

Numerical Approximation of Reaction and Diffusion Systems in the Mammalian Cell Using Homogenization and Compartment Modelling

Qasim Ali Chaudhry

KTH - Royal Institute of Technology, Stockholm
Sweden

July 05, 2010

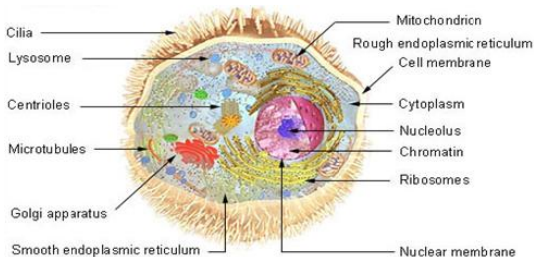


Outline

- 1 Introduction
- 2 Mathematical Model
 - Modelling Assumptions and Technique
 - Quantitative Model
- 3 Homogenization
 - Homogenization Steps
- 4 Numerical Simulations
- 5 Compartment Modelling
 - A Compartment Model (CM)
- 6 Conclusions and Future Directions

Introduction

- The mathematical modeling of the diffusion and reaction of toxic compounds in the mammalian cells is a tough task due to their very complex geometry, heterogeneity, and the variation of their architecture.



Introduction (2)

- The presence of many thin membrane structures adds to the difficulty in the modeling.

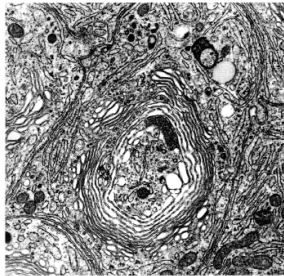


Figure: Epithelial rat cell showing Golgi-apparatus. © Dr. H. Jastrow

Introduction (3)

- This research work is in connection with the development of biochemical and mathematical model of the carcinogenic compounds in mammalian cells.
- The present investigations are motivated by a collaboration between the Numerical Analysis group at Royal Institute of Technology (KTH) and a research group at the Institute of Environmental Medicine, Karolinska Institute (KI).

Motivation and Challenge

- Polycyclic Aromatic Hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, they can be metabolized to reactive intermediates that react with protein and DNA, and thereby cause toxicity and cancer.
- The system is multi-scale system with respect to both space and time.

Motivation and Challenge

- Polycyclic Aromatic Hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, they can be metabolized to reactive intermediates that react with protein and DNA, and thereby cause toxicity and cancer.
- The system is multi-scale system with respect to both space and time.

Motivation and Challenge

- Polycyclic Aromatic Hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, they can be metabolized to reactive intermediates that react with protein and DNA, and thereby cause toxicity and cancer.
- The system is multi-scale system with respect to both space and time.

The Problem

To construct a Mathematical Model for the in vitro reactions and diffusion of carcinogenic compounds in the mammalian cells.

Mathematical Model

- Diffusion and reaction in the extracellular water.
- Diffusion and reaction in the cytoplasm and nucleus.
- Diffusion inside the membranes.
- Absorption and desorption between the different phases.

Reaction-Diffusion Mechanism in the Cell

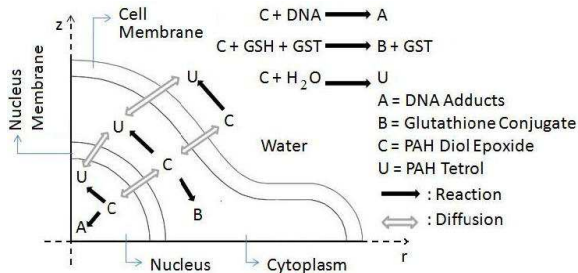


Figure: Quarter part of an axi-symmetric cell (not to scale). More like a flying saucer

Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

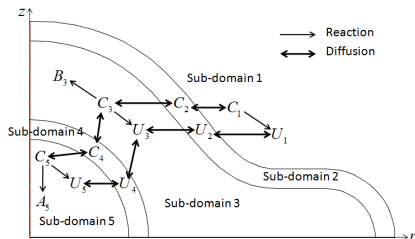
Modelling Assumptions

- On the smallest scale, cytoplasm consists of many thin membranes. We assume these membranes as layered structures.
- On the large scale, we assume that the volume of cytoplasm contains an unordered set of small-scale substructures, which are uniformly distributed over the volume.
- The physical and chemical properties of the cytoplasm and the membranes are uniform.
- We adopt the continuum hypothesis.
- The Jump in the concentration between the two sub-domains can be conveniently described by the partition coefficients.

Modeling Technique

For the numerical treatment of the model without changing the essential features of metabolism, Homogenization techniques have been implemented.

Quantitative Model



$$\frac{\partial}{\partial t}[C_{ij}] = \nabla \cdot (D(x)\nabla[C_{ij}]) + R_{ij}([C_{1j}], \dots, [C_{nj}], x), \quad x \in \Omega_j, \quad j = 1, \dots, m.$$

- Ω_j denotes the different sub-domains
- $[C_{ij}]$, $i = 1, \dots, n$ denotes the concentration of i -th species
- $D(x)$ is a diffusion coefficient
- R_{ij} represents the reaction

Interface Conditions

- Continuity of Flux
- Jump of concentrations

For $S = C, U$

$$[S_1] = K_{P,S}[S_2], \quad D_1 \frac{\partial}{\partial \mathbf{n}_1} [S_1] + D_2 \frac{\partial}{\partial \mathbf{n}_2} [S_2] = 0$$

$$[S_5] = K_{P,S}[S_4], \quad D_4 \frac{\partial}{\partial \mathbf{n}_4} [S_4] + D_5 \frac{\partial}{\partial \mathbf{n}_5} [S_5] = 0$$

$$[S_{3,w}] = K_{P,S}[S_{3,l}], \quad D_{3,w} \frac{\partial}{\partial \mathbf{n}_w} [S_{3,w}] + D_{3,l} \frac{\partial}{\partial \mathbf{n}_l} [S_{3,l}] = 0$$

where $\mathbf{n}_1 = -\mathbf{n}_2$, $\mathbf{n}_4 = -\mathbf{n}_5$ and $\mathbf{n}_w = -\mathbf{n}_l$.

Boundary & Initial Conditions

- At the outer boundary, Neumann Boundary Conditions are:

$$\frac{\partial}{\partial \mathbf{n}_1} [S_1] = 0$$

B and A are only restricted to the domains 3 (cytoplasm) and 5 (nucleus) resp.

$$\frac{\partial}{\partial \mathbf{n}_3} [B_3] = 0, \quad \frac{\partial}{\partial \mathbf{n}_5} [A_5] = 0$$

- At initial time, only the concentration of C_1 is non-zero:

$$[C_1]|_{t=0} = [C_0]$$

where all other species have zero concentration at $t = 0$.

Homogenization Technique for Cytoplasm

- A general methodology for replacing complex multiscale systems by the average/effective equations.
- Modify the reaction terms and diffusion time constant.
- Find an effective diffusion coefficient, $D_{3,S,\text{eff}}$ for the homogenized cytoplasm.
- Find the coupling conditions of the homogenized cytoplasm to the surrounding membranes.

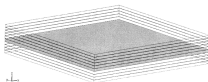
Homogenization Steps

Our modelling assumptions suggest two homogenization steps (iterated homogenization):

- On the smallest scale: periodic homogenization
- On the large scale: random homogenization

Finding Effective Diffusion Coefficient: Homogenization on the Smaller Scale

- Cytoplasm consists of layered structures/membranes



- The simplified form of the equation as

$$\delta_S \frac{\partial}{\partial t} [\hat{S}_3] = \nabla \cdot (\hat{D}_{3,s} \nabla [\hat{S}_3]) + \hat{k}_S [\hat{C}_3], \quad x \in G$$

Finding Effective Diffusion Coefficient: Homogenization on the Smaller Scale (2)

- For the effective concentrations \bar{S} ,

$$\delta_{S,\text{eff}} \frac{\partial}{\partial t} [\bar{S}_3] = \nabla \cdot (D_{3,S,\text{eff}} \nabla [\bar{S}_3]) + k_{S,\text{eff}} [\bar{C}_3]$$

- If the orientation of these thin membranes is different from the above direction, then using the rotation matrix T

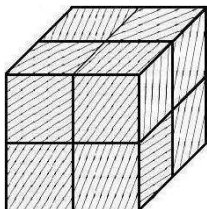
$$\delta_{S,\text{eff}} \frac{\partial}{\partial t} [\bar{S}_3] = \nabla_{(x',y',z')} \cdot (TD_{3,S,\text{eff}} T^t \nabla_{(x',y',z')} [\bar{S}_3]) + k_{S,\text{eff}} \bar{C}_3$$

Finding Effective Diffusion Coefficient: Homogenization on the Large Scale

- We assume that the cytoplasm contains an unordered set of the small sub-structures, which are uniformly distributed over the volume.
- The size of these sub-structures is very small as compared to the size of the cytoplasm.
- Orientation of the layers is random and uniformly distributed.
- No analytical expressions are known.
- We use Monte Carlo techniques for the estimation of effective diffusion coefficient.

Finding Effective Diffusion Coefficient: Homogenization on the Large Scale (2)

- Let the domain of each cube be, $\Omega = (0, L)^3$



- Divide each cube into N^3 sub-cubes, N is a positive integer:

$$\Omega_{ijk} = (x_{i-1}, x_i) \times (y_{j-1}, y_j) \times (z_{k-1}, z_k)$$

with $x_i = y_i = z_i = ih$, and $h = \frac{L}{N}$

Finding Effective Diffusion Coefficient: Homogenization on the Large Scale (3)

- Since the layered structures have no specific direction, so we use the transformation matrix T_{ijk}
- The mean value of $D_{3,S,eff}^N |_{\Omega_{ijk}}$ is denoted by $\bar{D}_{3,S,eff}^N$, It will hold (tested by Hanke M and Cabauatan-Villanueva M.C):

$$\bar{D}_{3,S,eff}^N \longrightarrow D_{3,S,eff}, \quad \text{for } N \longrightarrow \infty$$

Coupling of Homogenized Cytoplasm to the Surrounding Medium

- We consider the interface between Homogenized Cytoplasm (G_3) and Cell membrane (G_2),

$$[S_{3,\text{eff}}] = K_{P,S}[S_2]$$

$$D_{3,S,\text{eff}} \frac{\partial}{\partial \mathbf{n}_3} [S_{3,\text{eff}}] + D_2 \frac{\partial}{\partial \mathbf{n}_2} [S_2] = 0, \quad (\mathbf{n}_2 = -\mathbf{n}_3)$$

- Similar derivations can be made at the interface between the cytoplasm and the nuclear membrane.

Modeling in Comsol Multiphysics

In order to impose the interface conditions, a technique from the model library of the Chemical Engineering Module has been used. As an example, at the interface between the extracellular and cellular membrane, the interface conditions can be replaced by:

$$D_1 \frac{\partial}{\partial n_1} S_1 = m(S_2 - K_P S_1)$$

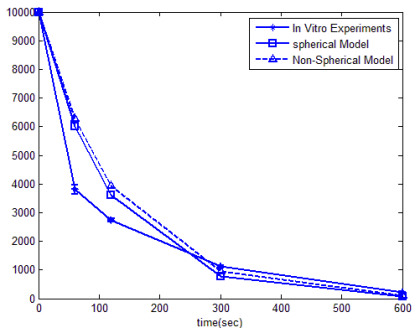
$$D_2 \frac{\partial}{\partial n_2} S_2 = m(K_P S_1 - S_2)$$

m is a (non-physical) very large constant. It is called penalty approach.

Simulation Results

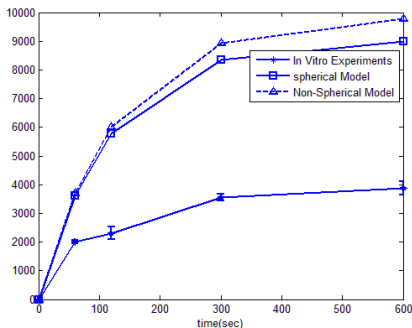
- The results of amount of different species in the model were compared with the in vitro cell experimental results.
- Simulations were performed in Comsol Multiphysics for spherical and non-spherical cell model
- Simulations were performed for a time span of 600 sec.

Comparison of Degradation of PAH Diol Epoxides (C_1)



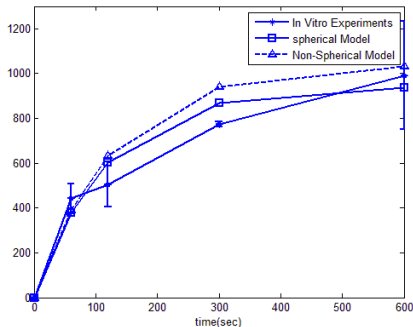
A nice agreement of the results of the in vitro experiments and the model in extracellular water.

Comparison of Formation of PAH Tetrols (U_1)



The large difference observed can be explained in part by the fact that some reactions, e.g. protein binding, have not been considered.

Comparison of Formation of Glutathione Conjugate (B_3)



A nice agreement of the results of the in vitro experiments and the model in the cytoplasm.

Compartment Modelling

- A compartment is a distinct, well stirred, and kinetically homogeneous amount of material.
- A compartmental system is made up of a finite number of compartments.
- These compartments interact by material flowing from one compartment to another.
- Compartment Modelling is often used to describe transport of material in biological systems.

Why to Use Compartment Modelling

- This is a standard modelling technique used in literature.
- Reduction of PDE Model to ODE Model thus decreasing the complexity and computational cost of the system of equations.

Why to Use Compartment Modelling

- This is a standard modelling technique used in literature.
- Reduction of PDE Model to ODE Model thus decreasing the complexity and computational cost of the system of equations.

Why to Use Compartment Modelling

- This is a standard modelling technique used in literature.
- Reduction of PDE Model to ODE Model thus decreasing the complexity and computational cost of the system of equations.

A Compartment Model (CM)

Jump in concentration: $[C_1] = K_P[C_{21}]$, $[C_3] = K_P[C_{23}]$

Concentration gradient: $([C_{23}] - [C_{21}])/\delta$

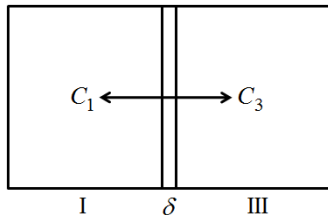
Fick's Law of diffusion:

$$\begin{aligned} \frac{d}{dt} C_1 &= \frac{DA}{\delta} ([C_{23}] - [C_{21}]) \\ &= \frac{DA}{K_P \delta} ([C_3] - [C_1]) \end{aligned}$$

or

$$V_1 \frac{d}{dt} [C_1] = \frac{DA}{K_P \delta} ([C_3] - [C_1])$$

$$V_3 \frac{d}{dt} [C_3] = \frac{DA}{K_P \delta} ([C_1] - [C_3])$$



A Compartment Model (CM), (2)

For Homogenized Cytoplasm

The effective Concentration will be used, hence we will replace $[S_3]$ by $[S_{3,\text{eff}}]$ in the cytoplasm, where

$$[S_{3,\text{eff}}] = \sigma_{S,\text{eff}}[S_3]$$

Quantitative Analysis

- The complete system of equations of Compartment Model was implemented in Matlab.
- Simulations were performed for a time span of 600 sec.
- The results of amount of different species in the model were compared with the 1D PDE Model.

Simulation Results: Quantitative Analysis

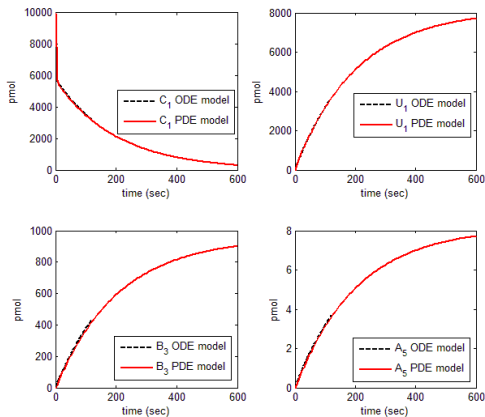


Figure: Comparison between CM (ODE) and PDE Model (1D)

Sensitivity Analysis

Parameter	Physical Values	For Sensitivity Analysis
D	1.0×10^{-12}	1.0×10^{-11}
$K_{P,C}$	1.2×10^{-3}	5.0×10^{-2}
$K_{P,S}$	8.3×10^{-3}	2.0×10^{-2}
k_B	3.7×10^3	3.7×10^5
k_A	6.2×10^{-3}	6.2×10^1

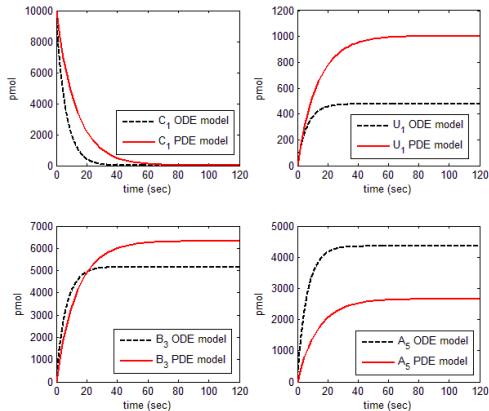


Figure: Comparison between CM (ODE) and PDE Model (1D)

Time Scale of Diffusion in the Compartments

Since

$$V_1[C_1] + V_3[C_3] = \text{Constant}$$

$$\text{Time Scale } (\tau) \approx K_P \delta / DA \left(\frac{1}{V_1} + \frac{1}{V_3} \right)$$

$$\tau \approx 1.25 \times 10^{-4}$$

- Concentration in the membrane is much higher than outside of it.
- Time scale for the CM is extremely small: membranes are very effective at transporting the stuff.
- Apparently, membranes have no role.
- However, from the in vitro experiments, it is an established fact that membranes act as reservoirs.

Conclusions

- For the approximation of reaction and diffusion system in complex cell geometry, a mathematical model in 2D is presented.
- Homogenization technique was used for Cytoplasm.
- Numerical results show nice agreement with the in vitro experimental results.

Conclusions

- For the approximation of reaction and diffusion system in complex cell geometry, a mathematical model in 2D is presented.
- Homogenization technique was used for Cytoplasm.
- Numerical results show nice agreement with the in vitro experimental results.

Conclusions

- For the approximation of reaction and diffusion system in complex cell geometry, a mathematical model in 2D is presented.
- Homogenization technique was used for Cytoplasm.
- Numerical results show nice agreement with the in vitro experimental results.

Conclusions (2)

- Compartment Model cannot capture some essential features of the metabolism. Hence, we need a more sophisticated model using PDEs as implemented in our homogenized cell model.

Future Directions

- To consider new cellular geometry like a fried egg sunny side up.
- To include new reaction-diffusion mechanisms in the model, and the models for different cell organelles such as Mitochondria.
- To include the stochastic effects.

References

- 1 Chaudhry Q. A. Numerical Approximation of Reaction and Diffusion Systems in Complex Cell Geometry, Licentiate Thesis, ISBN 978-91-7415-586-0, KTH (2010).
- 2 Dreij K, Chaudhry Q. A, Morgenstern R, Jernström B, Hanke M. A Homogenization Method for Efficient Calculation of Diffusion and Reactions of Lipophilic Compounds in Complex Cell Geometry (In preparation).

Thank You