Simulation of Transport of Lipophilic Compounds in Complex Cell Geometry

Qasim Ali Chaudhry [1] , Michael Hanke [2],
Ralf Morgenstern [3]
[1,2]School of Computer Science and Communication, Royal Institute of Technology, Stockholm, Sweden,
[3]Karolinska Institutet, Stockholm, Sweden
October 15, 2009

Outline

- Introduction
- Mathematical Model
- Simulation Results
- Future Work

Introduction

A cell is a fundamental unit of living organisms. Schematically, a human cell consists of outer cellular membrane, cytoplasm that contains lot of cell organelles i.e. mitochondria, Golgi apparatus, endoplasmic reticulum etc, then a nuclear membrane and finally a nucleus containing the most important hereditary material DNA.
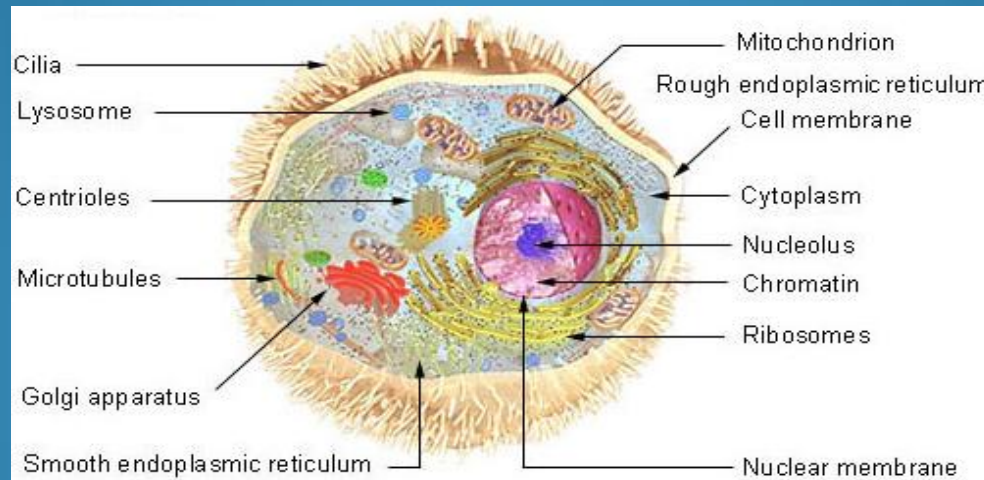
The Cell Structure*

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 and specially due to the presence of many thin membrane structures.
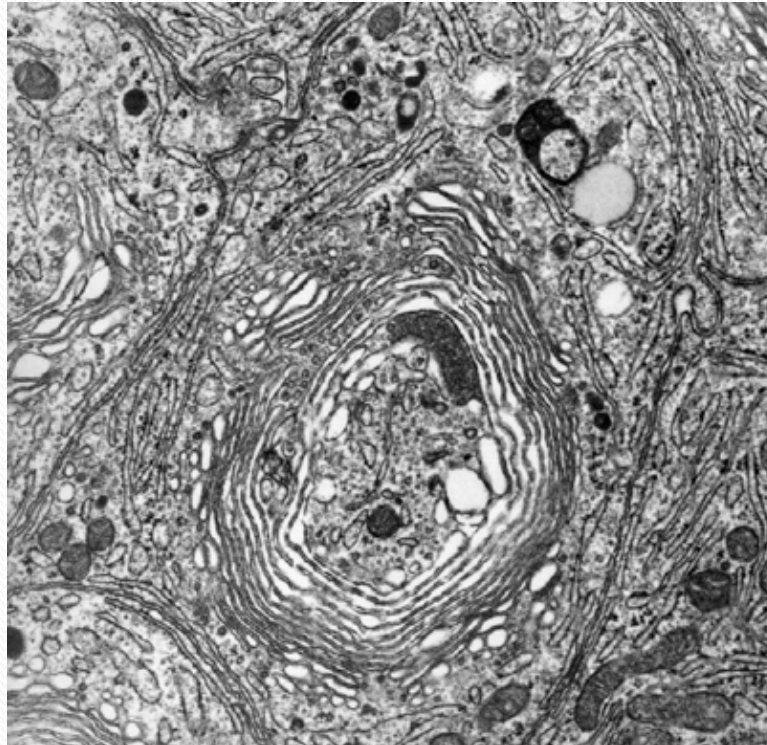
Real picture of an epithelial rat cell showing the Golgi-apparatus. Copyright Dr. H. Jastrow

?

Why this research work

➢ Since the polycyclic aromatic hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, so they can be metabolized to reactive intermediates that react with protein and DNA and thereby cause toxicity and cancer.

➢ Since the polycyclic aromatic hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, so they can be metabolized to reactive intermediates that react with protein and DNA and thereby cause toxicity and cancer.

➢ In order to understand the major principles that govern cellular fate of the reactive intermediates formed from PAH, and why some are carcinogens and others are not, we have implemented a Mathematical Model in Comsol Multiphysics for the in Vitro reactions and diffusions of carcinogenic compounds in the mammalian cells.

➢ Since the polycyclic aromatic hydrocarbons (PAH) are ubiquitous environmental pollutants formed from incomplete combustion, so they can be metabolized to reactive intermediates that react with protein and DNA and thereby cause toxicity and cancer.

➢ In order to understand the major principles that govern cellular fate of the reactive intermediates formed from PAH, and why some are carcinogens and others are not, we have implemented a Mathematical Model in Comsol Multiphysics for the in Vitro reactions and diffusions of carcinogenic compounds in the mammalian cells.

➢ The system is a multi-scale system with respect to both space and time

Mathematical Model

Mathematical Model

➢ Diffusion and reaction in the extracellular.

Mathematical Model

- ➢ Diffusion and reaction in the extracellular.
- ➢ Diffusion and reaction in the cytoplasm and nucleus.

Mathematical Model

➢ Diffusion and reaction in the extracellular.

➢ Diffusion and reaction in the cytoplasm and nucleus.

➢ Diffusion inside the membranes.

Mathematical Model

➢ Diffusion and reaction in the extracellular.
➢ 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
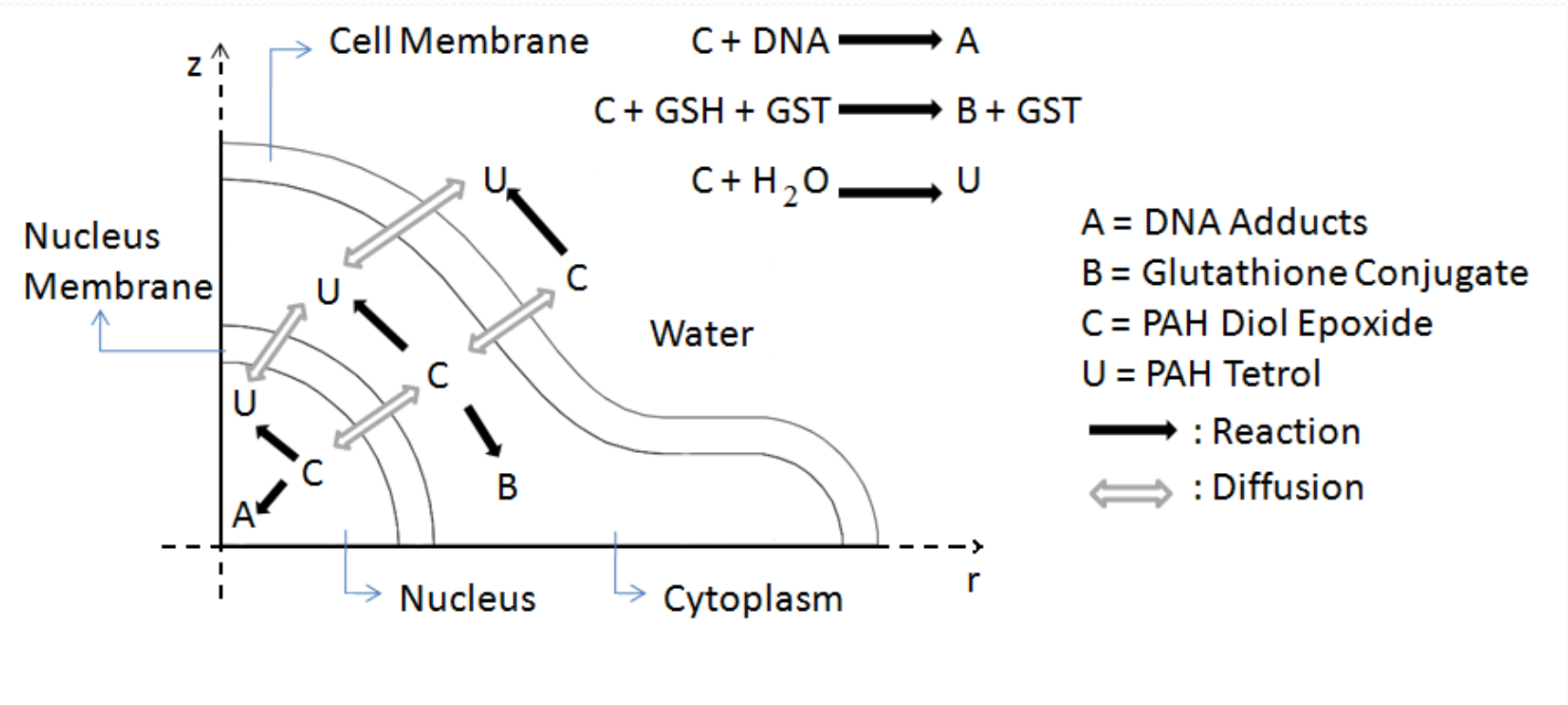
Quarter part of an axi-symmetric cell (not to scale)

Modeling Technique

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

➢ For the homogenized cytoplasm, effective diffusion coefficient $D_{3,\text{eff}}$ has been used.

Quantitative Model

$$\frac{\partial}{\partial t} C_{ij} = \nabla.(D_{ij}(x)\nabla C_{ij}) + R_{ij}(C_{1j}, C_{2j},...,C_{nj},x) \quad , \quad x \in \Omega_j \quad , \quad i = 1,...,n$$

$\Omega_j, j = 1,...m$ denotes the different sub-domains.

C_{ij} is the concentration of the *i*-th species.

D_{ij} is the diffusion tensor.

$R_{ij} \equiv 0$ in the membranes.

Interface Conditions

➤ Continuity of Flux
➤ Jump of concentrations over the membranes can be conveniently described by the use of partition coefficient $K_{p,s}$

$$S_1 = K_{p,s} S_2 \qquad D_1 \frac{\partial S_1}{\partial \mathbf{n}_1} + D_2 \frac{\partial S_2}{\partial \mathbf{n}_2} = 0$$

$$S_5 = K_{p,s} S_4 \qquad D_4 \frac{\partial S_4}{\partial \mathbf{n}_4} + D_5 \frac{\partial S_5}{\partial \mathbf{n}_5} = 0$$

$$S = C, U$$

Boundary & Initial Conditions

➤ Bounded extracellular medium i,e,

$$\frac{\partial S_1}{\partial n_1} = 0$$

➤ *B* and *A* are restricted in sub-domains 3 and 5 respectively, so

$$\frac{\partial B_3}{\partial n_3} = 0 \qquad , \qquad \frac{\partial A_5}{\partial n_5} = 0$$

➤ Initial Condition

$$C_1 = C_0 \mid_{t=0}$$

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

$$D_1 \frac{\partial S_1}{\partial \mathrm{n}_1} = M(S_2 - K_{p,s}S_1)$$

$$D_2 \frac{\partial S_2}{\partial \mathrm{n}_2} = M(K_{p,s}S_1 - S_2)$$

M is a (non-physical) very large constant

Simulation Results

Simulation Results

➢ Simulations were performed for spherical and non-spherical cell model.

Simulation Results

➢ Simulations were performed for spherical and
  non-spherical cell model.

➢ Simulations were performed for a time span of 600 sec.

Simulation Results

➢ Simulations were performed for spherical and non-spherical cell model.

➢ Simulations were performed for a time span of 600 sec.

➢ The comparisons between the results of concentrations of different species with respect to the time in the model were compared with the actual results taken from the in-vitro experiments using mammalian cells.

# Comparison of Degradation of PAH Diol Epoxides
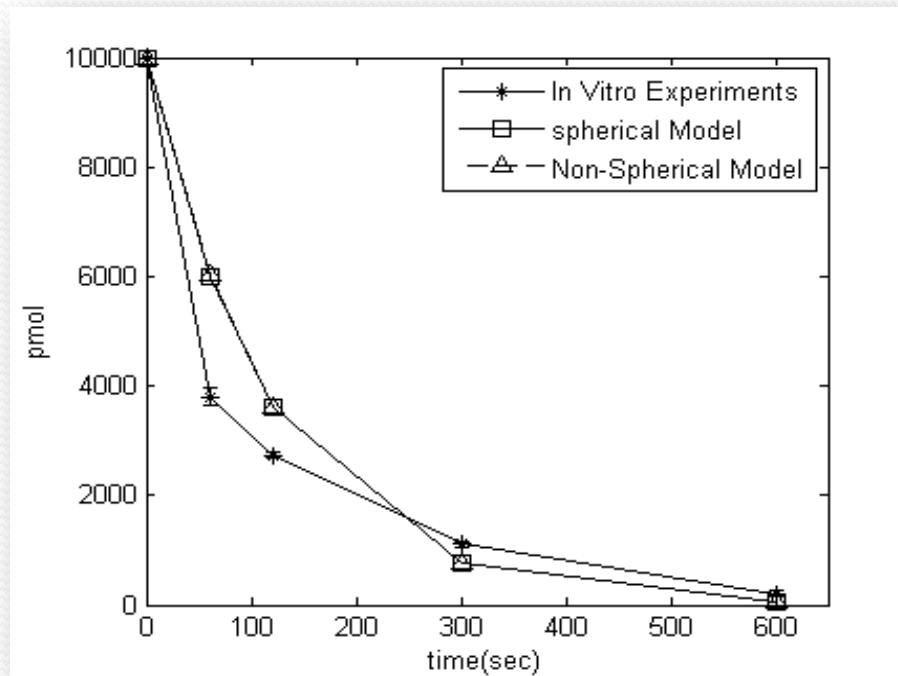
A very nice agreement of the results of in vitro experiments and the model in extracellular water.

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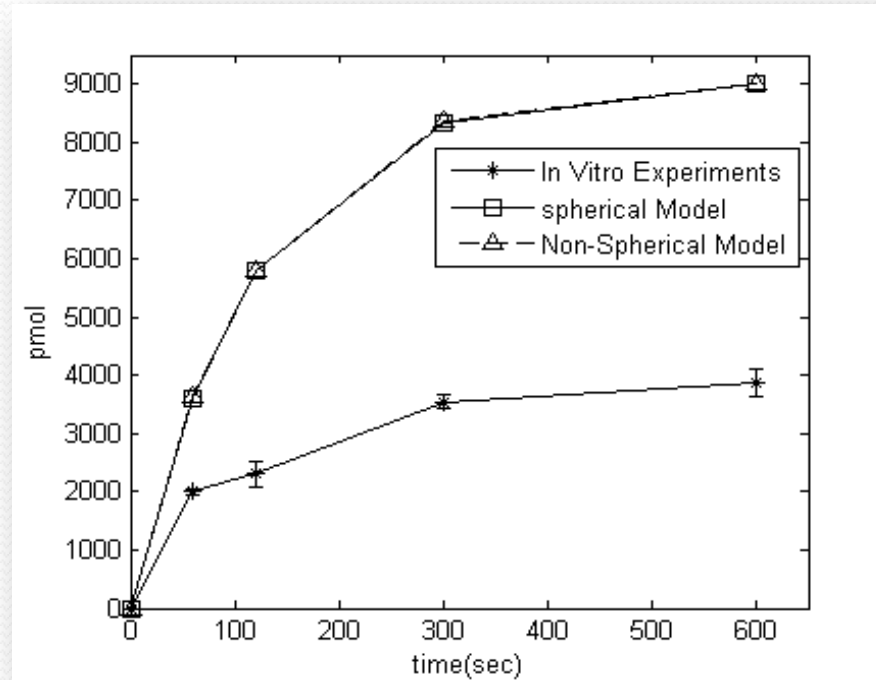
The large difference observed can be explained in part by the fact that some reactions, e.g. protein binding, have not been considered.

Comparison of Formation of Glutathione Conjugate
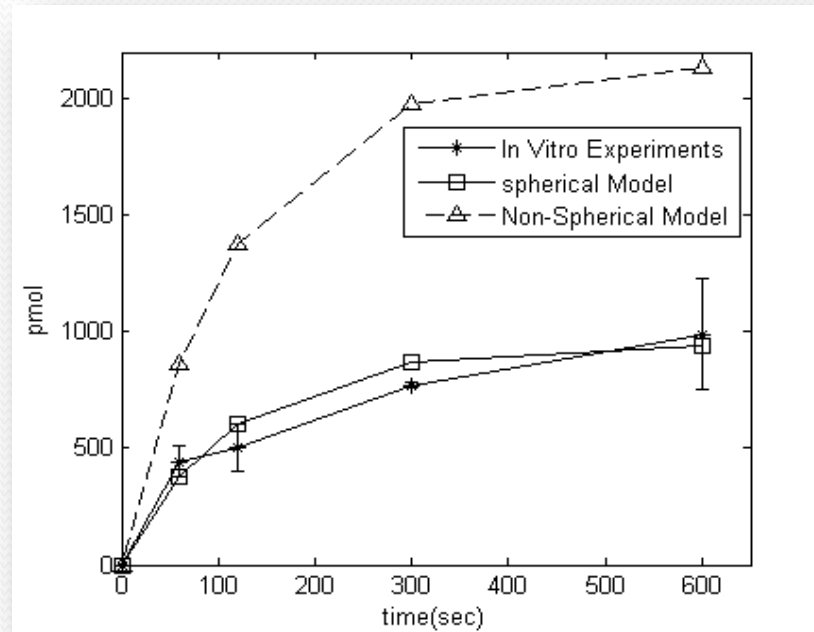
A nice agreement of the results of in vitro experiments and the spherical model, but there is a difference in the case of non spherical cell model. The reason is that, the shape of the cellular architecture has been considerably varied, which varies the concentration a lot.

Future Work

Future Work

➢ To go to higher Dimensions.

Future Work

- To go to higher Dimensions.
- To include new reaction mechanisms.

Future Work

➢ To go to higher Dimensions.

➢ To include new reaction mechanisms.

➢ To include stochastic effects.

Acknowledgments

Thank you very much