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Growth Study of Cancer within Organ through the Models on Stochastic Non-linear Programming

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Abstract The growth and loss of cancer cell population within an organ are influenced by their birth, death and migration processes. These issues may be observed during the presence and absence of chemotherapy also. In this paper, stochastic non-linear programming problems were formulated for getting the decision parameters on growth and loss of cancer cells in an organ subject to the constraints of its related health indicators. While formulating the objective function and subjective constraints based on the derived statistical measures in the works of Tirupathi Rao et. al. [9,10]. The decision parameters of the developed programming problem are predicted and analyzed the dynamics of cancer cell size in different situations.

Keywords: Stochastic Non-linear Programming, Cancer Growth, Birth-death and migration processes.

1. INTRODUCTION

Tumor comprises of normal and malignant cells. These cells in tumor may undergo the processes of mitosis to increase their off springs. The process of cell reproduction in an organ of any living body is regulated with its genetical instructions. Environmental conditions, food habits, culture and living styles, etc of an individual along with usual mechanism of cell division are also playing vital role in such instructions. Destruction and reconstruction of normal cells are getting the changing patterns due to the influence of continuous modifying cells. Experimental studies have more advantages for predicting the cell behaviour of growth, transforming and loss protocols. Contrary they have many practical limitations due to cost and other feasibilities. Mathematical modelling studies are the meaningful alternatives to handle the said objectives. The measures like optimal sizes of different cells subject to the wanted health

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standards of the patient can be derived by proper modelling of physiological and genetical phenomena of cells with the frame work of mathematical theory. Counting processes are some prominent mathematical tools to study the mechanism of cell's proliferation and their consequent behaviours.

On the other hand, predictions with mathematical modelling may provide the indicators in more deterministic environment. In practice, most of the processes are influenced by random and chance causes. Hence the model construction should be stochastic rather than certainty. Statistical measures basing on the stochastic models will provide the most relevant picture about the prevailing conditions on growth, loss and transformation of cell processes. These measures shall be utilised for developing the programming problems with objectives of efficient health management. Usual cell division process involves the reproducing of new cells to compensate the wear and tear of the existing cells due to several reason. However the newly introduced cell volume should always be within the range of spoiled cells. This regulating mechanism is the failure issue with respect to cancer causing cells. The study deals with formulation of optimization programming problems with the objective of exploring the decision parameters, which regulates the cancer growth and loss dynamics.

The dynamics of metastasis processes from the tumor are observed in secondary sites is studied through a mathematical model [1]. Computation of two stage and multi stage continuous time dependent tumor incidence rates can be done with stochastic models [2,3,7]. Growth of cancer cells, formation of metastasis and the growth behaviour of age dependent cancer were studied with stochastic models [4,5,6]. The metastatic progression of cancer cells in the secondary site under the treatment of chemotherapy is assessed through computational mathematical models [8]. Optimal drug administration procedures, including two stage and three stage cancer chemotherapy are designed with stochastic programming models [9,10,11,12].

In all the above models the growth/ loss processes of different types of cells are assessed with pure and linear birth, death processes for two/three stage dependent cancer growth. However, the spread/ invasion of cancer cells during their initial formation and at the stage of metastasis is also influenced by their migration and expansion of their colonies in new sites. This study considered developed stochastic models on spread of cancer cell growth by using linear birth, death and migration processes [9,10]. The study formulated stochastic programming problems for exploring the optimal decision parameters of growth, loss and invasion rates of cancer cells during normal and chemotherapy periods. All the developed stochastic programming problems are designed with multiple objectives such as minimizing the average number of cancer causing cells, maximizing the average number of healthy/ normal cells, maximizing the variability of cancer causing cells, minimizing the variability of healthy cells, etc. They have common constraints such as expected number of normal cells should be in wanted threshold limits; the expected number of cancer causing cells should not exceed specific danger limit, the variance of normal cells must be in closed range, the variance of cancer causing cells should be in broader range.

The above developed problems have the limitations that they are formulated with the assumptions of handling the multiple problems independently and separately. However, the growth/ loss processes of different types of cells will be happened simultaneously. Keeping this research gap in mind, some stochastic non linear programming problems were formulated with the ratio of average normal and average malignant cells. Hence these problems will deal the sizes of different type of cells among cancer patients. The concept of migration/invasion of cancer cells among the neighbouring parts of the organ in the body, particularly during metastasis is considered unlike previous studies. These models have further discussed the behaviour of cancer growth during drug absence and cancer restriction during drug administration.

2. MULTI-OBJECTIVE PROGRAMMING PROBLEMS

The statistical measures derived in the generalised stochastic model and particular cases with respect to chemotherapy are used to develop non-linear programming problems. The objective is to predict the decision parameters involved in the dynamics of cancer tumor, such way that those decision parameters will leads to optimise the given objective functions. In this context, the study proposed some stochastic programming problems with various constraints.

The mean and variance counts of normal and malignant cells in an organ are considered, which were derived through the study referred in Tirupathi Rao et al [10]. Among healthy people, the average size of normal cells is more than average size of malignant cells in any organ. When the conversion process of normal cells to malignant cells is initiated, the situation will be irreversible and the healthy person will be transformed to a cancer patient. Once the malignancy formation was confirmed, the growth of such cancerous cells will be at faster rate.

Considering the notations used in Tirupathi Rao et.al in [10] as

λ_{11}: Growth rate of normal staged cells in the primary tumor

λ_{21}: Growth rate of malignant staged cells in the primary tumor

λ_{32}: Growth rate of migrant malignant staged cells in the secondary tumor

μ_{11}: Loss rate of normal staged cells in the primary tumor

μ_{21}: Loss rate of malignant staged cells in the primary tumor

μ_{32}: Loss rate of migrant malignant staged cells in the secondary tumor

δ_{11}: Transformation rate of normal staged cells into the malignant stage cells in the primary tumor

δ_{21}: Migration rate of malignant staged cells in the primary tumor to the secondary tumor

δ_{32}: Emigration rate of immigrant malignant staged cells in the secondary tumor to other parts

N_0: Initial number of normal staged cells (in the primary Tumor)

M_0: Initial number of malignant staged cells (in the primary Tumor)

The status of health is considered to be under control as long as the average number of normal cells is more than average number of malignant cells. In other words the ratio of average normal cells to average malignant cells shall be more than unity. However, the situation seems to be alarmed when the ratio is less than unity.

Let E_1 be that ratio defined as $E_1 = \frac{\text{Average size of Normal Cells}}{\text{Average size of Malignant Cells}} > 1$

The objective function is to Maximize R_{E1}, where

$$R_{E1} = \left\{ \left[N_0\, e^{At} \right] / \left[\frac{\delta_{11} N_0 e^{At}}{A - B} + \left(M_0 - \frac{\delta_{11} N_0}{A - B} \right) e^{Bt} \right] \right\}$$

The fluctuations in the average number of normal cells in any organ shall be low as it indicates the status of healthy cells is consistent. Hence less volatility in the average number of normal cells is wanted. Contrary to the above situation, consistency in the growth of malignant cells is a threat to survival of the patient. Thus more fluctuations among the average number of malignant cells is a welcoming situation. Hence, more volatility in the average number of malignant cells is wanted. This study has proposed the second programming problem based on the objective of the ratio between variance of normal cells on variance of malignant cells.

$$E_2 = \frac{\text{Variance of normal cells at a point of time}}{\text{Variance of malignant cells at a point of time}} < 1$$

The objective Function is to Minimize R_{E2}, where

$$R_{E2}=\left\{\left[\frac{DN_0e^{At}}{A}\left(e^{At}-1\right)\right]/\left[\begin{array}{l}\dfrac{\delta_{11}N_0e^{At}}{A-2B}+(F+2E)\\ \quad\times\left\{\begin{array}{l}\dfrac{\delta_{11}N_0e^{At}}{(A-2B)(A-B)}\\ \quad-\left(M_0-\dfrac{\delta_{11}N_0}{A-B}\right)\dfrac{e^{Bt}}{B}\end{array}\right\}\\ +\dfrac{\delta_{11}^2N_0D}{A}\left(\dfrac{e^{2At}}{2(A-B)^2}+\dfrac{e^{At}}{(A-2B)B}\right)\\ -\dfrac{\delta_{11}(E-\delta_{11})N_0e^{At}}{(A-2B)B}\\ -\left(\dfrac{\delta_{11}N_0D-\left(A-B\right)\left(E-\delta_{11}\right)N_0}{(A-B)B}\right)\\ \quad\times\dfrac{\delta_{11}e^{(A+B)t}}{(A-B)}-\dfrac{\delta_{11}N_0e^{2Bt}}{(A-2B)}\\ +(F+2E)e^{2Bt}\left(\dfrac{\delta_{11}N_0-(A-2B)M_0}{2(A-2B)(A-B)^2B}\right)\\ +\delta_{11}{}^2N_0e^{2Bt}\left(\dfrac{2(A-B)(\delta_{11}-E)+D\delta_{11}}{2(A-2B)(A-B)^2}\right)\end{array}\right]\right\}$$

For healthy maintenance of average number of normal cells over average number of malignant cells, the constraints that are to be satisfied are

$$\left[N_0\,e^{At}\right]>\left[\frac{\delta_{11}N_0e^{At}}{A-B}+\left(M_0-\frac{\delta_{11}N_0}{A-B}\right)e^{Bt}\right]$$

and

$$\left[\frac{DN_0e^{At}}{A}\left(e^{At}-1\right)\right] < \left[\begin{array}{l} \frac{\delta_{11}N_0e^{At}}{A-2B}+(F+2E)\left\{\begin{array}{r}\frac{\delta_{11}N_0e^{At}}{(A-2B)(A-B)} \\ -\left(M_0-\frac{\delta_{11}N_0}{A-B}\right)\frac{e^{Bt}}{B}\end{array}\right\} \\ +\frac{\delta_{11}^2N_0D}{A}\left(\frac{e^{2At}}{2(A-B)^2}+\frac{e^{At}}{(A-2B)B}\right) \\ -\frac{\delta_{11}(E-\delta_{11})N_0e^{At}}{(A-2B)B} \\ -\left(\frac{\delta_{11}N_0D-(A-B)(E-\delta_{11})N_0}{(A-B)B}\right)\frac{\delta_{11}e^{(A+B)t}}{(A-B)} \\ -\frac{\delta_{11}N_0e^{2Bt}}{(A-2B)}+(F+2E)e^{2Bt}\left(\frac{\delta_{11}N_0-(A-2B)M_0}{2(A-2B)(A-B)^2B}\right) \\ +\delta_{11}{}^2N_0e^{2Bt}\left(\frac{2(A-B)(\delta_{11}-E)+D\delta_{11}}{2(A-2B)(A-B)^2}\right) \end{array}\right]$$

The fluctuations in growth of average number of normal cells are also harmful to the health. Therefore the growth of normal cells should be maintained with consistency. The average size of normal cells should be within threshold limits. Similarly consistent growth of malignant cells also threat to the health. For the above consideration we have the following constraints

$$C_1 \le N_0\, e^{At} \le C_2$$

$$\left[\frac{\delta_{11}N_0e^{At}}{A-B}+\left(M_0-\frac{\delta_{11}N_0}{A-B}\right)e^{Bt}\right] \le C_3$$

$$\left[\frac{DN_0e^{At}}{A}\left(e^{At}-1\right)\right] \le C_4$$

$$\left[\begin{array}{l} \frac{\delta_{11}N_0e^{At}}{A-2B}+(F+2E)\left\{\frac{\delta_{11}N_0e^{At}}{(A-2B)(A-B)}-\left(M_0-\frac{\delta_{11}N_0}{A-B}\right)\frac{e^{Bt}}{B}\right\} \\ +\frac{\delta_{11}^2N_0D}{A}\left(\frac{e^{2At}}{2(A-B)^2}+\frac{e^{At}}{(A-2B)B}\right) \\ -\frac{\delta_{11}(E-\delta_{11})N_0e^{At}}{(A-2B)B} \\ -\left(\frac{\delta_{11}N_0D-(A-B)(E-\delta_{11})N_0}{(A-B)B}\right)\frac{\delta_{11}e^{(A+B)t}}{(A-B)}-\frac{\delta_{11}N_0e^{2Bt}}{(A-2B)} \\ -(F+2E)e^{2Bt}\left(\frac{\delta_{11}N_0-(A-2B)M_0}{2(A-2B)(A-B)^2B}\right) \\ -\delta_{11}^2N_0e^{2Bt}\left(\frac{2(A-B)(\delta_{11}-E)+D\delta_{11}}{2(A-2B)(A-B)^2}\right) \end{array}\right]\geq C_5$$

where

C_1, C_2 - lower and upper threshold limits of normal cells

C_3 - warning limit on the average size of malignant cells

C_4 - upper allowable limits on the volatility of normal cells

C_5 - wanted lower limit on the volatility of malignant cells

$A=\lambda_{11}-\delta_{11}-\mu_{11}$; $B=\lambda_{21}-\mu_{21}-\delta_{21}$; $D=\lambda_{11}+\delta_{11}+\mu_{11}$; $E=\lambda_{32}-\mu_{32}-\delta_{32}$; $F=\lambda_{21}+\mu_{21}+\delta_{21}$; The non negative decision parameters under study are $\lambda_{11}\geq 0$, $\delta_{21}\geq 0$, $\lambda_{21}\geq 0$, $\lambda_{32}\geq 0$, $\mu_{11}\geq 0$, $\mu_{21}\geq 0$, $\delta_{21}\geq 0$, $\mu_{32}\geq 0$, $\delta_{32}\geq 0$. The numerical results for the developed problem have been solved using Lingo 8.0 and it is presented in the appendix I & II.

2.1. Special Case

For the homogeneous processes, the growth and loss rate of cells are assumed to be constant and usually growth rate of malignant cells is more during vacation period than regimen period, and loss rate of malignant cells is more during regimen period than vacation period. In order to study the effects of drug in between regimen period and vacation period, a linear function is defined using loss and growth rates of cells at various stages.

The growth and loss rate of cells during the drug administration period and vacation periods are considered to be rational decision parameters. The drug effectiveness on the tumor is evaluated through a scalar quantity $\{a_k\}$ defined in between 0 and 1. The growth, migration/transformation and loss rate of cells can be represented as $\lambda_{ij} = \left[a_k\lambda_{ijl} + (1-a_k)\lambda_{ijl}\right], \delta_{ij} = \left[a_k\delta_{ijl} + (1-a_k)\delta_{ijl}\right]$ and $\mu_{ij} = \left[a_k\mu_{ijl} + (1-a_k)\mu_{ijl}\right]$ respectively, where i= 1, 2, 3: cells at normal stage, cells at malignant stage, cells at migrant malignant stage, j=1, 2: primary tumor, secondary tumor, l=0, 1: drug absence, drug presence. In this approach, Tirupathi Rao et al [9] developed a model for this special case in the form of PDE is as follows,

$$
\begin{aligned}
\frac{\partial k(u,v;t)}{\partial t}
&= \left\{ \begin{array}{l}
-\left[\begin{array}{l} \left(a_1\lambda_{111} + (1-a_1)\lambda_{110}\right) + \left(a_2\delta_{111} + (1-a_2)\delta_{110}\right) \\ \quad + \left(a_5\mu_{111} + (1-a_5)\mu_{110}\right) \end{array} \right] \\
+\left(a_5\mu_{111} + (1-a_5)\mu_{110}\right)e^{-u} + \left(a_1\lambda_{111} + (1-a_1)\lambda_{110}\right)e^{u} \\
+\left(a_2\delta_{111} + (1-a_2)\delta_{110}\right)e^{v-u}
\end{array} \right\} \frac{\partial k(u,v;t)}{\partial u} \\
&\quad + \left\{ \begin{array}{l}
-\left[\begin{array}{l} \left(a_3\lambda_{211} + (1-a_3)\lambda_{210}\right) + \left(a_6\mu_{211} + (1-a_6)\mu_{210}\right) \\ + \left(a_7\delta_{211} + (1-a_7)\delta_{210}\right) \end{array} \right] \\
+\left(a_3\lambda_{211} + (1-a_3)\lambda_{210}\right)e^{v} + \left[\begin{array}{l} \left(a_6\mu_{211} + (1-a_6)\mu_{210}\right) \\ + \left(a_7\delta_{211} + (1-a_7)\delta_{210}\right) \end{array} \right] e^{-v}
\end{array} \right\} \frac{\partial k(u,v;t)}{\partial v} \\
&\quad + \left\{ \begin{array}{l}
-\left[\begin{array}{l} \left(a_4\lambda_{321} + (1-a_4)\lambda_{320}\right) + \left(a_8\mu_{321} + (1-a_8)\mu_{320}\right) \\ + \left(a_9\delta_{321} + (1-a_9)\delta_{320}\right) \end{array} \right] \\
+\left[\left(a_8\mu_{321} + (1-a_8)\mu_{320}\right) + \left(a_9\delta_{321} + (1-a_9)\delta_{320}\right)\right]e^{-v} \\
+\left(a_4\lambda_{321} + (1-a_4)\lambda_{320}\right)e^{v}
\end{array} \right\} k(u,v;t)
\end{aligned}
$$

For the above model, moments were derived [9]. Multi-objective programming problem similar to the earlier problem is constructed to predict the decision parameter as defined above. Let and be the ratio average number of normal to the average number malignant stage cells and the ratio of variance of number of normal cells and variance number of malignant stage cells in an organ respectively. The objective function in this context is to maximise and minimise, subject to the similar type of constraint as in (2). A numerical result for this programming problem is illustrated in the appendix III & IV.

3. RESULTS

The results in appendix-I reveals that $R_{E1} > 1$ and it is an increasing function of N_0 & t, decreasing function of M_0 & C_1 in an organ when all the other parameters are constant. The Parameter, λ_{11} is an increasing function of N_0 and decreasing function of C_1; λ_{32} is decreasing function of C_1; μ_{11} is an increasing function of N_0, decreasing function of C_1 & t in an organ when all other parameters are constant.

Appendix II shows that $R_{E2} < 1$ and it is an increasing function of N_0, decreasing function of C_4; μ_{11} is an increasing with N_0 & M_0, decreasing function of C_3, t; λ_{21} is decreasing function of N_0 & M_0, increasing function of C_3; δ_{21} is decreasing function of N_0, increasing function of M_0 & C_1; μ_{21} is an increasing function of C_1 and decreasing function of t; δ_{21} is an increasing function of N_0 & M_0; λ_{32} is decreasing function of M_0; δ_{32} is decreasing function of M_0 and increasing function of C_5 when all other parameters are constant.

From appendix III, it is observed that $R^*_{E1} > 1$ and it is an increasing function of N_0 & C_3 and decreasing function of M_0, C_1 and t in an organ when all other parameters are constant. The parameter, μ_{11} is an increasing function of N_0 and decreasing function of C_1 when all other parameters are constant.

Results in appendix IV implies that $R^*_{E2} < 1$ and it is an increasing function of M_0 and decreasing function of C_1, C_5 & t in an organ when all other parameters are constant. The parameter, $\boldsymbol{\mu}_{11}$ is an increasing function of M_0 & C_4 and decreasing function of C_1, C_2, t; λ_{11} is decreasing function of C_1 & t and increasing function of C_2 & C_4; λ_{21} is decreasing with C_2 & C_4; δ_{21} is an increasing function of C_2; $\boldsymbol{\mu}_{21}$ is decreasing function of C_2 & C_4; δ_{21} is decreasing function of C_2 & C_4 and increasing function of C_5 in an organ when all parameters are constant. The above results may helps to medical practitioner to understand the behavior of cancer cells dynamics for monitoring the medication of the patients.

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Appendix-I

Table 1: Values of R_{E1}, λ_{11}, λ_{21}, μ_{11}, δ_{11}, μ_{21}, δ_{21}, λ_{32}, μ_{32}, δ_{32} for Varying values of one value of the following No, Mo, C_1, C_2, C_3, C_4, C_5, t when other parameters are constants

N_0	M_0	C_1	C_2	C_3	C_4	C_5	t	R_{E1}	λ_{11}	λ_{21}	μ_{11}	δ_{11}	μ_{21}	δ_{21}	λ_{32}	μ_{32}	δ_{32}
2000000	10000	1500	100000	20000	20000	2000	5	180.627	8.882	0	10.321	36544620	18272310	1827231	1826027	0	0
2400000	10000	1500	100000	20000	20000	2000	5	218.779	9.105	0	10.581	75407000	75406990	4979865	75389540	0	0
4400000	10000	1500	100000	20000	20000	2000	5	411.272	9.850	0	11.447	1.12E+08	4262401	111603700	430525.8	0	0
5900000	10000	1500	100000	20000	20000	2000	5	556.734	10.211	0	11.867	5666278	2833140	2833140	2833140	0	
6800000	10000	1500	100000	20000	20000	2000	5	644.289	10.386	0	12.070	62153740	31016830	31076910	48579460	0	0
2000000	**11500**	1500	100000	20000	20000	2000	5	75.039	8.033	0	9.333	7709715	3854858	3854858	15266270	0	0
2000000	**11600**	1500	100000	20000	20000	2000	5	74.392	8.033	0	9.333	8683161	4341551	4341611	13073250	0	0
2000000	**11900**	1500	100000	20000	20000	2000	5	72.516	8.033	0	9.333	5305491	2652746	2652746	10491720	0	0
2000000	**12200**	1500	100000	20000	20000	2000	5	70.733	8.033	0	9.333	3959923	1979962	1979962	7796039	0	0
2000000	**12300**	1500	100000	20000	20000	2000	5	70.158	8.033	0	9.333	8004854	4002428	4002428	4043522	0	0
2000000	10000	**1800**	100000	20000	20000	2000	5	84.983	6.403	0	7.667	12552920	6275458	6276458	6273374	0	0
2000000	10000	**2200**	100000	20000	20000	2000	5	83.394	4.963	0	6.187	8108677	8108679	0.097606	8062127	0	0
2000000	10000	**2400**	100000	20000	20000	2000	5	83.653	4.436	0	5.642	12144250	6072124	6072130	6074350	0	0
2000000	10000	**3700**	100000	20000	20000	2000	5	78.441	2.478	0	3.598	5942739	2871370	2971370	11857580	0	0
2000000	10000	**3900**	100000	20000	20000	2000	5	77.863	2.301	0	3.410	743803.9	371803.8	371951.2	22188730	0	0
2000000	10000	1500	**6700**	20000	20000	2000	5	86.295	0.000	0	1.300	73.07846	68.82262	5.526815	4.55E+08	0	0
2000000	10000	1500	**7700**	20000	20000	2000	5	86.295	0.000	0	1.300	5072903	2536455	2536449	39746710	0	0
2000000	10000	1500	**7900**	20000	20000	2000	5	86.295	0.000	0	1.300	37495440	1874842	1874821	29215330	0	0
2000000	10000	1500	**8000**	20000	20000	2000	5	86.295	0.000	0	1.300	5507542	2753775	2753768	41056450	0	0
2000000	10000	1500	**9000**	20000	20000	2000	5	86.295	0.000	0	1.300	9255649	4627828	4627822	4629429	0	0
2000000	10000	1500	100000	**11800**	20000	2000	5	56.093	0.149	0	0.988	1576849	788424.9	788425	3049827	0	0
2000000	10000	1500	100000	**11900**	20000	2000	5	56.093	0.149	0	0.988	1581102	790551	790551.3	3058432	0	0
2000000	10000	1500	100000	**12000**	20000	2000	5	56.093	0.149	0	0.988	1590804	795402.6	795402.6	3080123	0	0
2000000	10000	1500	100000	**12600**	20000	2000	5	56.093	0.149	0	0.988	2344374	1172187	1172187	4588596	0	0
2000000	10000	1500	100000	**12900**	20000	2000	5	56.093	0.149	0	0.988	2704485	1352243	1352243	5307245	0	0
2000000	10000	1500	100000	20000	**18300**	2000	5	56.093	0.000	0	0.840	66709.5	0.397108	667098.9	2590724	0	0
2000000	10000	1500	100000	20000	**18400**	2000	5	56.093	0.000	0	0.840	1417195	1417195	0.103996	1420050	0	0
2000000	10000	1500	100000	20000	**18500**	2000	5	56.093	0.106	0	0.946	949068.9	0.471694	949069.2	3732372	0	0
2000000	10000	1500	100000	20000	**18600**	2000	5	56.093	0.000	0	0.840	4764890	0.118173	4764891	4771071	0	0
2000000	10000	1500	100000	20000	**19200**	2000	5	56.093	0.126	0	0.966	6458706	3229353	3229353	3231027	0	0
2000000	10000	1500	100000	20000	20000	**2700**	5	56.093	0.000	0	0.840	1275474	637737.5	637737.3	637595.5	0	0
2000000	10000	1500	100000	20000	20000	**2800**	5	56.093	0.000	0	0.840	2728183	1364092	1364092	1363881	0	0
2000000	10000	1500	100000	20000	20000	**2900**	5	56.093	0.000	0	0.840	1302425	651212.9	651212.7	651047.1	0	0
2000000	10000	1500	100000	20000	20000	**3000**	5	56.093	0.000	0	0.840	2094202	1047101	1047101	1046750	0	0
2000000	10000	1500	100000	20000	20000	**3100**	5	56.093	0.000	0	0.840	2121201	1060601	1060601	1060308	0	0
2000000	10000	1500	100000	20000	20000	2000	**10**	203.165	0.000	0	0.389	0	0.161437	0.298588	0	9950450	9950450
2000000	10000	1500	100000	20000	20000	2000	**11**	213.835	0.000	0	0.354	0	0.160153	0.262704	0	4264431	4264431
2000000	10000	1500	100000	20000	20000	2000	**12**	224.578	0.000	0	0.324	0	0.051818	0.339886	0	7977364	7977372
2000000	10000	1500	100000	20000	20000	2000	**13**	235.396	0.000	0	0.299	0	0.154174	0.211018	0	4537569	4537563
2000000	10000	1500	100000	20000	20000	2000	**14**	246.288	0.000	0	0.278	0	0.115582	0.226756	0	15080390	15080390

Table 2: Values of R_{E2}, λ_{11}, λ_{21}, μ_{11}, δ_{11}, μ_{21}, δ_{21}, λ_{32}, μ_{32}, δ_{32} for Varying values of one value of the following No, Mo, C_1, C_2, C_3, C_4, C_5, t when other parameters are constants

N_0	M_0	C_1	C_2	C_3	C_4	C_5	t	R_{E2}	μ_{11}	λ_{11}	λ_{21}	δ_{11}	μ_{21}	δ_{21}	λ_{32}	μ_{32}	δ_{32}
1500000	10000	15000	100000	20000	20000	2000	4	2.43E-12	1.012874	0.188599	0.325218	1.408405	1.27278	1.285118	1.308657	1.320963	1.333308
1600000	10000	15000	100000	20000	20000	2000	4	2.50E-12	1.019791	0.179351	0.323554	1.394069	1.27286	1.285201	1.308739	1.320881	1.333226
1700000	10000	15000	100000	20000	20000	2000	4	2.57E-12	1.037922	0.181945	0.322177	1.380163	1.27299	1.285328	1.308867	1.320754	1.333099
1800000	10000	15000	100000	20000	20000	2000	4	2.80E-12	1.057889	0.188106	0.321635	1.367000	1.27304	1.285379	1.308917	1.320704	1.333049
1900000	10000	15000	100000	20000	20000	2000	4	3.71E-12	1.111234	0.196796	0.294271	1.342069	1.26922	1.285559	1.308664	1.320956	1.333301
1000000	**12000**	15000	100000	20000	20000	2000	4	2.22E-13	0.719593	0	0.330333	2.416038	1.726813	1.739151	1.707038	1.004646	1.016219
1000000	**13000**	15000	100000	20000	20000	2000	4	2.21E-13	0.719843	0	0.330083	2.416090	1.726839	1.739177	1.707071	1.004608	1.016182
1000000	**14000**	15000	100000	20000	20000	2000	4	2.50E-13	0.720097	0	0.329825	2.416148	1.726866	1.739204	1.707103	1.004571	1.016144
1000000	**15000**	15000	100000	20000	20000	2000	4	2.32E-13	0.720345	0	0.329579	2.416200	1.726893	1.739231	1.707136	1.004533	1.016106
1000000	**17000**	15000	100000	20000	20000	2000	4	2.23E-13	0.720844	0	0.329082	2.416306	1.726947	1.739285	1.707201	1.004457	1.016031
1000000	15000	11000	100000	20000	20000	2000	4	3.95E-12	1.234198	0.296411	0.185051	1.437599	1.279613	1.280825	1.308803	1.320818	1.333163
1000000	15000	12000	100000	20000	20000	2000	4	9.93E-13	0.759149	0	0.288784	1.477684	1.256640	1.268978	1.310926	1.318694	1.331039
1000000	15000	15000	100000	20000	20000	2000	4	2.32E-13	0.720345	0	0.329579	2.416200	1.726893	1.739231	1.707136	1.004533	1.016106
1000000	15000	16000	100000	20000	20000	2000	4	1.99E-13	0.725045	0	0.308744	2.509700	1.765575	1.777913	1.741843	0.971318	0.982892
1000000	15000	17000	100000	20000	20000	2000	4	9.72E-12	1.01345	2.14E-06	5.18E-03	23.33575	1.500010	21.83574	1.308684	1.320936	1.333281
1000000	15000	15000	18000	20000	20000	2000	4	7.87E-13	0.720345	1.00E-06	0.329582	1.729747	1.383667	1.396006	1.380318	1.249303	1.261648
1000000	15000	15000	18500	20000	20000	2000	4	4.40E-13	0.720381	0	0.32951	1.793661	1.415607	1.427945	1.421507	1.208114	1.220459
1000000	15000	15000	19000	20000	20000	2000	4	4.21E-13	0.720344	0	0.329578	1.824150	1.430867	1.443205	1.431459	1.198161	1.210506
1000000	15000	15000	19500	20000	20000	2000	4	2.77E-13	0.720396	0	0.329481	2.143457	1.590498	1.602836	1.562705	1.066916	1.079261
1000000	15000	15000	20500	20000	20000	2000	4	8.12E-13	0.720713	2.78E-04	0.329464	1.469508	1.253534	1.265873	1.330759	1.298861	1.311206
1000000	15000	15000	100000	10500	20000	2000	4	9.01E-13	0.876923	0	0.167242	1.744070	1.352726	1.435510	1.330979	1.299142	1.001382
1000000	15000	15000	100000	11500	20000	2000	4	2.35E-13	0.86201	0	0.187915	3.183191	2.110389	2.122727	2.095699	0.535862	0.546267
1000000	15000	15000	100000	12500	20000	2000	4	4.64E-13	0.845344	0	0.204571	2.121949	1.579763	1.592101	1.567729	1.062391	1.074236
1000000	15000	15000	100000	15500	20000	2000	4	3.63E-13	0.795353	0	0.254563	2.299204	1.668391	1.680729	1.654002	0.976390	0.987964
1000000	15000	15000	100000	16500	20000	2000	4	2.77E-13	0.778676	0	0.271249	2.343534	1.690560	1.702899	1.654135	0.976257	0.987831
1000000	15000	15000	100000	20000	15000	2000	4	1.80E-12	0.85196	0	0.197956	1.542635	1.290107	1.302445	1.308052	1.321569	1.333914
1000000	15000	15000	100000	20000	15400	2000	4	1.16E-12	0.884958	1.68E-05	0.156753	1.541508	1.285432	1.297771	1.336983	1.292638	1.039068
1000000	15000	15000	100000	20000	15600	2000	4	1.23E-12	0.885092	1.42E-05	0.156658	1.541182	1.285289	1.297628	1.332723	1.296897	1.035336
1000000	15000	15000	100000	20000	16200	2000	4	2.76E-13	0.726772	5.99E-05	0.299884	2.123640	1.568949	1.581287	1.546764	1.082857	1.095202
1000000	15000	15000	100000	20000	16800	2000	4	7.47E-13	0.819101	2.41E-05	0.214394	1.563204	1.327006	1.269668	1.364981	1.264639	1.073646
1000000	15000	15000	100000	20000	20000	2500	4	2.32E-13	0.720345	0	0.329579	2.416200	1.726893	1.739231	1.707136	1.004533	1.016106
1000000	15000	15000	100000	20000	20000	6000	4	1.47E-12	0.919801	0	0.130126	1.525676	1.318193	1.257409	1.365074	1.264547	1.064045
1000000	15000	15000	100000	20000	20000	6300	4	5.92E-12	0.872884	0	0.177042	1.452350	1.244969	1.257308	1.365093	1.264527	1.065543
1000000	15000	15000	100000	20000	20000	6500	4	2.04E-12	0.871963	0	0.177963	1.520323	1.312545	1.257704	1.365108	1.264513	1.066756
1000000	15000	15000	100000	20000	20000	6700	4	4.69E-12	0.870705	0	0.179221	1.454775	1.246181	1.258520	1.365123	1.264497	1.068185
1000000	15000	15000	100000	20000	20000	2000	2.2	1.43E-13	1.414743	8.52E-02	0.579418	3.550334	4.154235	1.305056	4.544316	0.612441	4.77E-02
1000000	15000	15000	100000	20000	20000	2000	2.6	1.51E-12	1.371976	0.236458	0.465993	1.103336	1.346254	1.358593	1.385282	1.244338	1.256683
1000000	15000	15000	100000	20000	20000	2000	3	2.27E-12	1.269788	0.17297	0.276614	1.280628	1.286652	1.367408	1.309467	1.320154	1.332499
1000000	15000	15000	100000	20000	20000	2000	3.2	2.31E-12	1.230368	0.221546	0.302896	1.270914	1.285144	1.297489	1.308645	1.320975	1.33332
1000000	15000	15000	100000	20000	20000	2000	3.4	1.98E-12	1.145377	0.217539	0.30722	1.325921	1.268723	1.292256	1.308683	1.320938	1.333283

Appendix-III

Table 3: Values of R_{E1}*, λ_{11}, λ_{21}, μ_{11}, δ_{11}, μ_{21}, δ_{21}, λ_{32}, μ_{32}, δ_{32} for Varying values of one value of the following No, Mo, C_1, C_2, C_3, C_4, C_5, t when other parameters are constants

N_0	M_0	C_1	C_2	C_3	C_4	C_5	a	t	R_{E1}*	λ_{11}	λ_{21}	μ_{11}	δ_{11}	μ_{21}	δ_{21}	λ_{32}	μ_{32}	δ_{32}
900000	15000	15000	100000	20000	20000	2000	0.8	5	32.16829	0.0000	0	1.0236	1211127	609279.3	605033	609064.4	0	0
1000000	15000	15000	100000	20000	20000	2000	0.8	5	37.39539	0.0000	0	1.0499	999638.5	509373.4	498454.9	509065.3	0	0
1100000	15000	15000	100000	20000	20000	2000	0.8	5	42.68605	0.2222	0	1.2626	9866534	4976753	4976752	5004174	0	0
1500000	15000	15000	100000	20000	20000	2000	0.8	5	64.3578	0.0000	0	1.8967	1268591	643117.1	643117.4	642871.7	0	0
1600000	15000	15000	100000	20000	20000	2000	0.8	5	69.87906	0.2376	0	2.1168	0	0.737548	0.389091	21183500	0	0
1000000	10000	15000	100000	20000	20000	2000	0.8	5	56.09311	0.2184	0	1.2356	5287489	2713226	2713226	2697283	0	0
1000000	12000	15000	100000	20000	20000	2000	0.8	5	46.74423	0.2184	0	1.2356	1177038	597671.7	597671.5	597321.9	0	0
1000000	13000	15000	100000	20000	20000	2000	0.8	5	43.14854	0.0000	0	1.0499	5254613	5240339	0.84015	1443713	0	0
1000000	16000	15000	100000	20000	20000	2000	0.8	5	35.05819	0.2892	0	1.2356	3637327	21.04845	3598775	3644842	0	0
1000000	18000	15000	100000	20000	20000	2000	0.8	5	31.16284	0.2184	0	1.2356	5265390	2660720	2660719	2673957	0	0
1000000	15000	9000	100000	20000	20000	2000	0.8	5	44.14736	0.0000	0	1.1776	4174923	2099790	2085701	2098993	0	0
1000000	15000	9500	100000	20000	20000	2000	0.8	5	43.5187	0.0000	0	1.1641	1569810	800057.6	782740.7	799580.1	0	0
1000000	15000	10000	100000	20000	20000	2000	0.8	5	42.90521	0.0000	0	1.1513	2690647	1354633	1343994	1354203	0	0
1000000	15000	10500	100000	20000	20000	2000	0.8	5	42.30568	0.0000	0	1.1391	2439011	1240420	1216518	1239996	0	0
1000000	15000	11000	100000	20000	20000	2000	0.8	5	41.71905	0.0000	0	1.1275	2600714	1309450	1299058	1309450	0	0
1000000	15000	15000	19900	20000	20000	2000	0.8	5	37.39541	0.1878	0	1.2356	3617848	0.202456	3564740	3619308	0	0
1000000	15000	15000	20000	20000	20000	2000	0.8	5	37.39541	0.1874	0	1.2356	9533674	4820638	4759160	4875382	0	0
1000000	15000	15000	20100	20000	20000	2000	0.8	5	37.39539	0.1870	0	1.2356	917652.9	461579.4	461565.5	461584.1	0	0
1000000	15000	15000	20200	20000	20000	2000	0.8	5	37.39539	0.1865	0	1.2356	910470.2	463534.4	454049.9	463603.8	0	0
1000000	15000	15000	20400	20000	20000	2000	0.8	5	37.3954	0.1857	0	1.2356	2300279	1162867	1148322	1162361	0	0
1000000	15000	15000	25000	20100	20000	2000	0.8	5	37.39539	0.0000	0	1.0499	999638.5	509373.4	498454.9	509065.3	0	0
1000000	15000	15000	25000	20800	20000	2000	0.8	5	37.39539	0.2184	0	1.2356	1445398	733957.1	734442.1	733871	0	0
1000000	15000	15000	25000	23000	20000	2000	0.8	5	37.39539	0.2184	0	1.2356	1364695	693288.6	680784.2	693259.3	0	0
1000000	15000	15000	25000	26000	20000	2000	0.8	5	37.3954	0.0000	0	1.0499	3331710	1698525	1661188	1699872	0	0
1000000	15000	15000	25000	27000	20000	2000	0.8	5	37.3954	0.0000	0	1.0499	3331710	1698525	1661188	1699872	0	0
1000000	15000	15000	25000	20000	16000	2000	0.8	5	37.39539	0.0238	0	1.0855	1089898	1087999	1.53954	1094147	0	0
1000000	15000	15000	25000	20000	17000	2000	0.8	5	37.39541	0.0791	0	1.1436	4682985	670476.8	4030890	52604363	0	0
1000000	15000	15000	25000	20000	22000	2000	0.8	5	37.39541	0.0000	0	1.0499	6510144	3303077	3301521	3290099	0	0
1000000	15000	15000	25000	20000	25000	2000	0.8	5	37.3954	0.3707	0	1.4132	0	0.95181	0.041668	5599786	0	0
1000000	15000	15000	25000	20000	26000	2000	0.8	5	37.3954	0.4046	0	1.4488	1523368	1517837	3.857991	1530907	0	0
1000000	15000	15000	25000	20000	20000	1700	0.8	5	37.39541	0.0000	0	1.0499	2468722	0.224227	2390568	8663331	0	0
1000000	15000	15000	25000	20000	20000	1800	0.8	5	37.39539	0.1857	0	1.2356	835005.8	423121.6	423103.6	423106.1	0	0
1000000	15000	15000	25000	20000	20000	2100	0.8	5	37.39539	0.2184	0	1.2356	1393735	706626.5	706626.5	706507.2	0	0
1000000	15000	15000	25000	20000	20000	2200	0.8	5	37.3954	0.0000	0	1.0499	4155987	2140046	2140049	2131713	0	0
1000000	15000	15000	25000	20000	20000	2400	0.8	5	37.3954	0.0000	0	1.0499	5426272	66638.89	5369617	1402979	0	0
1000000	15000	15000	25000	20000	20000	2000	0.8	3.0	49.28016	0.0274	0	1.7772	1094620	1093251	0.347921	1095885	0	0
1000000	15000	15000	25000	20000	20000	2000	0.8	3.4	46.93586	0.2730	0	1.8170	495074.8	0.841872	495075.4	1963122	0	0
1000000	15000	15000	25000	20000	20000	2000	0.8	5.4	34.94492	0.0000	0	0.9722	3463125	3425514	0.089082	3507366	0	0
1000000	15000	15000	25000	20000	20000	2000	0.8	5.6	33.70467	0.0000	0	0.9374	3231719	3231721	0.097025	814438.3	0	0
1000000	15000	15000	25000	20000	20000	2000	0.8	6.4	28.604	0.1706	0	0.9666	1300107	1300108	0.010517	1299538	0	0

Appendix-IV

Table 4: Values of R_{E2}*, λ_{11}, λ_{21}, μ_{11}, δ_{11}, μ_{21}, δ_{21}, λ_{32}, μ_{32}, δ_{32} for Varying values of one value of the following No, Mo, C_1, C_2, C_3, C_4, C_5, t when other parameters are constants

N_0	M_0	C_1	C_2	C_3	C_4	C_5	a	t	R_{E2}*	μ_{11}	λ_{11}	λ_{21}	δ_{11}	μ_{21}	δ_{21}	λ_{32}	μ_{32}	δ_{32}
400000	10000	15000	100000	20000	20000	2000	0.8	3	1.14E-12	1.0560	0.2108	0.2493	1.3344	1.3372	1.0916	1.3845	1.4105	1.4352
500000	10000	15000	100000	20000	20000	2000	0.8	3	5.67E-13	0.9987	0.2189	0.3890	1.3075	1.3358	1.1405	1.4852	1.3099	1.3346
800000	10000	15000	100000	20000	20000	2000	0.8	3	2.61E-13	0.9833	0.0847	0.3653	2.1476	1.3358	2.0758	1.6461	1.1490	1.1247
900000	10000	15000	100000	20000	20000	2000	0.8	3	1.59E-12	1.1433	0.2100	0.4198	1.3118	1.3358	1.3292	1.3855	1.4095	1.4342
1000000	10000	15000	100000	20000	20000	2000	0.8	3	1.80E-12	1.1703	0.1999	0.4129	1.3030	1.3358	1.3505	1.3856	1.4094	1.4341
1000000	11000	15000	100000	20000	20000	2000	0.8	3	1.83E-12	1.1705	0.1997	0.4125	1.3030	1.3358	1.3504	1.3856	1.4094	1.4341
1000000	12000	15000	100000	20000	20000	2000	0.8	3	1.84E-12	1.1707	0.1995	0.4120	1.3030	1.3358	1.3504	1.3856	1.4094	1.4341
1000000	13000	15000	100000	20000	20000	2000	0.8	3	1.85E-12	1.1709	0.1994	0.4116	1.3030	1.3358	1.3503	1.3856	1.4094	1.4341
1000000	14000	15000	100000	20000	20000	2000	0.8	3	1.88E-12	1.1711	0.1992	0.4112	1.3030	1.3358	1.3503	1.3856	1.4094	1.4341
1000000	16000	15000	100000	20000	20000	2000	0.8	3	1.89E-12	1.1772	0.2115	0.4218	1.3026	1.3358	1.3543	1.3852	1.4098	1.4345
1000000	10000	10000	100000	20000	20000	2000	0.8	3	2.03E-12	1.2240	0.2577	0.4705	1.2925	1.3523	1.3770	1.3899	1.4051	1.4298
1000000	10000	13000	100000	20000	20000	2000	0.8	3	2.03E-12	1.1965	0.2468	0.4863	1.3030	1.3358	1.4033	1.3856	1.4094	1.4341
1000000	10000	16000	100000	20000	20000	2000	0.8	3	1.85E-12	1.1363	0.1626	0.3967	1.3029	1.3358	1.3375	1.3855	1.4095	1.4342
1000000	10000	17000	100000	20000	20000	2000	0.8	3	1.66E-12	1.0904	0.1161	0.3808	1.3026	1.3358	1.3219	1.3852	1.4099	1.4345
1000000	10000	18000	100000	20000	20000	2000	0.8	3	1.49E-12	1.0350	0.0526	0.3485	1.3027	1.3358	1.2978	1.3852	1.4098	1.4344
1000000	10000	10000	13000	20000	20000	2000	0.8	3	4.11E-12	1.2293	0.2450	0.4633	1.2933	1.3581	1.3828	1.3891	1.4059	1.4306
1000000	10000	10000	14000	20000	20000	2000	0.8	3	2.00E-12	1.2282	0.2557	0.4507	1.2997	1.3498	1.3731	1.3874	1.4076	1.4323
1000000	10000	10000	15000	20000	20000	2000	0.8	3	1.86E-12	1.2226	0.2659	0.4493	1.3093	1.3421	1.3731	1.3893	1.4058	1.4305
1000000	10000	10000	16000	20000	20000	2000	0.8	3	1.89E-12	1.2215	0.2647	0.4488	1.3093	1.3421	1.3727	1.3893	1.4058	1.4305
1000000	10000	10000	19000	20000	20000	2000	0.8	3	3.57E-12	1.2215	0.2647	0.4488	1.3093	1.3421	1.3727	1.3893	1.4058	1.4305
1000000	10000	10000	100000	6000	20000	2000	0.8	3	1.65E-13	1.3429	0.0045	0.1967	0.8051	1.1764	1.1637	27.8915	1.0971	0.2705
1000000	10000	10000	100000	8000	20000	2000	0.8	3	1.08E-12	1.1914	0.0135	0.1262	1.3551	0.7743	1.8848	2.2967	0.7124	1.0352
1000000	10000	10000	100000	9000	20000	2000	0.8	3	1.08E-12	1.2914	0.0312	0.2748	0.8163	1.0020	1.3494	1.4769	0.2786	0.2835
1000000	10000	10000	100000	10000	20000	2000	0.8	3	2.08E-13	1.2271	0.0198	0.3178	4.2613	4.4370	1.3494	4.3662	0.1086	0.1135
1000000	10000	10000	100000	14000	20000	2000	0.8	3	7.17E-13	1.3088	0.2371	0.4633	0.8001	1.0171	1.3180	1.3906	0.2836	0.2886
1000000	10000	10000	100000	20000	15000	2000	0.8	3	1.98E-12	1.2066	0.2241	0.5016	1.2865	1.3729	1.3976	1.4060	1.3890	1.4137
1000000	10000	10000	100000	20000	16000	2000	0.8	3	2.07E-12	1.2077	0.2313	0.4894	1.2844	1.3627	1.3874	1.3939	1.4012	1.4259
1000000	10000	10000	100000	20000	17000	2000	0.8	3	2.05E-12	1.2178	0.2363	0.4665	1.2933	1.3583	1.3830	1.3894	1.4056	1.4303
1000000	10000	10000	100000	20000	18000	2000	0.8	3	2.07E-12	1.2251	0.2473	0.4556	1.2965	1.3526	1.3773	1.3869	1.4081	1.4328
1000000	10000	10000	100000	20000	19000	2000	0.8	3	1.97E-12	1.2273	0.2574	0.4496	1.3023	1.3490	1.3728	1.3877	1.4074	1.4320
1000000	10000	10000	100000	20000	20000	18000	0.8	3	4.17E-12	1.3897	0.4688	0.5551	1.2802	1.3935	1.3227	1.3762	1.4189	1.6483
1000000	10000	10000	100000	20000	20000	20000	0.8	3	3.81E-12	1.3317	0.4071	0.6104	1.0980	1.2920	1.3411	1.3814	1.4137	1.4383
1000000	10000	10000	100000	20000	20000	21000	0.8	3	2.25E-13	1.2034	0.1564	0.4881	4.4802	1.5643	4.4509	2.3499	0.4596	0.4701
1000000	10000	10000	100000	20000	20000	22000	0.8	3	2.24E-13	1.2033	0.1553	0.4870	4.5536	1.5643	4.5243	2.3400	0.4694	0.4800
1000000	10000	10000	100000	20000	20000	23000	0.8	3	2.26E-14	1.2782	0.3547	0.6115	63.4283	1.8054	63.1579	1.5786	1.2164	1.2411
1000000	10000	10000	100000	20000	20000	2000	0.8	2.5	2.18E-13	1.4503	0.2000	0.5917	4.5465	1.5645	4.8240	4.6329	0.8940	0.8978
1000000	10000	10000	100000	20000	20000	2000	0.8	3.4	2.23E-13	1.1734	0.1980	0.2527	1.6698	1.3116	1.5864	5.4597	0.8551	0.8798
1000000	10000	10000	100000	20000	20000	2000	0.8	3.8	1.53E-13	1.1514	0.0945	0.0109	0.8654	0.6326	0.2327	0.3241	1.6480	1.6529
1000000	10000	10000	100000	20000	20000	2000	0.8	4.0	2.26E-23	0.9312	0.0379	0.0984	2.2591	1.0861	2.1647	0.3449	0.8422	1.0230
1000000	10000	10000	100000	20000	20000	2000	0.8	4.8	9.80E-24	0.6561	0.0482	0.2260	3.3709	1.4835	2.7213	0.3501	0.2129	0.8665

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