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RESEARCH ARTICLE

OPTIMIZATION MODELS ON MANAGEMENT OF MULTIPLE SCLEROSIS

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ABSTRACT

This paper has discussed the programming problems for optimal management of Multiple Sclerosis (MS) based on stochastic modeling of MS by Tirupathi Rao *et al.* [9].The proposed problems deal with the objectives of minimizing the expected size of MS, maximizing the expected size of oligodendrocytes and minimizing the variance of oligodendrocytes. The constraints are formulated with the minimum limit on expected size of oligodendrocytes, maximum limit on expected size of MS causing cells and maximum limit on variance of oligodendrocytes. The decision variables like growth and loss rates of MS causing cells; growth and loss rates of oligodendrocytes are obtained from the study. The patterns of the objective functions and decision variables are observed and arrived to the conclusions. This study will useful for provide the indicators of MS so as monitoring of the disease control can be planned.

INTRODUCTION

The prime function of a nerve cell is to make neurological communication in central nervous system which includes Brain, spinal cord and other peripheral organs of the body. The neuron communication is in the form of electrical impulses with ions through axon and dendrites. The axons are covered with fatty substance of white material (myelin) which act as an insulation to the nerve cell from the cross exposure of axons of other nerve cells. Multiple sclerosis is an inflammatory demyelination disease that damages the myelin sheath. It refers to forming of scars on myelin sheath with different depths and spread at multiple places. There are no specific reasons attributed to cause Multiple Sclerosis. However, some of the hypotheses are related with genetics, infections, inflammations and environmental risk factors for getting MS. Pathophysiology of MS is more complex and heterogeneous than any other disease of nervous disorder. Primarily it deals with disease of demyelination. It affects CNS, spinal cord and finally damages the nerve functioning immune system which attacks the nervous system. Neurological central CNS will create problem in conduction of nerves system results from axonal demyelination and destruction. However inflammation and oedema will reach Blood Brain Barrier (BBB) also contributes this tissue damage in CNS. In MS the new response is initiated at off side CNS when antigen is assembled in a self succeeding antigen as such myelin. It is further succeeded as macrophase and it subsequently presented through T-cells. The T-cells combined with antigen become activated and release cytokines including gamma interferon and inter lukanes in turn further influence demyelination cells. They are passing through the BBB to CNS so as cytokines and T-cells further activate and amplify the response of immunity.

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In CNS, activated T-cells will continuously release the pro-inflammatory cytokines. Other inflammatory cells including B-cells and macrophases, which enter to the CNS through BBB will produce antibodies and directly attack myelin and oligodendrocytes. When the macrophase is functioning with CNS, they have adverse effect on myelin surrounded to axon. Oligodendrocytes myelinates the axons in CNS ensuring the insulation process of axon and transmits the nerve ionic impulses quickly. An MS extravagation sensitive with T-cells become mis-program the antigen presenting cell of demyelination. As a result, T-cells will release cytokines to aggravate similar B-cells, T-cells and Macrophases. Then T-cells are able to break the BBB (membrane of blood vessel) and enters to CNS. Once they were inside CNS, the auro aggressive T-cells will release cytokines and activate B cells, Macrophases and microglia propogates the cytokines inflammation. The macrophases and microglia releases the B-cells and produce antibodies and spread of cytokines put together will destroy the myelin sheath. The pathophysiology of MS and its related functions with CNS and immunity system reveal the following two important contents. (1) The oligodendrocytes will generate/ supplement the Myelin sheath with the white material made up of proteins as insulation on the axon when the body is free from infections/ inflammations (here onwards it is referred as formation of Myelin sheath substance). (2) The combined influence of B-cells, T-cells, Microglia, Macrophase and cytokines with the act of intervening the infected T-cell from blood vessel to CNS through BBS during the exposure of the body to viral/bacterial attacks will create multiple scars on the axon with different depths and spread (here on words it is referred as formation of MS causing substance), The formation of MS substances will destroy the myelin sheath and the formation of myelin sheath will reduce the MS substances. Hence we may treat that the events of formation/destruction of both MS substance/ Myelin sheath are complementary. Due to the prevailing

situations of health conditions, the events of growth/loss of MS substance/ myelin sheath are uncertain and purely random in nature. New symptoms of MS occurring in discrete attacks (relapsing forms) and slow accumulation of MS over time (progressive forms) are the major different forms of these attacks. Presence of this disorder will effect whole nervous system so as the neurological communications. The intensity of the disease has to be assessed with the size and variability levels of MS spread and myelin sheath. Another feature of this disease is, symptoms may go away completely, but permanent neurological problems often occur, especially as the disease advances [10]. It has many hidden affects on neurological functions. Most of the times the symptoms of MS are un recognized. They are in submissive stage and the person who is having this disease may not even feel the presence of the disease. Moreover, clinical methods and diagnostic procedures are also not at that much advanced stage to quantify and screen the severity of the disease as like other diseases of nervous system. The symptoms of MS have to be identified well in advance before the attack comes to clinical stage. Hence there is a need of asses the cause and effect of MS through mathematical protocols. This objective of the study has attracted our attention to model the disease with applied stochastic processes and optimization methods.

Hodgkin and Huxley [1] pioneered the works of neuronal modeling and they have described the quantitative method for membrane current and its application to conduction and excitation in nerve cells. Christina Wolfson [2] proposed mathematical modeling on MS understanding by developing probabilistic models to the natural history of multiple sclerosis. It is a significant breakthrough on measuring MS through quantitative formats. Confavreux and Wolfson [3] developed Mathematical models for individualized outcome estimates in the studies of multiple sclerosis. Albert et.al.[4,5] have proposed a Markov model for sequences of ordinal data from a relapsing-remitting disease and applied time series modeling to study the activity in multiple sclerosis. Yakovlen et.al. [6] proposed Stochastic formulation of a clock model for temporally regulated generation of oligodendrocytes. Rachael Miller et.al. [7] developed Hidden Markov Models to lesion count data of individual multiple sclerosis patients and described the behavior of lesions over time. Ollivier Hyrien[8] developed a stochastic model to find the generation of oligodendrocytes. The model validation was carried out with time-lapse data. Tirupathi Rao et. al.[9] derived various statistical measures by developing a stochastic model for growth/loss processes of MS and oligodendrocytes. The referred literature has revealed a room for developing the stochastic programming for optimal management of MS as there are no studies in this direction so far. The study is focused on development of stochastic programming problem for optimal management of the disease by getting the indicators on the growth and loss rates of MS substance and extent of myelin sheath. The study includes the following steps.

1. Considered the works of Tirupathi Rao et. al. [9] to get the developed stochastic model with an approach of differential equations and derived mathematical formulae for statistical measures such as mean & variance of MS substance cells, Mean & variance of myelin sheath's extent.
2. Development of stochastic Non-linear programming problems with the objectives of minimizing the average spread of MS substance, maximizing the average expansion of myelin sheath and minimizing the variability in myelin sheath's expansion.
3. Formulation of subjective constraints by maintaining the minimum average size of myelin sheath (more than some wanted level); by maintaining the maximum average size of MS substance (less than some undesired level); by fixing the target on the maximum variability in expansion of myelin sheath (variance of myelin sheath's expansion should be less than some targeted level); and by achieving some minimum variability on MS substance (variance of MS substance should be more than some specific level).
4. Numerical calculations for objective functions, decision variables for the fixed values of the other parameters of the programming problem with mathematical software LINGO.
5. Analyzing the behaviour of the developed programming models with respect to objective function, growth/loss rates of MS substance and myelin sheath.
6. Drawing conclusions about the changing patterns of objective function and decision variables by various influencing factors.

This study is useful to understand the status of the disease and also to suggest the treatment policies for optimal management of the disease.

Stochastic Model

This section provides the highlights of developed stochastic model by Tirupathi Rao *et al.* [9] based on Bivariate Markovian processes of MS substance & myelin sheath density with birth and death processes. The postulates of the model are according to the generation and eradication of both MS substance and myelin sheath by including the pathophysiology of MS and CNS. Model construction was carried out on the frame work of stochastic nature in growth and spread of MS substance and its counter material on myelin sheath. The assumptions of the model includes, the events of either formation or eradication of MS substance will be in non-overlapping intervals of time; the events are statistically independent; 'i' is the number of MS substance cells; 'j' is the number of discrete cells in myelin sheath at time 't'; λ_1', λ_2', are the growth rates of MS substance cells, myelin sheath discrete units respectively per unit time; 'μ_1', 'μ_2' are the loss rates of MS substance cells, myelin sheath discrete units respectively per unit time; I_0, J_0 are the initial sizes of MS substance cells, myelin sheath discrete units respectively. The Postulates of the model includes, the probability of growth of a MS substance cell during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $i\lambda_1\Delta t + o(\Delta t)$; the probability of growth of a myelin sheath discrete unit during (t, t+ Δt) given that there exists 'j' discrete myelin sheath units during (0,t) is $j\lambda_2\Delta t + o(\Delta t)$; the probability of loss of a MS substance cell during (t, t+ Δt) given that there exists 'i' MS substance cells during (0,t) is $i\mu_1\Delta t + o(\Delta t)$; the probability of loss of a discrete unit of myelin sheath during (t, t+ Δt) given that there exists 'j' discrete units of myelin sheath during (0,t) is $j\mu_2\Delta t + o(\Delta t)$; the probability of no growth in MS substance cells during (t, t+ Δt) given that there exists 'i' such cells during (0,t) is $1 - (i\lambda_1\Delta t + o(\Delta t))$; the probability of no growth in the discrete units of myelin sheath during (t, t+ Δt) given that there exists 'i' such cells during (0,t) is $1 - (j\lambda_2\Delta t + o(\Delta t))$; the probability of no loss to MS substance cells during (t, t+ Δt) given that there exists 'i' such cells during (0,t) is 1-($i\mu_1\Delta t + o(\Delta t)$; the probability of no loss to discrete units of myelin sheath during (t,t+Δt) given that there exists 'j' such cells during (0,t) is $1 - (j\mu_2\Delta t + o(\Delta t))$ and the probability of happening more than one events during Δt time is $o(\Delta t)^2$.

If $p_{i\ j}(t)$ is the joint probability of 'i' MS substance cells and 'j' discrete units of myelin sheath per unit time 't' then the difference differential equations are

$$\left.\begin{aligned}
&p'_{ij}(t) = -p_{i,j}(t)\left[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)\right] + p_{i-1,j}(t)(i-1)\lambda_1 + \\
&p_{i+1,j}(t)(i+1)\mu_1 + \quad p_{i,j-1}(t)(j-1)\lambda_2 + \\
&p_{i,j+1}(t)(j+1)\mu_2; \qquad i,j \geq 1 \\
&p'_{0,0}(t) = \mu_1 p_{1,0}(t) + \mu_2 p_{0,1}(t) \\
&p'_{1,0}(t) = -(\lambda_1+\mu_1)p_{1,0}(t) + \mu_2 p_{1,1}(t) + 2\mu_1 p_{2,0}(t) \\
&p'_{0,1}(t) = -(\lambda_2+\mu_2)p_{0,1}(t) + \mu_1 p_{1,1}(t) + 2\mu_2 p_{0,2}(t)
\end{aligned}\right\} \quad (1)$$

The initial conditions are $p_{i\,j}(0) = 1\ \forall\ I,J > 0;\ p_{i\,j}(0) = 0\ \forall\ i = 0, j = 0$

The differential equations of the model

Let $m_{i\ ,\ j}(t)$ denote the joint moments of order (r,s) of MS substance cells and discrete units of myelin sheath at time 't'. Using the

relations in (1) along with cumulant generating functions, the differential equations of the model are

$$\left.\begin{aligned}
&\tfrac{d}{dt}m_{1,0}(t) = (\lambda_1 - \mu_1)m_{1,0}(t)\\
&\tfrac{d}{dt}m_{0,1}(t) = (\lambda_2 - \mu_2)m_{0,1}(t)\\
&\tfrac{d}{dt}m_{2,0}(t) = (\lambda_1 + \mu_1)m_{1,0}(t) + 2(\lambda_1 - \mu_1)m_{2,0}(t)\\
&\tfrac{d}{dt}m_{0,2}(t) = (\lambda_2 + \mu_2)m_{0,1}(t) + 2(\lambda_2 - \mu_2)m_{0,2}(t)\\
&\tfrac{d}{dt}m_{1,1}(t) = (\lambda_1 - \mu_1) + (\lambda_2 - \mu_2)m_{1,1}(t)
\end{aligned}\right\} \quad (2)$$

The statistical measures of the model

Solving the differential equations in (2) and by assuming I_0 and J_o as the initial sizes of MS substance and size discrete units of myelin sheath.

Expected number of MS substance cells at time 't' is

$$m_{1,0}(t) = e^{(\lambda_1-\mu_1)t} + I_0 \quad (3)$$

Expected number of discrete units in myelin sheath at time 't' is

$$m_{0,1}(t) = e^{(\lambda_2-\mu_2)t} + J_0 \quad (4)$$

The variance of number of MS substance cells at time 't' is

$$m_{2,0}(t) = (\lambda_1 + \mu_1)\left[\frac{e^{(\lambda_1-\mu_1)t}(e^{(\lambda_1-\mu_1)t}-1)}{\lambda_1-\mu_1} + \frac{I_0(e^{2(\lambda_1-\mu_1)t}-1)}{2(\lambda_1-\mu_1)}\right] \quad (5)$$

The variance of number of discrete units in myelin sheath at time 't' is

$$m_{0,2}(t) = (\lambda_2 + \mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2} + \frac{J_0(e^{2(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right] \quad (6)$$

Stochastic Optimization Programming Problems

This section deals with development of three different optimization-programming problems based on the results from (3) to (6). It is with the decision variables like growth rate of MS substance cells per unit time (λ_1), growth rate of discrete units in myelin sheath per unit time (λ_2), loss rate of MS substance cells per unit time (μ_1) and the loss rate of discrete units in myelin sheath per unit time(μ_2), etc. This section has considered some more assumptions in addition to the assumptions of section 2. Let 't' be the time of observation, let 'A' be the average allowable maximum number of MS substance cells, let 'B' be the average minimum required number of discrete units in myelin sheath, let 'C' be the minimum wanted variance of MS substance cells and let 'D' be the maximum specified/targeted variance of discrete units in myelin sheath for maintaining the optimal health standards in MS patient.

Problem-1: As the spread of MS substance is a harming device of neurological functions, the health caretaking measures have to be taken with an aim of minimizing the MS intensity. It is an optimization programming problem for minimizing the number of MS substance cells. Expected number of MS substance cells is obtained from the relation (3). Hence, the objective function is to Minimize the value of $Z_1 = e^{(\lambda_1-\mu_1)t} + I_0$ (7)

The constraint that the average number of MS substance cells should not exceed certain wanted level say A. Therefore the constraint with the unwanted limit of MS substance cells is

$$e^{(\lambda_1-\mu_1)t} + I_0 \le A; \quad (8)$$

As the MS growth is unwanted, more fluctuation/volatility in the sizes of MS substance cells is wanted and hence a constraint is formulated with a minimum desired variability 'C' of MS. Therefore the constraint with the minimum variability of MS is

$$(\lambda_1 + \mu_1)\left[\frac{e^{(\lambda_1-\mu_1)t}(e^{(\lambda_1-\mu_1)t}-1)}{\lambda_1-\mu_1} + \frac{I_0(e^{(\lambda_1-\mu_1)t}-1)}{2(\lambda_1-\mu_1)}\right] \ge C; \quad (9)$$

The decision variables are growth rate of MS substance cells per unit time (λ_1) and loss rate of MS substance cells per unit time (μ_1). Hence, $\boldsymbol{\lambda_1 and\ \mu_1 \ge 0}$ (10)

In summary the formulated non linear programming problem is

$$\left.\begin{aligned}
&Minimize\ Z_1 = e^{(\lambda_1-\mu_1)t} + I_0\ ;\\
&\text{Subject to the constraints}\\
&e^{(\lambda_1-\mu_1)t} + I_0 \le A;\\
&(\lambda_1 + \mu_1)\left[\frac{e^{(\lambda_1-\mu_1)t}(e^{(\lambda_1-\mu_1)t}-1)}{\lambda_1-\mu_1} + \frac{I_0(e^{(\lambda_1-\mu_1)t}-1)}{2(\lambda_1-\mu_1)}\right] \ge C;\ \text{and } \boldsymbol{\lambda_1},\ \mu_1 \ge 0
\end{aligned}\right\} \quad (11)$$

Problem-2: The growth intensity of discrete units in myelin sheath is a friendly device of neurological functions. There fore health care measures may be planned with an aim of maximizing the growth of it. This problem is with the objective of maximizing the average size of discrete units in myelin sheath. The expected number of discrete units in myelin sheath at time 't' is derived from the relation (4).

Hence, the objective function is to $Maximize\ Z_2 = e^{(\lambda_2-\mu_2)t} + J_o$ (12)

The constraint is on a minimum average number of discrete units in myelin sheath 'B'. Hence the constraint with the wanted levels of discrete units in myelin sheath is $e^{(\lambda_2-\mu_2)t} + J_0 \ge B;$ (13)

As the growth of discrete units in myelin sheath is a positive phenomena, less fluctuation in the sizes of discrete units in myelin sheath is wanted. A constraint is formulated with maximum and unwanted variability 'D' of discrete units in myelin sheath, which implies $(\lambda_2 + \mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2} + \frac{J_o(e^{(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right] \le D;$ (14)

The decision variables are growth rate of discrete units in myelin sheath per unit time (λ_2) and loss rate of discrete units in myelin sheath per unit time (μ_2). $\boldsymbol{\lambda_2 and\ \mu_2 \ge 0}$ (15)

In summary the formulated non linear programming problem is

$$\left.\begin{aligned}
&Maximize\ Z_2 = e^{(\lambda_2-\mu_2)t} + J_o\ ;\\
&\text{Subject to the constraints:}\\
&e^{(\lambda_2-\mu_2)t} + J_0 \ge B;\\
&(\lambda_2 + \mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2} + \frac{J_o(e^{(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right] \le D;\ \boldsymbol{\lambda_2},\ \mu_2 \ge 0
\end{aligned}\right\} \quad (16)$$

Problem-3: This section deals with the problem of minimizing the variability of discrete units in myelin sheath. Variance of number of discrete units in myelin sheath is obtained from the relation (6). Therefore, the objective function is

$$Mininimize\ Z_3 = (\lambda_2 + \mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2} + \frac{J_0(e^{(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right] \quad (17)$$

The constraints and the non-negative restrictions are similar to that of the problem 2. Therefore, the resulting Non linear programming problem is

$$\left.\begin{aligned} &Mininimize\, Z_3 = (\lambda_2+\mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2}+\frac{J_0(e^{(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right];\\ &\text{Subject to the constraints}\\ &e^{(\lambda_2-\mu_2)t}+J_0 \geq B;\\ &(\lambda_2+\mu_2)\left[\frac{e^{(\lambda_2-\mu_2)t}(e^{(\lambda_2-\mu_2)t}-1)}{\lambda_2-\mu_2}+\frac{J_o(e^{(\lambda_2-\mu_2)t}-1)}{2(\lambda_2-\mu_2)}\right]\leq D; \quad \text{and } \lambda_2,\ \mu_2 \geq 0 \end{aligned}\right\} (18)$$

Analysis

The initial sizes of MS substance and discrete units in myelin sheath are presented with I_0 and J_0. The values Z_1, Z_2, and Z_3 are computed for the given values of A, B, C, D and t to the problems 1, 2 and 3.

Problem-1:

The patterns of objective function values and the decision parameters are observed with a hypothetical numerical data set for NLPP, presented in the relation (11).

- Further it is observed that the growth rate of MS substance cells (λ_1) is less than loss rate of MS substance cells (μ_1) in all the above mentioned four cases.

Problem-2

The patterns of objective function values and the decision parameters are observed with a hypothetical numerical data set for NLPP in (16)

The observations with the results in Table-2 are as below.

- Maximum expected number of discrete units in myelin sheath (Z_2) is an increasing function of the initial size of discrete units in myelin sheath (J_0), the growth rate of discrete units in myelin sheath (λ_2) is a decreasing function of the initial size of discrete units in myelin sheath (J_0), the loss rate of discrete units in myelin sheath (μ_2) become equal to zero with respect to initial size of discrete units in myelin sheath (J_0) when the other parameters are constant.

Table 1. Values of (λ_1), (μ_1) and (Z_1) for the given values of .(I_0), (A), (C) and (t)

Initial size of MS(I_0)	Max. avg. no. of MS cells (A)	Max. Var. in the size MS cells (C)	time for study (t)	growth rate of MS (λ_1)	loss rate of MS (μ_1)	Average size of MS (Z_1)
160	250	210	2	31.104	51.9294	160
170	250	210	2	27.3635	49.2386	170
180	250	210	2	24.2539	46.4799	180
190	250	210	2	21.7434	43.5174	190
200	250	210	2	19.55	41.4469	200
150	**260**	210	2	27.2225	50.7281	150
150	**270**	210	2	27.088	50.4773	150
150	**280**	210	2	26.9866	50.2884	150
150	**290**	210	2	24.7952	46.2048	150
150	**300**	210	2	26.316	49.0388	150
150	250	**220**	2	28.6668	51.4804	150
150	250	**230**	2	40.3461	60.3897	150
150	250	**240**	2	41.297	60.8688	150
150	250	**250**	2	45.3717	65.1194	150
150	250	**260**	2	48.9234	67.833	150
150	250	210	**2.1**	27.469	47.6672	150
150	250	210	**2.2**	39.2685	57.3245	150
150	250	210	**2.3**	41.4124	58.625	150
150	250	210	**2.4**	47.1742	62.1941	150
150	250	210	**2.5**	49.1156	63.778	150

The results in Table-1 reveal that

- The minimum expected number of MS substance cells(Z_1) is an increasing function of Initial size of MS substance cells(I_0), the growth rate of MS substance cells(**λ_1**), the loss rate of MS substance cells(**μ_1**) are decreasing functions of initial size of MS substance cells(I_0), when the other parameters are constant.
- The minimum expected number of MS substances cells (Z_1) is no way related to maximum allowable average number of MS substances cells (A), the growth rate of MS substances cells (λ_1), the loss rate of MS substance cells (μ_1) are the increasing functions of maximum allowable average number of MS substance cells (A), when the other parameters are constant.
- The minimum expected number of MS substance cells(Z_1) is independent of maximum allowable variance of MS substance cells(C), the growth rate of MS substance cells(λ_1), the loss rate of MS substance cells (μ_1) are the increasing functions of maximum allowable variance of MS substance cells(C), when the other parameters are constant.
- Minimum expected number of MS substance cells(Z_1) is independent of change of time(t), But growth rate (λ_1) and loss rate(μ_1) of MS substance cells are increasing functions of time(t) when the other parameters are constant.
- Maximum expected number of discrete units in myelin sheath (Z_2), The growth rate of discrete units in myelin sheath (λ_2) and the loss rate of discrete units in myelin sheath (μ_2) are independent of change of minimum required average number of discrete units in myelin sheath (B) when the other parameters are constant.
- Maximum expected number of discrete units in myelin sheath (Z_2) and the growth rate of discrete units in myelin sheath (λ_2) are increasing functions of maximum allowable variability in discrete units in myelin sheath (D). The loss rate of discrete units in myelin sheath (μ_2) become equal to zero and has no influence on maximum allowable variability in discrete units in myelin sheath (D) when the other parameters are constant.
- Maximum expected number of discrete units in myelin sheath (Z_2) and the loss rate of discrete units in myelin sheath (**μ_2**) are independent of change of time (t) whereas the growth rate of discrete units in myelin sheath (**λ_2**) is a decreasing function of time (t), when the other parameters are constant.

Problem-3:

The patterns of objective function values and the decision parameters are observed with a hypothetical numerical data set for NLPP in (18).

Table 2. Values of (λ_2), (μ_2) and (Z_2) for the given values of .(J_0), (B), (D) and (t)

Initial size of Oligs.(J_0)	Min. Avg. no. of Oligos. (B)	Min. Avg. size in Oligos. (D)	time for study (t)	growth rate of Oligos. (λ_2)	Loss rate of Oligos. (μ_2)	Average size of Oligos. (Z_2)
100	60	120	2	0.5898	0	103.2534
110	60	120	2	0.5602	0	113.0666
120	60	120	2	0.5336	0	122.9076
130	60	120	2	0.5095	0	132.7707
140	60	120	2	0.4876	0	142.6517
100	**60**	120	2	0.5898	0	103.2534
100	**70**	120	2	0.5898	0	103.2534
100	**80**	120	2	0.5898	0	103.2534
100	**90**	120	2	0.5898	0	103.2534
100	**100**	120	2	0.5898	0	103.2534
100	60	**130**	2	0.6167	0	103.433
100	60	**140**	2	0.642	0	103.6114
100	60	**150**	2	0.666	0	103.7887
100	60	**160**	2	0.6887	0	103.9649
100	60	**170**	2	0.7103	0	104.14
100	60	120	**2.1**	0.5617	0	103.2534
100	60	120	**2.2**	0.5362	0	103.2534
100	60	120	**2.3**	0.5129	0	103.2534
100	60	120	**2.4**	0.4915	0	103.2534
100	60	120	**2.5**	0.4718	0	103.2534

Table 3. Values of (λ_2), (μ_2) and (Z_3) for the given values of .(J_0), (B), (D) and (t)

Initial size of Oligs.(J_0)	Min. Avg. no. of Olgos. (B)	Min. Avg. size in oligos. (D)	time for study (t)	growth rate of Oligos. (λ_2)	Loss rate of Oligos. (μ_2)	Average size of Oligos. (Z_3)
130	70	250	2	0.5569	0	301.8629
140	70	250	2	0.4985	0	331.7458
150	70	250	2	0.4429	0	366.7493
160	70	250	2	0.3897	0	408.6487
170	70	250	2	0.3387	0	460.1535
130	**80**	250	2	0.5569	0	301.8629
130	**90**	250	2	0.5569	0	301.8629
130	**100**	250	2	0.5569	0	301.8629
130	**110**	250	2	0.5569	0	301.8629
130	**120**	250	2	0.5569	0	301.8629
130	70	**260**	2	0.5888	0	299.4126
130	70	**270**	2	0.6192	0	297.7925
130	70	**280**	2	0.6482	0	296.826
130	70	**290**	2	0.6761	0	296.3823
130	70	**300**	2	0.6908	0	296.3241
130	70	250	**2.1**	0.4922	0	332.419
130	70	250	**2.2**	0.4343	0	369.2015
130	70	250	**2.3**	0.3824	0	413.4335
130	70	250	**2.4**	0.3356	0	466.7699
130	70	250	**2.5**	0.2933	0	531.4711

The observations with the results in Table-3 are as below

- Minimum variance of discrete units in myelin sheath (Z_3) is an increasing function of the initial size of discrete units in myelin sheath (J_0), the growth rate of discrete units in myelin sheath **(λ_2)** is a decreasing function of the initial size of discrete units in myelin sheath (J_0), the loss rate of discrete units in myelin sheath **(μ_2)** has no influence on the initial size of discrete units in myelin sheath (J_0) when the other parameters are constant.
- Minimum variance of discrete units in myelin sheath (Z_3), the growth rate of discrete units in myelin sheath **(λ_2),** the loss rate of discrete units in myelin sheath **(μ_2)** are independent of change of minimum required average number of discrete units in myelin sheath (B), when other parameters are constant.
- Minimum variance of discrete units in myelin sheath (Z_3) is a decreasing function of maximum allowable variability in discrete units in myelin sheath (D), the growth rate of discrete units in myelin sheath (λ_2) is an increasing function of the maximum allowable variability in discrete units in myelin sheath (D), the loss rate of discrete units in myelin sheath (μ_2) has no influence on maximum allowable variability in discrete units in myelin sheath (D) when the other parameters are constant.
- Minimum variance of discrete units in myelin sheath (Z_3) is an increasing function of time (t), the growth rate of discrete units in myelin sheath **(λ_2)** is a decreasing function of time (t), the loss rate of discrete units in myelin sheath **(μ_2)** has no influence on time (t), when the other parameters are constant.

Conclusions

All the three developed NLPP's in section-3 are solved with LINGO and the results are presented in Tables-1, 2&3 respectively. The study has obtained decision variables such as the growth and loss rates of MS substance size; the growth and loss rates of discrete units in myelin sheath and the objective function values in the respective programming problems. As per Table-1, the optimal (minimum) expected size of MS substance is positively influenced by its initial size. The death rate of MS substance is a controlled variable and it is decreasing with increased initial size of MS substance. Growth rate of MS substance is increased when the existing average size of MS substance is increased. The loss rate of MS substance is more when there is more variance of MS substance which may indicates that the increasing volatility in MS substance size is a positive contributing factor for loss rate of MS substance. The optimality program has suggested the increased loss rate of MS substances over a period of time.

The results in Table-2 reveal that the optimal (maximum) size of discrete units in myelin sheath is positively correlated with its initial size. The programming problem has suggested the decrease loss rate of discrete units in myelin sheath. Further, the optimality levels of discrete units in myelin sheath are increased when the minimum existing size of them are increasing. It may conclude that the increase in growth rate of discrete units in myelin sheath is with increase in "minimum required size of discrete units in myelin sheath". The results of Table-3 reveal that the optimal (minimum) variability for discrete units in myelin sheath is having the positive relation with its initial sizes. It supports the proposition that the variance is decreasing when the initial size is of discrete units in myelin sheath is small. It has also concluded that there is a decrease in the growth rate of discrete units in myelin sheath when the initial size of discrete units in myelin sheath is increasing. The variance of size in discrete units in myelin sheath is having positive correlation with respect to time. Whereas the growth rate of discrete units in myelin sheath is having the negative correlation with time.

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