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Stochastic Programming on Optimal Drug Administration for Three-Stage Cancer Chemotherapy Treatment

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Abstract In this paper, a stochastic programming problem is formulated for optimal drug administration to the cancer patients under chemotherapy. A stochastic model for three-stage cancer growth[1] has been considered for formulating the objective function and constraints. The objective of the problem is to maximize the drug efficacy subject to the constraints on the admissible protocols of healthy drug administration. The health status of the patient during drug presence and its absence can be evaluated through the developed model. Numerical illustrations were given for better understanding the model. This study will have extensive uses for health care industry in optimal chemotherapy.

Keywords Optimal Drug Administration, Stochastic Programming, Cancer Chemotherapy, Healthcare Management

1. Introduction

Cancer is a disease of division or proliferation of cells on abnormal, uninterrupted and continuous manner after formal initiation of cancer causing cell after mutant behaviour of a normal cell. The formation of malignancy is a resulting stage of transformation of normal cell division. This mechanism may be in stages, such as (i) Forming of mutant cell from normal cell (stage I); (ii) Formulation of pre malignant cell from mutant cell (stage II); and (iii) further transformation of pre-malignant cell in to malignant cell (stage-III). We will observe the faster growth rate among cell division when a normal cell is converted in to a malignant cell. It may be due to many unexplained reasons. In fact, there is no exact proposition on the cause of formation and growth of cancer cells. The genetical impacts, inactivation of alleles, formation location of cancer causing cell, the type of tissue and many more similar reasons may be the influencing factors of cancer growth. Identification of cancer at initial stages will be helpful to avoid the ultimate risk of death. The living body system has its own system of regulation and control over cell division and growth/loss processes of cells. The immunity system of the body will act as a defensive mechanism to protect the existing normal cells from invading mutant cells. This situation may leads to a considerable loss of white blood cells (WBC). Sometimes the active immune system may be responsible for the count of WBC beyond the upper threshold limit, which may cause the problems like leukemia (blood cancer). Hence the size of WBC either way at abnormal extremes is unwanted.

Chemotherapy is a treatment of cancer control with a combination of drugs, usually administered in cycles with different intensified spells within the cycle. It has some considerable negative impacts also. It may harm some healthy and normal cells, though the objective of drug administration is to kill the cancer causing cells. In such cases, the WBC may come to the rescue of protecting normal and healthy cells. Consequently, there is a possibility of WBC loss. Continuous drug administration leads to health hazards due to the loss of normal cells and white blood cells. Hence, the patient needs periodic health checkups to assess the status levels of WBC. If the loss of WBC is considerably high then they have to be allowed to drug vacation to get recovery from the chemical toxicity of drugs. However, drug vacation may leads to re-aggravate the growth of mutant cell population. Therefore, both long-term drug administration and long-term drug vacation are unwanted. Regarding the drug dosage levels, drug administration above the required quantity will harm the natural immunity system by killing both normal and white blood cells. On the other hand, the drug quantity less than the required level will make the body drug resistant. Hence, there is a need of maintaining the optimal levels in drug doses for chemotherapy patient. The growth and loss behaviour of both normal and mutant cells are greatly influenced by the condition of drug administration and drug vacation.

The applications of engineering optimal control theory to investigate the drug regimen for reducing an exponential tumor cell population have been studied[2,3]. The cancer chemotherapy optimization and computing models were developed by branching processes[4]. Toxicity limits are

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used to develop a model on optimal control for cancer chemotherapy[5,6]. The treatment of tumor over a fixed period of time by the repeated administration of a single drug is described by an optimal parameter selection model of cancer chemotherapy[7]. A protocol for drug administration to the tumor with immune resistance was mathematically modeled[8]. A single drug administration was applied for optimal cancer chemotherapy[9]. Optimized drug regimens by an efficacy-toxicity in cancer chemotherapy were modeled mathematically[10]. Stochastic model for optimal drug administration in cancer chemotherapy have been developed[11]. The problem of optimal administration of chemotherapeutic agents has been discussed for the treatment of brain tumors[12]. Treatment dependent malignancy growth was modeled with stochasticity and a stochastic programming approach is used for optimal drug administration in the treatment of two-stage cancer[13,14]. An approach of stochastic programming problem was developed for optimal drug administration for cancer chemotherapy[15].

There was much emphasis on the usage of mathematical modeling on the studies of cancer growth by deterministic and stochastic assumptions. Very few available evidences are there in stochastic modeling of cancer growth during chemotherapy and also on optimization modeling of drug administration. In this study, a stochastic programming problem is developed for maximizing the drug effectiveness in 3-stage cancer chemotherapy. The phenomena of cell division, growth and loss of various stages are modeled with stochastic assumptions by Tirupathi Rao et.al[1]. Three-way Poisson process was used to develop the basic stochastic model. The mathematical formulae for the expected number of cells at stage-I, stage-II and stage-III; the variance of number of cells at stage-I, stage-II and stage-III were derived. These derived relations have been used for formulating the objective function and the constraints of the proposed programming problem. The constraint on healthy threshold limits of WBC is also considered. The decision parameters like rate of growth of mutant (stage-I) cells, premalignant (stage-II) cells, malignant (stage-III) cells; the rate of transformations from mutancy (stage-I) to pre-malignancy (stage-II), from pre-malignancy (stage-II) to malignancy (stage-III); and the death rates of mutant (stage-I) cells, premalignant (stage-II) cells, malignant (stage-III) cells in a tumor, etc are obtained with the study.

2. Stochastic Model and Statistical Components

It is assumed that a mutant (stage-I) cell may be either transformed to a premalignant (stage-II) cell or it may get death. A premalignant (stage-II) cell is either transformed to malignant (stage-III) cells or it may get death. The malignant (stage-III) cell either divided in to further malignant cells or it may get death. The behaviour of the cell division is influenced by the presence and absence of drug. The Statistical measures such as Average number of mutant (stage-I) cells; Average number of premalignant (stage-II) cells; and Average number of malignant (stage-III) cells during drug administration are denoted by $E(N_A)$, $E(M_A)$ and $E(K_A)$ respectively and Similarly the average number of cells in stage-I, stage-II and stage-III during drug vacation are denoted by $E(N_V)$, $E(M_V)$ and $E(K_V)$ respectively. The patient's health status during presence and absence of drug are to be considered as complementary event. Therefore, the total effect of cell loss/growth is a linear combination of both drug presence and its absence. Let 'X' be the number of cells in a specific category. Then the expected number of cells during the drug administration and drug vacation is defined as aE(X)+(1-a)E(X); where a=1, when drug is administered; a=0, when drug is not administered.

Let $\alpha_1, \beta_1, \gamma_1$ be the rates of generation of stage-I cells from normal cells; stage II cells from stage-I; stage-III cells from stage-II respectively during drug presence. Let λ_1, δ_1, θ_1 be the rates of deaths cells from stage-I, stage-II, stage-III respectively during drug presence. Similarly the rates of generation of stage-I, stage-II and stage-III cells are $\alpha_0, \beta_0, \gamma_0$ during drug absence. λ_0, δ_0, θ_0 are the rates of deaths of stage-I, stage-II and stage-III cells during drug absence. It is assumed that $\alpha, \beta, \gamma, \lambda, \delta, \theta$ are the linear combinations expressed as $\alpha = a.\alpha_0+(1-a).\alpha_1$; $\beta = b.\beta_0+(1-b).\beta_1$; $\gamma = c.\gamma_0+(1-c).\gamma_1$; $\lambda = d.\lambda_0+(1-d).\lambda_1$; $\delta = e.\delta_0+(1-e).\delta_1$; $\theta = f.\theta_0+(1-f).\theta_1$ for a, b, c, d, e, f, g are equal to either '0' or '1'. The schematic diagram show below shall explain the above mechanism of cell division and growth in detail.

From the work of Tirupathi Rao et.al. (2012), the derived relations from the model are

The expected number of mutant (stage-I) cells in a tumor at time t during drug administration is

$$E(N_A) = \left[\frac{(1-a)\alpha_1}{(1-d)\lambda_1 + (1-b)\beta_1} . [1 - e^{-((1-d)\lambda_1 + (1-b)\beta_1)t}](1 - N_0) \right] \tag{2.1}$$

The expected number of premalignant (stage-II) cells in a tumor at time t during drug administration is

$$E(M_A) = \left[\frac{(1-a)\alpha_1 . (1-b)\beta_1)}{[(1-d)\lambda_1 + (1-b)\beta_1][(1-d)\lambda_1 + (1-b)\beta_1 - (1-f)\delta_1 - (1-c)\gamma_1]} - \frac{N_0(1-b)\beta_1}{[(1-d)\lambda_1 + (1-b)\beta_1 - (1-f)\delta_1 - (1-c)\gamma_1]} \right] . e^{-[(1-d)\lambda_1 + (1-b)\beta_1)]t}$$

$$-\left[\frac{(1-a)\alpha_1.(1-b)\beta_1}{[(1-f)\delta_1+(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1]}\right.$$
$$\left.-\frac{N_0(1-b)\beta_1}{[(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1]}-M_0\right]e^{-[(1-f)\delta_1+(1-c)\gamma_1]t}$$
$$+\frac{((1-a)\alpha_1)((1-b)\beta_1)}{[(1-f)\delta_1+(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1]} \quad (2.2)$$

The expected number of malignant (stage-III) cells in a tumor at time t during drug administration is

$$E(K_A)=\left[\frac{(1-a)\alpha_1.(1-b)\beta_1.(1-c)\gamma_1}{[(1-f)\delta_1+(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1]}\right.$$
$$\left.-\frac{N_0(1-b)\beta_1(1-c)\gamma_1}{[(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1]}-M_0(1-f)\delta_1\right].$$
$$\frac{e^{-[(1-f)\delta_1+(1-c)\gamma_1]t}}{[(1-f)\delta_1+(1-c)\gamma_1-(1-g)\theta_1]}-\left[\frac{(1-a)\alpha_1.(1-b)\beta_1.(1-c)\gamma_1}{(1-g)\theta_1[(1-d)\lambda_1+(1-b)\beta_1-(1-g)\theta_1]}\right.$$
$$\frac{N_0.(1-b)\beta_1.(1-c)\gamma_1}{[(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1-(1-g)\theta_1]}$$
$$\left.-M_0(1-d)\lambda_1\right]\frac{e^{-[(1-g)\theta_1]t}}{[(1-f)\delta_1+(1-c)\gamma_1-(1-g)\theta_1]}+K_0\frac{e^{-[(1-g)\theta_1]t}}{[(1-f)\delta_1+(1-c)\gamma_1-(1-g)\theta_1]} \quad (2.3)$$
$$+\left[N_0(1-b)\beta_1(1-c)\gamma_1-\frac{(1-a)\alpha_1.(1-b)\beta_1.(1-c)\gamma_1}{(1-d)\lambda_1+(1-b)\beta_1}\right].$$
$$\frac{e-[(1-d)\lambda_1+(1-b)\beta_1]t}{[(1-d)\lambda_1+(1-b)\beta_1-(1-f)\delta_1-(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1-(1-g)\theta_1]}$$
$$-\frac{(1-a)\alpha_1.(1-b)\beta_1.(1-c)\gamma_1}{(1-g)\theta_1[(1-f)\delta_1-(1-c)\gamma_1][(1-d)\lambda_1+(1-b)\beta_1]}$$

The expected number of mutant (stage-I) cells in a tumor at time t during drug vacation is

$$E(N_v)=\frac{a\alpha_0}{d\lambda_0+b\beta_0}[1-e^{-[d\lambda_0+b\beta_0]t}(1-N_0)]\left[\frac{a\alpha_0.b\beta_0}{(d\lambda_0+b\beta_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}\right.$$
$$\left.-\frac{N_0b\beta_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}\right]e^{-[d\lambda_0+b\beta_0]t}-\left[\frac{a\alpha_0.b\beta_0}{(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}\right. \quad (2.4)$$
$$\left.-\frac{N_0b\beta_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}-M_0\right]e^{-[(f\delta_0+c\gamma_0)]t}+\frac{a\alpha_0.b\beta_0}{(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0)}$$

The expected number of premalignant (stage-II) cells in a tumor at time‘t’ during drug vacation is

$$E(M_v)=\left[\frac{a\alpha_0.b\beta_0.c\gamma_0}{(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}-\frac{N_0b\beta_0.c\gamma_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}-M_0.f\delta_0\right]\frac{e^{-(c\gamma_0+f\delta_0)t}}{(f\delta_0+c\gamma_0-g\theta_0)}$$
$$-\left[\frac{a\alpha_0.b\beta_0.c\gamma_0}{g\theta_0[d\lambda_0+b\beta_0-g\theta_0]}-\frac{N_0b\beta_0.c\gamma_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)(d\lambda_0+b\beta_0-g\theta_0)}-M_0.c\gamma_0\right].$$
$$\frac{e^{-g\theta_0t}}{(f\delta_0+c\gamma_0-g\theta_0)}+K_0\frac{e^{-g\theta_0t}}{(f\delta_0+c\gamma_0-g\theta_0)}+\left[N_0b\beta_0c\gamma_0-\frac{a\alpha_0.b\beta_0.c\gamma_0}{(d\lambda_0+b\beta_0)}\right]$$
$$+\frac{e^{-[d\lambda_0+b\beta_0]t}}{(d\lambda_0+b\beta_0-g\theta_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}+\frac{a\alpha_0.b\beta_0.c\gamma_0}{g\theta_0(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0)} \quad (2.5)$$

The expected number of malignant (stage-III) cells in a tumor at time‘t’ during drug vacation is

$$E(K_V)=\left[\frac{a\alpha_0.b\beta_0.c\gamma_0}{(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}-\frac{N_0b\beta_0.c\gamma_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}-M_0.f\delta_0\right]\frac{e^{-(c\gamma_0+f\delta_0)t}}{(f\delta_0+c\gamma_0-g\theta_0)}$$
$$-\left[\frac{a\alpha_0.b\beta_0.c\gamma_0}{g\theta_0[d\lambda_0+b\beta_0-g\theta_0]}-\frac{N_0b\beta_0.c\gamma_0}{(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)(d\lambda_0+b\beta_0-g\theta_0)}-M_0.c\gamma_0\right].$$
$$\frac{e^{-g\theta_0t}}{(f\delta_0+c\gamma_0-g\theta_0)}+K_0\frac{e^{-g\theta_0t}}{(f\delta_0+c\gamma_0-g\theta_0)}+$$
$$+\frac{e^{-[d\lambda_0+b\beta_0]t}}{(d\lambda_0+b\beta_0-g\theta_0)(d\lambda_0+b\beta_0-f\delta_0-c\gamma_0)}+\frac{a\alpha_0.b\beta_0.c\gamma_0}{g\theta_0(f\delta_0+c\gamma_0)(d\lambda_0+b\beta_0)} \quad (2.6)$$

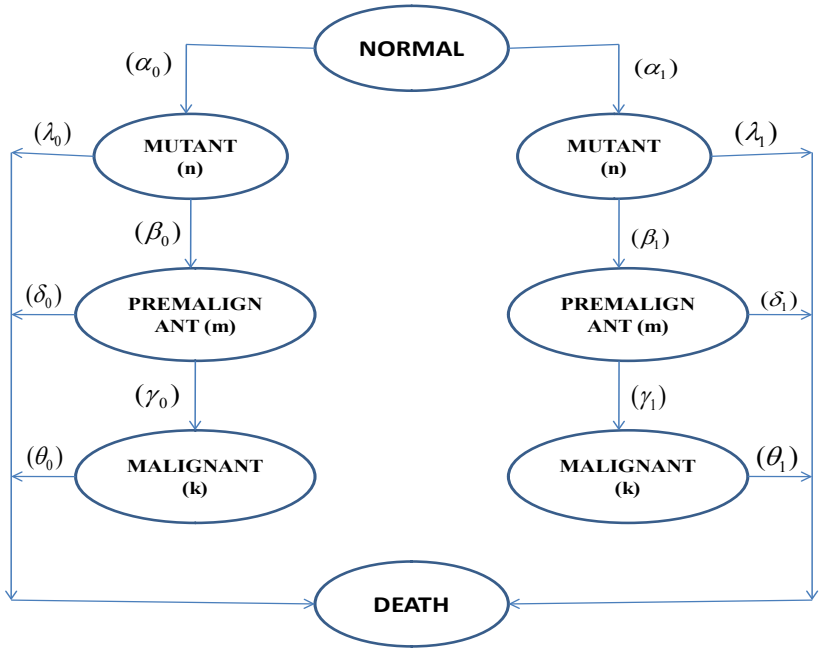

Figure 1. The schematic diagram for the spread of 3 stage cancer

3. Stochastic Programming Problem

in this section, the procedure for formulation of optimizations programming problem is discussed. The objective is on maximizing the drug's net effectiveness (pooling the positive, negative effectiveness) of drug on killing of cancer causing cells at all stages.

3.1. Notation and Terminology

i : Number of drug cycles in overall treatment of chemotherapy; i=1,2,… l ;

l **:** Maximum number of drug cycles;

j : Number of spells of drug administration in each cycle; j=1,2, …k;

k : Maximum number of drug spells within a cycle;

r : Number of drug vacation periods in the total treatment process; r=1,2, … $l-1$;

s : Number of days within a period of drug vacation; s=1,2, … ω;

ω : Maximum number of days within a drug vacation period.

a_{ij}: Number of units of drug doses in i^{th} cycle and j^{th} spell of drug administration (DA);

p_{ij} : Positive (+ ve) effect of one unit DA on a mutant(stage-I) cell during i^{th} cycle and j^{th} spell;

q_{ij}: Negative (- ve) effect of one unit DA on a mutant(stage-I)cell during i^{th} cycle and j^{th} spell;

b_{ij}: +ve effect of one unit DA on a premalignant (stage-II) cell during i^{th} cycle and j^{th} spell;

c_{ij} : -ve effect of one unit of DA on one premalignant (stage-II) cell during i^{th} cycle and j^{th} spell;

u_{ij} : +ve effect of one unit DA on one malignant (stage-III) cell during i^{th} cycle and j^{th} spell;

v_{ij} : - ve effect of one unit of DA on one malignant (stage-III) cell during i^{th} cycle and j^{th} spell;

α_{ij}: Loss of WBC in one unit of DA for killing of one stage-I cell in i^{th} cycle and j^{th} spell;

β_{ij}: Loss of WBC in one unit of DA for killing of one stage-II cell in i^{th} cycle and j^{th} spell;

γ_{ij}: Loss of WBC in one unit of DA for killing of one stage-III cell in i^{th} cycle and j^{th} spell;

$\mathbf{d_{rs}}$**:**+ve impact ofone unit of drug vacation (DV) time on one "stage-I" cell in r^{th} DV period, s^{th} day;

$\mathbf{e_{rs}}$**:** - ve impact of one unit time of DV on one "stage-I" cell in r^{th} DV period and s^{th} day;

$\mathbf{f_{rs}}$**:** +ve impact of one unit time of DV on one "stage-II" cell during r^{th} DV period and s^{th} day;

$\mathbf{g_{rs}}$**:** - ve impact of one unit time of DV on one "stage-II" cell during r^{th} DV period and s^{th} day;

$\mathbf{m_{rs}}$**:** +ve impact of one unit time of DV on one "stage-III" cell during r^{th} DV period and s^{th} day;

$\mathbf{n_{rs}}$**:** - ve impact of one unit time of DV on one "stage-III" cell during r^{th} DV period and s^{th} day;

$\boldsymbol{\lambda_{rs}}$**:** Loss of WBC per unit time of DV due to growth of one "stage-I" cell in r^{th} DV period, s^{th} day;

$\boldsymbol{\delta_{rs}}$**:** Loss of WBC per unit time of DV due to growth of one "stage-II" cell in r^{th} DV perood, s^{th} day;

$\boldsymbol{\theta_{rs}}$**:** Loss of WBC per unit time of DV due to growth of one "stage-III" cell in r^{th} DV period, s^{th} day;

$\mathbf{t_{rs}}$ **:** The number of time units in r^{th} DV Period and s^{th} day ; for r = 1,2, … $l-1$; s = 1,2,….n

$\mathbf{T_{x,y,z}}$**:** Total +ve /-ve (x) effect of treatment during drug presence/absence(y) while targeting the Mutant/ Premalignant/ Malignant (z) cell population.

Where x=1: If drug has positive effectiveness; x =0: If drug has negative effectiveness

y=1: If Drug is present; y=0: If Drug is absent

z=1: If the cell is in "stage-1" ; z=2: If the cell is in "stage-2"; z=3: If the cell is in "stage-3";

$\mathbf{W_{X,Y,Z}}$**:** Total loss/growth(X) of WBC during drug presence/absence(Y) while targeting to destroy Mutant/ Premalignant/Malignant (Z) cell population.

Where X=1: If there is Growth of WBC; X =0: If there is Loss of WBC

Y=1: During Drug Presence; Y=0: During Drug Absence

Z=1: For Mutant cell; Z=2: For Premalignant cell; Z=3: For Malignant cell

$\mathbf{W_U}$**,** $\mathbf{W_L}$: The desired optimal upper & lower limits of healthy sizes of WBC during treatment.

$\mathbf{N_U}$**,** $\mathbf{N_L}$: The critical target upper & lower limits on size of the mutant (stage-I) cells

$\mathbf{M_U}$**,** $\mathbf{M_L}$**:** The critical target limit upper & lower limits on size of the premalignant (stage-II) cells.

$\mathbf{K_U}$**,** $\mathbf{K_L}$: The critical target upper and lower limits on size of the malignant (stage-III) cells

3.2. Programming Problem for Drug Administration

With the mentioned Terminology and notation,

$$T_{111}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .p_{ij} \Rightarrow \ E(T_{111})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .p_{ij}\ E(N_A) \tag{3.2.1}$$

$$T_{011}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .q_{ij} \ \Rightarrow \ E(T_{011})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .q_{ij}\ E(N_A) \tag{3.2.2}$$

Implies the net effect of drug administration on one mutant (stage-I) cell is

$$Z_1=A.E(N_A);A\geq 0\ ;\text{Where } A=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .(p_{ij}-q_{ij});\ \text{usually } p_{ij}\geq q_{ij} \tag{3.2.3}$$

$$T_{112}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .b_{ij} \ \Rightarrow E(T_{112})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .b_{ij}\ E(M_A) \tag{3.2.4}$$

$$T_{012}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .c_{ij} \ \Rightarrow \ E(T_{012})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .c_{ij}\ E(M_A) \tag{3.2.5}$$

Implies the net effect of drug administration on a premalignant (stage-II) cell is

$$Z_2=B.E(M_A);B\geq 0\ ;\text{Where } B=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .(b_{ij}-c_{ij});\ \text{usually } b_{ij}\geq c_{ij} \tag{3.2.6}$$

$$T_{113}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}.u_{ij} \ \Rightarrow \ E(T_{113})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .u_{ij}\ E(K_A) \tag{3.2.7}$$

$$T_{013}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .v_{ij} \ \Rightarrow \ E(T_{013})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .v_{ij}\ E(K_A) \tag{3.2.8}$$

so as the net effect of drug administration on a malignant (stage-III) cell is

$$Z_3=C.E(K_A);C\geq 0\ ;\text{Where } C=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .(u_{ij}-v_{ij});\ \text{usually } u_{ij}\geq v_{ij} \tag{3.2.9}$$

By considering 3.2.3, 3.2.6 and 3.2.9; the overall effect of drug administration on all the 3 types of cell population is

$$Z=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ [(p_{ij}-q_{ij})+(b_{ij}-c_{ij})+(u_{ij}-v_{ij})] \tag{3.2.10}$$

and Z is to be maximized.

Regarding the constraints of the problem

$$W_{011}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\alpha_{ij}\ \Rightarrow\ E(W_{011})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\alpha_{ij}\ E(N_A) \tag{3.2.11}$$

The constraint with respect to WBC loss count on mutant cells (stage-1) is

$$E(W_{011})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\alpha_{ij}\ E(N_A)\le (W_U-W_L) \tag{3.2.12}$$

$$W_{012}=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\beta_{ij}\ \Rightarrow\ E(W_{012})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\beta_{ij}\ E(M_A) \tag{3.2.13}$$

The constraint with respect to WBC loss count on premalignant (stage-2) cells is

$$E(W_{012})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\beta_{ij}\ E(M_A)\le (W_U-W_L) \tag{3.2.14}$$

$$W_{013}=\sum_{i=1}^{l}\sum_{j=1}^{k} \gamma_{ij}\ .a_{ij}\ \Rightarrow\ E(W_{013})=\sum_{i=1}^{l}\sum_{j=1}^{k} \gamma_{ij}\ .a_{ij}\ E(K_A) \tag{3.2.15}$$

The constraint with respect to WBC loss count on malignant (stage-3) cells is

$$E(W_{013})=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}\ .\gamma_{ij}\ E(K_A)\le (W_U-W_L) \tag{3.2.16}$$

Putting (3.2.12), (3.2.14) and (3.16) together, the constraint with respect to the loss count of WBC is

$$\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}[\alpha_{ij}E(N_A)+\beta_{ij}E(M_A)+\gamma_{ij}E(K_A)]\le (W_U-W_L) \tag{3.2.17}$$

The constraints with minimum feasible eradicate Mutant (stage-I) cells in a tumor during drug administration at time 't' is

$$NCL\ge E(N_A) \tag{3.2.18}$$

Similarly the constraints with Premalignant (stage-II) cell population at time t is

$$E(M_A)\ \le\ M_U \tag{3.2.19}$$

For Malignant (stage-III) cell population at time t is

$$E(KA)\le KU \tag{3.2.20}$$

And the decision parameters are

$$\alpha_1\ge 0,\ \beta_1\ge 0,\gamma_1\ge 0,\lambda_1\ge 0,\delta_1\ge 0,\theta_1\ge 0 \tag{3.2.21}$$

The resulting optimization problem for drug administration is

$$\left.\begin{array}{c} \text{Maximise } Z=A.E(N_A)+B.E(M_A)+C.E(K_A); \\ \text{where } A=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}(p_{ij}-q_{ij});B=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}(b_{ij}-c_{ij});C=\sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}(u_{ij}-v_{ij}) \\ E(N_A);\ E(M_A) \text{ and } E(K_A) \text{ are obtained from the relations 2.1; 2.2 and 2.3 respectively} \\ \text{Subject to the constraints} \\ \sum_{i=1}^{l}\sum_{j=1}^{k} a_{ij}(\alpha_{ij}E(N_A)+\beta_{ij}E(M_A)+\gamma_{ij}E(K_A))\le (W_U-W_L); \\ E(N_A)\le N_L;\ E(M_A)\le M_L;\ E(K_A)\le K_L \\ \text{and } \alpha_1,\beta_1,\gamma_1,\lambda_1,\delta_1,\theta_1\ge 0 \end{array}\right\} \tag{3.2.22}$$

3.3. Programming Problem for Drug Vacation

As chemotherapy is a double-edged weapon in cancer treatment. It has its effect on the health of the patient during its administration as well as during its vacation also. Long time drug administration demands the recovery to the patient from the

toxic exposure of the drug. This period will act as a stimulant to reactivate the natural immune system. The duration of drug absence should also be handled with optimal care for effective positive results in the process of chemotherapy. Hence there is a need of studying the optimal drug vacation.

From the Notation and Terminology

$$T_{101}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} d_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{101})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} d_{rs}\ .t_{rs}\ E(N_V) \tag{3.3.1}$$

$$T_{001}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} e_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{001})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} e_{rs}\ .t_{rs}\ E(N_V) \tag{3.3.2}$$

Which implies the net impact of drug vacation on one mutant (stage-I) cell is

$$H_1=D.E(M_V);D\geq 0\ ;\text{Where } D=\sum_{r=1}^{l-1}\sum_{s=1}^{n} t_{rs}\ .(d_{rs}-e_{rs});\ \text{usually } d_{rs}\geq e_{rs} \tag{3.3.3}$$

$$T_{102}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} f_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{102})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} f_{rs}\ .t_{rs}\ E(M_V) \tag{3.3.4}$$

$$T_{002}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} g_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{002})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} g_{rs}\ .t_{rs}\ E(M_V) \tag{3.3.5}$$

Which implies the net impact factor of drug vacation on a premalignant (stage-II) cell is

$$H_2=E.E(M_V);E\geq 0\ ;\text{Where } E=\sum_{r=1}^{l-1}\sum_{s=1}^{n} t_{rs}\ .(f_{rs}-g_{rs});\ \text{usually } f_{rs}\geq g_{rs} \tag{3.3.6}$$

$$T_{103}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} m_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{103})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} m_{rs}\ .t_{rs}\ E(K_V) \tag{3.3.7}$$

$$T_{003}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} n_{rs}\ .t_{rs} \ \Rightarrow\ E(T_{103})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} n_{rs}\ .t_{rs}\ E(K_V) \tag{3.3.8}$$

So as net impact of drug vacation on a malignant (stage-III) cell is

$$H_3=F.E(K_V);F\geq 0\ ;\text{Where } F=\sum_{r=1}^{l-1}\sum_{s=1}^{n} t_{rs}\ .(m_{rs}-n_{rs});\ \text{usually } m_{rs}\geq n_{rs} \tag{3.3.9}$$

By considering 3.3.3, 3.3.6 and 3.3.9 the overall effect of drug vacation on all the 3 types of cell population is

$$H=\sum_{r=1}^{l-1}\sum_{s=1}^{n} t_{rs}\ [(d_{rs}-e_{rs})+(f_{rs}-g_{rs})+(m_{rs}-n_{rs})] \tag{3.3.10}$$

and H is to be maximized.

Regarding the constraints of the problem

$$W_{101}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \lambda_{rs}\ .t_{rs} \ \Rightarrow\ E(W_{101})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \lambda_{rs}\ .t_{rs}\ E(N_V) \tag{3.3.11}$$

The constraint with respect to WBC loss count on mutant cells (Stage-I) is

$$E(W_{101})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \lambda_{rs}\ .t_{rs}\ E(N_V)\leq W_U-W_L \tag{3.3.12}$$

$$W_{102}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \delta_{rs}\ .t_{rs} \ \Rightarrow\ E(W_{102})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \delta_{rs}\ .t_{rs}\ E(N_V) \tag{3.3.13}$$

The constraint with respect to WBC loss count on premalignant cells (stage-II) is

$$E(W_{102})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \delta_{rs}\ .t_{rs}.E(M_V)\leq W_U-W_L \tag{3.3.14}$$

$$W_{103}=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \theta_{rs}\ .t_{rs} \ \Rightarrow\ E(W_{103})=\sum_{r=1}^{l-1}\sum_{s=1}^{n} \theta_{rs}\ .t_{rs}\ E(K_V) \tag{3.3.15}$$

The constraint with respect to WBC loss count on malignant (stage-III) cells is

$$E(W_{103})=\sum_{r=1}^{l-1}\sum_{s=1}^{n}\theta_{rs}\ .t_{rs}.E(K_V)\le(W_U-W_L) \tag{3.3.16}$$

Putting (5.12), (5.14) and (5.16) together, the constraints with respect to the loss count of WBC is

$$\sum_{r=1}^{l-1}\sum_{s=1}^{n}t_{rs}[\alpha_{rs}.E(N_V)+\beta_{rs}.E(M_V)+\gamma_{rs}.E(K_V)]\le(W_U-W_L) \tag{3.3.17}$$

The constraint with mutant cell population during drug vacation at time‘t’ is

$$E(N_V)\le N_U \tag{3.3.18}$$

Similarly for premalignant cell population at time t is

$$E(M_V)\le M_U \tag{3.3.19}$$

For malignant cells at time t is

$$E(K_V)\le K_U \tag{3.3.20}$$

And the decision parameters are

$$\alpha_0\ge 0,\beta_0\ge 0,\gamma_0\ge 0,\lambda_0\ge 0,\delta_0\ge 0,\theta_0\ge 0 \tag{3.3.21}$$

The resulting optimization problem for recovery of health during drug vacation is

$$\left.\begin{array}{c}\text{Maximize } H=D.E(N_V)+E.E(M_V)+F.E(K_V);\\ \text{where}\quad D=\sum_{r=1}^{l-1}\sum_{s=1}^{n}t_{rs}\ (d_{rs}-e_{rs});\ \ E=\sum_{r=1}^{l-1}\sum_{s=1}^{n}t_{rs}\ (f_{rs}-g_{rs})\ \ F=\sum_{r=1}^{l-1}\sum_{s=1}^{n}t_{rs}\ (m_{rs}-n_{rs})\\ E(N_V);\ E(N_V)\text{ and }E(N_V)\text{ are obtained from the relations 2.4; 2.5 and 2.6 respectively}\\ \text{Subject to the Constraints}\\ \sum_{r=1}^{l-1}\sum_{s=1}^{n}t_{rs}[\alpha_{rs}.E(N_V)+\beta_{rs}.E(M_V)+\gamma_{rs}.E(K_V)]\le W_U-W_L\\ E(N_V)\le N_U;\ E(M_V)\le M_U;\ E(K_V)\le K_U\\ \text{and}\ \ \alpha_0,\beta_0,\gamma_0,\lambda_0,\delta_0,\theta_0\ge 0\end{array}\right\} \tag{3.3.22}$$

Table 4.1. For fixed values of t_1=2; N_0=7.6x10^7; M_0=9.71x10^5; K_0=9.8 x10^6; W_U=5.5x10^6; W_L=3.5x10^6; N_U=1.5x10^5; N_L=1.29x10^5; M_U=11.5x10^5; M_L=9.7x10^5; K_U=1.2x10^6; K_L= 10

i	j	t_1	Z	α_1	β_1	γ_1	λ_1	δ_1	θ_1
2	3	2	326087.00	21693930.00	159.85	2.65	29.96	7.18	4.68
3	3	2	562520.60	281982.20	0.00	0.00	8.31	2.08	2.77
4	3	2	614949.70	281206.80	0.00	0.00	8.30	2.08	2.77
5	3	2	650158.90	30655.57	0.00	0.00	5.42	1.35	1.81
3	2	2	415770.60	4389245.00	0.00	0.00	48.21	9.22	16.07
3	3	2	548223.40	3350696.00	0.00	1.17	9.90	2.47	0.96
3	4	2	805050.70	501992.40	0.00	0.00	14.74	3.69	4.91
3	5	2	815016.20	3174.90	0.00	0.00	26.83	0.14	8.94
3	3	4	1062309.00	879201800000.00	11824.47	0.00	20434730.00	444.10	592.13
3	3	5	594452.60	290250.90	0.00	0.00	12.48	3.11	4.15
3	3	6	416058.40	1945520.00	0.00	0.34	504.38	1.67	1.54
3	3	10	415770.60	4233.26	0.00	4.00	33.86	2.92	0.00

Table 4.2. For fixed values of t_1=2; N_0=7.6x10^7; M_0=9.71x10^5; K_0=9.8 x10^6; W_U=5.5x10^6; W_L=3.5x10^6; N_U=1.5x10^5; N_L=1.29x10^5; M_U=11.5x10^5; M_L=9.7x10^5; K_U=1.2x10^6; K_L= 10^5

R	S	t_0	Z	α_0	β_0	γ_0	λ_0	δ_0	θ_0
2	3	2	795500	0.12	9.38	0.07	987908000	2.51	1.03
3	3	2	858000	10.44	9.33	0.00	709826.70	2.44	0.31
4	3	2	960000	4630.80	0.00	0.00	14.01	15.81	2.05
5	3	2	1745500	4.46	5.84	1.59	31421320	28.66	3.53
2	2	2	560000	0.74	14070.42	5.63	0.00	2.93	89.23
2	4	2	772000	15640.39	291.49	0.00	1966773000	269232900	1.83
2	6	2	1256000	144.83	63272.05	0.00	280880300	90812300	0.27
2	8	2	2066000	2614.79	0.07	0.00	5215209	0.08	0.26
2	3	4	821000	194.56	0.00	0.00	7472348000000	1.07	5.88
2	3	6	821000	5149.97	2.70	0.00	114082.20	0.07	8.02
2	3	8	821000	112061.70	300.06	0.00	17540360000	20827270000	474656700
2	3	10	610500	0.19	23168.39	4.51	3237.88	1.50	0.00

4. Numerical Illustration & Sensitivity Analysis

In order to understand the model behaviour, a hypothetical data is considered. Decision parameters like growth, loss and transformation rates of cells among the 3stages, are obtained at different values of initial number of stage-1 cell (N_0), Initial number of stage-2 cells (M_0), and initial number of stage-3 cells (K_0), WBC upper limit (W_U), WBC lower limit (W_L), lower and upper limits of stage-1 cells (N_L,N_U), lower and upper limits of stage-2 cells (M_L,M_U), lower and upper limits of stage-3 cells (K_L,K_U), etc. $\alpha_1,\beta_1,\gamma_1,\lambda_1,\delta_1,\theta_1$ and $\alpha_0,\beta_0,\gamma_0,\lambda_0,\delta_0,\theta_0$ are obtained from the above non linear programming problems during drug administration and drug vacation for varying hypothetical values of i, j, r, s, t by using LINGO 8.0 and the results are presented in table – 4.1 and table-4.2.

From the table 4.1 it is observed that Z (drug efficacy) is an increasing function of number of drug administration cycles and number of spells within the cycle when all other parameters are constant. It may indicate that increasing number of drug cycles and spells within a cycle will increase the drug efficacy. It is also observed that the parameters $\alpha_1,\beta_1,\gamma_1,\lambda_1,\delta_1,\theta_1$ are decreasing functions of number of drug administration cycles. It may indicate that the increasing number of drug cycles will decrease the generation and transformation of the stage-I, stage-II and stage-III cells. It is also observed that the parameter α_1 is decreasing function and β_1 is invariant of change of number of spells within cycle. It may indicate that increasing number of spells within a cycle will decreases generation of stage-I cells and invariant of change of stage-II cells. It is further observed that Z is decreasing function of time 't' when all other parameters are constant implies that longevity of drug administration above the required time may decrease drug efficacy. It is further observed that parameter $\alpha_1,\beta_1,\gamma_1,\lambda_1,\delta_1,\theta_1$ are decreasing functions and γ_1 is increasing function of time 't'. It may be due to continuous drug administration will decrease the rate of generation of stage-I and stage-II cells but increase the transformation rate of stage-III cells from stage-II.

From the table 4.2 it is observed that Z is an increasing function of number of DVP and number of days within the DVP when all other parameters are constant. It is also observed that $\gamma_0,\delta_0,\theta_0$ are increasing functions and λ_0 is decreasing function of number of DVP. It may indicate that increasing number of DVP during drug vacation will increase the transformation of stage-III from stage-II cells and death of stage-II and stage-III cells but decreases the death of stage-I cells. It is further observed that parameters γ_0,θ_0 are decreasing function of number of days with in DVP. It may indicate that an increase of the number of days within DVP will decrease the transformation and death of stage-III cells. It is also observed that the Z is decreasing function of time when all other parameters are constant. It is further observed that β_0,γ_0 are increasing function, λ_0 is decreasing function of time t. It may indicate that increasing the drug vacation time increases the generation of the stage-II and stage-III cell population.

5. Summary and Conclusions

In cancer, chemotherapy the drug administration in spells with various quantities of mixed drugs. It is also to be implemented with drug vacation periods with various lengths of time units (say number of days). Either continuous and long spells drug administration or continuous long days of drug vacation are unwanted in a proper treatment of cancer. While developing the programming problem in two cases, during drug administration and during drug vacation separately, we have assumed that the behaviour of growth/loss of cancer cells and normal cells are complementary during these periods. Our study has explored the decision variables like threshold limits on drug administration times (minimum & maximum); duration of drug vacation periods, dosage level (quantum) of drug in each spell; number of cycles of drug administration; number of drug vacation spells; The times between two drug vacations and drug administration's etc.

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