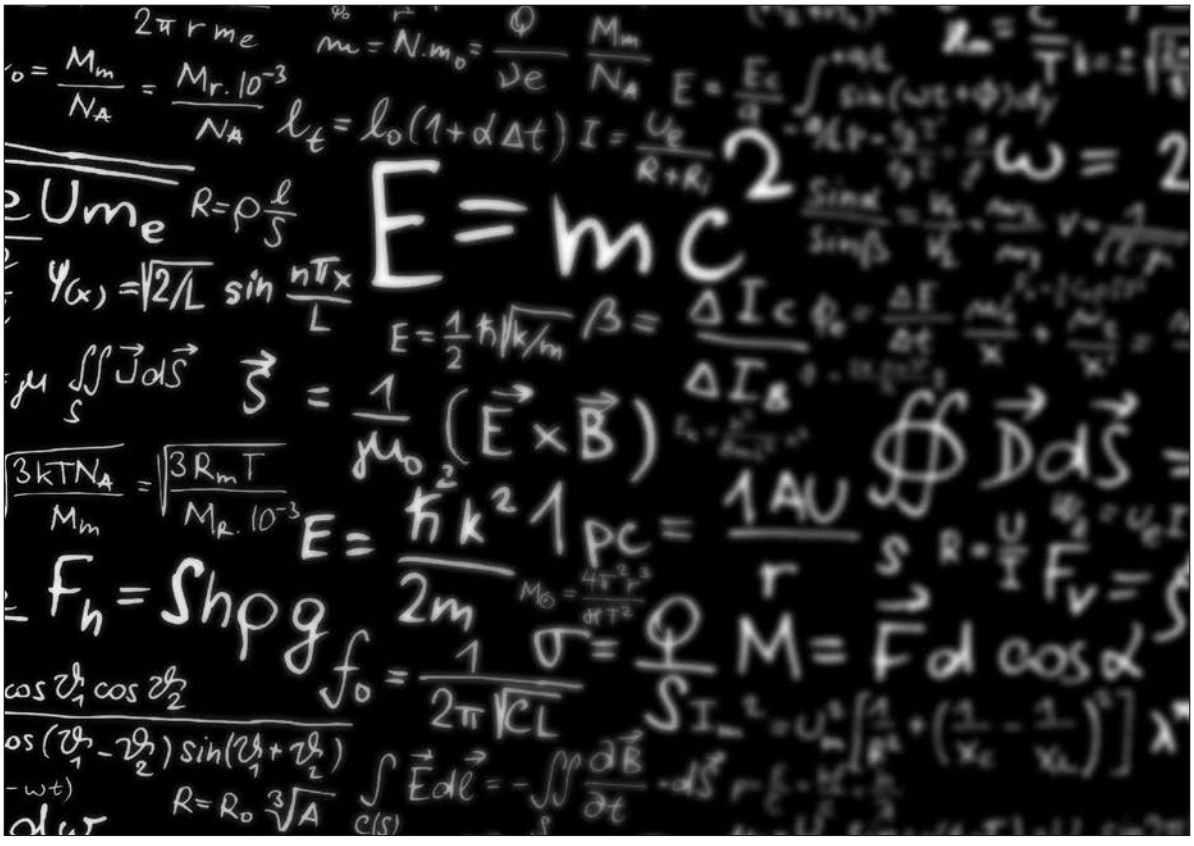

Asian Journal of Mathematics & Statistics

ISSN 1994-5418

science alert

ANSInet
an open access publisher
http://ansinet.com

Asian Journal of Mathematics and Statistics 7 (2): 60-67, 2014
ISSN 1994-5418 / DOI: 10.3923/ajms.2014.60.67

Applications of Mathematical Models on Tumor Growth Rate

[1]Atanu Bhattacharjee and [2]B. Satheesan
[1]Division of Clinical Research and Biostatistics, Malabar Cancer Centre, Kerala, India
[2]Department of Surgical Oncology, Malabar Cancer Centre, Kerala, India

Corresponding Author: Atanu Bhattacharjee, Division of Clinical Research and Biostatistics, Malabar Cancer Centre, Kerala, India

ABSTRACT

New Statistical method on delay differential equation is proposed for growth rate modeling. The method is compared with two conventional approaches, illustrating the application on mice tumor growth data. Significance drug treatment effect is observed through different methods. The proposed method can be applied in tumor growth data.

Key words: Gompertz curve, Bayesian, MCMC, iteration, delay differential equation

INTRODUCTION

The analysis of change of tumor growth through *in vivo* experiment is prevailing method to observe the treatment effects of cancer. Generally, treatment effects are compared through randomization. The growth data is observed with repeated measurements of each subject in different time points. Then repeated observations are considered as time dependent variables with outcomes of specific treatment effect. The interest of treatment effect study is to look on the tumor growth over the time of study period.

Longitudinal data analysis is inevitable tool for tumor growth modeling. Regressions modeling with covariates and data exploration are choice of work with longitudinal data analysis (Bhattacharjee and Nath, 2013; Diggle and Kenward, 1994). The rate of growth curve can be observed through differential equations. Differential equation is widely accepted tool for growth curve modeling. The mathematical modelings on growth curve through differential equation are widely elaborated area on different drug treatment effect (Kim and Lee, 2012). The curve fitting is another approach for growth curve modeling. The fitted line and prediction obtained through curve modeling becomes useful for future drug treatment effectiveness. The Gompertz curve is widely explored area in time series data modeling. Recently, it is also illustrated on growth curve modeling. The extension of general Gompertz curve as time dependent is useful for growth modeling. This study is aimed to the comparison of different modeling techniques on tumor curve growth. The Bayesian approach in the longitudinal data modeling, delay differential equation is applied for growth and Gompertz curve with MCMC techniques are applied for the tumor growth modeling. The analysis is performed on secondary data on tumor growth in mice. The detailed about data is elaborated in data methodology section.

DATA METHODOLOGY

The secondary data is considered from the study of Rygaard and Spang-Thomsen (1997). The data of 46 mice are considered as model illustration. The data contained with longitudinal

observations of tumor volume (Y_{ij}) is with four groups of mice. The groups (i = 1, 2, 3 and 4) are based on types of treatment as given to them. The treatment i = 1, is the group of control and i = 2, 3 and 4 are of having treatment with 10, 20 and 25 mg kg^{-1} cisplain, respectively. The objective is to compare the treatment effect among mice. The growths of tumor of the mice are considered as response of interest. The raw data is presented in Fig. 1.

Mixed effect model: Mixed models are well accepted tool for longitudinal data analysis, due to easily available in different software. It is assumed that the measurements of single subject having different unobserved random effects. These unobserved random effects are useful to describe the relation between repeated measurements (Cheng *et al.*, 2010).

In linear models, the parameters of interest are supposed to be identical for all the individuals. In clinical trial, the inter-individual correlation and variability crack this usual assumption. The ideal way to tackle the problem is modeled the parameters by sum of fixed and random effects. The mixed effect model (sum of fixed and random) is useful in clinical trial data analysis (Lindstrom and Bates, 1990; Samson *et al.*, 2006; Samson *et al.*, 2007). In generally the tumor growth does not consider the contribution of the treatments. These models are inappropriate to find the best treatment in sensitive disease like cancer. The study is involved with mixed model on the size of tumor growth. In longitudinal data analysis the mixed model (Diggle and Kenward, 1994) is defined as Eq. 1:

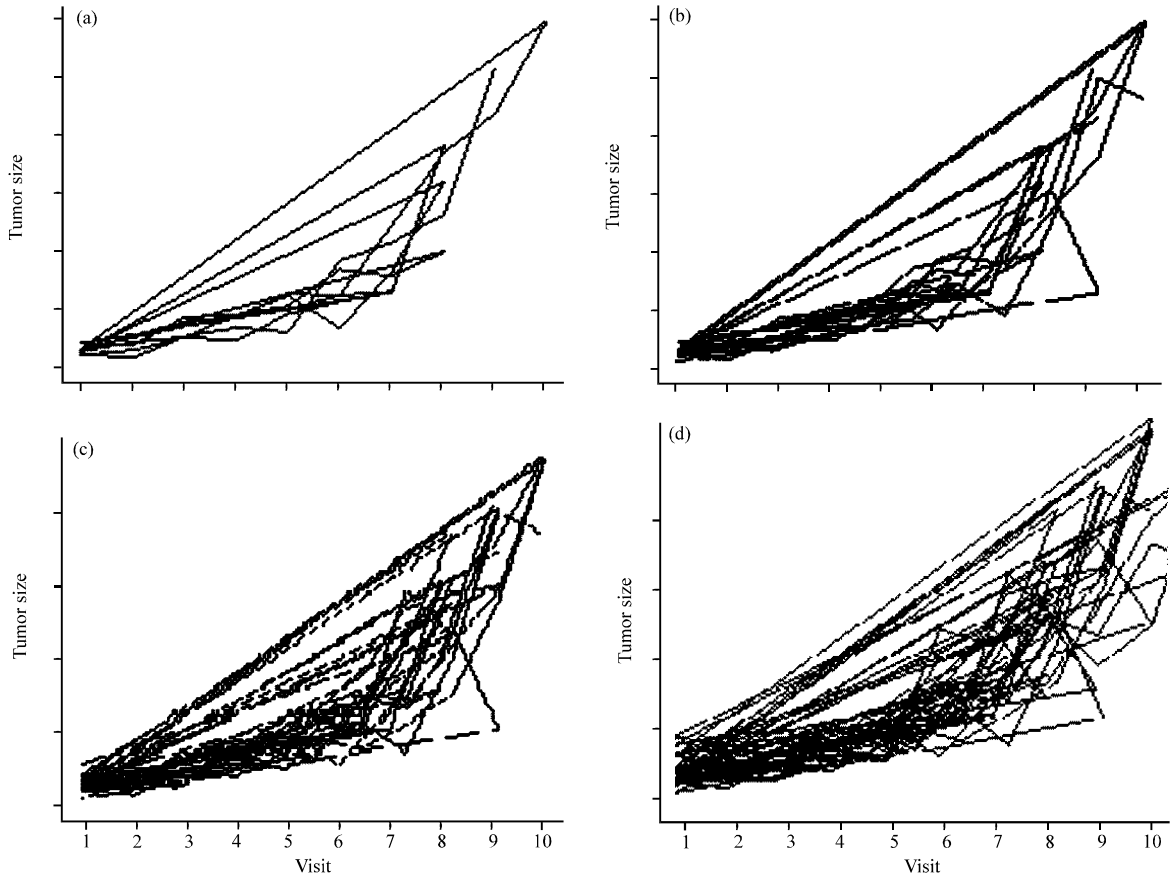

Fig. 1(a-d): Visit wise changes of growth rate in different subjects, Group (a) 0, (b) 1, (c) 2 and (d) 3

$$Y = X'_{it}\beta + Zi\gamma_i + \varepsilon_{it} \quad (1)$$

The observations on time t is defined as t = 1,... .... T_i. The terms ε_{it} and γ_i (both are independent) are the error and lag correlation terms, respectively. It is assumed that $\gamma_i \sim (0, \sigma^2_y)$ and $\varepsilon_{it} \sim (0, \sigma^2_s)$. There are different ways to get estimate of the random effects. The work is contributed through the effects of MLE. However, the consideration of covariance structure is important during estimation. It is natural the observations of same individual will be correlated. The application of autocorrelation structure is simple and useful in presences of different correlation structure. The independent factors are considered as fixed when it is well controlled. Here, the treatment effect is considered as fixed effect. The random independent factor is considered; when no control exist over the factor. The subject or individual effect is considered as the random effect. The Bayesian approach is considered to obtain the result on mixed effect models. The MCMC is applied in R to obtain the result with Bayesian approach. The iteration having convergence is considered for the analysis. In comparison to frequentist approach, the Bayesian inference gives the inference about parameters in terms of probability based on the conditional on the observed data of the response of interest. The estimates can be applied for replication of the experiment in another aspect. The MCMC is used through simulation to compute the result on mixed effect modeling. A total of 10,000 burns are run for computation. The posterior estimates are detailed with highest posterior density estimates. The graphical exploration is given in Fig. 2.

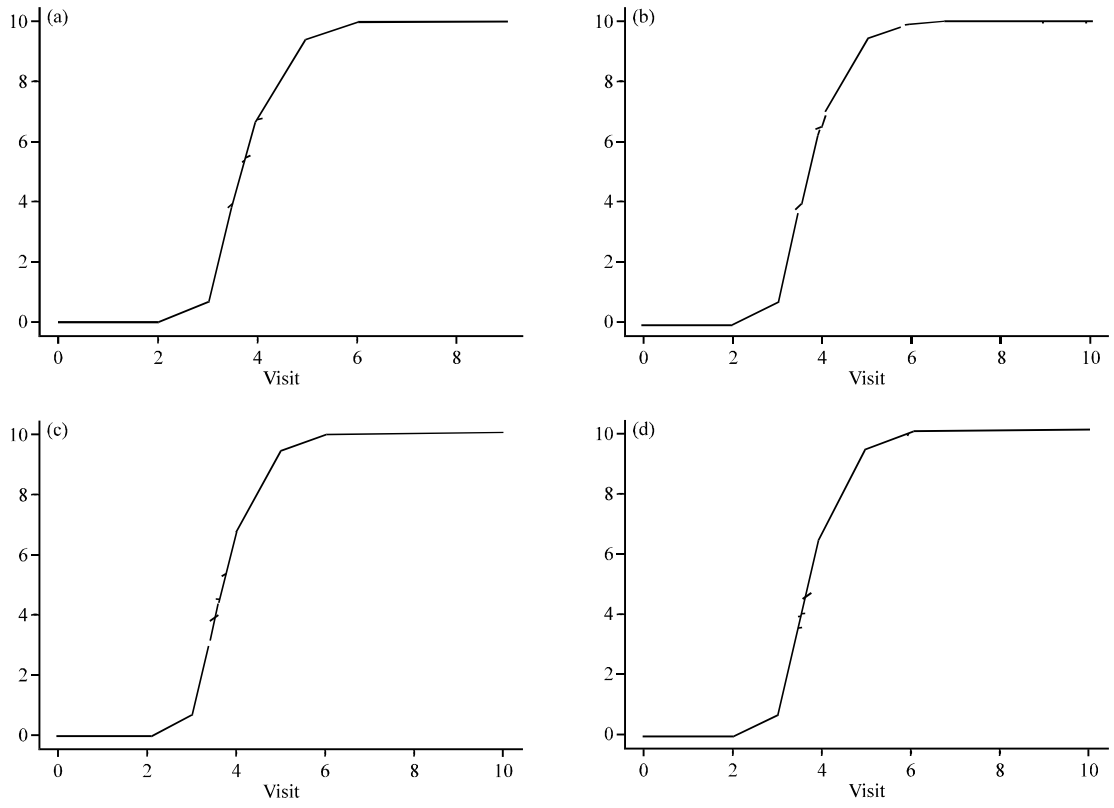

Fig. 2(a-d): Fitted growth model applied in different treatment trough mixed effect model, Group (a) 0, (b) 1, (c) 2 and (d) 3

Gompertz curve: The tumor growth models through clinical trial data are proposed and discussed with Gompertz curve (Norton, 1982, 1986). The therapeutic comparison and pattern of kinetic growth are also well discussed (Skipper and Schabel, 1982). The limitation of Gompertz growth curve is also applied and discussed (Laird, 1969; Winsor, 1932). Gompertz model is found suitable in clinical trials design (Norton and Simon, 1986; Perloff *et al*., 1986). However, the validity of Gompertzian model is found poor in breast cancer data (May, 1975). In this study, the model is applied to describe the tumor growth rate *in vivo* mice cell through the duration of growth. Gompertz curve is a time dependent mathematical model. It is very much useful to define the tumor dynamics, where least growth is observed in the initial period Eq. 2:

$$Y(t) = A\exp\left[-\exp\left(\frac{\mu e}{A}(\lambda - t)\right)+1\right] \tag{2}$$

The model is useful to fit the data with nonlinear least square methods by considering the features of the parameters. However, it is difficult to define the cellular growth through the Gompertz curve. In some cases, the model can be generated with error due to absence of real functional relation between response and covariates of interest. The mathematical assumption can be avoided through the model free spline method (Mackey and Glass, 1977, Birch,1999). In this work, the model free spline method is applied in the growth data. The graphical presentation of fitted curves are detailed in Fig. 3.

Delay differential equation: Delay of tumor growth after or without treatment is natural process. The delay differential equation is the extension over ordinary differential equation. It is preferable to use delay differential equation when the delay is natural process of the system. The growth of tumor is measured with delay differential equation. It is assumed that the delay on the growth of the treatment will be natural. The different treatment effect on tumor growth are

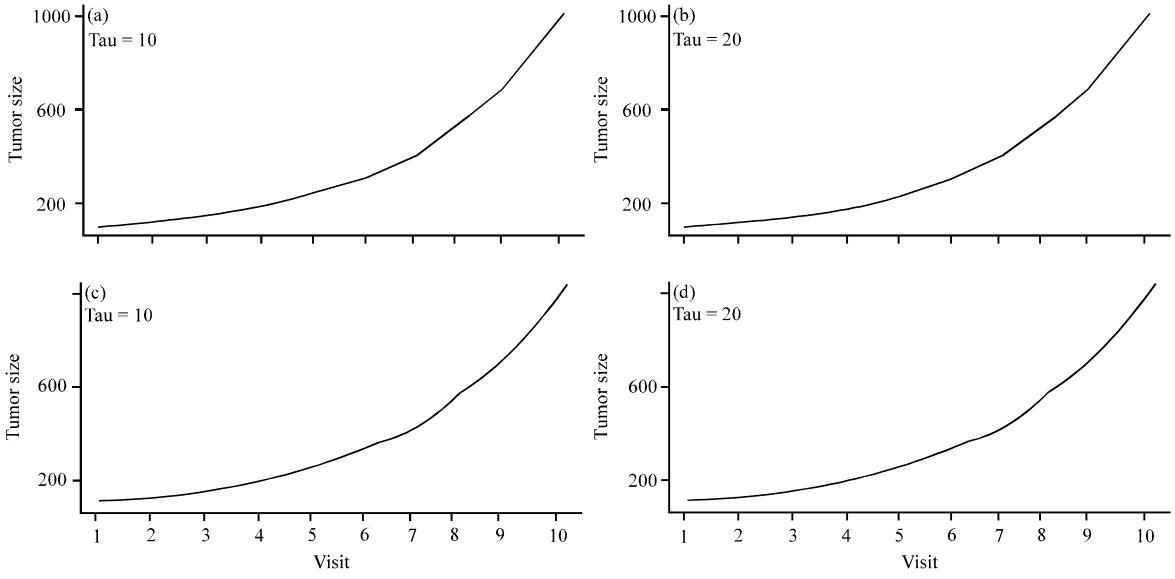

Fig. 3(a-d): Fitted growth curve applied in different visits through Gompertz curve, (a, b) Group 0 and (c, d) Group 1

compared and measured through delay differential equation. The delay differential is applied in population growth (Tziperman *et al.*, 1994) a nd temperature measurement (Bellen and Zennaro, 2003). The basic ingredient of delay differential is the acceptance of past values as the time series manner. The detailed literatures about application of delay differential equation are well discussed (Hale and Lunel, 1993).

The delay differential equation is based on dependent variables having past value. It can be written as Eq. 3-4:

$$Y'(t) = f(t, y(t), y(t-u_1), y(t-u_2), \ldots y(t-u_n)), \text{ for } t_0 \le t \le t_F \tag{3}$$

$$Y(t) = \varphi(t), \text{ for } t \le t_0 \tag{4}$$

$Y'(t) = \varphi(t)$ is the right-hand derivative of y with respect to t, u is the delay. (t-u) is the argument of delay and y(t-u) is value of delay. The term $\varphi(t)$ is past time observation of the dependent variables. The above equation can be generalized with:

$$Y'(t) = f(t.y(t), y(\delta_1(t, y(t))), \ldots y(\delta_n(t, y(t))))), \text{ for } t_0 < t \le t_f$$

$Y(t) = \varphi(t)$, for $t \le t_0$ having delay functions $(\delta_i(t, y(t)), i = 1,,,,, n$ and $(\delta_i(t, y(t)) \le t$.

The detailed mathematical elaborations are given in application part. The derivative of the solution t is dependent on the past value of t i.e., t-1. The equation can be simplified with Eq. 5-6:

$$Y' = -Y(t-1) \tag{5}$$

$$Y(t-1) = 1 \text{ for } t \in [-1, 0] \tag{6}$$

The delay differential equation is elaborated on chaotic production of white cell (Mackey and Glass, 1977). The equation is:

$$Y' = ay_t \frac{1}{1 + y_t} \tag{7}$$

by:

$$Y_t = y(t-u) \text{ and } Y_t = 0.5, \text{ for } t \le 0$$

In this study, the model is extended with Eq. 8-9:

$$Y' = aY_t + \frac{1}{1 + \frac{1}{y_t^c}} + bY \tag{8}$$

$$Y_t = Y(t+u) \text{ and } Y_t = 0.5, \text{ for } t \le 0 \tag{9}$$

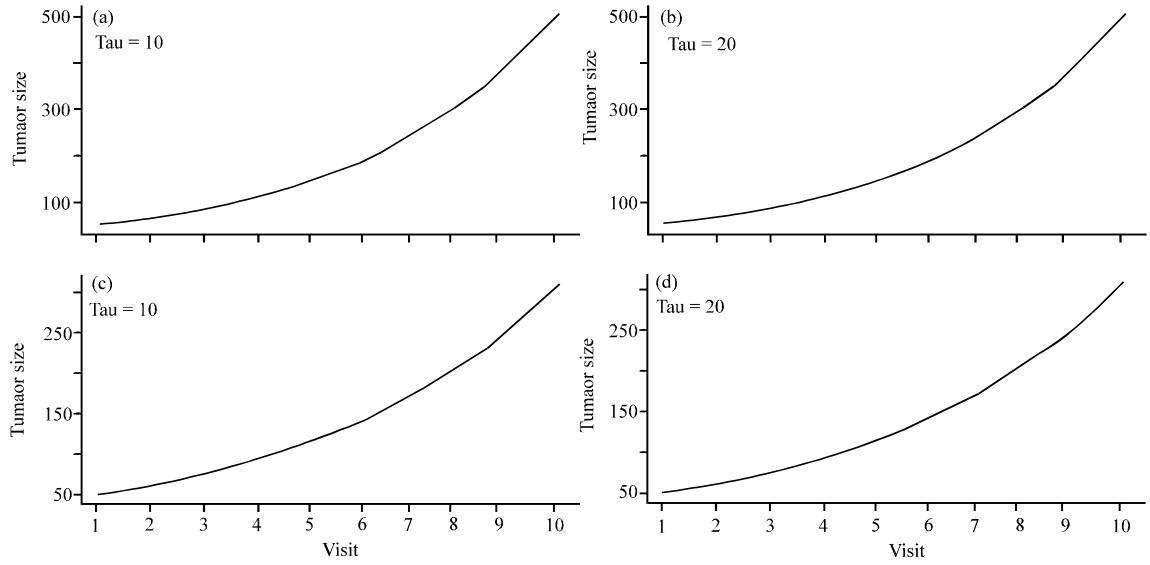

Fig. 4(a-d): Fitted growth curve applied in different visits through delay differential equation, (a, b) Group 2, (c, d) Group 3

The term b is the increase rate. The initial value for y' is the size of tumor growth in presence of gene on earlier time (u). The progress of tumor size is dominated by Eq. 10:

$$\frac{1}{1+\frac{1}{y_t^c}} \tag{10}$$

The desolve function in R is used to solve the delay differential equation. The initial past value and past derivatives are selected based on optimum value of simulation and lag value function.

Application of delay differential equation: Here y is the current size of tumor, y_u is the size at time, b is the rate of induction size of tumor. The first term in the equation for y_ is the introduction of size of tumor before treatment, as the size of time u. The equation generated for basic of a and b. b = 046, 042, 033 and 026 are assumed for the group1, 2, 3 and 4, respectively. The corresponding value of a is observed with 1.36, 1.34, 0.74 and 0.51, respectively. The model is implemented in R. The graphical changes of the rate are given in Fig. 4. The group wise growth comparison can be observed through the graphical expression. The rate of tumor size changes are also detailed in figures.

DISCUSSION

Tumor growth is an emerging issue in cancer clinical research. The area is widely explored in mathematics, statistics and cancer research. The growth rate of tumor is explored with non linear equation (Savage, 2010) and differential equation (Lowengrub *et al*., 2010). Generally, the tumor growth rate is explored without consideration of inequity of cured and uncured tumor. The failed or uncured tumor may also re-grow after treatment failure. This study is illustrated to tumor growth modeling through differential equation, mixed modeling and Gompertz curve. The

statistical modeling in tumor growth size is important in terms of treatment effect. The primary endpoint of cancer treatment is tumor size growth rate. Differential equation is suitable choice to capture the growth rate. However, the growth of tumor sometimes becomes delayed due to several biological factors. The ordinary differential is not suitable for this purpose. The delay differential equation can be applied to address the issue. Contributing factors to reduce the tumor size are also important. Sometimes, the specific drug plays contributing role for rapid growth of tumor. Statistical modeling to explore the relation between tumor size and treatment effect can be carried out through modeling. It is natural that no linear relation between the tumor growth and treatment exists in the problem. In those circumstances, the non-linear modeling is crucial to point out the relation between response and covariates.

CONCLUSION

The fit of tumor growth data from 46 mice to investigate the effect of cisplain is studied. The data are fitted well by the delay differential equation, Gompetrz model and Mixed model. The prior distribution is used for mixed model to obtain the posterior mean estimates of the parameters. The growth curve theory is well-launched in biostatistics area. The detailed progresses of growth models are also elaborated. The application of modeling in untreated tumor growth and treated tumor growth is different. The comprehensive comparison of mathematical and statistical modeling in not carried out. The study is contributed only on treated tumor having re-growth. The study is contributed with extension of delay differential equation on tumor re-growth and dose response. Statistical inference on tumor growth through treatment effect can be carried out in different manners. However, there is a gap between applications of statistical modeling in kinetic cell modeling and irradiated tumor re-growth on tumor volume. The limitation can be overcome in near future through proper illustration. The reason may be due to lack of application of proper statistical modeling. The attempts are made on the available data having treatment effect. The new approach through delay differential equation may be considered for other tumor growth modeling.

REFERENCES

Bellen, A. and M. Zennaro, 2003. Numerical Methods for Delay Differential Equations: Numerical Mathematics and Scientific Computation. The Clarendon Press/Oxford University Press, New York, ISBN: 9780198506546, Pages: 395.

Bhattacharjee, A. and D.C. Nath, 2013. Dependent prior: An application in spinal anaesthesia drug treatment effect comparison. Pak. J. Stat. Oper. Res., 9: 293-303.

Birch, C.P.D., 1999. A new generalized logistic sigmoid growth equation compared with the richards growth equation. Ann. Bot., 83: 713-723.

Cheng, J., L.J. Edwards, M.M. Maldonado-Molina, K.A. Komro and K.E. Muller, 2010. Real longitudinal data analysis for real people: building a good enough mixed model. Stat. Med., 29: 504-520.

Diggle, P. and M.G. Kenward, 1994. Imformative drop-out in longitudinal data analysis. J. Applied Stat., 43: 49-93.

Hale, J.K. and S.M.V. Lunel, 1993. Introduction to Functional Differential Equations (Applied Mathematical Sciences, Volume 99). Springer, New York, USA., ISBN-13: 9780387940762, Pages: 447.

Kim, P.S. and P.P. Lee, 2012. Modeling protective anti-tumor immunity via preventative cancer vaccines using a hybrid agent-based and delay differential equation approach. PLoS Comput. Biol., Vol. 8. 10.1371/journal.pcbi.1002742

Laird, A.K., 1969. Dynamics of growth in tumors and in normal organisms. Natl. Cancer Inst. Monogr., 30: 15-28.

Lindstrom, M.L. and D.M. Bates, 1990. Nonlinear mixed-effects models for repeated measures data. Biometrics, 46: 673-687.

Lowengrub, J.S., H.B. Frieboes, F. Jin, Y.L. Chuang, X. Li, P. Macklin, S.M. Wise and V. Cristini, 2010. Nonlinear modelling of cancer: Bridging the gap between cells and tumours. Nonlinearity, 23: 1-9.

Mackey, M.C. and L. Glass, 1977. Oscillation and chaos in physiological control systems. Science, 197: 287-289.

May, R.M., 1975. Stability and Complexity in Model Ecosystems. 2nd Edn., Princeton University Press, Princeton, USA.

Norton, I., 1982. Cell kinetics in Normal Tissues and in Tumors of the Young. In: Cancer in the Young, Levine, A.S. (Ed.). Masson, New York, pp: 53-82.

Norton, L. and R. Simon, 1986. The Norton-Simon hypothesis revisited. Cancer Treat. Rep., 70: 163-169.

Norton, L., 1986. Implications of kinetic heterogeneity in clinical oncology. Seminars Oncol., 2: 231-249.

Perloff, M., L. Norton, A. Korzun, W. Wood, R. Carey, V. Weinberg and J.F. Holland, 1986. Advantage of an *Adriamycin combination* plus Halotestin after initial cyclophosphamide, methotrexate, 5-fluorouracil, vincristine and prednisone for adjuvant therapy of node-positive stage II breast cancer. Proc. Am. Soc. Clin. Oncol., 5: 70-70.

Rygaard, K. and M. Spang-Thomsen, 1997. Quantitation and Gompertzian analysis of tumor growth. Breast Cancer Res. Treatment, 46: 303-312.

Samson, A., M. Lavielle and F. Mentre, 2006. Extension of the SAEM algorithm to left-censored data in non-linear mixed-effects model: Application to HIV dynamics model. Comput. Stat. Data Anal., 51: 1562-1574.

Samson, A., M. Lavielle and F. Mentre, 2007. The SAEMalgorithm for group comparison tests in longitudinal data analysis based on non-linear mixed-effects model. Stat. Med., 26: 4860-4875.

Savage, H., 2010. A nonlinear ODE model of tumor growth and effect of immunotherapy and chemotherapy treatment in colorectal cancer. Department of Mathematics, May, 2010. http://scholarship.claremont.edu/cgi/viewcontent.cgi?article=1020 and context=hmc_theses.

Skipper, H.E. and F. Schabel Jr., 1982. Quantitative and Cytokinetic Studies in Experimental Tumor Systems. In: Cancer Medicine, Holland, J.F. and E. Frei (Eds.). 2nd Edn., Lea and Febiger, Philadelphia, pp: 636-648.

Tziperman, E., L. Stone, M.A. Cane and H. Jarosh, 1994. El nino chaos: Overlapping of resonances between the seasonal cycle and the pacific ocean-atmosphere oscillator. Science, 264: 72-74.

Winsor, C.P., 1932. The gompertz curve as a growth curve. Proc. Natl. Acad. Sci., 18: 1-8.