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Stochastic Optimization Models for Cancer Chemotherapy

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Aims: The study is conducted with the objective of deriving the growth and loss rates of cancer causing cells by formulating two optimization problems based on Two Stage Stochastic Model for Cancer Cell growth developed by Srinivasa Rao and Tirupathi Rao [10]. It has significant usage in development of decision support systems for optimal drug administration by health care industry for cancer chemotherapy protocols.
Study Design: The study is designed for developing the optimization programming problems with two different aims. The primary one 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.
Methodology: The study is further analyzed with the simulated numerical illustrations. The optimization results on the decision parameters were explored and the interpretations were made accordingly. The basic methodology is divided in to two parts. In part-1 the formulation of programming problems was carried out through theoretical notion of Stochastic programming. In part-2 the decision variables were obtained through the numerical illustrations. Interpretations on the cancer chemotherapy and effectiveness of treatment are arrived.

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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 genetic instructions. A normal cell should act as per the regulating directions of genetic instructions of 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 et al. [1] 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 et al. [2] studied the Conflicting objectives in chemotherapy with drug resistance using system of differential equations in a cycle non-specific chemotherapy. Andrew J. Coldman [3] 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. [4] 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. [5] 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. [6] 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. [7], reviewed the Mathematical models applied to the optimal design of the cancer chemotherapy for effective treatment of colorectal cancer. Michael Engelhart et al. [8] 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. [9] 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 Ra and Tirupathi Srinivasa Rao [10]. 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

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

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

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

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

$$V[N(t)] = \left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t})\right]^2 + N_0(N_0-1)e^{-2(d_1+\beta)t} + \left(\frac{2\lambda N_0}{d_1+\beta}\right)(1-e^{-(d_1+\beta)t})(e^{-(d_1+\beta)t}) \quad + s\left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0 e^{-(d_1+\beta)t}\right] \left[1-\left\{\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0 e^{-(d_1+\beta)t}\right\}\right] \quad \text{... (1.3)}$$

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

$$V[M(t)] = \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]^2 + N_0(N_0-1)\left[\frac{\beta}{d_1+\beta-d_2}(e^{-d_2t}-e^{-(d_1+\beta)t})\right]^2 + M_0(M_0-1)e^{-2d_2t} + 2N_0M_0\beta e^{-d_2t}\left[\frac{(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2}\right] + 2\left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right] \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left\{\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\} \left\{1-\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\} \quad \text{..(1.4)}$$

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

$$E[L(t)] = \left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right] + \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right] \quad \text{... (1.5)}$$

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

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

$+\left(\frac{2\lambda N_0}{d_1+\beta}\right)(1-e^{-(d_1+\beta)t})(e^{-(d_1+\beta)t}) + \left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right]$

$\left[1-\left\{\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right\}\right] + \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]^2 +$

$N_0(N_0-1)\left[\frac{\beta}{d_1+\beta-d_2}(e^{-d_2t}-e^{-(d_1+\beta)t})\right]^2 + M_0(M_0-1)e^{-2d_2t}$

$+2\left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]$

$+2N_0M_0\beta e^{-d_2t}\left[\frac{(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2}\right] + \left\{\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] +\right.$

$\left.+\left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\}\left\{1-\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] +\right.$

$\left.\left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\} - 2\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]$

$\left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2}\right]$

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

$\left[\frac{\lambda M_0}{d_1+\beta}e^{-d_2t}(1-e^{-(d_1+\beta)t}) + N_0M_0e^{-(d_1+\beta+d_2)t}\right] + 2\left\{\left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right]\right.$

$\left.\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\}$ ... (1.6)

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

The Expected value of T is

$$E(T) = \frac{\beta + d_2}{(d_1+\beta)d_2} \quad \ldots \quad (1.7)$$

The variance of T is

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

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,

$$\text{Min } Z = \left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0 e^{-(d_1+\beta)t}\right] + \left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0 e^{-d_2t}\right] \quad (2.1)$$

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

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

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

$$\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left(\frac{N_0\beta}{d_1+\beta-d_2}\right)(e^{-d_2t}-e^{-(d_1+\beta)t}) + M_0 e^{-d_2t} \le M \quad (2.3)$$

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

$$\left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t})\right]^2 + N_0(N_0-1)e^{-2(d_1+\beta)t} + \left(\frac{2\lambda N_0}{d_1+\beta}\right)(1-e^{-(d_1+\beta)t})(e^{-(d_1+\beta)t}) + \left[\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right]\left[1-\left\{\frac{\lambda}{d_1+\beta}(1-e^{-(d_1+\beta)t}) + N_0e^{-(d_1+\beta)t}\right\}\right] \le VN2 \tag{2.4}$$

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

$$\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right]^2 + N_0(N_0-1)\left[\frac{\beta}{d_1+\beta-d_2}(e^{-d_2t}-e^{-(d_1+\beta)t})\right]^2 + M_0(M_0-1)e^{-2d_2t} + 2N_0M_0\beta e^{-d_2t}\left[\frac{(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2}\right] + 2\left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left\{\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\}\left\{1-\left[\frac{\lambda\beta}{d_1+\beta}\left\{\frac{1-e^{-d_2t}}{d_2} - \frac{e^{-d_2t}-e^{-(d_1+\beta)t}}{d_1+\beta-d_2}\right\}\right] + \left[\frac{\beta N_0(e^{-d_2t}-e^{-(d_1+\beta)t})}{d_1+\beta-d_2} + M_0e^{-d_2t}\right]\right\} \le VM2 \tag{2.5}$$

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 $\lambda \ge 0$; $\beta \ge 0$; $d_1 \ge 0$; $d_2 \ge 0$;

Problem -2:

The objective is to Minimize

$$Z = \frac{\beta + d_2}{(d_1+\beta)d_2} \tag{2.6}$$

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.

Then the constraint with this context is

$$e^{-(d_1+\beta)t} \leq T1 \tag{2.7}$$

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

Then the constraint with this context is

$$\frac{\beta}{d_1+\beta-d_2}\left[e^{-d_2 t}-e^{-(d_1+\beta)t}\right] \leq T2 \tag{2.8}$$

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

Then the constraint with this context is

$$1-\left(\frac{d_1-d_2}{d_1+\beta-d_2}\right)e^{-(d_1+\beta)t}-\left(\frac{\beta}{d_1+\beta-d_2}\right)e^{-d_2 t} \leq T3 \tag{2.9}$$

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

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

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

The applicability of the above model has a very broad spectrum. These models can be used for assessing the cancer severity either in any organ such as liver, breast, prostate, cervix, bladder, lungs, etc; or in any tumor or in tissue, muscle or in all over body or the systems like digestive system, endocrinology, blood circulation, respiratory systems, nervous system, etc.

3. NUMERICAL ILLUSTRATIONS AND SENSITIVITY ANALYSIS

From Table 1, It is observed that the objective of minimizing the expected number of mutant cells (Z_1) is an increasing function; death rate of mutant cells (d_1) is a decreasing function; death rate of malignant cells (d_2) is a decreasing function; of Time (t) when the other parameters are constants. The objective of minimizing the expected number of mutant cells (Z1) is a decreasing function; transition rate of mutant cells to malignant cells (β) is an increasing function; the death rate of malignant cells (d2) is an increasing function; the death rate of mutant cells (d1) is a decreasing function; the arrival rate of mutant cells (λ) is a

decreasing function of Initial Size of malignant cells (M0) when the other parameters are constants. The objective function (Z1) an increasing function; the rate of transition from mutant to malignant (β) is a decreasing function; The rate of death of malignant cells (d2) is a decreasing function; the rate of death of mutant cells (d1) is an increasing function; the rate of arrivals of mutant cells (λ) is an increasing function of the expected size of malignant cells (M) as the other parameters are constant. The objective function (Z1) is a decreasing function; the rate of death of mutant cells (d1) is an increasing function of Variance of maximum target limit of mutant cells (VN2) when all other parameters are constant. The objective function (Z1) is a decreasing function; the rate of transition cells from mutant to malignant cells (β) is an increasing function; the death rate of malignant cells (d2) is an increasing function; the death rate of mutant cells (d1) is a decreasing function; and the arrival rate of mutant cells (λ) is a decreasing function; of maximum limit on variance of malignant cells (VM2) when the other parameters are constant.

Table 1. The values of the parameters and the objective function for different constants

T	N_0	M	N	M	V	V	V	V	λ	d_1	d_2	β	Obj. Fun.
0.0000	15	25	35	45	15	35	10	35	86.905	41014	1.42E	53323	94.36499
0.0000									39.223	11510	6.72E	39376	94.36502
0.0000									65.199	78481	1.07E	14211	94.36517
0.0000									78.183	57746	3.72E	84627	94.36534
0.0000									60.777	38726	3.03E	76200	94.36539
0.0000	15	25	35	45	15	35	10	35	86.905	41014	1.42E	53323	94.36499
	14								1.01E	68086	3.36E	2.355	15.0001
	13								12447	83142	2.37E	2.337	15.00001
	12								1.59E	1.06E	2.47E	2.333	15.00001
	11								9.85E	66241	8.32E	2.353	15.00019
0.0000	15	24	35	45	15	35	10	35	79.396	40509	1.69E	58367	94.36498
		24							140.91	13473	2.01E	32873	94.36508
		23							956.02	45862	1.23E	48422	94.36566
		22							1273.5	45982	6.91E	36333	94.36591
		21							1381.9	46011	5.88E	33480	94.36599
0.0000	15	25	35	45	15	35	10	35	86.905	41014	1.42E	53323	94.36499
			34						88.879	41132	1.42E	52140	94.36499
			33						88.824	41129	1.42E	52172	94.36499
			32						86.996	41019	1.42E	53268	94.36499
			28						120.86	42778	7.62E	35684	94.36501
0.0000	15	25	35	50	15	35	10	35	121.66	42537	9.21E	38088	94.365
				53					132.46	42848	5.54E	34982	94.36503
				57					146.74	43188	4.86E	31576	94.36504
				59					346.78	45010	9.17E	13359	94.36519
				62					662.06	45646	2.56E	69946	94.36543
0.0000	15	25	35	45	15	33	10	35	220.70	37777	4.40E	17926	100.9809
						30			931.06	32003	1.47E	34718	108.5415
						27			134.42	24846	7.23E	19967	114.6863
						24			335.94	21650	9.65E	66405	120.0002
						21			149.28	17198	4.28E	12346	124.7494
0.0000	15	25	35	45	15	35	10	35	86.905	41014	1.42E	53323	94.36499
								33	106.77	42006	9.47E	43399	94.365
								27	219.36	44234	2.47E	21122	94.36508
								23	505.26	45429	4.47E	91671	94.36531
								19	1181.8	45954	8.01E	39157	94.36584

From Table 2, It is observed that the rate of cell transition from mutant stage to malignant stage (beta) is an increasing function; The rate of death of cancer cell at mutant stage (d1) is an increasing function; The rate of death of cancer cells at malignant stage (d2) is a decreasing function; and The objective of minimizing the duration of cancer causing cell (Z2) is a decreasing function of time (T) when the other parameters are constant. The rate of cell transition from mutant stage to malignant stage (β) is not having any pattern, and the objective of minimizing the duration of cancer causing cell (z2) is a decreasing function; the death rate of malignant cells (d2) is a decreasing function of maximum targeted time of cell in malignant stage (T3) when the other parameters are constants. The rate of death of malignant cell (d2) is a decreasing function and the objective of minimizing the duration of cancer causing cell (Z2) is an increasing function of maximum limit in the variance of stay of cancer causing cell in the tumor (VT) when the other parameters are constant.

Table 2. The values of the parameters and the objective function for different constants

T	T1	T2	T3	VT	d_1	d_2	β	Objective function (Z_2)
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	14975.60	0.955068	27449.02	0.677 4695
	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			9812.13	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	21574.60	1.058336
				4	9231.42	0.543887	17533.60	1.204503
				5	7212.66	0.491588	13764.07	1.334823
				6	12275.34	0.451994	23510.76	1.453543

4. CONCLUSION

The main focus of this work is on formulation of stochastic optimization programming problem for getting the decision parameters of chemotherapy based on the results of stochastic models developed by Srinivasa Rao and Tirupathi Rao [10]. Multi objective stochastic optimization problems were designed by considering the models on average size and variances of number of cells at mutant and malignant stages. The former problem is on minimization of average size of tumor with the constraints of restriction on the maximum size of expected number and minimum volatility of cancer causing cells; the latter problem is on minimization of average duration of cancer causing cells during the time of treatment with the constraints of maximum expected duration and minimum variability duration of cancer causing cell in mutant stage, in malignant stage and from mutant stage to malignant stages.

The formulated programming problems are presented in section 2 as problem 1 and 2. The numerical illustrations were given in section-3, which were the results of several decision variables by solving the developed non linear programming problems. The other prime concern of the numerical illustration is to observe the patterns of objective function is achieved.

The results in Table 1 have provided the evidence that the average number of mutant cells is in increasing trend with respected to time period during the drug vacation. The death rate of mutant and malignant cells are decreased when the duration of drug vacation is more. The death rate of malignant cells (d_2) is increasing when the initial size of malignant cells are increasing during chemotherapy; whereas the death rate of mutant cells (d_1) is decreasing when the initial size of malignant cells are increasing. Further the arrival rate of mutant cells (λ) is decreasing when there is increment in the Initial Size of malignant cells (M_0). The death rate of malignant cells (d2) is a decreasing function when the existing expected size of malignant cells is increasing. However the death rate of mutant cells (d1) and the arrival rate of mutant cells (λ) are increasing when the expected size of malignant cells (M) are increasing. The death rate of mutant cells (d_1) is increasing when the variability in the target limit of mutant cells (VN2) is increasing may be due to increased volatility leads to increase the generation of mutant cells.

The results in Table 2 reveal that the rate of cell transition from mutant stage to malignant stage (β) is increasing with time. function; The death rate of cancer cell at mutant stage (d_1) is increasing and the death rate of cancer cells at malignant stage (d_2) is decreasing with time period during chemotherapy. This indicates the targeting cell killing with the administered drug is achieving its objective. The death rate of malignant cells (d_2) is a decreasing when maximum targeted time of cell in malignant stage (T_3) is increasing. The death rate of malignant cell (d_2) is decreasing when maximum limit in the variance of stay of cancer causing cell in the tumor (VT) is increasing.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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