A SIMPLIFIED SPHERICAL CELL MODEL WITH THE INCLUSION OF NUCLEAR ENVELOPE FOR THE REACTION-DIFFUSION MECHANISM

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ABSTRACT: *Aspiration of this particular work is to recapitulate the effects of harmful lipophilic chemical compounds in a V79 mammalian cell. A detailed mathematical model, with the presence of plasma/nuclear membranes, was developed earlier to draw information about toxicity level of these chemical compounds in different subdomains of the cell. Inclusion of plasma/nuclear membranes in the model made the model complex and multiscale with reference to space. To diminish the level of intricacy of detailed model, a new simplified model is developed here by replacing plasma/nuclear membranes by construing membrane flux employing Fick's law of diffusion. Results obtained from newly developed simplified model are compared with the results of previously developed detailed model to highlight the exclusion effect of plasma/nuclear membranes on toxicity level.*

INTRODUCTION

The vital element of our life is known as a cell and is generally resides of plasma membrane, cytoplasm, nuclear envelop, nuclear membrane and nucleus. Our body is composed of trillions of cells and these cells carry out a number of intricate tasks like soaking up nutrients from food, fabricate antibodies, and transmit signals from our brain to the whole body [1,2]. So, a well-functioned cell is indispensable for life. Polycyclic aromatic hydrocarbons (PAHs) are harmful lipophilic chemical compounds that are ever present in the environment and can enter in our body through breathing or direct skin exposure to these compounds and affect our cells. They enter in a cell through cellular membrane where they react in different subdomains of the cell to produce toxic compounds and finally reach to the nucleus where they react with DNA to produce DNA adducts [3]. A detailed model was developed previously with the presence of plasma/nuclear membranes to draw information about concentrations of these toxic compounds in different subdomains of the cell [4]. Presence of these plasma/nuclear membranes made the model complex and multiscale with respect to space. Our focal point is to develop a new simplified model in this paper that can draw same information with less time and computational labor. This can be done by replacing plasma/nuclear membranes using membrane flux technique employing Fick's law of diffusion.

MATHEMATICAL MODEL

Mathematical model presented in this paper describes the reaction-diffusion system of chemical compound Benzo(a)pyrene diol epoxide (BPDE); denoted by *C* here, in a mammalian cell. 2D axi-symmetric detailed model was developed previously with the presence of plasma/nuclear membranes. Membranes act as protective reservoirs but their presence makes the model multiscale with reference to space. So, a new simplified model is constructed here by replacing plasma/nuclear membranes by construing membrane flux employing Fick's law of diffusion [5].

Figure-1 shows the reaction and diffusion of chemical compound BPDE in different subdomains of the cell. In extracellular medium, which is domain 1, BPDE forms tetrols after undergoing the hydrolysis process and diffuse to the second domain that is cytoplasm. In cytoplasm, BPDE *(C)* forms tetrols *(T)*, protein adduct *(A)* and GSH conjugation

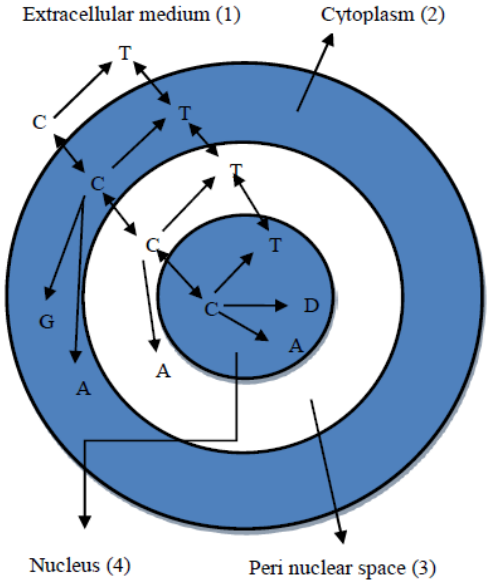

Fig-1, computational domains and reactions taking place within the cell

(G) after reacting with water, protein and glutathione *(GSH)* in the presence of glutathione transferases *(GSTs)* respectively and diffuse to the peri nuclear space. In peri nuclear space *C* reacts with protein resulting in formation of protein adduct *A* and finally diffuse to the nucleus where it reacts with water, protein and DNA and produce tetrols, protein adduct and DNA adduct respectively. DNA adducts can cause extreme damage to DNA. These dented cells put off the normal control system of cell overgrowth and these cells tend to grow with additional characteristics like change in the cell structure and fabricate new enzymes.

BASIC ASSUMPTIONS

To develop the modeling strategy we use the assumptions described in [6]. Following assumption is mainly related to the present work.

- Molecules exhibit normal flux for transportation through one domain to another and their tangential component is negligible.

Under the above assumption, the plasma/nuclear membranes will be replaced by construing membrane flux employing Fick's law of diffusion. Remaining geometric properties will

be identical with the geometrical properties of the previous detailed model.

Table – 2, shows fundamental geometric constants

Constants	Value	Symbol
Volume of one cell	3×10^{-15}	V_1
Thickness of membrane	1.127252×10^{-8}	Mt
Volume of nucleus	10% of V_1	V_n
Volume of cell medium	10^{-5}	V_w
Thickness of peri nuclear space	30×10^{-9}	Pnsize

CHEMICAL REACTIONS USED FOR SIMPLIFIED MODEL

The distribution of the material in each subdomain is defined by concentration. To distinguish the representation of concentration in each domain index "i" is used where $i = 1,2,3,4$. For example C_1 is used to represent the concentration of BPDE in extracellular medium. D is symbolized for diffusion coefficient and K_T is used for reaction rate constant.

SUBDOMAIN-1

Chemical reactions for each subdomain are given below and details of the rate constants are given in table – 3.

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

where *T* stands for Tetrols.

Its governing equations are as follows:

$$\frac{\partial C_1}{\partial t} = \nabla.(D_E \nabla C_1) - K_T C_1 ,$$

$$\frac{\partial T_1}{\partial t} = \nabla.(D_E \nabla T_1) + K_T C_1,$$

where *D* is the diffusion. Similarly, we can get the equations for the other subdomains

Table - 3, chemical constants for the model [6].

Symbol	Constant	Value
D_E	Rate of diffusion in extra cellular medium	10^{-9}
D_P, D_N	Rate of diffusion in nucleus and pn space	2.5×10^{-10}
D_{CM}, D_{PM}, D_{NM}	Diffusion rate in cellular/peri nuclear/nuclear membrane	10^{-12}
K_{PC}	Partition coefficient for *C*	1.2×10^{-3}
K_{PT}	Partition coefficient for *T*	8.3×10^{-3}
K_{GH}	Formation rate of GSH conjugate in homogenized cytoplasm	0.242908
K_{TH}	Formation rate of tetrol in homogenized cytoplasm	0.005744
K_A	Formation rate of protein adduct	0.3256
K_D	DNA adduct formation rate	6.2×10^{-3}
K_T	Tetrol formation rate	7.7×10^{-3}
K_{AH}	Protein adduct formation rate in homogenized cytoplasm	0.242908
D_{2C}	Diffusion rate in cytoplasm for *C*	4.06×10^{-10}
$\sigma_{C,H}$	Scaling factor for *C*	212.39
$\sigma_{T,H}$	Scaling factor for *T*	31.34
D_{2T}	Diffusion rate in cytoplasm for *T*	2.42×10^{-10}

SUBDOMAIN-2

Cytoplasm has a very complex and dense structure and it adds to the difficulty in model construction. So, homogenization technique is being used for the numerical treatment of cytoplasm and effective equations are used which were derived earlier in [6]. During homogenization process, effective diffusion constant and effective reaction rates as summarized in table- 2.

Following are the governing chemical reactions used for cytoplasm:

$$C + H_2O \xrightarrow{K_{TH}} T$$

$$C + Protein \xrightarrow{K_{AH}} A$$

$$C + GSH \xrightarrow{K_{GH}} G$$

SUBDOMAIN-3

Chemical reactions used for perinuclear space are:

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

$$C + Protein \xrightarrow{K_A} A$$

SUBDOMAIN-4

In this subdomain, *C* reacts with water to form *T*. Chemical reactions used for nucleus are:

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

$$C + Protein \xrightarrow{K_A} A$$

$$C + DNA \xrightarrow{K_D} D$$

INITIAL AND BOUNDARY CONDITIONS

It is assumed that the outer boundary of the cell is isolated which means there is no outward flux therefore, Neumann boundary condition holds

$$\frac{\partial S_1}{\partial \mathbf{n_1}} = 0, \qquad \text{where } S = C, T$$

Initially only *C* is present where all other species *T*, *G*, *P* and *D* are zero. So, the concentration at initial stage is given by

$$C = C_0$$

INTERFACE CONDITIONS

For the sake of transportation, the flux between two subdomains is defined in the following way.

Flux between extra cellular medium and cytoplasm:

$$\boldsymbol{D_1}\frac{\partial S_1}{\partial \mathbf{n_1}} = \frac{D_{CM}}{K_{PS}\delta}(S_{2,h} - S_1) \quad \boldsymbol{D_{2C}}\frac{\partial S_2}{\partial \mathbf{n_2}} = \frac{D_{CM}}{K_{PS}\delta}(S_1 - S_{2,h})$$

Flux between cytoplasm and peri nuclear space

$$\boldsymbol{D_{2C}}\frac{\partial S_{2,h}}{\partial \mathbf{n_2}} = \frac{D_{PM}}{K_{PS}\delta}(S_3 - S_{2,h}) \quad \boldsymbol{D_3}\frac{\partial S_3}{\partial \mathbf{n_3}} = \frac{D_{PM}}{K_{PS}\delta}(S_{2,h} - S_3)$$

Flux between peri nuclear space and nucleus

$$\boldsymbol{D_3}\frac{\partial S_3}{\partial \mathbf{n_3}} = \frac{D_{NM}}{K_{PS}\delta}(S_4 - S_3) \qquad \boldsymbol{D_4}\frac{\partial S_4}{\partial \mathbf{n_4}} = \frac{D_{NM}}{K_{PS}\delta}(S_3 - S_4)$$

Where $S_i = C_i, T_i; i = 1,2,3,4$ and δ denotes membrane thickness. The motivation of this model is to investigate whether this model produce approximately same results as of detailed model.

EXECUTION OF MODEL IN COMSOL MULTIPHYSICS

Comsol Multiphysics is used for model implementation. This software uses finite element method for solution (Stockholm, 2008). To solve the system of linear PDEs, UMFPACK method is used. UMFPACK method works on the principle of LU decomposition method [7, 8].

RESULTS AND DISCUSSION

Our main objective for developing new simplified model was to reduce the complexity of the detailed model and to draw same information about the concentrations of harmful chemical compounds in different subdomains of the cell with

less time; therefore the comparison between newly developed simplified model and previously developed detailed model is given below.

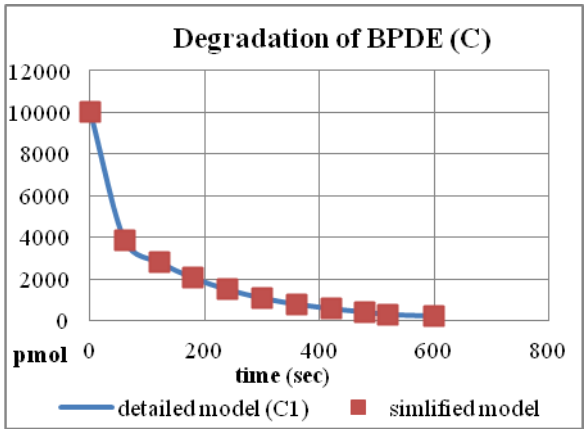

Figure (A) - comparison for degradation of BPDE between detailed and simplified model in extracellular egion.

Figure (A) shows comparison for BPDE between detailed and simplified model and it is observable that results for both the models are approximately same which means that our new model has provided same results with less time and computational labor.

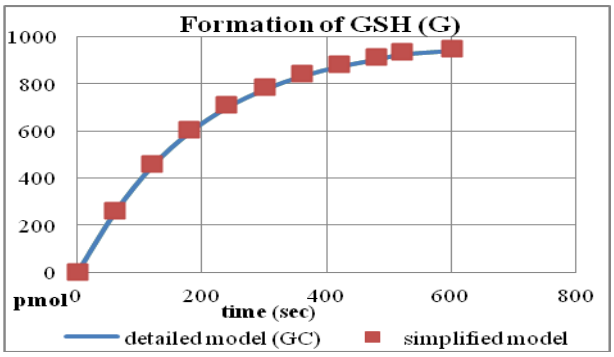

Figure (B) - comparison for formation of GSH (*G*) in cytoplasmic region.

Figure (B) shows the results for GSH in cytoplasmic region and it is apparent form the figure that results for both the models are similar.

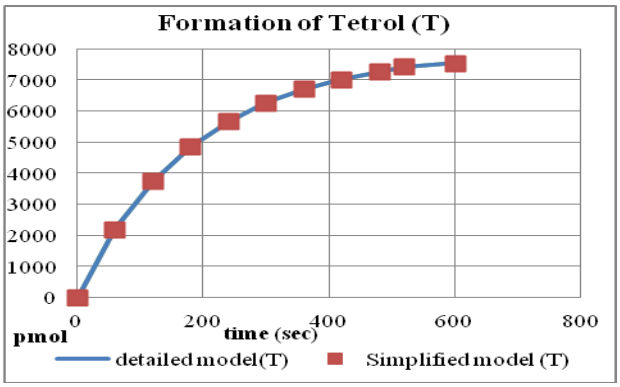

Figure (C) – comparison for formation of tetrols (*T*)

Figure (C) shows the comparison for formation of tetrols for both the models and it is obvious form the figure that both the models yield similar results.

CONCLUSION

Our focal point for developing new simplified model was to reduce the complexity of previously developed detailed model and to extract same information about the toxicity level of lipophilic chemical compounds in different subdomains of the cell in less time. The comparison for the results of both models is shown above and it turns out to be similar. This means that if we replace plasma/nuclear membranes by construing membrane flux employing Fick's law of diffusion, then it has no effect on toxicity level of chemical compounds and therefore detailed spherical model can be replaced by simplified spherical model for less time consumption and computational ease.

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