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A mathematical Model for Mycolactone toxin Reaction and diffusion in cell cytoplasm

Short Research Article

Abstract

The study of mechanisms and transport of proteins inside cells provide understanding of the dynamics of biological systems and give clues to biological effect of drugs on our system. Reaction-diffusion mechanisms inside cells control various cell functions from adhesion, haptotaxis, chemotaxis to cytoskeletal rearrangement. The theorectical model presented in this work aims to model activation of proteins in a biological cell. In our previous paper on mathematical model for mycobacterium invasion of tissues, (Nyarko et al 2017), we reported that mycolactone activation of the WASP in the cytoplasm of cells leads to tissue necrosis in the Bururli ulcer disease. We provide two approaches to model reaction-diffusion in the cytoplasm: first the system of reaction-diffusion arising from mycolactone and WASP interactions are solved in a 3D domain with mycolactone toxin allowed to diffuse into the cytoplasm through the cell membrane to bind the WASP whiles defining a flux boundary condition on the cell membrane for the mycolactone, and restricting the WASP to the cytoplasm compartment. In the second model, we use the idea of periodicity to develop a topological setup for a layer of tissue that constitutes aggregation of similar cells. The model is solved using the coefficient form of PDE in Comsol Multiphysics. In the numerical simulation we compare the performance of three sparse direct solvers (UMFPACK, SPOOLES and PARDISO) on a 64-bit windows HP-Z1 workstation machine with 16GB RAM. The model is a contribution to the understanding of drug diffusion in the cell and most importantly to the understanding of the etiology of Buruli ulcer disease.

Keywords: Reaction diffusion, Periodicity, Mycolactone, Buruli ulcer.
2018 Mathematics Subject Classification: 53C25; 83C05; 57N16

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1 Introduction

Buruli ulcer (BU), is an infectious disease in immunocompetent humans and caused by *Mycobacterium ulcerans* (M. ulcerans) [16]. The disease involves the skin and subcutaneous adipose tissue and is characterized by a painless nodule, papule, plaque and normally evolves into a painless ulcer with characteristically undermined edges [20].
BU is one of the most neglected tropical diseases that largely affect the poor in remote rural areas [20,17]. The human pathogen *Mycobacterium ulcerans* secrets the diffusible lipid (*Mycolactone*), which induces the formation of open skin lesions referred to as Buruli ulcers [9, 12]. *Mycolactone* operates by diffusing through the cell membrane into the cytoplasm to react/bind and hijack the *Wiskott-Aldrich syndrome protein* (WASP) family of actin-nucleating factors. This reactions lead to over production of actin filament in the cell with a resultant effect of cytoskeletal rearrangement leading to apoptosis and necrosis of the dermis, panniculus, and deep fascia [12]. WASP is involved in the pathogenesis of many immune-related disorders and it is a key regulator of actin dynamics. Human patients deficient in WASP suffer from *Wiskott-Aldrich Syndrom*, a severe form of immunodeficiency where immune system cells have abnormal actin-based motility and platelets do not form normally. Secondly, mutations in the gene encoding WASP results in an immune system disorder and affected individuals die unless they receive bone marrow transplant. Other related disorders like thrombocytopenia, eczema, and immunodeficiency in humans also exist due to specific mutations in WASP [13,8, 5, 2]. The use of reaction-diffusion models to measure mobility of protein transport and interaction inside the cell nucleus and the influence of cell membrane boundaries on computions have been documented (see [18, 19] and the references there in). Understanding the functions and regulation of WASP and its activation in cells is a major step to understanding the etiology of many dsisease, including BU and *Wiskott-Aldrich syndrome*.
The paper is arrange as follows: In Section 2 we introduce the cytoplasm and importance of mathematical modeling in biology to reduce experimental cost. The reaction of *mycolactone* and WASP in the cytoplasm and compleses formed is introduced in section 3. In section 4 we introduce the evolution equations and the coupling of the $2D$ plane and $3D$ domain of the cell in Comsol Multiphysics, followed by a topological set-up of periodic arrangement of similar cells in a layer of tissue. The numerical simulations and comparism of three direct solvers is discused in Section 5. Finally, a discussion of the results is provided in Section 6.

2 Motivation

Mathematical models for biological systems and infectious disease modeling has in recent years received much attention because of the role mathematics play to reduce otherwise complicated and costly experimental procedures. The cytoplasm is a compartment of the cell where diverse cell surface receptors trigger global structural rearrangements in response to external signals. The reaction of *mycolactone* and the receptor protein (WASP) in the cytoplasm of cells discribed above lead to a system of reaction-diffusion equations whose solution explains events in the cell at the subcellular levels. In [14] it is clear that events at the subcellular level affect the ulcer formation at the macro-scale as described for cancer cells.

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3 Model Formulation

We propose a mathematical model for *mycolactone* toxin reaction and diffusion in the cytoplasm of a cell. To simplify the model we assume a uniform and homogeneous cytoplasm, and discuss Comsol Multiphysics-based methods in the study of intracellular reactions and the formation of complexes on the surface of the cytoplasm of a cell. In the model, the WASP referred to as the receptor and denoted by (R) is restricted to remain in the cytoplasm while the *mycolactone* toxin, referred to as the ligand and denoted by (m) is allowed to freely diffuse into the cell from the extracellular space to react/bind with the WASP to form the complex (Rm). Concentrations in the model will be denoted by u_i, $i \in \{R, m, Rm\}$. The index i shows the reacting species and the complex(s) formed.
The WASP and the complex formed in the cytoplasm do not diffuse out of the cytoplasm, but rather, there is accumulation of these complex on the surface of the cytoplasm. By this approach the total concentration of the complex can be computed. The concentration of receptors in the cytoplasm is assumed to be constant. This implies that a saturation level is reached in the complexes formed when all binding sites on the receptors are fully bound. Such situations lead to simple linear dynamics for the reactions terms. In [3, 11, 7], the standard procedure of adsorption and desorption of surface reactions on cytoplasm membrane have been considered for polycyclic aromatic hydrocarbons using homogenization methods and Comsol multiphsics for the numerical simulations. The Comsol Multiphysics has predefined equations and in-built material libraries that give several options to model reaction and diffusion of compounds with an additional opportunity to restrain complexes/species and reactions to specific compartments whiles the complexes can also be coupled to other reactions.

4 Mathematical model

We begin the modeling process with a reaction diffusion process in an arbitrary cell as in [1]. The cell will be represented by a three dimensional domain denoted by $\Omega \subseteq \mathbb{R}^3$ with a boundary denoted by $\partial\Omega$ (see Figure 1 and Figure 2). We shall denote the concentration of the WASP in the cytoplasm of the cell by u_R. The capabilities of Comsol Multiphysics allow us to restrict the concentration of WASP to the cytoplasmic compartment and allow the *mycolactone* toxin to diffuse into the cytoplasm throung its boundary which is the cell membrane. *Mycolactone* enters the cell through some part of its membrane denoted by Γ. To model the interface Γ (a part of the cell bounday), we use the multiphysics capabilities of Comsol Multiphysics to intersect the cell membrane with a rectangular plane. This gives the 2D rectangular plane (see Figure 2), in this way we allow the *mycolactone* to diffuse into the cytoplasm of the cell through the 2D rectangular plane. The reversible binding of *mycolactone* to WASP in the cytoplasm leads to a complex Rm according to the equation:

$$\mathrm{R+m} \underset{\mathrm{k_{-1}}}{\overset{\mathrm{k_1}}{\rightleftharpoons}} \mathrm{Rm}$$

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From the law of mass action the model is described by the system of equations:

$$\begin{cases} \dfrac{\partial u_m}{\partial t} = \nabla \cdot \big(D_m \nabla u_m\big), & t > 0, \Gamma \\ \dfrac{\partial u_R}{\partial t} = \nabla \cdot \big(D_R \nabla u_R\big) + k_{-1} u_{Rm} - k_1 u_R u_m, & t > 0, \Omega \\ \dfrac{\partial u_{Rm}}{\partial t} = D_{Rm} \nabla^2 u_{Rm} + k_1 u_R u_m - k_{-1} u_{Rm}, & t > 0, \Omega \end{cases} \tag{4.1}$$

The first equation in (4.1) describe the diffusion of mycolactone through the 2D boundary (Γ) and it is assumed that no reactions take place in the cell membrane. The second equation describe the reaction and diffusion of *mycolactone* and WASP in the cytoplasm. The third equation in (4.1) describe the formation of complexes in the cell cytoplasm and k_1 and k_{-1} are constant reaction rates.
At the interface between the cytoplasm and the extracellular region, we have continuity of the concentrations $u_{m,i}$ across the interface therefore the following flux conditions are defined:

$$u_{m,ext} = u_{m,cyt}, \qquad t > 0, \partial\Omega_{int}, \tag{4.2}$$

where the subscripts cyt, int, and ext denote cytoplasm, interface, and extracellular space respectively.
The model is supplemented with the bounday conditions:

$$\begin{aligned} D_m \nabla u_m \cdot n = d_m \nabla u_{m,cyt} \cdot n - k_1 u_{m,cyt} u_R, &\quad t > 0, \partial\Omega_{int}, \\ D_R \nabla u_R \cdot n = -(k_1 u_{m,cyt}) u_R, &\quad t > 0, \partial\Omega_{int}, \\ D_{Rm} \nabla u_{Rm} \cdot n = 0, &\quad t > 0, \partial\Omega_{int}, \end{aligned}$$

For brevity, we introduce the following variables for the concentrations $u_{m,i}$ in the different compartments of the domain Ω:

$$u_m = \begin{cases} u_{m,ext}, & \text{if } x \in \Omega_{ext}, \\ u_{m,cyt}, & \text{if } x \in \Omega_{cyt}. \end{cases} \tag{4.3}$$

Finally, the system of equations is supplemented with the following initial conditions:

$$u_m(0,x) = u_m^{\text{in}}(x), \quad \text{in } \Gamma, \tag{4.4}$$

$$u_R(0,x) = u_R^{\text{in}}(x), \; u_{Rm}(0,x) = 0, \quad \text{in } \Omega_{cyt}. \tag{4.5}$$

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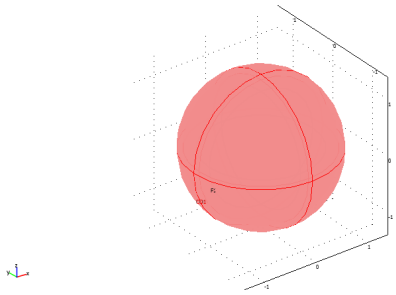

Figure 1:

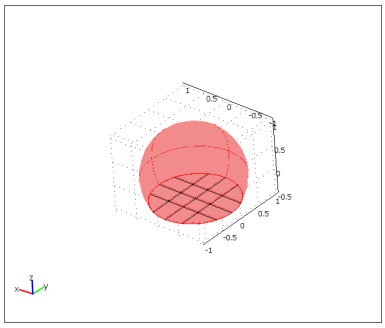

Figure 2:

4.1 Model Implementation in Comsol Multiphysics

We solve the problem using COMSOL Multiphysics version $3.5a$ using the coefficient form PDE with the variables fully coupled. This software uses the finite element method for the discretization with respect to the spatial independent variable [4]. The direct (non-iterative) method of solving finite element computations is used in this study. COMSOL Multiphysics has in-built direct and iterative solvers which can be selected depending on the type of problem being solved, and the symmetric nature of the matrix. In this study we use the UMFPACK solver. Let u_h be the numerical approximation of u, then in the numerical treatment we follow these steps:

- We get an initial solution of the finite element discretized problem on a coarse mesh.
- Set a tolerance $TOL > 0$. Then the global discretization error denoted by $\| E \|$ is estimated using the local discretization error denoted by $\| E \|_T$.

$$\underbrace{\| u - u_h \|^2}_{GlobalError} = \sum_{T \in Z_h} \underbrace{\| u - u_h \|^2}_{LocalError} \tag{4.6}$$

where

$$\| E \|_T = \| u - u_h \|_T \leq TOL \tag{4.7}$$

- The mesh is refined by subdividing the elements into finer mesh. This procedure is repeated until the error tolerance level is reached by every element in the discretized domain. In this study $TOL = 10^{-6}$
  Details of the initial concentrations and parameters used are given in section 4.3 below. The numerical solution in figure 3 shows the surface plot for the concentraction of *mycolactone* when it is allowed to diffuse into the cytoplasm in an alternating order. Figure 4 shows the surface plot for the concentration of *mycolactone* when it is allowed to flow into the cytoplasm through the center of Γ.

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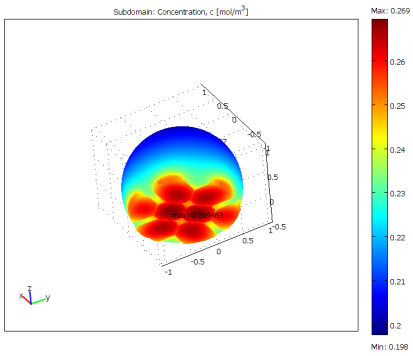

Figure 3:

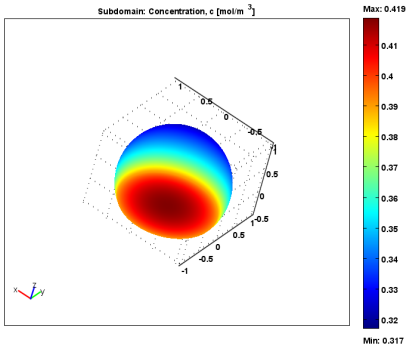

Figure 4:

In the next section we describe a second approach to model the reaction and diffusion in the cell using the idea of periodicity. The decription of a simplified model of the topological setup is given below.

4.2 Topological setup of the tissue in the model

The setup below describes a simplified model of the tissue as used in the model. Let $\Omega \subset \mathbb{R}^2$ be a bounded Lipschitz domain with periodic arrangements of cells and the reference unit cell $Y = (0,1)^2$ be an open set in $\mathbb{R}^2$. Copies of Y spans the entire region of Ω as shown on the left of Figure 5. By this representation, Ω is a layer of tissue with cells periodically arranged on the extra-cellular matrix (ECM). Therefore a layer of tissue constitutes an aggregation of similar cells.
Within the unit cell Y, we define a geometrical structure Y_{cell} as the cytoplasm (ie. a closed subset of Y) and $Y_{ext} = Y \backslash Y_{cell}$ the extracellular space. Then the cell membrane separate Y_{cell} and Y_{ext}, this is modeled as one-dimensional boundary and denoted by $\Gamma^* \subset Y$.

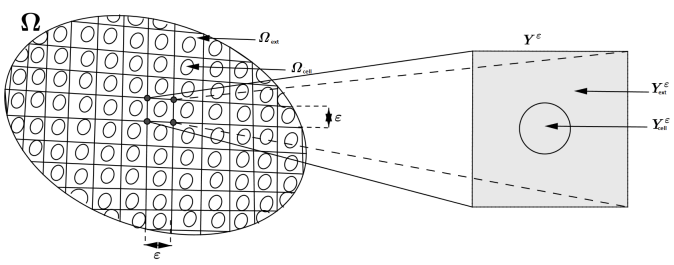

Figure 5: *Periodic arrangement of cells on ECM*

Furthermore we assume that any two neighboring subdomains Y_{cell} do not touch each other and the two parts of the unit cell satisfy $\bar{Y}_{cell} \cap \bar{Y}_{ext} = \Gamma^*$ (where $\bar{Y}$ denote the closure of Y). Therefore $\Gamma^* = \partial Y_{cell}$ and $\bar{Y}_{cell} \subset Y$ such that $Y = Y_{cell} \cup Y_{ext} \cup \Gamma^*$.

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In line with [3, 6], the following assumptions and conditions are made on the model:
(i) the concentration of the toxin on the cell membrane boundary are in rapid equilibrium; (ii) one elementary cell (Y) consists of both the cytoplasm and extracellular space therefore, Y_{cell} and Y_{ext} have strictly positive measure on $\bar{Y}$ with $\partial Y_{cell} \cup Y_{ext} = \emptyset$; (iii) the boundary of the extracellular space (Y_{ext}) is sufficiently regular therefore Y_{ext}, is an open set with a local Lipschitz boundary; (iv) the Continuum hypothesis is adopted to enable molecules in the cell and extracellular space to be described using concentration u_i, $i \in \{m, R, Rm\}$; (v) the cytoplasm and the cell membrane have constant physical and chemical properties; (vi) the flux through the membrane is normal to the surface of the membrane .
For a small parameter ε we generate copies of cells $\varepsilon Y_i^\varepsilon$ of regular mesh of size ε to span the domain $\Omega \subset \mathbb{R}^2$. Denote each re-scaled cell by $Y_i^\varepsilon = (0, \varepsilon)^2$ (see Figure.5) for $1 \leq i \leq N(\varepsilon)$. The number of cells in the domain of Ω is given by $N(\varepsilon) = \varepsilon^{-1} \mid \Omega \mid$. Then each cell now become homeomorphic to Y by a linear homeomorphism Π_i^ε with ratio of magnification ε^{-1} $(\Pi_i^\varepsilon : Y_i^\varepsilon \longrightarrow Y)$. It holds that

$$Y_{cell_i}^\varepsilon = (\Pi_i^\varepsilon)^{-1} (Y_{cell}) \tag{4.8}$$

$$Y_{ext_i}^\varepsilon = (\Pi_i^\varepsilon)^{-1} (Y_{ext}) \tag{4.9}$$

The domain Ω_{ext}^ε and $\Omega_{cell}^\varepsilon$ are assumed to be extracellular space and cytoplasm of cell respectively.
It holds further that $\Omega^\varepsilon = \Omega_{cell}^\varepsilon \cup \Omega_{ext}^\varepsilon$ and $Y^\varepsilon = Y_{cell}^\varepsilon \cup Y_{ext}^\varepsilon \cup \Gamma^\varepsilon$.
The extracellular space $\Omega_{ext}^\varepsilon \subset \Omega$.
That is

$$\Omega_{ext}^\varepsilon = \Omega \backslash \bigcup_{i=1}^{N(\varepsilon)} Y_i^\varepsilon \tag{4.10}$$

and

$$\Omega_{cell}^\varepsilon = \bigcup_{i=1}^{N(\varepsilon)} Y_i^\varepsilon \tag{4.11}$$

Also define the boundary of the extracellular space by

$$\partial \Omega_{ext}^\varepsilon = \partial \Omega \cup \partial \Omega_{cell}^\varepsilon \tag{4.12}$$

where $\partial \Omega_{cell}^\varepsilon = \Gamma^*$ is the cell membrane boundary.
For $T > 0$, let $S\colon = (0, T)$ denote the time interval. The space-time domain then becomes $Q\colon = S \times \Omega$ and $Q^\varepsilon\colon = S \times \Omega_z^\varepsilon \quad \forall z \in \{cell, ext\}$. It suffices to state that the domain Y_{cell}^ε as well as the domain Y_{ext}^ε of this repetition are $Y-$periodic in the language of Homogenization Theory. Therefore, periodic Homogenization methods can also be used to compute solutions for the problem. Periodicity allows us to simulate one cell as a true representation of the tissue. This reduces computational cost and CPU memory.

4.3 Coupling of the Subdomains

The geometry used in the numerical simulation consists of an extracellular space Y_{ext} and an inner subdomain representing the cytoplasm surface Y_{cell}. This is separated by the cell membrane. The extracellular space and the cytoplasm are represented by squares

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of size 1 and 0.5 respectively (see Figure 6). Figure 7 shows the initial coarse mesh of our domain, whiles table 1 and 2, details the performance of the three sovlvers in terms of; degree's of freedom, time, memory and the number of elements used in the solution, on a 64-bit windows HP-Z1 workstation machine with 16GB RAM. In Y_{cell} the following parameter were used $D_R = D_{Rm} = 1.0m^2s^{-1}$, $k_1 = 0.5$, $k_{-1} = 0.1s^{-1}$, $D_m = 3.0m^2s^{-1}$. In the extracellular space (Y_{cell}) $D_R = D_{Rm} = 0$. Since the WASP and complexes formed are restricted to the cytoplasm.

$$n.\nabla u_{Rm} = 0 \quad \text{on} \quad \partial Y_{cell}. \tag{4.13}$$

$$\int_{Y_{ext}} u_m dA = 0.5mol/m^3 \tag{4.14}$$

$$\int_{Y_{cell}} u_R dA = 1.0mol/m^3 \tag{4.15}$$

are initial conditions for the *mycolactone* toxin and WASP respectively. This implies, at time zero $(t = 0)$ WASP is present in Y_{cell} and *mycolactone* is present in the extracellular space (Y_{ext}).

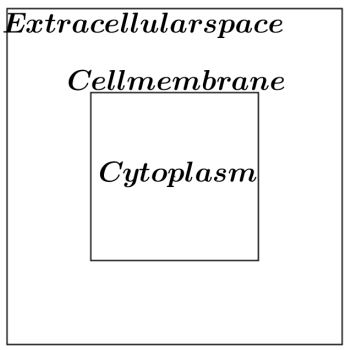

Figure 6:

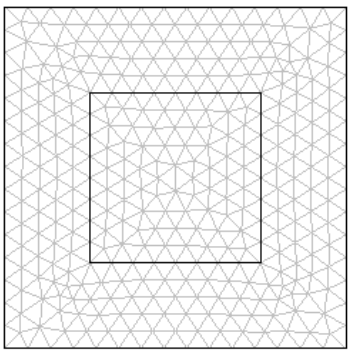

Figure 7:

5 Numerical results

We present numerical results in the form line and surface plots obtained by COMSOL Multiphysics. The results here were obtained by integrating the concentrations over respective subdomains or compartments. The black, blue and red lines in figure 8 represent WASP, *mycolactone* toxin, and complexes formed respectively. The numerical solutions are computed using three direct solvers namely: UMFPACK, SPOOLES (Sparse object oriented linear equation solver) and PARDISO (Parallel direct sparse solvers). Figures 9 and 10 are surface plots showing the concentration of *mycolactone* (u_m) in $2D$ and $3D$ respectively. The arrow plot in figure 9, shows direction of flow of *mycolactone* from the extracellular space into the cytoplasm.

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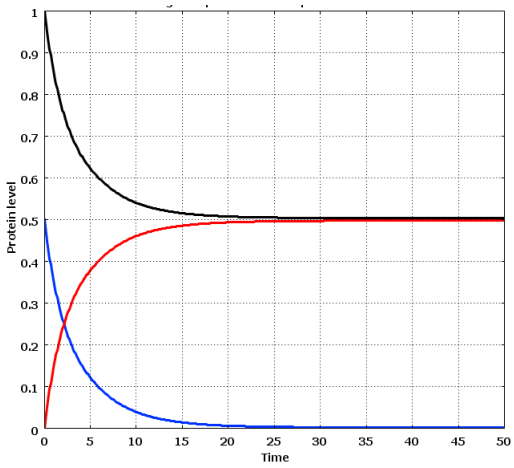

Figure 8: *plot shows the formation of complexes* (Rm) *and reduction of* m *and* R

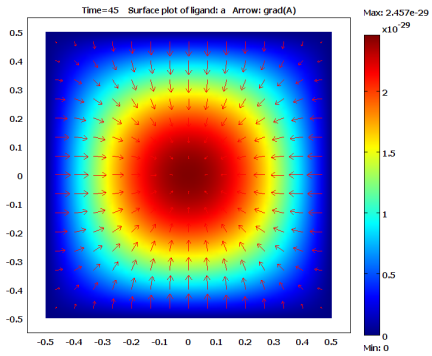

Figure 9:

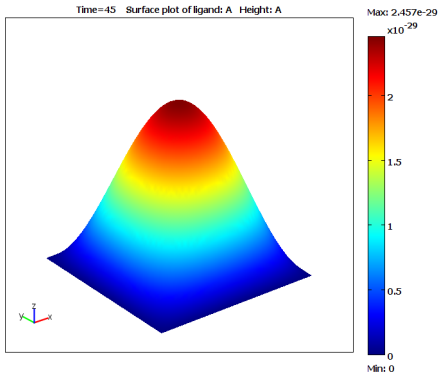

Figure 10:

Table 1: Performance of solvers on a coarse mesh

Solver	♯ dof's	Time (sec.)	Memory (GB)	Elements
UMFPACK	42440	131.804	566	648
SPOOLES	42440	87.961	596	648
PARDISO	42440	36.339	595	648

The tables 1 and 2 show the performance of the solvers. In the numerical simulation, about 95% of the time used by the solvers were used in the matrix factorization step. The

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Table 2: Performance of solvers on a fine mesh

Solver	♯ dof's	Time (sec.)	Memory (GB)	Elements
UMFPACK	42440	134.774	701	2592
SPOOLES	42440	88.78	712	2592
PARDISO	42440	35.726	665	2592

general observation is that the number of degrees of freedom solved for are the same in both meshes (coarse and fine). An increase in the number of mesh elements increases the computational time and memory requirement increase which is expected.
The UMFPACK solver takes the longest time to solve the linear system of equations. It is more than three times slower than the time taken by PARDISO and about one and a half times slower than the SPOOLES solver. In terms of memory requirement, the SPOOLES solver requires the largest memory and UMFPACK rquires the least in the coarse mesh. There is a little deviation when the mesh elements increased from 648 to 2592. The SPOOLES solver still requires the largest amount of memory followed by UMFPACK and PARDISO respectively. From tables 1 and 2 it can be observed that in terms of memory requirement and computational time, the PARDISO solver performs better than SPOOLES and UMFPACK although on a coarse mesh the UMFPACK requires less memory.

6 Conclusion

The coupled system of reaction-diffusion equations were solved in the cytoplasm of the cell. The concentration distributions in figures 3,4, 9 and 10 shows that the maximum concentration of the *mycolactone* is at the center of the domain.
For the numerical treatment of reactions in a periodic geometry, computing quasi-periodicity in tissue modeling is introduced. This technique allows us to simulate one cell as a true representation of the tissue, and drastically reduce computational costs and CPU memory.

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