

**COMPARTMENTAL SYSTEM OF REACTION AND DIFFUSION  
MECHANISM OF CARCINOGENIC POLYCYCLIC AROMATIC  
HYDROCARBONS IN MAMMALIAN CELL**

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**Abstract:**

The effect of ubiquitous carcinogen pollutants in mammalian cells is the source of several problems. Carcinogenic compounds present in environment as persistent pollutants become the root of carcinoma, toxicity or cancer when they react with hereditary material. To study the cellular exposure of reaction and diffusion mechanism of these carcinogenic compounds in mammalian V79 cell earlier, mathematical modeling with the set of spatially distributed system (PDEs) was developed. In this paper, compartmental modeling approach have used with the inclusion of perinuclear space. The system reduced the spatially distributed, i.e., Partial differential equations (PDEs) system to the temporal, i.e., Ordinary differential equations (ODEs) system, thus reducing the complexity and computational cost. The compartmental system has been simulated computationally in Virtual Cell using homogenization technique. The quantitative consideration of the results of spatially distributed system and temporal system shows a nice agreement. We can extend the compartmental system adding more compartments, reaction and diffusion processes.

**Keywords:** Carcinogenic, Cell, Reaction and Diffusion, Homogenization.

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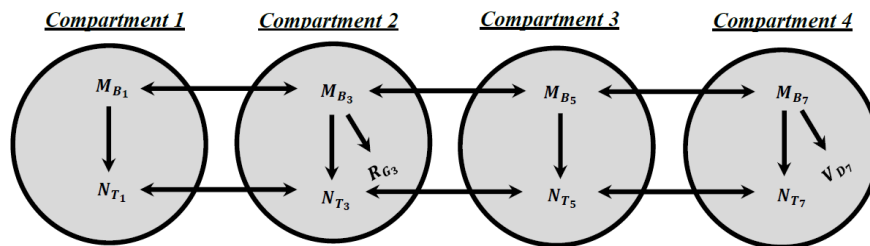
## 1. Introduction

Intra-cellular modeling of reaction and diffusion mechanism is a challenging task due to complex cell architecture. The complexity in the biological system makes the involvement of mathematics essential as many mathematical models are increasingly used to deal with these problems. Schematically, cell is composed by cell membrane, cytoplasm, nuclear envelope, perinuclear space, nuclear membrane and nucleus [1]. Polycyclic aromatic hydrocarbons are the potent atmospheric pollutants produced due to incomplete combustion of organic substances. BPDE (Benzo[a]pyrene) is one of the reactive carcinogenic compounds of PAHs which react with genetic material DNA of the cell and may turn into tumor or cancer [2,3]. In the current study, compartment modeling approach is used for the intracellular dynamics of the carcinogenic compounds of PAHs; it is a standard modeling approach used to describe reaction and transportation mechanism in biological system [4-7]. In addition to the system developed in [8,9] perinuclear space has been added. The complete system of reaction and diffusion processes gives rise to a system of temporal equations (ODEs). The purpose of the development of compartmental system is to reduce the computational expenses and complexity of the set of equations as compared to the spatially distributed system developed earlier [10]. We are considering here four subdomains for our compartmental system with well mixed material namely extracellular medium, cytoplasm, perinuclear space and nucleus, whereas the membrane flux have been taken the place of cell membrane, nuclear envelope and nuclear membrane using the Fick's Law and law of mass action. To make our compartmental system numerically treatable the homogenization approach is also used here for handling complex compartment of cell (i.e. cytoplasm) which was derived in [8]. Cytoplasm includes cytosol and many small organelles such as endoplasmic reticulum, Golgi apparatus, microtubules, ribosomes, mitochondria etc., perform different functions within the cell, and due to the presence of these tiny organelles it is a very difficult task to model them separately. Therefore, an effective equation attained by homogenization approach considerably decreases the heterogeneity of the system. The other compartments i.e. extracellular medium, perinuclear space and nucleus can be treated easily using modern computational simulations for solving temporal equations as these compartments have a simple geometry as compared to the cytoplasm. A part of this research work was also published in [13].

## 2. Experimental

### Compartmental System

The system delineates the uptake of diffusion and reaction dynamics of lethal compounds in mammalian cell. Compartmental system accommodates extracellular medium, cytoplasm, perinuclear space and nucleus. Extracellular medium is the outside environment of the cell consists of water. Cytoplasm is that segment of cell between cell membrane and nuclear envelope that include cellular organelles and cytosol. Nuclear envelope is a barrier which monitors the import and export of molecules in and outside the nucleus. Nucleus carries ancestral material and is encompassed by nuclear membrane [1].



**Fig. 1.** Compartmental System demonstrating reaction- diffusion process in and outside the mammalian cell. The model consists of mainly four compartments.

One of the prototypes carcinogenic chemical compounds of PAHs is BPDE (Benzo pyrene diol epoxide) which was earlier used in [8, 9] is denoted as  $M_B$  in this mathematical system. BPDE undergo hydrolysis process within and outside the cell where water is available to form tetrols.

**Table I:** Species and process representation

Benzo[a]pyrene diol epoxide (BPDE)	$M_B$
Benzo pyrene tetrols (BPT)	$N_T$
GSH conjugate	$R_G$
DNA adducts	$V_D$
Diffusion	↔
Reaction	→

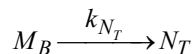
Here tetrols are denoted as  $N_T$ .  $M_B$  reacts with water to yield  $N_T$  in extracellular medium. There is no reaction taking place in membranes. When  $M_B$  and  $N_T$  come to the second compartment (cytoplasm),  $M_B$  reacts with water to yield  $N_T$  (tetrols), secondly  $M_B$  reacts with glutathione transferees to yield  $R_G$  (glutathione conjugate). Again,  $M_B$  and  $N_T$  come to the perinuclear space by diffusing through nuclear envelope and here  $M_B$  undergoes hydrolysis process to yield  $N_T$ . Lastly, when  $M_B$  and  $N_T$  reach the nucleus by diffusion where  $M_B$  reacts with water to yield  $N_T$  and  $M_B$  reacts with DNA resulting in  $V_D$  (DNA adduct) thereby engender toxicity, tumor or cancer. Thus our compartmental modeling technique provides a tool to investigate the fate of carcinogenic compounds in mammalian cells. An index is added to distinguish the concentrations between the different compartments. For example we denote  $M_B$  in extracellular medium by  $M_{B_1}$ . Fig 1 demonstrates the compartmental system in and outside the mammalian cell.

**Governing Equations**

Set of ordinary differential equations obtained from compartment modeling is given as:

➤ **Compartment 1 (Extracellular Medium)**

The carcinogenic chemical compound  $M_B$  (BPDE) undergoes hydrolysis process in this compartment and the following reaction takes place



The above reaction gives rise to the following system of ordinary differential equations:

$$V_1 \frac{d}{dt} M_{B_1} = \frac{DA_1}{K_{P,M_B} \delta} \left( \frac{M_{B_3,eff}}{\sigma_{M_B}} - M_{B_1} \right) - V_1 k_{N_T} M_{B_1}$$

$$V_1 \frac{d}{dt} N_{T_1} = \frac{DA_1}{K_{P,N_T} \delta} \left( \frac{N_{T_3,eff}}{\sigma_{N_T}} - N_{T_1} \right) + V_1 k_{N_T} M_{B_1}$$

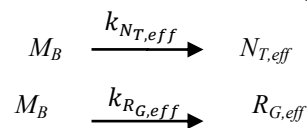
where,  $D$  is the diffusion and  $\delta$  is the thickness of membranes.  $K_{P,M_B}$ ,  $K_{P,N_T}$  are the partition coefficients for BPDE and tetrols.  $k_{N_T}$  is the formation rate constant for tetrols.  $V_1$  is the volume of extracellular medium.  $M_{B_1}$ ,  $N_{T_1}$  are the concentrations of BPDE and BPT respectively outside the cell. The above differential equations are obtained using the Fick's first law of diffusion and the law of mass action. The first part represents the diffusion part whereas the second part of the equations represents the reaction part.

**Table II:** Geometry constants for the system.

Constants	Value	Units
Volume of extracellular medium ( $V_1$ )	663666.67	$\mu\text{m}^3$
Volume of one cell	3000	$\mu\text{m}^3$
Volume of cytoplasm ( $V_2$ )	2690.9662	$\mu\text{m}^3$
Volume of perinuclear space ( $V_3$ )	9.033755368	$\mu\text{m}^3$
Volume of nucleus ( $V_4$ )	300	$\mu\text{m}^3$
Area of cell membrane ( $A_1$ )	1005.9235	$\mu\text{m}^2$
Area of nuclear envelope ( $A_2$ )	222.2385791	$\mu\text{m}^2$
Area of nuclear membrane ( $A_3$ )	217.8977843	$\mu\text{m}^2$
Perinuclear space thickness	0.003	$\mu\text{m}$
Membrane thickness	0.0113	$\mu\text{m}$

### ➤ Compartment 2 (Cytoplasm)

Two types of reactions occur in this compartment.  $M_B$  reacts with water to form  $N_{T,eff}$  (tetrols), secondly  $M_B$  reacts with glutathione transferees to form  $R_{G,eff}$  as shown below:



These chemical reactions give rise to the following equations:

$$V_2 \frac{d}{dt} M_{B_3} = \frac{DA_1}{K_{P,M_B} \delta} \left( M_{B_1} - \frac{M_{B_3,eff}}{\sigma_{M_B,eff}} \right) + \frac{DA_2}{K_{P,M_B} \delta} \left( M_{B_5} - \frac{M_{B_3,eff}}{\sigma_{M_B,eff}} \right) - V_2 \left( \frac{k_{N_T,eff} + k_{R_G,eff}}{\sigma_{M_B,eff}} \right) M_{B_3}$$

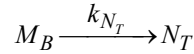
$$V_2 \frac{d}{dt} N_{T_3} = \frac{DA_1}{K_{P,N_T} \delta} \left( N_{T_1} - \frac{N_{T_3,eff}}{\sigma_{N_T,eff}} \right) + \frac{DA_2}{K_{P,N_T} \delta} \left( N_{T_5} - \frac{N_{T_3,eff}}{\sigma_{N_T,eff}} \right) + \frac{k_{N_T,eff}}{\sigma_{M_B,eff}} M_{B_3}$$

$$V_2 \frac{d}{dt} R_{G_3} = V_2 \frac{k_{R_G,eff}}{\sigma_{M_B,eff}} M_{B_3}$$

where  $\sigma_{M_B,eff}$ ,  $\sigma_{N_T,eff}$  are the scaling factors for BPDE.  $k_{N_T,eff}$  and  $k_{R_G,eff}$  are the formation rate constants for  $N_T$  and  $R_G$  respectively in homogenized cytoplasm.

### ➤ Compartment 3 (Perinuclear Space)

In this compartment  $M_B$  reacts with water to form  $N_T$ .



The above chemical reactions give rise to the following equations:

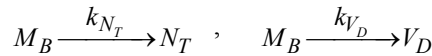
$$V_3 \frac{d}{dt} M_{B_5} = \frac{DA_2}{K_{P,M_B} \delta} \left( \frac{M_{B_3,eff}}{\sigma_{M_B,eff}} - M_{B_5} \right) + \frac{DA_3}{K_{P,M_B} \delta} (M_{B_7} - M_{B_5}) - V_3 k_{N_T} M_{B_5}$$

$$V_3 \frac{d}{dt} N_{T_5} = \frac{DA_2}{K_{P,N_T} \delta} \left( \frac{N_{T_3,eff}}{\sigma_{N_T,eff}} - N_{T_5} \right) + \frac{DA_3}{K_{P,N_T} \delta} (N_{T_7} - N_{T_5}) + V_3 k_{N_T} M_{B_5}$$

where  $V_5$  is the volume of perinuclear space and  $A_2$  is the area of nuclear envelope.

### ➤ Compartment 4 (Nucleus)

In this compartment  $M_B$  takes place two types of chemical reactions. Firstly  $M_B$  reacts with water to form  $N_T$  and  $M_B$  reacts with DNA resulting in  $V_D$  (DNA adduct).



The following equations are obtained from the above chemical reactions:

$$V_4 \frac{d}{dt} M_{B_7} = \frac{DA_3}{K_{P,M_B} \delta} (M_{B_5} - M_{B_7}) - V_4 (k_{N_T} + k_{V_D}) M_{B_7}$$

$$V_4 \frac{d}{dt} N_{T_7} = \frac{DA_3}{K_{P,N_T} \delta} (N_{T_5} - N_{T_7}) + V_4 k_{N_T} M_{B_7}$$

$$V_4 \frac{d}{dt} V_{D_7} = V_4 k_{V_D} M_{B_7}$$

Where,  $V_4$  is the volume of nucleus and  $A_3$  is the area of nuclear membrane.

### Initial Condition

We assume that  $M_B$  (BPDE) at initial time is non-zero and all other chemical species are zero.

### 1. Results and Discussion

We are presenting here a compartmental system demonstrating the diffusion and reaction mechanism of carcinogenic compounds in cell, which is numerically treated. The system is simulated in Virtual Cell [11] for the time span of 1200 seconds. The chemical parameters used in the model are given in Tab 3 [8].

symbol	constant	value
$k_{N_T}$	$N_T$ (Tetrols) formation rate	0.0077
$k_{V_D}$	$V_D$ (DNA adduct) formation rate	0.0062
$D$	Diffusion in membranes	$10^{-12}$
$K_{P,M_B}$	Partition coefficient for $M_B$	0.0012
$K_{P,N_T}$	Partition coefficient for $N_T$	0.0083
$k_{R_G,eff}$	$R_G$ (GSH conjugate) formation rate in homogenized cytoplasm	0.242908
$k_{N_T,eff}$	$N_T$ (Tetrols) formation rate in homogenized cytoplasm	0.005744
$\sigma_{M_B,eff}$	Scaling factor for $M_B$	212.39
$\sigma_{N_T,eff}$	Scaling factor for $N_T$	31.34



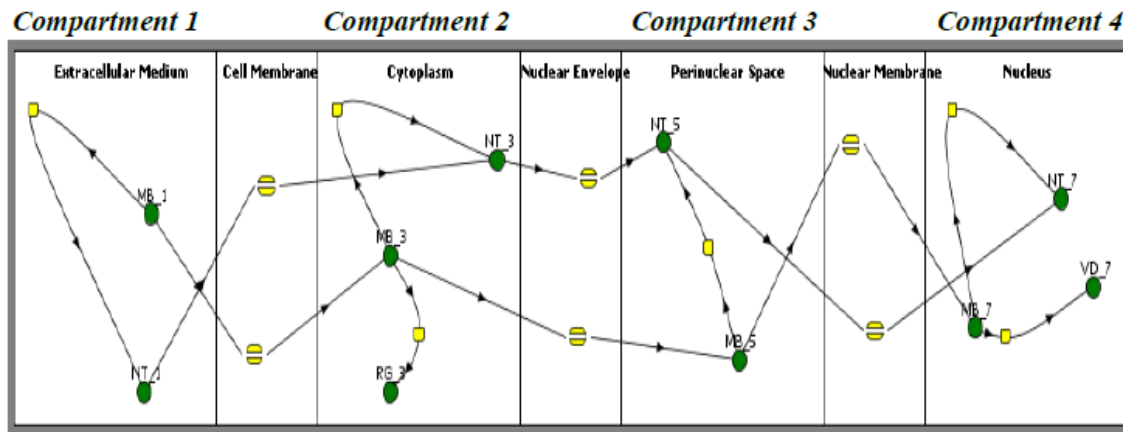
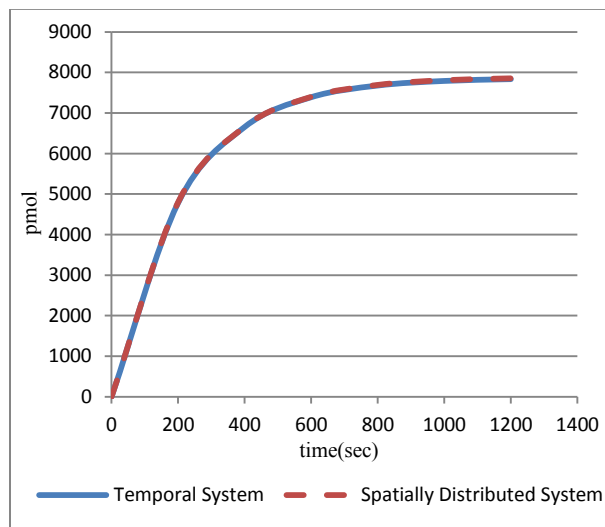
Computational simulations provide us a framework to treat our compartmental system with numeric based tools, manage the set of temporal (ODEs) equations quickly and get better results. Virtual Cell is the distinctive web-based computational software for construction and simulation of cellular dynamics. It provides mathematicians and cellular biologists an environment where they can create simple or complex models not only as a temporal model but also as a spatially distributed model [12]. Fig. 2 portrays the diffusion and reaction mechanism within and outside the cell in four compartments image taken from the virtual cell. The green icon ● is indicating chemical species,  is the flux in membranes, and  is showing reactions in all compartments. Comparison of the numerical results of temporal system shows reasonable agreement with the spatially distributed system as shown in figures 3, 4, 5 and 6.

Fig. 3 demonstrates the formation of  $N_T$  (BPT) in extracellular medium and fig. 4 demonstrates the degradation of  $M_B$  (BPDE) in and outside the cell and both figure exhibit that there is no difference between the numerical results of spatially distributed system and temporal system.

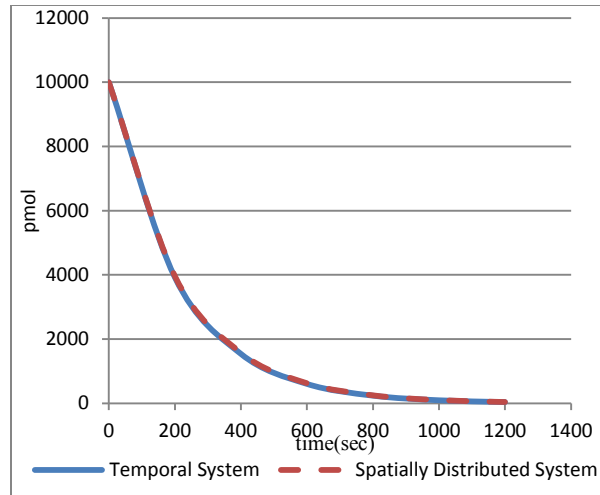


**Fig. 2.** Virtual cell image of reaction and diffusion process. The model was implemented in a freely available software named VCell. In the model, reaction phenomena is only available in aqueous compartments. The membranous parts do not have reaction phenomena; only diffusion part takes place there.



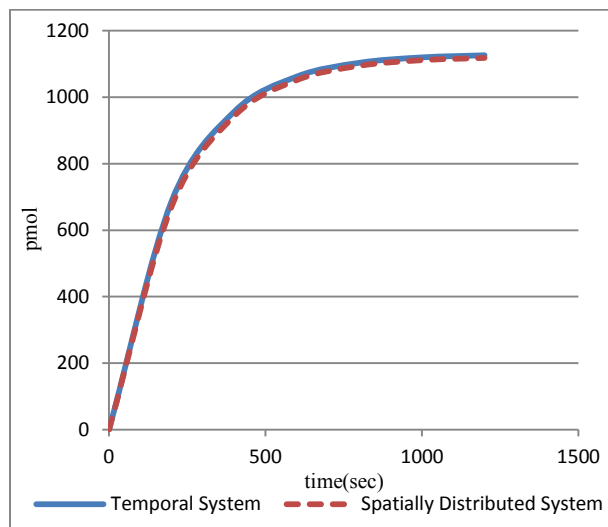
**Fig. 3.** Formation of  $N_T$  (BPT) in extracellular medium. The comparison was made between the spatially distributed and temporal model.

Similarly fig. 5 demonstrates the formation of  $R_G$  (GSH conjugate) in cytoplasm. The temporal system displays a nice agreement with the results of spatially distributed system, both results demonstrating the rapid initial formation of  $R_G$  reaching about 1100 pmol after 1200 seconds.



**Fig. 4.** Degradation of  $M_B$  (BPDE) in complete cell. The comparison was made between the spatially distributed and temporal model.

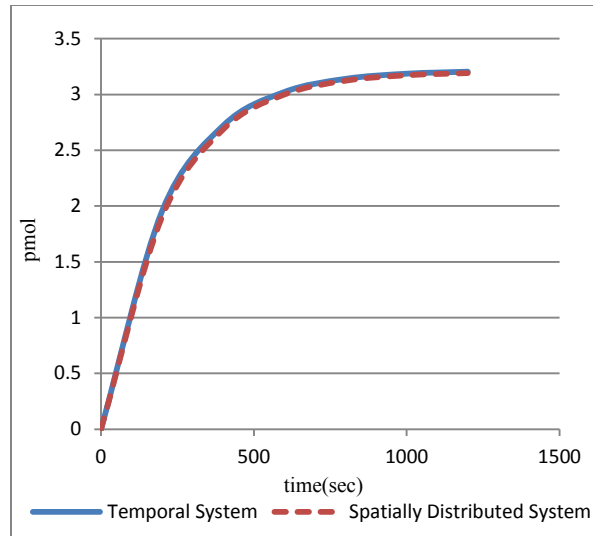
Fig. 6 demonstrates the formation of  $V_D$  (DNA adduct) in nucleus and the results of spatially distributed system and temporal system displays a rapid initial formation of  $V_D$  reaching about 3.20 pmol after 1200 seconds. Since the numerical results of spatially distributed system have already been compared against the experimental results [6] therefore the spatially distributed system was only compared with the temporal system, where the nice agreement between the numerical results really justifies the approach of this current model.



**Fig. 5.** Formation of  $R_G$  (GSH conjugate) in cytoplasm. The comparison was made between the spatially distributed and temporal model.

To make our compartmental system numerically treatable mathematical approach of homogenization was used which reduced the computational expenses and complexity and allowed us to treat the ordinary differential equations easily for numerical solution.





**Fig. 6.** Formation of  $V_D$  (DNA adduct) in nucleus. The comparison was made between the spatially distributed and temporal model.

The main assumption for the well-mixed compartmental system is that the diffusion is much fast as compared to the reactions. The above results show that the compartmental system has the potential to depict mechanism of reactive and carcinogenic compound (benzo pyrene diol epoxide).

## 2. Conclusions

We conclude that in future we may replace the system of partial differential equations with the system of ordinary differential equations because the temporal (ODEs) model reduces the degrees of freedom. It also reduces the complexity and computational expenses of the system as compared to the spatially distributed (PDEs) system. Later, this model can be further developed by adding more reaction and diffusion processes, and also by adding new sub-domain, e.g., crista and matrix of mitochondria.

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