary condition. The implementation was carried out with Comsol Multiphysics software. The result showed some symmetry which is not unexpected due to the constant Dirichlet boundary condition.

We considered a general model in Chapter 4 where the Dirichlet boundary value was computed from the reaction-diffusion model on the cell membrane. The model for the reactiondiffusion on the cell membrane was obtained and implemented both with Matlab and Comsol Multiphysics, taking care of the jumped coefficients of the model problem in the two subdomains on the membrane. As expected, the symmetry structure of the result obtained in Chapter 3 was lost in the result obtained in Chapter 4 (see Figure 6.1).

Based on the general model of Chapter 2 and the result of the model implementation in Chapter 4, we were able to couple the two models in the last chapter. We have thus been able to achieve our goal of giving a complete description and modeling of a reaction diffusion in cell membrane.

As an outlook, in Chapter 4, we have assumed a certain pattern for the reactions of the two chemical species on the cell membrane. A possible improvement on this would be to obtain the probabilistic rate of reactions of these chemical species from experimental data. This will result in a new pattern for the chemical reactions on the cell membrane and thus new results can be arrived at. Furthermore, extension to non-stationary problems can be considered and improvements is also possible as regards the geometry modeling with Comsol Multiphysics.



Figure 6.1: Comparison of the numerical solutions of the pure diffusion models. 6.1(a), 6.1(c): Numerical solution of the diffusion model with constant Dirichlet data g. 6.1(b), 6.1(d): Numerical solution of the diffusion model with non-constant Dirichlet data g.

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Eidesstattliche Erklärung

Ich, Saheed Ojo Akindeinde, erkläre an Eides statt, dass ich die vorliegende Diplomarbeit selbständig und ohne fremde Hilfe verfasst, andere als die angegebenen Quellen und Hilfsmittel nicht benutzt bzw. die wörtlich oder sinngemäß entnommenen Stellen als solche kenntlich gemacht habe.

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