NUMERICAL APPROXIMATION OF DEGRADATION OF PLASMID DNA IN RAT PLASMA

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ABSTRACT: The scientific study revealed that the transport of plasmid Deoxyribonucleic acid (pDNA) towards the target sites played a vital role in creating a hurdle in gene delivery. In this study, the kinetic model of degradation of all the topoforms of pDNA namely super-coiled, open-circular and linear, have been discussed. The resulting system of ordinary differential equations (ODEs) has been numerically treated using various schemes, where the numerical results have been found to be in good agreement with the exact solutions. Further, it has been observed that, DTM gives more accurate results as compared with the results obtained by other numerical techniques.

Key words: pDNA, ordinary differential equations, DTM, topoforms, RK4, BDF.

INTRODUCTION

Biotechnology and computational biology are a rapid growing and an important area of research work particularly in the field of pharmacokinetics and pharmaceutical sciences. It has many clinical applications, and one of them is gene therapy. In this process, it is expected that *in vivo*, the proteins will be produced by the body's own mechanisms. Gene delivery is a complicated process, which gives rise to some important issues which needs to be addressed. One of the important issues is the transportation of pDNA towards the target sites and the other is the conversion of pDNA to its topoforms. Mathematical modeling of degradation of all the three topoforms of pDNA, namely super-coiled, open-circular and linear, is an important area of research work, because the transportation of these topoforms towards their target sites play a vital role in creating an obstacle in the process of gene delivery. The kinetic model of degradation of pDNA was studied by Houk *et al.* (1999). They constructed a kinetic model for this purpose in rat plasma. They also performed different experiments in vitro at 37°C in order to calculate the amount of the three topoforms in rat plasma. It was observed by Hirose and Ohaba (1993) that super coiled has more rapid rate as compared to the rate of open-circular particularly when observed in initial hours after transfection. Gosse *et al*. (1965) determined the fate of DNA when it was injected in mammals.

Mathematical modeling of cell, where the prediction of DNA in the presence of GST was the main problem of research, was discussed in detail by Dreij *et al*. (2011 and 2012). Thierry *et al*. (1997) performed the experiments in which they observed that in first 20 min, the degradation of pDNA was very small, whereas during the next 40 min, the amount of super-coiled was detected. Lechardeur *et al*. (1999) concluded that, in cytosol, the metabolic in-efficiency and in-stability of pDNA caused hurdles and obstacles, and reduced the efficiency of gene delivery system.

The kinetic model of the degradation of all the three topoforms of plasmid DNA namely, super-coiled, open-circular and linear topoform was discussed in detail by Houk *et al.* (1999) which is represented below:

$$SC \xrightarrow{k_{sc}} OC \xrightarrow{k_{oc}} LI \xrightarrow{k_{li}}$$

where *SC* stands for super-coiled, *OC* denotes the open-circular, and *LI* stands for linear plasmid topoform. k_{SC} is the rate constant for the degradation of super-coiled, k_{OC} is the rate constant for the degradation of open-circular, and k_{li} stands for the rate constant for the degradation of linear topoform. The above kinetic system gives rise to the following system of ordinary differential equations:

$$\frac{dSC}{dt} = -k_{SC}SC \quad (1)$$

$$\frac{dOC}{dt} = k_{SC}SC - k_{OC}OC \quad (2)$$

$$\frac{dLI}{dt} = k_{OC}OC - k_{li}LI \quad (3)$$

In this study, we have the aim to solve the above system of ODEs using different techniques, e.g., Backward Difference Formula (BDF), Runge-Kutta Method (RK4) and Differential Transform Method (DTM). BDF and RK4 are well known and quite famous numerical methods. A brief description of DTM is given below:

Differential Transform Method: Differential Transform Method is a semi analytical method, which provides the solution in series form. An important phenomenon of DTM is that, it gives a closed form solution. Zhou (1986) introduced the idea of DTM which can be used to solve

linear and non-linear initial value problems. There are many applications of this method, e.g, in electric circuit analysis and biological problems etc. Initially, this method was only for ordinary differential equations but DTM was developed by Chen and Ho (1999) for partial differential equations.

DTM uses polynomial Taylor series for the solution of differential equations. Since the higher order Taylor series method is very costly to use for solving higher order equations, therefore DTM is entirely different from this scheme. Above all it gives a better accuracy for small number of terms unlike Taylor series method. Thus the proposed method, i.e., DTM is rather cheap and can easily be implemented to solve linear as well as non-linear differential equations to get better results. The basic definition of DTM is given below:

Consider a function $u(x)$, the differential transformation of which is written in the form as under

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

where the inverse of the differential Transformation given above will be defined as:

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

If x_0 to be taken as zero, then the function $u(x)$ takes the form of a finite series and is defined as under

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

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

From the above relation, it is clear that the DTM is based on the Taylor series.

Ayaz (2004); Arikoglu and Ozkol (2007); Kangalgil and Ayaz (2009) provided some fundamental results of 1-dimensional transformation, which are listed in Table-1.

Table-1. Some results of the 1-dimensional transformation Method

Original function	Transformed function
$y(t) = a(t) \pm b(t)$	$Y(k) = A(k) \pm B(k)$
$y(t) = \beta a(t)$	$Y(k) = \beta A(k)$
$y(t) = \partial a(t)/\partial t$	$Y(k) = (k+1)A(k+1)$
$y(t) = u(t)v(t)$	$Y(k) = \sum_{n=0}^{k} U(k-n)V(n)$

Now we apply DTM to the system of equations (1-3), which gives rise to the following system of equations. Eq. (1) takes the form as

$$SC(k+1) = -\frac{1}{(k+1)} k_{SC} SC(k) \qquad (4)$$

Eq. (2) becomes

$$OC(k+1) = \frac{1}{(k+1)}[k_{SC} SC(k) - k_{OC} OC(k)] \qquad (5)$$

Finally, eq. (3) takes the following form

$$LI(k+1) = \frac{1}{(k+1)}[k_{OC} OC(k) - k_{li} LI(k)] \qquad (6)$$

RESULTS AND DISCUSSION

The results obtained by solving the system of equations (4-6) using DTM were compared with the exact solution. The values of the rate constants were derived from Houk *et al.* (1999), and are presented in Table-2.

Table-2. Kinetic parameters used for isolated plasmid DNA in rat plasma

Parameter/Constant	Symbol	Value $[s^{-1}]$
Rate constant for the degradation of super-coiled topoform	k_{SC}	0.01
Rate constant for the degradation of open-circular topoform	k_{OC}	0.0005
Rate constant for the degradation of linear topoform	k_{li}	0.001

In order to see the comparison of the results with different numerical schemes, the system of differential equations was solved using Runge-Kutta (RK4) and Backward Difference Formula (BDF). Both numerical schemes were efficiently used to solve the system of differential equations. System of equations was solved for a time span of 60min. The profiles of all the topoforms have been shown in Figure-1.

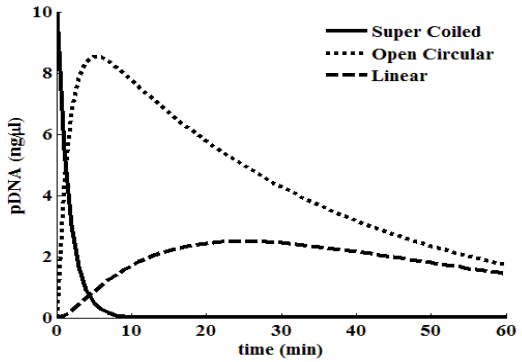

Figure-1. Profiles of topoforms of pDNA (super-coiled, open-circular and linear plasmids).

The error at different time steps between the exact solution of all the topoforms and the solution obtained using RK4, BDF and DTM has been calculated, and is shown in Table-3. Total error between the exact solution and BDF is calculated to be 1.0780E-11, whereas the total error between the exact solution and RK4 is 1.6859E-13. Finally the total error between the exact solution and DTM was calculated which is 3.4347E-14. The results clearly show that the error using DTM is approximately 3 order less than the error obtained using BDF, whereas it is approximately more than 1 order less than the error obtained using RK4.

Table-3. Numerical error between the exact solutions and some numerical techniques

	|Exact – BDF|			**|Exact - RK4|**			**|Exact –DTM|**		
Time (sec)/ Species	**SC**	**OC**	**L**	**SC**	**OC**	**L**	**SC**	**OC**	**L**
0	0	0	2.9104E-15	0	0	2.9104E-15	0	0	2.9104E-15
6	5.3291E-15	7.7716E-16	1.5970E-16	1.7764E-15	9.9920E-16	1.9678E-16	0	1.1102E-15	1.9494E-16
12	8.8818E-15	7.1054E-15	1.5339E-15	5.3291E-15	0	1.9980E-15	1.7764E-15	1.1102E-15	1.9719E-15
18	3.1974E-14	3.1086E-14	9.4803E-16	5.3291E-15	8.8818E-16	9.3502E-16	3.5527E-15	0	8.7257E-16
24	8.4377E-14	8.6597E-14	3.7106E-15	4.4409E-15	2.6645E-15	1.1692E-15	0	8.8818E-16	1.1692E-15
30	1.7586E-13	1.8696E-13	7.9103E-15	7.9936E-15	2.2204E-15	2.8380E-15	0	8.8818E-16	2.5882E-15
36	3.3129E-13	3.4905E-13	1.7378E-14	7.9936E-15	3.9968E-15	2.4217E-15	0	1.3323E-15	2.1025E-15
42	5.5511E-13	5.8620E-13	3.0656E-14	3.5527E-15	8.8818E-16	2.0053E-15	8.8818E-16	0	2.0053E-15
48	8.6597E-13	9.1305E-13	5.0543E-14	8.8818E-15	5.7732E-15	6.6613E-16	8.8818E-16	8.8818E-16	2.4286E-16
54	1.2736E-12	1.3456E-12	7.2879E-14	3.9968E-14	3.8192E-14	4.0384E-15	0	1.7764E-15	1.8319E-15
60	1.7764E-12	1.8732E-12	1.0265E-13	1.7764E-15	5.3291E-15	1.4155E-15	0	1.7764E-15	1.5821E-15
$\sum Errors$	5.1088E-12	5.3796E-12	2.9128E-13	8.7041E-14	6.0951E-14	2.0594E-14	7.1054E-15	9.7700E-15	1.7472E-14
Total Error	1.0780E-11			1.6859E-13			3.4347E-14		

Thus we conclude that the results of DTM give better solution as compared to other numerical techniques. Later, this method will be used for this system in order to find optimal parameters, where the optimization scheme will be used as discussed by Chaudhry *et al*. (2009).

REFERENCES

Arikoglu A. and I. Ozkol. Solution of fractional differential equations by using differential transform method. Chaos Soliton Fract, 34(5): 1473-1481 (2007).

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).

Chen C. K. and S. H. Ho. Solving partial differential equations by two-dimensional differential transform method. Appl. Math Comput, 106(2-3): 171-179 (1999).

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).

Dreij K., Q. A. Chaudhry, J. Zhang, K. Sundberg, B. Jernström, M. Hanke and R. Morgenstern. In silico modeling of the intracellular dynamics of

polycyclic aromatic hydrocarbons. Toxicol Lett, 211: S60–S61 (2012).

Gosse C., J. B. L. Pecq, P. Defrance and C. Paoletti. Initial degradation of deoxyribonucleic acid after injection in mammals. Cancer Res, 25: 877–883 (1965).

Hirose S. and R. Ohaba. Supercoiling facilitates the assembly of active chromatin. In: Andoh T, Ikeda H, Oguro M, eds. Molecular Biology of DNA Topoisomerases. Boca Raton, FL: CRC Press: 87-93 (1993).

Houk B. E., G. Hochhaus and J. A. Hughes. Kinetic modeling of plasmid DNA degradation in rat plasma. AAPS PharmSci, 1(4): E9 (1999).

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).

Lechardeur D., K. J. Sohn, M. Haardt, P. B. Joshi, M. Monck, R. W. Graham, B. Beatty, J. Squire, H. O'Brodovich and G. L. Lukacs. Metabolic instability of plasmid DNA in the cytosol: a potential barrier to gene transfer. Gene Therapy, 6(4): 482-497 (1999).

Thierry A. R., R. Rabinovich, B. Peng, L. C. Mahan, J. L. Bryant and R. C. Gallo. Characterization of liposome-mediated gene delivery: Expression, stability, and pharmacokinetics of plasmid DNA. Gene Therapy, 4(3): 226-237 (1997).

Zhou J. K. Differential Transformation and its Applications for Electrical Circuits. Huazhong University Press, China (1986).