MATHEMATICAL MODELING OF REACTION-DIFFUSION MECHANISM OF PAH DIOL EPOXIDES IN A CELL

Q. A. Chaudhry, M. O. Ahmad, F. Ashraf, R. Ashraf and N. A. Chaudhry

Department of Mathematics University of Engineering & Technology, Lahore 54890, Pakistan
*Corresponding Author: alicq@kth.se

ABSTRACT: Mathematical modeling of reaction-diffusion mechanism of biological cell is facing severe problems. Earlier, we developed a mathematical model describing the intracellular dynamics. The resulting system of PDEs was handled numerically. Later, this model was reduced to a system of ODEs using standard compartment modeling approach, and was solved using BDF. In this study, we solved the system of ODEs using a semi analytical scheme known as Differential Transformation Method. The degradation of DEs in extra-cellular medium, and formation of DEs in cytoplasm and nucleus was observed, where the results of the model using DTM were compared against the results obtained from numerical techniques, which showed a very nice agreement. The main feature of DTM was that it gave a better solution. Therefore, one needs to have such a method, which may give a better solution with less error.

Key words: Reaction-diffusion, DTM, Mathematical modeling, PAH Diol Epoxides.

INTRODUCTION

Cell biology deals with the most fundamental unit of life, i.e., cell. Schematically, a mammalian cell consists of cell/plasma membrane, then a cytoplasm composed of many different tiny cell organelles like golgi apparatus, mitochondria, endoplasmic reticulum, etc., nuclear envelop/membrane enclosing the nucleus which contains the most important heredity material DNA. Mathematical modeling of a cell is not only an important research work but a challenging task as well because of its complexity. (Dreij *et al*. 2011) developed a first model describing the fate of polycyclic aromatic hydrocarbons in complex cell geometry. The diffusion-reaction mechanism gave rise to a system of PDEs. For the modeling purpose, some modeling assumptions were made by (Dreij *et al*. 2011), which have been adopted here.

For the reduction of complexity of the system of equations, compartment modeling approach is used which results in a system of ODEs, where the system of ODEs is numerically solved using Backward Differentiation Formula (BDF). For a large system of ODEs, numerical techniques sometimes give very accurate solution but in most of the cases, numerical error is large. Therefore, one needs to have such a method, which may give a better solution with less error. Thus, to solve our model, a semi analytical method, Differential Transformation Method (DTM) is used. DTM was used by many researchers for different problems, where they showed that DTM gives better accuracy as compared to other techniques (Chaudhry *et al*. 2014). This equation is also solved by Adomian Decomposition Method and Homotopy Analysis Method, the results of which are compared against the results obtained using DTM. The comparison shows that DTM is much efficient and effective method as compared to HAM and ADM. (Ibrahim and Ismail 2012) developed SIR epidemic model for constant vaccination strategy, which is handled using DTM. This method gives solution in the form of series which converges very fast as compared to other numerical methods. The main advantage of DTM is that this method provides the efficient solution of the given numerical problem without the help of Adomian's polynomial. According to author's knowledge, it is the first time that DTM is used for cell models.

MATERIALS AND METHODS

The model discussed in this work reported the uptake of chemical compounds from the environment into mammalian cells. The chemical compounds considered here were polycyclic aromatic hydrocarbons (PAHs), which were formed because of incomplete combustion and burning. PAHs were available in our environment in large quantity, where some were more carcinogenic. The intermediates, formed due to metabolism of PAHs, exposed to the nucleus of the cell where they reacted with the DNA of the cell, which probably caused toxic diseases like cancer and tumors. In order to understand the effect of these chemical compounds on cellular behavior, mathematical model was developed by (Dreij *et al*. 2011) where the reaction and diffusion processes took place. In the model presented here, the aim was to model the uptake of PAH Diol Epoxcides (PAH DEs) into the cell. DEs undergo the process of hydrolysis in extracellular medium as well as intracellular domains. From extracellular medium, it

diffused to the cytoplasm through cell membrane. Due to the process of hydrolysis and conjugation, PAH DEs were degraded to tetrols and glutatheoine conjugates. DEs further diffused to nucleus through nuclear membrane, where they reacted with the DNA of the cell to form DNA adducts. In this study, we were only interested to know the fate of PAH DEs in the presence of above mentioned processes.

Quantitative Model: *The model description discussed above leads to the following chemical reactions in different sub-domains:*

- **Sub-domain 1 (extracellular medium)**

$$DE_{wa} \xrightarrow{k_{tet}} Tet_{wa}$$

where DE_{wa} and Tet_{wa} denote the Diol Epoxides and tetrols respectively in extracellular sub-domain. Since we were interested to know the fate of DEs only, therefore the above chemical reaction gave rise to the following PDE:

$$\frac{\partial DE_{wa}}{\partial t} = \nabla.(D_{wa}\nabla DE_{wa}) - k_{tet}DE_{wa} \quad (1)$$

DE_{wa} stands for diffusion coefficient in sub-domain 1 i.e. extracellular, where k_{tet} represented the rate constant for the formation of tetrols.

- **Sub-domain 2 (cell membrane)**

Since sub-domain 2 was lipid membrane, no reaction took place in it. Only diffusion process was available, which gave rise to the following PDE:

$$\frac{\partial DE_{memc}}{\partial t} = \nabla.(D_{cm}\nabla DE_{memc}) \quad (2)$$

where DE_{memc} and D_{cm} represented the DEs and diffusion coefficient respectively in cell membrane.

- **Sub-domain 3 (cytoplasm)**

Cytoplasm mainly consists of water and tiny lipid membranes. If we resolve these tiny structures, we need to have a very small grid, thus making the model computationally highly expensive. In order to avoid this issue, the cytoplasm was homogenized as reported by (Dreij *et al*. 2011). Here, we will use the effective equations only. The chemical reactions presented in water part of cytoplasm were as under:

$$DE_{cy} \xrightarrow{k_{tet,eff}} Tet_{cy}$$
$$DE_{cy} \xrightarrow{k_{conj,eff}} Conj_{cy}$$

Here, $Conj_{cy}$ denotes the glutathione conjugates in cytoplasm. The above chemical reaction gave rise to the following PDE:

$$\sigma\frac{\partial DE_{cy}}{\partial t} = \nabla.(D_{cy,eff}\nabla DE_{cy}) - (k_{tet,eff} + k_{conj,eff})DE_{cy} \quad (3)$$

where σ represented the scaling factor, which appeared because of the homogenization procedure, and is defined as below

$$\sigma = \begin{cases} p_{water} + \frac{p_{mem}}{K_p}, & x \in \text{water part in cytoplasm} \\ \frac{1}{K_p}, & x \in \text{membrane part of cytoplasm} \end{cases}$$

where p_{water} and p_{mem} denoted the volume fraction of water and membranous parts of cytoplasm, respectively K_p represented the partition coefficient. $D_{cy,eff}$ in Eq. (3) stood for the effective diffusion coefficient which was derived by Dreij *et al*. (2011) using the iterative homogenization approach.

- **Sub-domain 4 (nuclear membrane)**

Like sub-domain 2, we have:

$$\frac{\partial DE_{memn}}{\partial t} = \nabla.(D_{nm}\nabla DE_{memn}) \quad (4)$$

- **Sub-domain 5 (nucleus)**

$$DE_{nu} \xrightarrow{k_{tet}} Tet_{nu}$$
$$DE_{nu} \xrightarrow{k_{add}} Add_{nu}$$

where Add_{nu} showed the DNA Adducts in nucleus. The above chemical reaction gave rise to the following PDE:

$$\frac{\partial DE_{nu}}{\partial t} = \nabla.(D_{nu}\nabla DE_{nu}) - (k_{tet} + k_{k_{add}})DE_{nu} \quad (5$$

Compartment Model: Compartment modeling technique is standard and quite common among the biologists and mathematicians, by which the complexity of system of equations was reduced. This approach was used in many biological studies by many scientists, (Dreij *et al*. 2011; Godfrey 1983; Holz and Fahr 2001; Jernström *et al*. 1996). A compartment model may contain a number of compartments, where each compartment was a well stirred and homogeneous mixture.

The complete set of equations (1-5) in different sub-domains would be replaced by the following equations using compartment modeling technique:

- **Sub-domain 1 (extracellular medium)**

$$\frac{d}{dt}n_{DE_{wa}} = \frac{D_{cm}A_{cm}}{K_p\delta}(DE_{cy,eff} - DE_{wa}) - k_{tet}n_{DE_{wa}} \quad (6$$

In this equation, and the following equations, DE_{wa} represented the concentration of DEs whereas $n_{DE_{wa}}$ showed the molar contents of DEs in extracellular dub-domain. Similar expressions will be followed for other species. $DE_{cy,eff}$ showing the effective concentration of DEs in cytoplasm, the expression of which is given as:

$$DE_{cy,eff} = \frac{DE_{cy}}{\sigma}$$

A_{cm} denotes the area, and δ stands for the thickness of cell membrane.

- **Sub-domain 3 (cytoplasm)**

$$\frac{d}{dt}n_{DE_{cy}} = \frac{D_{cm}A_{cm}}{K_p\delta}(DE_{wa} - DE_{cy,eff}) + \frac{D_{nm}A_{nm}}{K_p\delta}(DE_{nu} - DE_{cy,eff}) - \frac{k_{tot,eff} + k_{conj,eff}}{\sigma}n_{DE_{cy}} \quad (7)$$

where A_{nm} represents the area of nuclear membrane. Since the thickness of the membrane is same, therefore the thickness of the nuclear membrane is represented by δ again.

- **Sub-domain 5 (nucleus)**

$$\frac{d}{dt}n_{DE_{nu}} = \frac{D_{nm}A_{nm}}{K_p\delta}(DE_{cy,eff} \quad DE_{nu}) \quad (k_{tot} + k_{add})n_{DE_{nu}} \quad (8)$$

Differential Transformation Method (DTM): DTM was a semi-analytic scheme, which provided us a solution in the form of series. Unlike other numerical techniques, DTM gave us a closed form solution.

DTM used Taylor series for the solution of differential equations in the form of polynomial. This technique was entirely different from higher order Taylor series method because in Taylor series method when we solved it for higher order equations, it was computationally very expensive. This method gave better accuracy for small number of terms rather than Taylor series. The proposed method is very cheap for calculation and easily applicable to ordinary differential equation such as linear and non-linear to find the exact and approximate solution.

Basic Definition of DTM: *A differential Transformation* $U(k)$ *of a function* $u(x)$ *is in the form as given below.*

$$U(k) = \frac{1}{k!}\left[\frac{d^k u(x)}{dx^k}\right]_{x=x_0}$$

Here

Original function denotes $u(x)$

Transformed function denotes $U(k)$

The Inverse of differential Transformation is defined as below.

$$u(x) = \sum_{k=0}^{\infty} U(k)(x - x_0)^k.$$

When x_0 was taken as zero, then the above original function $u(x)$ would be defined in the form of finite series and above function could be expressed in the form as given below.

$$u(x) = \sum_{k=0}^{\infty} U(k)\,x^k$$

$$u(x) = \sum_{k=0}^{\infty} U(k)\frac{x^k}{k!}\left[\frac{d^k u(x)}{dx^k}\right]_{x=x_0}$$

From the above equation, we can see that the basic idea of DTM was based on Taylor series.

Some Fundamental Results of the one-dimensional transformation Method:

Some fundamental results of the one-dimensional transformation Method were given by (Chen and Liu 1998; Ayaz 2004; Kangalgil and Ayaz 2009), and are listed in Table-1.

Table-1. Showing some fundamental results of the one-dimensional transformation Method

Original function	Transformed function
$z(t) = a(t) \pm b(t)$	$Z(k) = A(k) \pm B(k)$
$z(t) = \beta a(t)$	$Z(k) = \beta A(k)$
$z(t) = \partial a(t)/\partial t$	$Z(k) = (k+1)A(k+1)$
$z(t) = \partial^s a(t)/\partial t^s$	$Z(k) = (k+1)(k+2)\ldots(k+s)A(k+s)$
$z(t) = u(t)v(t)$	$Z(k) = \sum_{l=0}^{k} U(k-l)V(l)$

By applying Differential Transformation Method to the system of Differential Equations (6-8), we got the following equations in different sub-domains:

- **Compartment 1 (extracellular medium)**

$$(k+1)n_{DE_{wa}}(k+1) = \frac{D_{cm}A_{cm}}{K_p\delta}(DE_{cy,eff}(k) - DE_{wa}(k)) - k_{tot}n_{DE_{wa}}(k)$$

$$n_{DE_{wa}}(k+1) = \frac{1}{(k+1)}\left[\frac{D_{cm}A_{cm}}{K_p\delta}(DE_{cy,eff}(k) - DE_{wa}(k)) - k_{tot}n_{DE_{wa}}(k)\right] \quad (8)$$

- **Compartment 3 (cytoplasm)**

$$(k+1)n_{DE_{cy}}(k+1) = \frac{D_{cm}A_{cm}}{K_p\delta}(DE_{wa}(k+1) - DE_{cy,eff}(k+1)) + \frac{D_{nm}A_{nm}}{K_p\delta}$$

$$(DE_{nu}(k+1) - DE_{cy,eff}(k+1)) - \frac{k_{tot,eff} + k_{conj,eff}}{\sigma}n_{DE_{cy}}(k+1)$$

$$n_{(}DE_{(}cy)(k+1) = 1/((k+1))[(D_{(}cm A_{(}cm)/(K_{(}p\,\delta)(DE_{(}wa(k+1) - DE_{(}(cy,eff)(k+1)) + (D_{(}nm A_{(}nm)/(K_{(}p\,\delta)(DE_{(}nu(k+1) \quad (9)$$

- **Compartment 5 (nucleus)**

$$(k+1)n_{DE_{nu}}(k+1) = \frac{D_{nm}A_{nm}}{K_p\delta}(DE_{cy,eff}(k) - DE_{nu}(k)) - (k_{tot} + k_{add})n_{DE_{nu}}(k)$$

$$n_{DE_{nu}}(k+1) = \frac{1}{(k+1)}\left[\frac{D_{nm}A_{nm}}{K_p\delta}(DE_{cy,eff}(k) - DE_{nu}(k)) - (k_{tot} + k_{add})n_{DE_{nu}}(k)\right] \quad (10)$$

RESULTS AND DISCUSSION

Cytoplasm of a cell has a very complex structure, containing watery part known as cytosol, and small membranous substructures. This complex and heterogeneous structure really adds not only the difficulty in the modeling, but computationally highly expensive. In order to avoid this issue, iterated homogenization technique was used. In this paper we have only used the results which were the outcome of the effective equations, which were derived earlier by Dreij *et al.* (2011). The resulting value of the scaling factor σ is given as:

$$\sigma = 2.1239 \times 10^{2}$$

It was shown by Dreij *et al*. (2011) that with the physical parameters, the system of partial differential equations could be replaced by a system of ordinary differential equations, because both systems gave identical results. Thus in this study, we dealt with the system of ODEs instead of handling PDEs. The resulting system of ODEs has been given in Eqs (6-8), which were obtained using Fick's law of diffusion following standard compartment modeling approach. The system of differential equations (6-8) were solved using Differential Transformation Method (DTM). DTM is a semi-analytic scheme, which provided us a solution in the form of series. Unlike other numerical techniques, DTM gave us a closed form solution. The transformed system is given in Eqs. (9-11). The chemical and physical constants which were used to solve the system, were derived by (Dreij *et al*. 2011; Jernström *et al*. 1996; Sundberg *et al*. 2002; Townsend *et al*. 1990), and are summarized in Table-2.

The results obtained by applying DTM were compared against the numerical results obtained by using Runge-Kutta and Backward Differentiation schemes. Runge – Kutta method was a numerical technique used to solve system of ODEs. BDF was a family of implicit methods for the numerical integration of ODEs. They were linear multi-step methods that, for a given function and time, approximate the derivative of that function using information from already computed times, thereby increasing the accuracy of the approximation. The comparison of the degradation of PAH DEs in extracellular medium, using the above mentioned three methods, were compared with each other in Figure-1. In Figure-2 and 3, the formation of PAH DEs in cytoplasm and nucleus, using three methods were compared respectively. The results in all the figures showed that the results obtained by DTM had an excellent agreement with the results by other numerical methods, which showed the importance of DTM because it was easy and less computationally expensive as compared to the pure numerical techniques. Another key feature of using DTM was that, If compared the results obtained using DTM with the analytical solution, it gave better accuracy as compared to the other techniques.

Table-2. Showing chemical and physical constants

Parameter/Constant	Symbol	Value
Diffusion coefficient in cell/nuclear membrane $[m^2 s^{-1}]$	D_{cm}	1×10^{-12}
Rate constant for forming Tetrols $[s^{-1}]$	k_{tet}	7.7×10^{-8}
Effective rate constant for forming Tetrols (in cytoplasm) $[s^{-1}]$	$k_{tet,eff}$	5.74×10^{-2}
Effective rate constant for forming GSH conjugates $[s^{-1}]$	$k_{conj,eff}$	2.43×10^{-1}
Rate constant for forming DNA Adducts $[s^{-1}]$	k_{add}	6.3×10^{-8}
Volume fraction of water in cytoplasm (%)	p_{water}	75
Volume fraction of membranes in cytoplasm (%)	p_{mem}	25
Partition coefficient	K_p	1.2×10^{-8}
Area of cell membrane $[m^2]$	A_{cm}	1.01×10^{-9}
Area of nuclear membrane $[m^2]$	A_{nm}	4.0×10^{-10}
Thickness of cell/nuclear membrane $[m]$	δ	1.13×10^{-1}
Initial amount of DEs in extracellular [pmol]	$DE_{wa,0}$	1×10^{4}
Volume of each compartment	V	1×10^{-6}

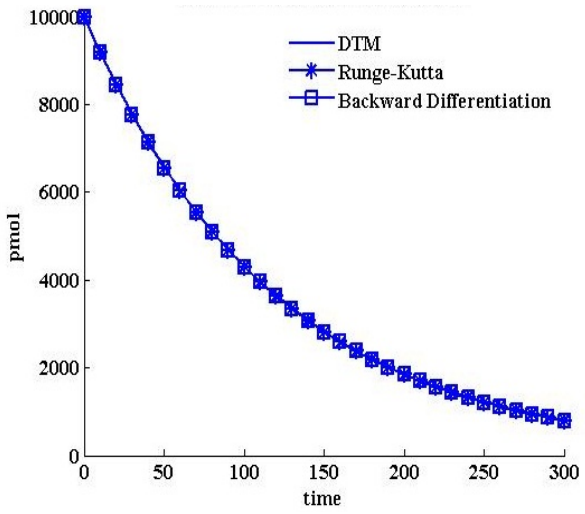

Figure-1. Showing degradation of PAH DEs in Extracellular sub-domain

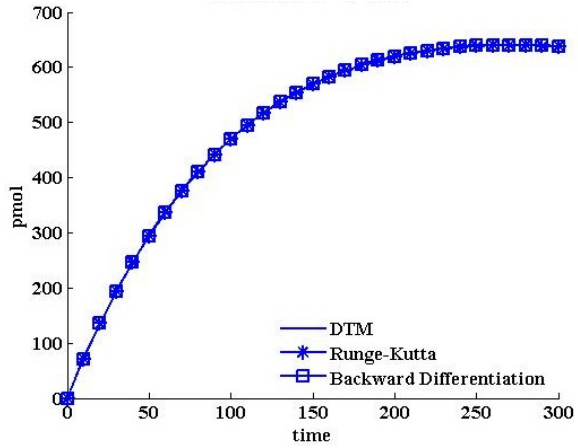

Figure-2. Showing formation of PAH DEs in Cytoplasm

The results obtained by applying DTM motivated the use of this method on extended and complex models. Later on this technique would be used with optimal parameters which would be obtained using different optimization techniques, used by (Chaudhry *et al*. 2009).

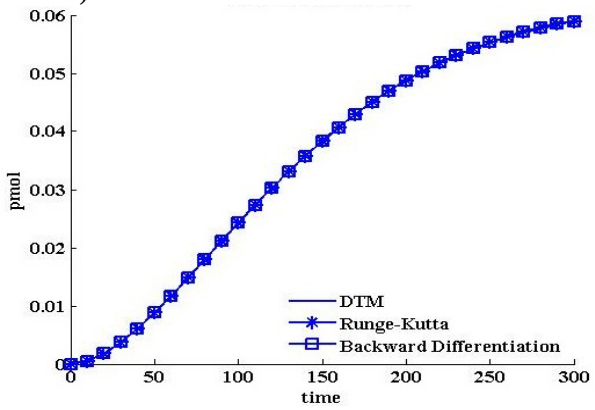

Figure-3. Showing formation of PAH DEs in Nucleus

REFERENCES

Ayaz F. Application of differential transform method to do differential-algebraic equations. Appl. Math Comput, 152(3): 649-657 (2004).

Chaudhry N. A., M. O. Ahmad and J. Ali. Constraint handling in genetic algorithms by a 2-parameter-exponential penalty function approach. Pakistan J. Sci, 61(3): 122-129 (2009).

Chaudhry Q. A., N. A. Chaudhry and Z. Zafar. Numerical approximation of degradation of plasmid DNA in rat plasma. Pakistan J. Sci, 66(1): 56-59 (2014).

Chen C. L. and Y. C. Liu. Solution of two point boundary value problem using the differential transformation method. J. Optimiz Theory App, 99(1): 23-35 (1998).

Dreij K., Q. A. Chaudhry, B. Jernström, R. Morgenstern and M. Hanke. A method for efficient calculation of diffusion and reactions of lipophilic compounds in complex cell geometry. PLoS ONE, 6(8): e23128 (2011).

Godfrey K. Compartment Models and their Applications. Academic Press, London (1983).

Holz M. and A. Fahr. Compartment modeling. Adv Drug Deliv Rev, 48(2): 249-264 (2001).

Ibrahim S. F. M. and S. M. Ismail. Differential transformation approach to a SIR epidemic model with constant vaccination. J. Am. Sci, 8(7): (2012).

Jernström B., M. Funk, H. Frank, B. Mannervik and A. Seidel. Glutathione Stransferase A1-1-catalysed conjugation of bay and fjord region diol epoxides or polycyclic aromatic hydrocarbons with glutathione. Carcinogenesis, 17(7): 1491–1498 (1996).

Kangalgil F. and F. Ayaz. Solitary wave solutions for the KdV and mKdV equations by differential transform method. Chaos Soliton Fract, 41(1): 464–472 (2009).

Sundberg K., K. Dreij, A. Seidel and B. Jernström. Glutathione conjugation and DNA adduct formation of dibenzo[a,l]pyrene and benzo[a]pyrene diol epoxides in V79 cells stably expressing different human glutathione transferases. Chem Res Toxicol, 15(2): 170–179 (2002).

Townsend K., A. Stretch, D. Stevens and D. Goodhead. Thickness measurements on V79-4 cells: A comparison between laser scanning confocal microscopy and electron microscopy. Int J Radiat Biol, 58(3): 499–508 (1990).