INCLUSION OF NUCLEAR ENVELOPE IN NON-SPHERICAL CELLULAR GEOMETRY

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ABSTRACT; *Mathematical modeling of drug diffusion system is a strenuous task due to the heterogeneous structure of mammalian cell. The difficulty level increases when the lipophilic compounds are taken into account. Earlier, 1D spherical shaped cell model was developed by considering spherical symmetry and further this model has been extended by adding nuclear envelope. In this paper 2D axi symmetric mathematical model is developed with non-spherical cellular geometry by inclusion of nuclear envelope that is very close to the real cellular geometry of cultured adherent cell used for in vitro experimental results. Homogenization techniques are used to reduce the complexity of cytoplasm. The numerical results obtained from non-spherical model are ratified against the in vitro experimental results.*

INTRODUCTION

It is essential to know the biology of the cell to understand the physical and chemical processes. The cell is a microscopic systemic and functional unit of living organism. The inherent features of cell are cell membrane, cytoplasm and nucleus. The cytoplasm has a very complex structure having many different organelles named as the endoplasmic reticulum, Golgi apparatus, mitochondria and the vacuole. The nucleus having nuclear membrane is encircled by a double layered membrane; named as nuclear envelope having nuclear pores on it that allow protein to pass, and the space between the membranes is known as perinuclear space.

In the presence of lipophilic compounds, the mathematical modeling of dense membranous structure in the cytoplasm is a very challenging task. Polycyclic aromatic hydrocarbons (PAHs) are a large class of chemical compounds which are formed by an incomplete burning process of organic material, which can be absorbed almost all internal organs [1,2]. These ubiquitous poisonous compounds react with DNA of the nucleus that may cause toxicity in the form of cancer [3,4]. Earlier, the spherical mathematical model was developed to scrutinize the behavior of the drug diffusion reaction procedure [5]. This model was also extended by placing the nuclear envelope in the intracellular structure [6]. The intention of these earlier developed models was to minimize the emergence of the amount of toxic compounds. In present research paper, non-spherical 2D axi symmetric mathematical model will be developed.

MATHEMATICAL MODEL

Spherical cell geometry may be a good estimation, but the cultured cells used in experimental system inhere more flat shape, where cell membrane is the only membrane that has changed the model into non-spherical shape meanwhile all other sub domains are spherical. So in present paper, we analyze the state by taking the cell shape roughly looks like a flying saucer [7].

Earlier a mathematical model was developed to study the diffusion reaction process for benzo[a]pyrene diol epoxide also known as B[a]P DE, is one of a group of PAHs, which

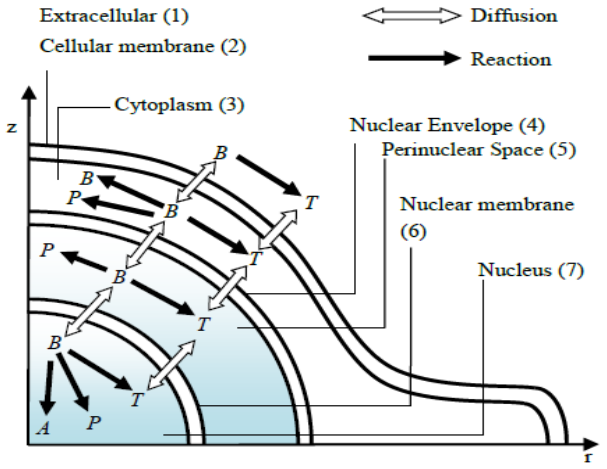


Figure 1. Showing Quarter part of Axi symmetric cellular geometry with Drug reaction diffusion process.

not only diffuse through membranes because of its lipophilic nature, but also take part in reaction-diffusion process throughout the cell, that reaches the nucleus where they affect its *DNA* resulting in damage of cell that leads to mutation, tumor and cancer. The following assumptions are made in this research paper:

1. The cell has cylindrical symmetry.
2. All the sub domains of cellular geometry are the perfect ball except cellular membrane.

Under the 1st assumption, the 3D cell geometry can be reduced into the 2D problem, while 2nd assumption is related to the change in shape of cell membrane which leads to non-spherical cellular geometry model. All other assumptions are taken into account from previous research work [5].

QUANTITATIVE MODEL

In order to describe the chemical compounds notations and symbols used in the mathematical model, the Table 1 is given and the non-spherical cellular geometry is shown in figure 1 which shows the drug diffusion and reaction process in each sub domain.

Table 1. Chemical names and their symbol

Chemical name	Symbol
B[a]P DE	*B*
Tetrols	*T*
GSH conjugate	*G*
Protein adduct	*P*
DNA adduct	*D*

The geometry of this model is composed of sub domains; extracellular medium, cellular membrane, cytoplasm, nuclear envelope, perinuclear space, nuclear membrane and nucleus. The chemical reaction of B[a]P DE *(B)* with water forms tetrols *(T)* in extracellular medium by hydrolysis process. In this model, *B* and *T* diffuse through the cellular membrane. In the sub domain of cytoplasm, *B* react with protein to form protein adducts *P*. In the presence of Glutathione S-transferases *(GSTs)*, *B* reacts with glutathione *(GSH)* to form glutathione conjugates *G*. In the chemical reaction with aqueous part *B* also forms Tetrols *(T)*. *B* and *T* again diffuse through the nuclear envelope and reach the perinuclear space where *B* reacts with water and proteins forming tetrols *(T)* and protein adduct *(P)*. Further *B* and *T* diffuse through the nuclear membrane and reach the nucleus, where the hydrolysis process takes place, forming tetrols and *B* reacts with *DNA* of nucleus forming *DNA* adducts (*D*).

Table 2. Fundamental geometric constants

Symbol	Constants	Value
V_1	Volume of one cell [m^3]	3×10^{-15}
MT	Thickness of membrane	1.127252×10^{-8}
V_N	Volume of nucleus [m^3]	10% of 3×10^{-15}
P_space	Thickness of perinuclear space [m]	30×10^{-9}

CHEMICAL REACTIONS

The chemical reactions for each sub domain is given below where the detail of each chemical rate constant and the diffusion rate for is given in Table 3.

Extracellular medium

$$B + H_2O \xrightarrow{K_T} T$$

Cytoplasm

The chemical reactions of the homogenized compounds are given by:

$$B + H_2O \xrightarrow{K_{HT}} T$$

$$B + GSH + GST \xrightarrow{K_{HG}} G$$

$$B + Protein \xrightarrow{K_{HP}} P$$

Perinuclear Space

$$B + H_2O \xrightarrow{K_T} T, \qquad B + Protein \xrightarrow{K_P} P$$

Nucleus

In nucleus *B* reacts with water, Protein and *DNA* of the nucleus and form Tetrols, protein adducts and *DNA* adducts respectively where *DNA* adducts are carcinogenic.

$$B + H_2O \xrightarrow{K_T} T, \quad B + Protein \xrightarrow{K_P} P, \quad B + DNA \xrightarrow{K_D} D$$

GOVERNING EQUATIONS

The transportation of the species is defined by concentration in each domain. An index *"i"* is used for the concentration to differentiate within sub domains. B_i and D_i are the concentration and diffusion coefficient of B[a]P DE for the i^{th} sub domain respectively.

1st Sub domain (Extracellular medium)

$$\frac{\partial B_1}{\partial t} = \nabla.(D_1 \nabla B_1) - K_T B_1 \qquad (1)$$

$$\frac{\partial T_1}{\partial t} = \nabla.(D_1 \nabla B_1) + K_T B_1 \qquad (2)$$

2nd, 4th and 6th Sub domains (Cell membrane, Nuclear envelope & Nuclear membrane)

In all above mentioned sub domains *B* and *T* only diffuse through their respective membranes such as:

$$\frac{\partial B_i}{\partial t} = \nabla.(D_i \nabla B_i) \qquad (3)$$

$$\frac{\partial T_i}{\partial t} = \nabla.(D_i \nabla T_i) \qquad (4)$$

i = 2, 4, 6

3rd Sub domain (Cytoplasm)

The presence of thin layers of water and lipids make the structure of cytoplasm more complex. The model becomes computationally expensive if a diffusion reaction system is observed by each organelle. Effective equations are acquired in [5] to reduce the complexity of model by implementing homogenization techniques. The homogenized diffusion coefficient for B[a]P DE and tetrols formation is represented by D_{BH} and D_{TH} respectively. The governing equations for the cytoplasm sub domain can be derived similarly as done earlier for subdomain 1.

5th Sub domain (Perinuclear space)

The perinuclear space contains protein and water. In the chemical reaction T and Protein adducts are also formed. The governing equations for this sub domain can be derived similarly as done earlier for subdomain 1.

7th Sub domain (Nucleus)

The governing equations for this sub domain can be derived similarly as done earlier for subdomain 1.

Boundary conditions

The assumption is made that the outer boundary of the cell is solitary, so the Neumann boundary condition holds at the outer boundary:

$$\frac{\partial B_1}{\partial n_1} = 0$$

Also the *G* and *D* are restricted to the 3rd & 7th sub domains respectively.

$$\frac{\partial G_3}{\partial n_3} = 0 \qquad \frac{\partial D_5}{\partial n_5} = 0$$

Initial Conditions

The initial value of all species is set to zero except B_1 i.e. $B_1=B_0$

Interface conditions

Interface conditions are needed at the boundary between two phases and partition coefficient is used for the transportation of concentration from one phase to another. In this research work *B* and *T* diffuse through the membrane from one sub domain to another. Conservation of mass gives rise to the equation of continuity between the different sub domains which means that the inflow is equal to outflow where an outward normal vector is denoted by n_i of the i^{th} sub domain where:

$$n_1 = -n_2 \qquad n_3 = -n_2 \qquad n_6 = -n_7$$

The interface conditions are given by:

$$S_1 = K_{PS} S_2 \qquad D_1 \frac{\partial B_1}{\partial n_1} = -D_2 \frac{\partial B_2}{\partial n_2}$$

$$S_5 = K_{PS} S_4 \qquad D_5 \frac{\partial B_5}{\partial n_5} = -D_4 \frac{\partial B_4}{\partial n_4}$$

$$S_7 = K_{PS} S_6 \qquad D_7 \frac{\partial B_7}{\partial n_7} = -D_6 \frac{\partial B_6}{\partial n_6}$$

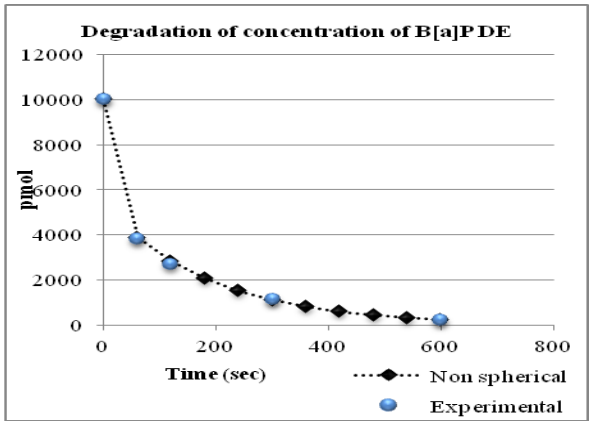
Table 3. Chemical constants of the model [5].

Symbol	Constant	Value
D_1	Diffusion rate in extracellular medium [m^2s^{-1}]	10^{-9}
D_2, D_4, D_6	Diffusive rate in membrane [m^2s^{-1}]	10^{-12}
D_5, D_7	Diffusion rate in nucleus & perinuclear space [m^2s^{-1}]	2.5×10^{-10}
K_{PB}	Partition coefficient for B	1.2×10^{-3}
K_{PT}	Partition coefficient for T	8.3×10^{-3}
K_{GH}	Formation rate of GSH conjugate in homogenized cytoplasm [s^{-1}]	0.242908
K_{TH}	Formation rate of tetrols in homogenized cytoplasm [s^{-1}]	0.005744
K_P	Formation rate of protein adducts [s^{-1}]	0.3256
K_D	Formation rate of DNA adducts [s^{-1}]	6.2×10^{-3}
K_T	Tetrols formation rate [s^{-1}]	7.7×10^{-3}
K_{PH}	Protein adduct formation rate in homogenized cytoplasm [s^{-1}]	0.242908
D_{BH}	Diffusion rate in cytoplasm for B [m^2s^{-1}]	4.06×10^{-10}
D_{TH}	Diffusion rate in cytoplasm for T [m^2s^{-1}]	2.42×10^{-10}
σ_{BH}	Scaling factor for B	212.39
σ_{TH}	Scaling factor for T	31.34

RESULTS AND DISCUSSIONS

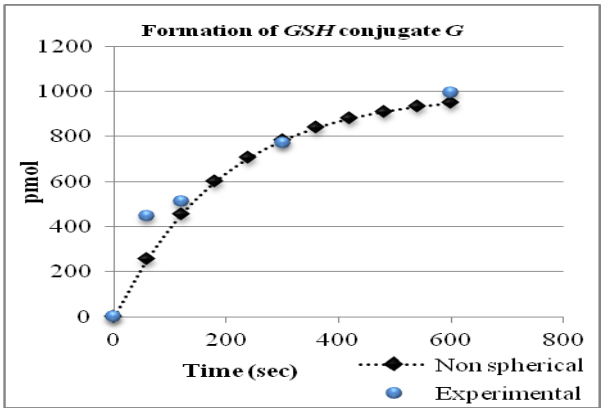
This model is executed in Comsol Multiphysics using the Reaction Engineering Lab. This software solves the problems by using finite element. System of linear PDEs is solved using UMFPACK method. UMFPACK method is based on the principle of the LU decomposition method [8].

The Non-spherical mathematical model is compared with the experimental in vitro results by using graphs. The comparison of the concentration of B[a]P DE in graph (A) which shows that the results of the model as well as the experimental results are quite nice and approximately same.



Graph (A). Shows the comparison of concentration of B[a]P DE in Extracellular region.

The graph B shows the comparison of the formation of *GSH* conjugates of the present non-spherical model and the experimental data where we see a nice agreement in the results.



Graph (B). Shows the comparison of the formation of *GSH* conjugate of Non-spherical model & Experimental in vitro results

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