

Stochastic Optimization Models for Cancer Chemotherapy

Abstract

In this study, an attempt is made to derive the rates of growth and loss of cancer causing cells by formulating two optimization problems based on Two Stage Stochastic Model for Cancer Cell growth developed by Srinivasa Rao,K. et.al.(2004). One objective is to minimize the expected intensity of cancer causing cells either in mutant or malignant stage, the other is to minimize the stay time of cancer causing cell in the tumor. The subjective constraints are designed with maximum expected levels and limits on variability size of cancer causing cells in mutant and malignant stages. The constraints of the other problem are the expected durations of cancer causing cell in mutant stage, in malignant stage, from mutant stage to malignant stage should not exceed to some targeted time; and the other constraint is on the maximum limit on the variability size of the tumor duration should not be more than some specified limit. The behavior of the models was analyzed with simulated data sets. This study has significant usage in development of decision support systems for optimal drug administration by health care industry for cancer chemotherapy protocols.

Keywords: Stochastic Optimization Model, Cancer Chemotherapy, Optimal Drug Administration

1. Introduction:

Chemotherapy is one of the techniques to treat cancer with chemicals. This may not cure the cancer completely but it can control the growth of tumor for some period. Therefore, chemotherapy should be applied in cycles with periodicity. Human being is one of the multi-cellular organisms where the cell functioning is governed by its genetical instructions. A normal cell should act as per the regulating directions of genetical cell division either for germinating another cell or to die. The cells, which revolt the signal for regulating the cell division shows a way to uninhibited growth and proliferation leads to form a tumor or cancer. The tumor escalation will be due to the spontaneous proliferation and dependent on time. The growth of mutant cell can be minimized by effective chemotherapy.

The main purpose of anti-cancer drug is to destroy cancer-causing cells, but in turn, it may harm both mutant and normal cells. Continuous drug administration leads to remarkable loss of white blood cells and ultimately affects the immunity system of body. This may harm the general health of the patient who is under treatment of chemotherapy. Hence, there is an absolute necessity on drug vacation to the patient for getting recovery from the toxicity effect of drug. At the same time, if the drug vacation period is too large, this leads in resuming the growth process of mutant cells. Therefore, drug vacation period and drug administration periods have to be optimally designed such that the control and resuming of cancer causing cells should not give adverse affect on normal cells. Another dimension of the cancer chemotherapy is on the quantity and frequency of drug in take during the treatment period. Less amount of drug may be ineffective to control the growth of cancer moreover; the regular administration of same drug in small quantities makes the mutant cell as drug resistance. The size of the tumor is a variable subject to various known and unknown reasons. The growth of the cancer causing cells is stochastic in nature. Therefore, the appropriate stochastic model will enable us to predict the dynamics of tumor sizes over a period. A sequential process in which decisions yield uncertain results in turn needs stochastic and dynamic programming models. The stochastic optimization is serving the analyst to take the decision under the presence of uncertainty. Usually, the growth of cells is merely stochastic in nature. Hence, formulation of appropriate stochastic optimization problem will help to determine the parameters behind decision variables.

Martin, R.B. et.al. (1992) studied a model for optimal control of tumor size to maximize the survival time of normal cells when cancer cells are resistant to chemotherapy. Costa, M. I. S. et.al. (1997) studied the Conflicting objectives in chemotherapy with drug resistance using system of differential equations in a cycle non-specific chemotherapy. Andrew J. Coldman (2000) developed stochastic models of chemotherapy for cancer to incorporate its concomitant effect on the normal system and derived overall measures of outcome by the model by incorporating the drug resistance in tumor and normal system growth functions. Andrzej Swierniak, et.al. (2003) described the Cancer chemotherapy as optimal control problem over a fixed horizon with dynamics of cancer chemotherapy by considering the general class of mathematical models. De Pillis LG et.al. (2007) investigated a mathematical model of tumor-immune interactions with chemotherapy and designed the strategies for optimal treatment. Further, they analyzed the dynamics of the model, characterized the optimal controls related to

drug therapy and discussed the numerical results on the optimal strategies. Tirupathi Rao. P. et. al. (2010) derived stochastic models for optimal drug administration in cancer chemotherapy by considering the time of mutant cell duration in the tumor during the drug administration and during drug absence periods. Jinghua Shi et.al. (2011), reviewed the Mathematical models applied to the optimal design of the cancer chemotherapy for effective treatment of colorectal cancer. Michael Engelhart et. al (2011) studied Optimal control methods related to selected cancer chemotherapy problems through Ordinary Differential Equation models for optimal schedules of the drugs. Tirupathi Rao, P. et.al. (2012) developed optimization-programming problem for designing drug administration strategies of chemotherapy for exploring the values of drug dosage level, drug administration period, drug vacation period, number of drug administration cycles and number of drugs applied within a cycle.

From the above information, it is observed that considerable work is reported on modeling the growth of cancer through stochastic assumptions. However, there is a little evidence of literature on the development of stochastic optimization programming, which helps in understanding the thresholds of the disease severity. In order to fill this area of gap, we have made efforts in formulating the stochastic programming problem for the effective drug administration of cancer chemotherapy based on Two Stage Stochastic Model for Cancer Cell growth by Srinivasa Rao, K. et al. (2004). The present work focuses on designing Multi objective stochastic optimization problems by considering the cells at both mutant and malignant stages. The first objective function is formulated to minimize the tumor size, and the second objective is to minimize the duration of cancer causing cells during the time of treatment. The constraints are designed with a view of restriction on the maximum limit of expected number and variability of cancer causing cells. The constraints of the second problem are with expected durations and variability of cancer causing cell in mutant stage, in malignant stage and from mutant stage to malignant stage, which should not exceed to some targeted time as well as some specified limit.

The two stage stochastic model for cancer growth during chemotherapy is considered for this study. If $P_{n,m}(t)$ is the probability of having 'n' cells in the stage of mutant and 'm' cells in state of malignant during time 't', then the characteristics of the model as below.

The average number of cancer causing cells in mutant stage at time 't' is

$$E[N(t)] = \frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \quad \dots (1.1)$$

94 The average number of cancer causing cells in malignant stage at time 't' is

$$95 \quad E[M(t)] = \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left(\frac{N_0\beta}{d_1 + \beta - d_2} \right) (e^{-d_2 t} - e^{-(d_1 + \beta)t}) + M_0 e^{-d_2 t} \quad \dots (1.2)$$

96 The variance of the number of cancer causing cells in the stage of mutant is

$$97 \quad V[N(t)] = \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) \right]^2 + N_0(N_0 - 1)e^{-2(d_1 + \beta)t} + \left(\frac{2\lambda N_0}{d_1 + \beta} \right) (1 - e^{-(d_1 + \beta)t}) (e^{-(d_1 + \beta)t})$$

$$98 \quad + \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] \left[1 - \left\{ \frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right\} \right] \quad \dots (1.3)$$

99 The variance of the number of cancer causing cells in malignant stage is

$$100 \quad V[M(t)] = \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right]^2 + N_0(N_0 - 1) \left[\frac{\beta}{d_1 + \beta - d_2} (e^{-d_2 t} - e^{-(d_1 + \beta)t}) \right]^2$$

$$101 \quad + M_0(M_0 - 1)e^{-2d_2 t} + 2N_0 M_0 \beta e^{-d_2 t} \left[\frac{(e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} \right]$$

$$102 \quad + 2 \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right]$$

$$103 \quad + \left\{ \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \right\}$$

$$104 \quad \left\{ 1 - \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \right\}$$

$$105 \quad \dots (1.4)$$

106 The expected number of cancer causing cells in both the stages of Mutant and Malignant is

$$107 \quad E[L(t)] = \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] + \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right]$$

$$108 \quad + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \quad \dots (1.5)$$

109 The variance of the number of cancer causing cells in both the stages of Mutant and Malignant is

$$110 \quad V[L(t)] = \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) \right]^2 + N_0(N_0 - 1)e^{-2(d_1 + \beta)t} + \left(\frac{2\lambda N_0}{d_1 + \beta} \right) (1 - e^{-(d_1 + \beta)t}) (e^{-(d_1 + \beta)t})$$

$$\begin{aligned}
 & + \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] \left[1 - \left\{ \frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right\} \right] \\
 & + \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right]^2 + N_0 (N_0 - 1) \left[\frac{\beta}{d_1 + \beta - d_2} (e^{-d_2 t} - e^{-(d_1 + \beta)t}) \right]^2 \\
 & + M_0 (M_0 - 1) e^{-2d_2 t} + 2 \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] \\
 & + 2 N_0 M_0 \beta e^{-d_2 t} \left[\frac{(e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} \right] + \left\{ \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \right. \\
 & \left. \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \right\} \left\{ 1 - \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \right. \\
 & \left. \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \right\} - 2 \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] \\
 & \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} \right] \\
 & \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + (N_0 - 1) e^{-(d_1 + \beta)t} \right] + \\
 & \left[\frac{\lambda M_0}{d_1 + \beta} e^{-d_2 t} (1 - e^{-(d_1 + \beta)t}) + N_0 M_0 e^{-(d_1 + \beta + d_2)t} \right] + 2 \left\{ \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] \right. \\
 & \left. \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \right\} \dots (1.6)
 \end{aligned}$$

The above mentioned study also derived the expected duration of the mutant cell and the variance of cancer causing cell duration in the tumor. If 'T' is time duration of a cancer causing cell in the tumor, then

$$\text{The Expected value of T is } E(T) = \frac{\beta + d_2}{(d_1 + \beta)d_2} \dots (1.7)$$

The variance of T is

$$V(T) = \frac{2d_1}{(d_1 + \beta)^3} + \frac{2d_2\beta}{(d_1 + \beta - d_2)} \left(\frac{1}{d_2^3} - \frac{1}{(d_1 + \beta)^3} \right) - \left(\frac{\beta + d_2}{d_1 + \beta - d_2} \right)^2 \dots (1.8)$$

2. STOCHASTIC OPTIMIZATION PROGRAMMING PROBLEMS:

The optimal stochastic programming problem was designed by considering the results of the earlier mentioned models. Problem -1 deals with the objective of minimizing the number of cancer causing cells in the tumor and problem-2 deals with the objective of minimizing the survival duration of cancer causing cell in the tumor.

Notations:

- λ : the rate of growth of cancer cells in the tumor
- β : the transition rate of a cell from mutant to malignant stage
- d_1 : the rate of death of a cell in mutant stage
- d_2 : the rate of death of a cell in malignant stage
- N_0 : Initial number of cells in mutant stage
- M_0 : Initial number of cells in malignant stage
- N : number of cells in mutant stage at time 't'
- M : number of cells in malignant stage at time 't'

Problem -1:

The objective function for the above said optimization problem is as follows,

$$\begin{aligned} \text{Min } Z = & \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] + \left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] \\ & + \left[\frac{\beta N_0 (e^{-d_2 t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2 t} \right] \end{aligned} \quad (2.1)$$

The subjective constraints are mostly with the average growths and the Volatility minimization.

The expected number of cancer causing cells in mutant stage must be within some targeted limit.

$$\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \leq N \quad (2.2)$$

The expected number of cancer causing cells in malignant stage must be within some targeted limit

$$\left[\frac{\lambda \beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2 t}}{d_2} - \frac{e^{-d_2 t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left(\frac{N_0 \beta}{d_1 + \beta - d_2} \right) (e^{-d_2 t} - e^{-(d_1 + \beta)t}) + M_0 e^{-d_2 t} \leq M \quad (2.3)$$

The variability on the number of cancer causing cells in mutant stage should within some healthy threshold limits. These limits are as close as possible to maintain the consistency in the health of

the patient. In other words, it is of minimizing the volatility in the size of the cancer causing cells in mutant stage. Therefore the constraint with this context is

$$\begin{aligned} & \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) \right]^2 + N_0(N_0 - 1)e^{-2(d_1 + \beta)t} + \left(\frac{2\lambda N_0}{d_1 + \beta} \right) (1 - e^{-(d_1 + \beta)t}) (e^{-(d_1 + \beta)t}) \\ & + \left[\frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right] \left[1 - \left\{ \frac{\lambda}{d_1 + \beta} (1 - e^{-(d_1 + \beta)t}) + N_0 e^{-(d_1 + \beta)t} \right\} \right] \leq VN2 \end{aligned} \quad (2.4)$$

Similarly, The variability on the number of cancer causing cells in malignant stage should also be within some healthy threshold limits. Therefore the constraint with this context is

$$\begin{aligned} & \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2t}}{d_2} - \frac{e^{-d_2t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right]^2 + N_0(N_0 - 1) \left[\frac{\beta}{d_1 + \beta - d_2} (e^{-d_2t} - e^{-(d_1 + \beta)t}) \right]^2 \\ & + M_0(M_0 - 1)e^{-2d_2t} + 2N_0M_0\beta e^{-d_2t} \left[\frac{(e^{-d_2t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} \right] \\ & + 2 \left[\frac{\beta N_0 (e^{-d_2t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2t} \right] \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2t}}{d_2} - \frac{e^{-d_2t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] \\ & + \left\{ \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2t}}{d_2} - \frac{e^{-d_2t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left[\frac{\beta N_0 (e^{-d_2t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2t} \right] \right\} \\ & \left\{ 1 - \left[\frac{\lambda\beta}{d_1 + \beta} \left\{ \frac{1 - e^{-d_2t}}{d_2} - \frac{e^{-d_2t} - e^{-(d_1 + \beta)t}}{d_1 + \beta - d_2} \right\} \right] + \left[\frac{\beta N_0 (e^{-d_2t} - e^{-(d_1 + \beta)t})}{d_1 + \beta - d_2} + M_0 e^{-d_2t} \right] \right\} \leq VM2 \end{aligned} \quad (2.5)$$

The decision variables of this problem are the parameters under study and they have to be non negative always. Therefore, the sign of the parameters under study are $\lambda \geq 0; \beta \geq 0; d_1 \geq 0; d_2 \geq 0$;

Problem -2:

$$\text{The objective is to Minimize } Z = \frac{\beta + d_2}{(d_1 + \beta)d_2} \quad (2.6)$$

This is influenced by the constraints as below,

The expected duration of cancer causing cell (which is in the mutant stage) must not exceed some targeted time say T1.

$$\text{Then the constraint with this context is } e^{-(d_1 + \beta)t} \leq T1 \quad (2.7)$$

The expected duration of cancer causing cell (leaving from mutant stage to malignant stage) should not exceed some targeted time say T2.

175 Then the constraint with this context is $\frac{\beta}{d_1 + \beta - d_2} [e^{-d_2 t} - e^{-(d_1 + \beta)t}] \leq T2$ (2.8)

176 The expected duration of cancer causing cell in malignant stage should not exceed some targeted
177 time say T3.

178 Then the constraint with this context is $1 - (\frac{d_1 - d_2}{d_1 + \beta - d_2})e^{-(d_1 + \beta)t} - (\frac{\beta}{d_1 + \beta - d_2})e^{-d_2 t} \leq T3$ (2.9)

179 It is suggestible that the stay time of cancer causing cell (in both formats) has to be as minimum
180 as possible and the variability in the stay of it is as volatile as possible. Hence, the constraint
181 with this context is considered as

$$182 \quad \frac{2d_1}{(d_1 + \beta)^3} + \frac{2d_2\beta}{(d_1 + \beta - d_2)} \left(\frac{1}{d_2^3} - \frac{1}{(d_1 + \beta)^3} \right) - \left(\frac{\beta + d_2}{d_1 + \beta - d_2} \right)^2 \leq VT \quad (2.10)$$

183 The decision variables of this problem are the parameters under study. They are always non
184 negative, which implies that $\beta \geq 0$; $d_1 \geq 0$; $d_2 \geq 0$;

185 **3. Numerical Illustrations and Sensitivity Analysis:**

186 from Table -1, It is observed that the objective of minimizing the expected number of mutant
187 cells is an increasing function of Time when the other parameters are constants. The objective of
188 minimizing the expected number of mutant cells is an increasing function of Initial Size of
189 malignant cells when the other parameters are constants. The objective function is a decreasing
190 function of the sizes of Mutant cells and it is an increasing function of malignant cells as the
191 other parameters are constant. The objective function is a decreasing function of maximum
192 target limit of the variance of mutant cells, and also the maximum target limit of malignant cells.

193 From table-2, It is observed that the rate of cell transition from mutant stage to malignant stage is
194 an increasing function of time. The rate of death of cancer cell at mutant stage is an increasing
195 function of time. The rate of death of cancer cells at malignant stage is a decreasing function of
196 time. The objective of minimizing the duration of cancer causing cell is a decreasing function of
197 time when the other parameters are constant. The rate of cell transition from mutant stage to
198 malignant stage is a decreasing function, and the objective of minimizing the duration of cancer
199 causing cell is a decreasing function of maximum targeted time of cell in malignant stage when
200 the other parameters are constants. The rate of death of malignant cell is a decreasing function
201 and the objective of minimizing the duration of cancer causing cell is an increasing function of

maximum limit in the stay of cancer causing cell in the tumor when the other parameters are constant.

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Annexure

239

Table-1:

240 The values of the Parameters and the objective function for different constants

T	N0	M0	N	M	VN1	VN2	VM1	VM2	Λ	d ₁	d ₂	B	Objective Function
0.0000001	150	250	350	450	15	35	10	35	86.9055	4101418	1.42E+12	533238.9	94.36499
0.0000003									39.22368	1151089	6.72E+11	39376.5	94.36502
0.0000005									65.1994	784816.8	1.07E+11	142112.9	94.36517
0.0000007									78.18334	577463.9	3.72E+10	84627.69	94.36534
0.000001									60.77714	387263.7	3.03E+10	76200.28	94.36539
0.0000001	150	250	350	450	15	35	10	35	86.9055	4101418	1.42E+12	533238.9	94.36499
	140								1.01E+09	68086830	3.36E+08	2.355	15.0001
	130								12447870	83142000	2.37E+08	2.337725	15.00001
	120								1.59E+09	1.06E+08	2.47E+08	2.333742	15.00001
	110								9.85E+08	66241200	8.32E+08	2.35312	15.00019
0.0000001	150	245	350	450	15	35	10	35	79.39644	4050977	1.69E+12	583679	94.36498
		240							14.09168	1347315	2.01E+12	3287344	94.36508
		235							956.0209	4586205	1.23E+10	48422.54	94.36566
		225							1273.595	4598284	6.91E+09	36333.83	94.36591
		210							1381.973	4601133	5.88E+09	33480.47	94.36599
0.0000001	150	250	350	450	15	35	10	35	86.9055	4101418	1.42E+12	533238.9	94.36499
			340						88.87913	4113256	1.42E+12	521400.1	94.36499
			330						88.82435	4112935	1.42E+12	521721.7	94.36499
			320						86.99623	4101974	1.42E+12	532682.9	94.36499
			280						120.8632	4277814	7.62E+11	356840.9	94.36501
			240						129.8648	4277819	7.62E+11	356836.5	94.36501
0.0000001	150	250	350	500	15	35	10	35	121.6671	4253773	9.21E+11	380882.7	94.365
				530					132.4606	4284828	5.54E+11	349827.1	94.36503
				570					146.7458	4318888	4.86E+11	315766.3	94.36504
				590					346.7819	4501058	9.17E+10	133590	94.36519
				620					662.0664	4564691	2.56E+10	69946.39	94.36543
0.0000001	150	250	350	450	15	33	10	35	220.7062	3777780	4.40E+11	179268	100.9809
						30			931.0644	3200337	1.47E+10	34718.11	108.5415
						27			134.4218	2484673	7.23E+11	199675	114.6863
						24			335.9447	2165026	9.65E+10	66405.79	120.0002
						21			149.2848	1719824	4.28E+11	123460.2	124.7494
						18			138.2624	1393166	5.06E+11	108608.9	129.0833
0.0000001	150	250	350	450	15	35	10	35	86.9055	4101418	1.42E+12	533238.9	94.36499
								33	106.7757	4200657	9.47E+11	433998.4	94.365
								27	219.3625	4423429	2.47E+11	211223.6	94.36508
								23	505.2633	4542971	4.47E+10	91671.78	94.36531
								19	1181.886	4595463	8.01E+09	39157.75	94.36584

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Table-2:

250 The values of the Parameters and the objective function for different constants

T	T1	T2	T3	VT	d1	d2	beta	Objective function
0.2	1	2	3	1	12054.71	0.949826	20551.81	0.6636236
0.3					15150.08	0.945025	24299.61	0.6518221
0.4					19457.98	0.940637	29624.61	0.6416776
0.5					24879.79	0.936631	36215.24	0.63289
0.1	2	2	3	1	14975.6	0.955068	27449.02	0.6774695
	3				14234.68	0.955067	26090.89	0.6774703
	4				15752.81	0.955068	28873.67	0.6774687
	5				15752.81	0.955068	28873.67	0.6774687
	6				13593.45	0.955067	24915.49	0.6774710
0.1	1	2	3	1	14085.69	0.955067	25817.79	0.6774704
		4			16570.36	0.955069	30372.27	0.677468
		5			16659.95	0.955069	30536.49	0.6774679
		6			9812.131	0.955063	17984.22	0.6774776
		7			15737.24	0.955068	28845.12	0.6774687
0.1	1	2	3.5	1	27243.68	0.943379	42833.82	0.6479349
			4	1	16694.72	0.935366	23970.45	0.6302153
			4.5		17946.75	0.929575	24262.65	0.6183883
			5		36563.34	0.925209	47354.97	0.6099268
0.1	1	2	3	3	11433.98	0.617596	21574.6	1.058336
				4	9231.425	0.543887	17533.6	1.204503
				5	7212.66	0.491588	13764.07	1.334823
				6	12275.34	0.451994	23510.76	1.453543

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