Some Studies on Stochastic Models and Its Applications

The present study involved three phases such as i) the development of bivariate linear birth and death processes of MS causing cells and oligodendrocytes. The developed stochastic models have been used to derive various statistical measures in the format of bivariate moments; ii) The derived statistical measures have been considered for developing optimization programming problems to minimize the intensity of multiple sclerosis and iii) Constructed quality assurance tools by developing the threshold limits for natural tolerance (control limits) and specification limits. These tools shall make use of MS health management and optimal drug administrations.

Dr. P. Kalpana, presently working as an Assistant Professor in the Department of Mathematics, VFSTR. The thrust areas of my research are Stochastic Modeling, Statistical Quality Control, Time Series Analysis and Agricultural Statistics. I have published a good number of research papers in reputed international journals.

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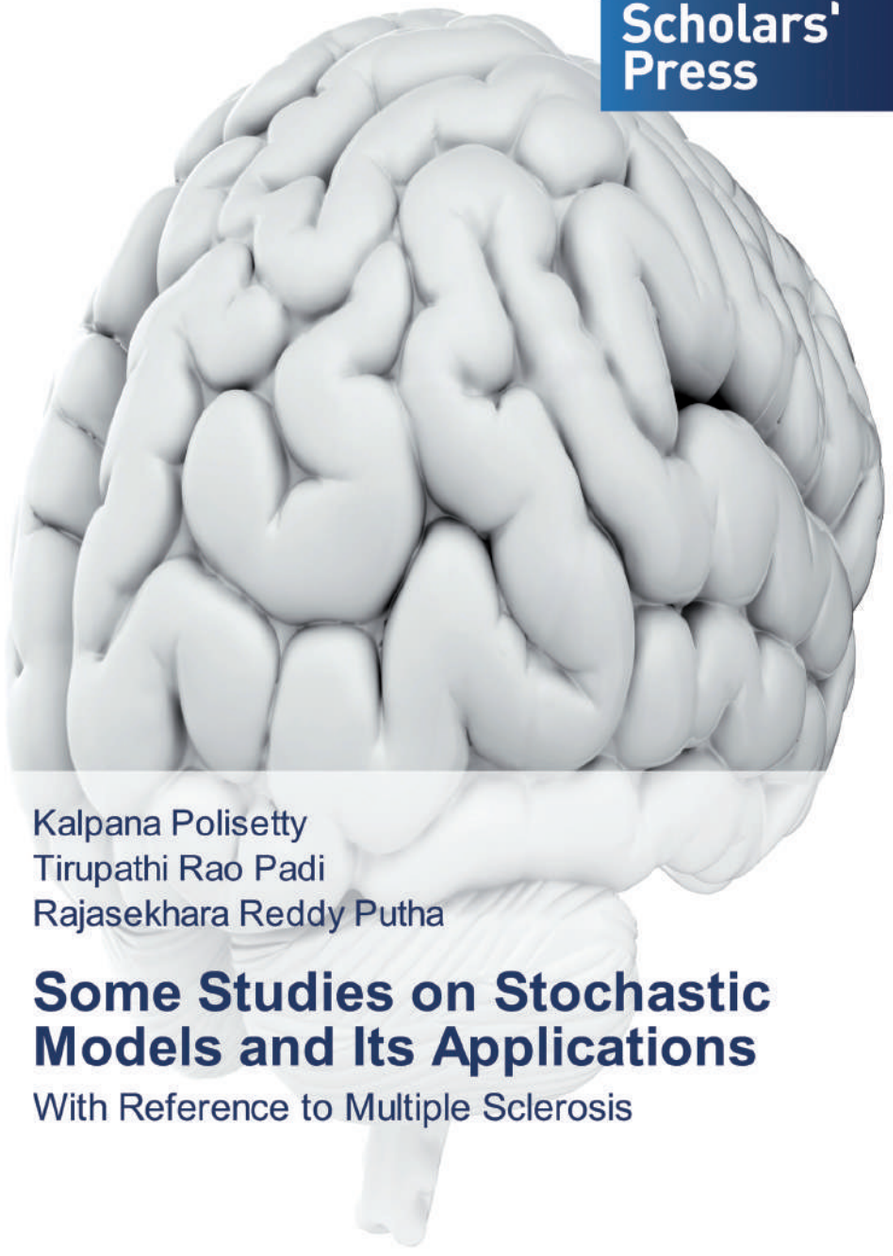

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With Reference to Multiple Sclerosis

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Title of Thesis

SOME STUDIES ON STOCHASTIC MODELS AND ITS APPLICATIONS WITH REFERENCE TO MULTIPLE SCLEROSIS

CONTENTS

CHAPTER-1

INTRODUCTION AND REVIEW OF LITERATURE

1.1 OVERVIEW ON PATHOGENESIS OF MULTIPLE SCLEROSIS

Immune System

Human body is able to recognize itself the foreign cells or any pathogen such as a virus, bacteria, fungus etc. entering in side. The immune system has a great network with organs, tissue, cells and bio molecules and it acts as defense to the body against things that are non self. When foreign substances are come to body the immune system identifies it automatically and removes these from the body. There are two types of immunities, namely innate immunity and acquired immunity. The former is the body's first line of defense with in the body by birth. It defends from wide variety of foreign substances and has nonspecific recognition mechanisms. Whereas the later is classified as an adaptive immunity, that is specific for a particular kind of foreign agent. This immunity has memory capacity to recognize foreign agent when it invades second time. But both require the concerted action of many cell types and signaling molecules. Theleukocytes or WBC fall into in the category of most immune cells. These cells are againdivided into three types namely phagocytes, lymphocytes, and auxiliary cells. The working nature of these cells has unique mechanism for defense, detecting and interacting antigens. These are immune stimulating components of foreign substances. Each immune cell is also able to interact with other immune cells to heighten or suppress the immune response.

Phagocytes (eating cells) mediate the innate immune system of antibodies and foreign substances. If any individual (foreign substances) comes to body, phagocytes ingest them and rid from the body. The other phagocytes are Macrophages and dendrite cells. Phagocytes in the brain are called microglia. Phagocytic cells have the capability to brain down ingested foreign agents into their molecular components and display them as antigens for recognition by T-cells. The immune response is depended on lymphocytes primarily B-cells and T-cells. The B-cells originate from bone marrow and related places. It shows the immunoglobulin proteins, or antibodies. When those antibodies recognize the antigens and activate the B-cells, these cells are soluble to antibodies. T-cells are also originated in bone marrow when

the thymus is in mature stage and they have a wider range of activities for destroying the pathogens.

Central Nervous System

The central nervous system (CNS) is made up of the brain and spinal cord. These components are responsible for coordinating the senses of the touch, taste, smell, sight, and hearing with appropriate response. There are two types of cells in CNS namely Neurons and Glia cells. Glia cells include astrocytes, oligodendrocytes and microglia. These are all only 50% of the total cell count. In CNS, different types of neurons conduct signals to, from, and within the system. Sensory neurons work is to transmit signals from the five sense organs to the CNS. Motor neurons are sending signal from the CNS to a muscles or a gland, telling it what to do. Association neurons connect the signals between sensors and motor neurons within the CNS. In the structure, neurons possess dendrites and attached to the cell body at end places. These dendrites capture sense of signals from outside the body to the nerves. Neurons have dendrites, which are the receivers of nerve signals, and axons of the neurons signalized the signal from the neurons to effector organs. Just as electric wires are insulated for efficient energy conduction, so are neurons.

Neurons are stimulated by mechanical force, pain, heat, light or chemical reactions, etc. A certain threshold crossing stimulation creates an electrical cascade which is called as action potential within the associated axon. During that time, ion channels in the axonal membrane opened and allowed the sodium ions flow into the neuron and potassium ions will go out of the neurons. The resulting of this will act as stimulus for the opening of ion channels at the next node of ranvier. Ions are moved through the axons to the next node. Here it catches the action that is necessary over there. Once an ion channel is opened, it is refractory or incapable of responding to further stimuli for a brief period of time. The white material or membrane of the axon, known as myelin will increase the speed of the action potential propagation by allowing the electrical impulses or signals to jump from one node to another node.

The endothelial cells are connected to the CNS through the capillaries in the brain. The connecting line from endothelial cells to capillaries is called blood-brain barrier (BBB). The work of BBB is to select the types of molecules and cells that can pass into brain. This BBB is supported by astrocytes, the most abundant glial cell type. The Astrocyte extenctions called pervivascular feet almost surround the brain capillaries. Hence there is a close relation

between astrocytes with the BBB positions in the CNS. There are two types of immune cells in the CNS. First one is astrocytes of glia cells and second is Microglia cells in CNS. The former surrounds the endothelial cells that compose BBB, later responds to antigens like circulating phagocytes-microglia constitute up to 20% of cells. Astrocytes secretes cytokine called tumour necrosis factor alpha which permibalizes BBB. Tumour necrosis factor alpha stimulates astrocytes for aiding the migration of circulating leukocytes in the brain by expressing inter-cellular adhesion molecules of astrocytes. T cells are also secreted by the cytokine of astrocytes to the site of inflammation.

Multiple Sclerosis

The meaning of Multiple sclerosis is “many scars”. The inflammatory episodes give visible damages in CNS. The scares also called as plaques visible as discolorations in the myelinated white matter of brain. When this problem is at cellular level, the effect of myelin breaks down and causes nerve impulses transmission become slowly. As a result, people with MS experience the symptoms like pain, numbness, tingling, or visual disturbances. Cyclic Inflammatory demyelination leads to the neuronal degeneration and loss of mobility. The Axon covered by insulating material Myelin which is made up by oligodendrocytes consists of specialized lipids and proteins. The gaps between myelinated segments of axons are called nodes of ranvier. At the nodes, the axon wall has protein channels so Ions flow into and out of the axon. Multiple Sclerosis is a disease which damages the white material (Myelin sheath) around the axon of the nerve. The problem of impaired nerve impulses will be observed due to this reason. MS can be identified by the presence of damage in Myelin sheath or multiple scars around axon, may not be considered as the early onset of disease.

When MS in progression, symptoms will be slowly visible. MS is of four types, namely relapsing-remitting, secondary progressive, progressive relapsing, and primary progressive. Relapsing-remitting MS (RRMS) shows periods of acute inflammatory action with transient upsurge of symptoms and full periods of recovery alternatively. Secondary progressive MS (SPMS) is exactly similar to RRMS with intermittent attacks followed by complete recovery periods. But, in due course of time, following each attack patient starts retaining the disability. Progressive Relapsing MS (PRMS) is rare type of MS. It is slow worsening and increasing disability from the starting of the disease. In this stage acute attacks of growing severity are shown that have great impact on progression of progressive relapsing

MS. Primary progressive MS (PPMS) is also identified by slow worsening of symptoms. These MS patients have without acute attacks.

The invisible signs and symptoms of MS may make it hard for some people to believe there is real illness occurring. MS has symptoms like sight, numbness, fatigue, tingling feeling, and weakness in only one leg or in a leg and arm on the same side of the body etc., in every day experience. The symptoms of MS are three types namely primary, secondary and tertiary. Primary symptoms are directly caused by the dymyelination process including vision problems, fatigue, and weakness. Secondary symptoms are including primary bladder problems, persistent urinary tract infections and loss of movement in an arm or leg etc. Tertiary symptoms are the social, emotional, and vocational effects of primary and secondary symptoms. Strength of nerve conduction decreases through spinal cord because of the physical injury to spinal cord and demyelination. Symptoms include inflammation of the optic nerve (optic neuritis), blurred vision and abnormal eye movement. A laboratory profile includes magnetic resonance imaging (MRI) of the patient and cross sectional images of the brain created by using MRI. Cerebrospinal fluid (CSF) increases antibody production and it is the standard laboratory test. When MS patients are in the initial stages, there are no visual differences between the normal health physical status persons and first stage MS patients. In this stage MS patients look like normal people. Criteria established for a positive diagnosis of MS includes number of attacks in combination with clinical and laboratory evidence.

Some symptoms of MS may be due to the result of lost axonal activity, whereas the initial symptoms directly connected to the inflammatory activity in the CNS.Neuropathic pain is shock like sensation at certain points. The pain related inflammation due to optic neuritis is stimulating visual disturbance and exacerbated by eye movements. Pain due to increase muscle tone directly leads to spasticity. Chronic nonspecific pain is commonly seen in general MS population including neck or back pain. Cognitive Dysfunctionleads a decreased ability to think, reasoning, concentration, and memory. The different levels of cognitive dysfunction are related with dymyelination degree in the brain. MS also affects the cognition indirectly leading to mental stress, anxiety, depression etc.

Pathogenesis and Modelling of MS

When the system is in the state of Autoimmunity, it faces the problems to distinguish between self derived (autologus) molecules and foreign (exgenous) molecules. During this period, the system confuses self and foreign molecules and it attacks against self molecules.

When the system is at the loss of self recognition phagocytes begin to ingest person's own healthy cells. Consideration of self molecules is called tolerance and its work is to develop the population sizes of the T-cells and B-cells. Self reactive lymphocytes are usually killed off when these are in maturation stage in the lymphatic system, but a small number survive and are present in the adult. These self reactive cells can be activated by the presentation of self antigens. The myelin component protein is acted as autolugous antigens to MS in the general theory of Autoimmunity. In the brain, inflammatory response brings phagocytes, whereas in case of MS, the oligodendrocytes that produce myelin are attacked and killed.

A chronic viral infection induces a normal immune response in which phagocytes break down infected tissues. The damaged tissue releases autologous molecules that are recognized by the rare self-reactive T cells. The self-recognition triggers a secondary immune response against the source of the self antigen. Molecular mimicryholds that certain viral epitopes are structurally similar to host epitopes. The similarity is great enough that T cells recognizing the viral epitope are also activated against the host epitope. Bystander activation explains the activation of self-reactive T-cells as the result of cytokine release during the inflammatory response against an invader. Self reactive T-cells are activated along with the rest of the local T-cell population and, if they happen to recognize a self antigen, an autoimmune response is generated.

Regarding the mechanism of central nervous system, axon of the nerve cell is considered to be the most vital organ to send the electronic impulses to and from between brain and the muscles of different organs. A white material referred as myelin sheath used to protect axon from cross interactions of other axons as it is a membrane surrounded to axon. The signal processing in nerve cells through axons are greatly influenced by the thickness of myelin sheath around the axon. Proteins and oligodendrocytes are the responsible substances which will generate the myelin formation. Simultaneously there is a possibility of loss of myelin sheath due to the influence of B-and T-cells as a resultant effect of infections and inflammations. This cause may be attributed as multiple sclerosis which creates scars or plaques at places, with different depth and expansions on myelin sheath. The effectiveness of neurological functions is depended on the healthy components of central nervous system. The performance abilities of the nerve cells have to be assessed through mathematical models because of the complex nature of the neuro functions. There is much evidence in the literature where mathematical models are prominently used for neuro functional studies.

Neuronal models based on Hodgkin and Huxley formalism was first described in 1952. In which they have discussed how further simplification of formulism enables mathematical analysis of the process of neural excitability. Modeling the neurological activities through mathematical methods is a breakthrough in understanding and assessment of the mechanisms in neural functions. Central nervous system being a major component of neurological communications is being worked with other biological systems with a network approach. Functioning of the physiological systems is considered to be dependable operating mechanisms with many subsystems. The immunity of the body system used to act as a defense mechanism protects the internal health from exogenous influences. However there is a possibility that the protecting mechanism may be weaken due to many unknown reasons. Consequently there is a possibility of vulnerable conditions to the healthsystem and it may lead to exposure of the risk of infections and inflammations to the body organs.

Quantification of MS

Magnetic resonance imaging (MRI) is very useful to observe the white matter abnormalities seen in MS and also MRI with gadolinium as a contrast agent can be extremely useful. Plaques that show enhancement with gadolinium are typically thought to be active MS lesions, with ongoing destruction of the blood-brain barrier. The disadvantage of MRI is a lack of specificity; other disease processes produce similar MRI findings. Cerebrospinal fluid (CSF) is useful for diagnosis of MS and excludes other disease processes like as infection or vasculitis. In MS, the CSF total white blood cell (WBC) count is normal in about two thirds of patients and less than 50 cells/μL, with rare exceptions. Thus, a very elevated WBC count in the cerebrospinal fluid warrants a more extensive search for an alternate diagnosis. In addition, there is typically an elevation of CSF immunoglobulin (Ig) levels relative to other protein components, suggesting intrathecal synthesis of Ig. A recent consensus statement indicates that qualitative comparison of the IgG fraction for the presence of CSF-specific oligoclonal bands (OCBs) could help diagnose MS. Optical coherence tomography (OCT) is a tool of MS imaging and useful for classify retinal modification in MS patients. OCT has emerged as a potential marker of axonal retinal degeneration in MS patients. Through OCT it is possible to find the rate of thinning of the ganglion cell/inner plexiform (GCIP) layer and the retinal nerve fiber layer MS patients.

Methods used for measuring atrophy (tissue loss)

Location	Method
Brain	Third ventricle width Third ventricle volume Brain width Corpus callosum width Volume on central brain slice Stereology Cerebrospinal fluid (CSF) volumes Brain parenchymal fraction (BPF) Whole brain ratio (WBR) Brain intracranial capacity ratio (BICCR) Fuzzy connectedness Probabilistic segmentation (SPM) Template driven segmentation (TDS) Medical Image Display and Analysis Software (MIDAS) Structural Image Evaluation using Normalization of Atrophy (SIENA)
Spinal cord	Manual outlining Semi automated outline of 3D axial images Automated whole cord volume measurement
Optic nerve	Manual outlining Semi automated outline of 3D axial images Automated whole cord volume measurement

1.2 REVIEW OF LITERATURE

In this section the reported research work was reviewed on 4 categories namely 1. Mathematical and Stochastic models on MS and related diseases. 2. Optimization models with mathematical and stochastic programming approaches for optimal drug administrations

and effective disease control managements. 3. Empirical data set modeling's using statistical techniques for MS disease, neurological and other related diseases. 4. Quality control tools in healthcare management.

Stochastic and Mathematical Modeling on MS and related diseases

Christina Wolfson (1984) described the course of disease by the movement of patients through well-defined disease states. He evaluated the effect of prognostic factors on transition from state to state based on two probabilistic models, semi-markov and the stochastic survival models. The feasibility and applicability of the two models are evaluated using data on MS patients and inferred that stochastic survival model is most appropriate.

David Greenhalgh (1988) developed a mathematical model for controlling an epidemic by the removal and isolation of infected people. The objective is maximization of expected number of people removed at some terminal time. Stochastic model is also developed under certain assumptions. Similar results are found in both the models. Confavreux *et al.* (1989) described disease trend by movements of patient's conditions through well-defined disease states. At first a markov model is developed with 278 reports of definite and probable MS cases but this model is not very meaningful for the individual patient, and limited studies of potential prognostic variables to dichotomous variables and univariate analyses. They have developed a stochastic survival model, and observed that it is difficult at theoretical level but easy in practical use.

Lawrence Joseph *et al.* (1990) discussed the statistical inference aspects about the input intensity of MS by assuming the output process as an infinite server queue with Poisson process with an empty queue at time= 0.

Albert (1994a, 1994b) proposed a finite Markov chain as a model to analyze progression of ordinal data in RRMS. This model provides an understanding of the stochastic nature of MS disease process. It allows for efficient estimation of important characteristics of the disease course such as mean first passage times, occupation times, and steady-state probabilities. Further he developed two different models for progression of MS from the data of RRMS disease. The first model is on RRMS data by a Poisson time series with a periodic trend in the mean, where mean is expressed as a function of a sinusoidal trend and past observations of the time series. The second model is on the behavior of RRMS by a Poisson time series in which changes in the mean follow a latent Markov chain.

Srinivasa Rao *et al.* (1996) developed a stochastic model for unidentified infectious individuals of Multiple sclerosis by assuming the spread of the infection follows Poisson process. Yakovlev *et al.* (1998) proposed a stochastic model of brain cell differentiation in culture to accommodate the experimental findings and the model is an age dependent branching process with two types of cells. The model is to find the analytical expressions for the average number of progenitor cells and of oligodendrocytes as functions of time. Parameters of this model are estimated by fitting of these functions through data on the average number of both types of cells at different time intervals. A biologically meaningful interpretation was provided for the observed pattern of oligodendrocyte generation.

Boucher *et al.* (1999) proposed a stochastic model to analyze the generation of oligodendrocytes for vitro base on the assumption of an arbitrary distribution function. The developed model provides good quantitative descriptions on movements of O-2A progenitor cells, oligodendrocytes and corresponding distributions. From the analysis it was suggested that the thyroid hormone gives effect in two stages, which reduces the expected duration of the mitotic cycle for progenitor cells, and it also increases the probability of their transformation into oligodendrocytes.

Von Collani *et al.* (1999) proposed a partial likelihood function to overcome the difficulty of their previous work proposed on branching stochastic process for developing a model of oligodendrocyte generation by O-2A progenitor cells under in vitro conditions. These conditions prohibit or invoke the ML techniques for estimation. It gives the consistent estimates of the parameters of the model under certain constraints. Computer simulations and data analyses are carried out for illustrating the usefulness of this approach.

Yakovlev *et al.* (2000) provided a stochastic explanation through different biological probable assumptions of the clock model based on the multi type age- dependent branching processes. This approach makes it possible to interpret the observed pattern of oligodendrocyte generation and its modification in the presence of thyroid hormone. Koen Van Leemput *et al.* (2001) developed a stochastic model for an automated segmentation of Multiple Sclerosis lesions through outlier detection for automated bias field correction and tissue classification of normal brain MR images.

Lecca *et al.* (2004) developed a stochastic model of lymphocyte recruitment in inflamed brain micro vessels by considering MS extravasations of lymphocytes. Rachel Mackay Altman (2004) proposed a graphical technique for evaluating the goodness of fit of a

stationary hidden markov model for a multiple sclerosis data. Ollivier Hyrien *et al.* (2005) analyzed the growth of cell clones data and developed stochastic model as an extension of the multi-type Bellman–Harris branching stochastic process. They have also developed a simulated pseudo likelihood method for parametric statistical inference under the above model. Proliferation and differentiation of cultured O-2A progenitor cells are analyzed with the developed model and methods.

Ollivier Hyrien *et al.* (2005) have developed another stochastic model by considering the generation of oligodendrocytes in cell culture based on the works ofBoucher *et al.*(J. Math. Biol.43 (2001)). The model is also extended with death of oligodendrocytes and compared the distributions of first mitotic cycle duration to the subsequent cycles of precursor cells.Rachel Mackay Altman *et al.* (2005) applied some hidden markov models developed by Albert (1994) to the lesion count data of individual multiple sclerosis patients. They also described the behavior of MS lesions over time by measuring the efficiency of the method and its validity check.

Mounira Rouainia *et al.* (2006) presented a method based on an automated stochastic model for detecting the MS lesions from MR images. Estimated tissue class distribution parameters categorized the image voxels (volume pixels) through the method after preprocessing the images and brain extraction. These followed intensity driven methods to fit the models to data. And by taking imaging artefacts such as partial volume effect, intensity homogeneities into account, voxels etc., are taken for characterizing Markov random fields (MRF) with references [K. Held *et al.* (1997), W. M. Wells *et al.* (1996) and Y. Zhang *et al.* (2001)].

Ollivier Hyrien *et al.* (2006) developed stochastic models with two objectives. The first one is on validating the assumptions behind their previously developed models to analyze the oligodendrocyte generation in cell culture. The other objective is to generate time-lapse data that may help bio mathematicians to build stochastic models of cell proliferation and differentiation under other experimental scenarios.

Phenyo E. Lekone *et al.* (2006) developed a stochastic discrete time susceptible-exposed-infectious-recovered (SEIR) model for infectious diseases for estimating parameters. Xiobai Li (2006) Constructed biologically interpretable queueing models for the longitudinal data of these lesion counts and these models describe the natural evolution of the lesions. For this purpose the infinite-server queue with Poisson arrival process and exponential service

(M/M/∞) is suggested. Based on appropriate assumptions, the likelihood function is derived for each model and fitted these models on relapsing remitting MS patient's data. He also discussed validation of proposed models, assumptions and examined the robustness of estimators.

Rachel MacKay Altman (2007) presented two mixed hidden markov models to capture the differences of covariate and random effects among the processes. These models are described through the generalized linear mixed models and MHMMs interpretations. They provided algorithms for the purpose of estimating the parameters and estimation properties illustrated through a simulation study. They have considered a data on lesion counts of relapsing remitting multiple sclerosis patients.

Petiot *et al.* (2007) analyzed the methodological challenges due to partly missing transition times in markov modeling of MS disability. The multiple imputation data were missing at random phenomena that data founded by Weibull model. The simulated results of multiple imputation estimates approximate to the full data set than the list wise deletion estimates.

Antti Saatinen *et al.* (2008) studied the dynamic behavior of a neuron by developing a model with simulation approach using stochastic differential equations and Brownian motion. Further a stochastic model is developed for granule cell in the ion channel function into gating variables of conductance.

Rasoul Khayati *et al.* (2008) have proposed a fully automatic segmentation of MS lesions in fluid attenuated inversion recovery (FLAIR) Magnetic Resonance (MR) images based on Bayesian classifier and adaptive mixtures method (AMM). Further Markov random field (MRF) model is used to derive the class conditional probability density function (CCPDF) with a priori probability of each class. The performance of proposed approach is compared with previous approaches including manual segmentation. The proposed approach is better than to previous works. They performed the comparison of lesions volume between the fully automated segmentation and the gold standard with correlation coefficient.

Stephanie Bricq *et al.* (2008) described a new automatic robust algorithm to segment multimodal brain MR images with MS lesions. They used a hidden markovian model to detect MS lesions. Douglas S. Goodin (2009, 2010) developed mathematical models for MS pathogenesis and observed the association between genetic tendency and environmental exposure of current changes in MS epidemiology. The model is appropriate to suggest the

genetic susceptibility of MS pathogenesis. This study underscores the importance of environmental contributions to MS pathogenesis. He developed another mathematical model of genetic susceptibility and analyzed epidemiological data of MS.

Broome *et al.* (2011) developed a mathematical model of cell death in MS based on Biochemical system theory, to test potential drug therapies and also to detect possible trigger points for the disease. This model is focused for reactive oxygen and nitrogen species, the permeability transition pore, apoptotic factors and the eventual cell death in the oligodendrocytes.

Tirupathi Rao *et al.* (2012) developed a bivariate stochastic model with linear birth and death processes for modeling the growth and loss of MS spread and the expansion of oligodendrocytes. Joint probability mass function is derived through difference differential equations with the assumptions and postulates of bivariate Poison processes. The statistical measures such as expected number and variance of MS causing cells; expected number and variance of oligodendrocytes; correlation coefficient between MS causing cells and oligodendrocytes are derived. The model behavior was analyzed through numerical illustrations by computing statistical measures through derived formula. Henry C. Tuckwell (2013) considered linear Stochastic partial differential equation models on line segments with one and two components for representing the neural anatomy.

Models for Optimization Methods

Martin *et al.* (1993) developed a model for analysis of optimal strategy for the distribution of vaccine during measles epidemic with strategies of minimizing the probability of exposure and to control it with vaccination. Frederik Barkhof *et al.* (1997) reviewed successful achievement of MRI-monitored trials with present state and identifying priorities for future research facilitates. They identified the strategies to optimize the uses of MRI in monitoring disease activity of MS treatment.

Alexander Zorin *et al.* (2000) presented computer-intensive simulation techniques to overcome the difficulty in estimation of model parameters and their statistical properties. The Kiefer-Wolfowitz procedure is used for stochastic optimization methods to maximize the estimated likelihood function. A possibility of modeling the process of oligodendrocyte generation in vitro as a multi-type Bellman-Harris branching stochastic process is explored.

Urszula Ledzewicz *et al.* (2000) developed non cell-cycle specific mathematical models for drug resistance in a treatment of disease. They formulated optimal control problems of chemotherapy to study the quantitative structure of optimal controls. Hem Raj josh (2002) derived a system of ODEs for describing interaction of HIV and T-cells in immune system. He explored the optimal control models for drug treatment strategies. The optimality system is derived and solved it numerically with a Runge-Kutta fourth order scheme.

Mark S. Freedman *et al.* (2004) studied the levels of outcomes in treatment of multiple patients by physicians. He hasalso reviewed the recommendations given by Canadian Multiple Sclerosis Working Group (CMSWG) and Bashir*et al.* (2002), in which they have discussed the criteria of optimal and suboptimal responses to disease-modifying therapies (DMTs). The importance of regular and standardized clinical assessment with the evaluation of disease progression also explained.

Graeme A. Forster *et al.* (2007) examined the importance of the time scale for control of epidemic. They derived analytical results of mean field approximation for the optimal treatment regimes that minimizes the total cost of epidemics. Juan Luis Ruiz-Pena *et al.* (2008) optimized multiple sclerosis treatment by avoiding subjective interpretation. A software based tool was developed to automatize the recommendations of Canadian multiple sclerosis patients.

Matthew W. Tanner *et al.* (2008) formulated a stochastic programming problem for the optimal vaccination policy in two phases one is when vaccine supply is limited and another is on cost- benefit scenario for controlling diseases under parameter uncertainty.Panos M. Pardalos *et al.* (2009) overviewed the applications of mathematical optimization programming and data mining in medicine for radiation therapy, microarray data analysis and computational neurosis. Martial L. Ndeffo *et al.* (2010) discussed the methods of optimal control of a pathogen, which is capable of infecting multiple hosts with different rates of transmission within and between species.

Vicente Pico–Ramirez *et al.* (2010) developed procedures on usage of stochastic optimal control theory for the treatment of human disease. Here, time dependent uncertainties are modeled as Ito processes. The problems optimality conditions are derived with stochastic maximum principle. Gradient method and a stochastic version of the Runge-Kutta method are derived and these methods iteratively used for solving boundary value problem. The need of

optimal control theory in development of clinical insight and diagnosing illness under uncertainties in model parameters are explained.

Byung-Jun Yoon (2011) proposed a stochastic optimization algorithm to find effective optimization of combinatory drugs and to analyze the concentration change of a specific drug affects the overall drug response. The performance of the algorithm is based on various drug response functions. Elsa Hansen *et al.* (2011) provided analytical solutions for optimal control to minimize the outbreak size (or infectious burden) under the assumption of limited control resources. They derived optimal control policies for isolation, for vaccination and for combined isolation-vaccination.

Algoul *et al.* (2011) described multi drug scheduling method using multi objective genetic algorithm. The optimum dosages by trading-off between cell killing and toxic side effects of chemotherapy are computed with this method.

Tirupathi Rao (2012) developed and analyzed a stochastic model for blood glucose level in type-2 diabetes mellitus patients and derived the optimal control policies of glucose regulatory system. Ludwig Kuznia (2012) studied the solution procedure of mixed integer programming subject to chance constraints. Stochastic programs and clinical/medical data transformed into model to evaluate decision making during the treatment phase is outlined. Khalid Hattaf *et al.* (2012) presented a delay differential equation with optimal control that describes the interactions between human immune deficiency virus (HIV), CD4+ T cells and cell-mediated immune response.

Tirupathi Rao (2012) developed stochastic modeling and optimization problem for studying blood glucose and insulin regulatory system suitable for management of type-2 diabetes. Stochastic programming problem is developed for maintaining the optimized glucose and insulin levels in the blood. An objective function is formulated for maximizing the energy release subject to the constraints on the consumption of glucose for different purposes. Tirupathi Rao *et al.* (2013) developed three optimization programming problems for managing the multiple sclerosis disease through stochastic models. The programming problems are formulated based on statistical measures of MS.

Statistical and Data Related Models of MS

Andrej Y. Yakovlev*et al.* (1998) developed advanced quantitative analysis of proliferation and differentiation of oligodendrocyte type 2 astrocyte (O-2A) progenitor cells

at the clonal level. Sormani *et al.* (2001) summarized statistical models for MRI enhancing lesion counted data. Negative Binomial and Poisson models are developed for studying the profiles of MS patients. They found their data set is better in Negative Binomial model comparing to Poisson model. Further, applications of the parameterization of lesion counts are discussed and used computer simulations for estimating sample size.

Vercoulen *et al.* (1998) developed a model for factors involved in the perpetuation of fatigue in chronic fatigue syndrome (CFS). The hypothesized model was tested on patients with CFS and on fatigue patient with (MS). The model was formulated by cause and effect relationships. An integral test of this model was performed by statistical technique, structural equation models in modeling the patients with CFS.

Sormani *et al.* (1999, 2012) calculated statistical power by means of computer simulations using MRI data obtained from untreated RRMS patients scanned for 9 months. They have evaluated the estimated powers of stability by analyzing the same procedure on random subsets of the original data. They further discussed the applications of parameterization of lesion counts data, and presented computer simulations for the sample size estimation.

Petr Lansky *et al.* (1999) constructed a neural network model for two interconnected parts of a dendritic and a trigger zone which was considered with the white noise action and periodic inputs on the dendritic zone. The developed model shows that variability of the depolarization potential is decreased from the dendritic to the trigger zone for sub threshold behavior. Nicola De Stefano *et al.* (2001) evaluated axonal damage and its contribution to disability at different stages of multiple sclerosis. Proton magnetic resonance spectroscopic image is preformed and N-acetyl aspirate (NAA) used in MS patients.

Orhun H. Kantarci *et al.* (2002) determined multiple sclerosis course and severity considering genetic contribution in course and severity of MS. Gehrmann *et al.* (2003) analyzed Multiple Sclerosis through piecewise exponential model by utilizing piecewise constant hazard rates and a Poisson model in identifying covariates. They significantly influence sustained progression in determining the size and form of the effect of these covariates. Lie Wang *et al.* (2005) studied microcosmic changes of brain's white mater in multiple sclerosis patients by Texture analysis. They have used the texture information of MR image. Further they applied the gray level co-occurrence matrix approach to image analysis of normal appearing white mater of MS patients on MR. The study considered the

characteristic parameters such as statistical attribute, energy, contrast, deviation, inverse difference moment and entropy. Using texture parameters a diffusion model was developed to study the brain white matter of MS patients. Sormani *et al.* (2005) estimated the distribution of the effect of interferon beta-1b (IFβ-1b) in terms of reduction of active T_2 lesions in MS patients and investigated the distribution using a fixed and a random effects model.

Skundric (2005) reviewed relapsing-remitting experimental autoimmune encephalomyelitis (EAE) models along with its limitations and advantages of acute and relapsing disease. He discussed the relapse regulation mainly the immune and molecular mechanisms of neuro inflammation, oligodendrocyte damage, myelin loss and axonal degeneration. The cell death time is following a two parameter gamma distribution, in this situation the lapse of time between the occurrences of cell death and the occurrences of cell degeneration is considered to be exponentially distributed.

David J. Mock *et al.* (2006) developed an in vitro murine glial precursor cell model. This model reproduces the important features of HHV-6-mediated cell cycle captures previously observed in human glial precursors by Dietrich *et al.* (2004). Inmaculada B. Aban *et al.* (2007) described methods for over diseased data using the negative binomial distribution resulting from Poisson-Gamma mixture. They compared small sample properties of the likelihood based tests and their performances to those of t-test and of Wilcoxon test; showed there is gain in efficiency when using the likelihood based methods comparing to the t-test and Wilcoxon test. All these findings are based on MRI lesion counts data of MS.

Brian C. Haly *et al.* (2009) described unbiased treatment effect estimated through modeling disease process of MS. Simulated data were generated from Poisson and Normal distribution to mimic outcomes from phase I/II clinical trials of RRMS patients under a constant or changing disease process model. Orest Bolbocean *et al.* (2009) determined the diagnostic yield of Transcranial Magnetic Simulation (TMS) in MS and evaluated the strength of correlation between clinical disability and motor evoked potential abnormalities in different stages of progression of MS. Clelia Di Serio *et al.* (2009) developed a model for unobserved heterogeneity in MS longitudinal data to understanding the impact of prognostic factors in MS severity. They investigated both the randomness and ordinal responses affecting MS data through Bayesian P-Spline and also generalized additive mixed models (GAMMS) used for investigating splines and the role of MS prognostic factors.

Brian C. Healy *et al.* (2010) investigated a method to evaluate treatment switching approach of treatment changes after one MS relapse. Negative binomial and Cox regression models were used to control the potential clinical confounders, relapse severity, relapse duration, age, disease duration and presence of previous/combination therapy. Mallikarjuna Rao Rettiganti (2010) used Negative binomial and Poisson-Inverse Gaussian distributions to fit the over dispersed data and these distributions have been used for simulating MRI data for the power analysis of the tests. Nonparametric tests are used in RRMS clinical trials data.

Igor I. Stepanov *et al.* (2012) illustrated discreminant analysis. It gives an accurate assessment of the californa verbal learning test learning curve in that suitable predictor variables are selected. They developed a mathematical model including best predictor variables with discreminant functions. This model helps to detect the early signs of memory impairment in multiple sclerosis patients. Joanne H. Wang *et al.* (2011) described a genetic association of multiple sclerosis using multi-step logistic regression protocol. ANCOVA is also used to compare clinical characteristics of individuals with various degrees of risks.

Hartmut B. F. Pohl *et al.* (2011) characterized a model of genetically induced adult oligodendrocyte death. The RAG-1 (Recombination Activating Gene-1) model is used to understand the sequels of adult oligodendrocyte death in the absence of primary axonal injury and reactive cells of the adaptive immune system. Shirani *et al.* (2012) investigated an association study between interferon beta exposure and disability progression of relapsing remitting MS patients. They have used a multivariable Cox regression model with interferon beta treatment consist of a time-varying covariate to check the above mentioned investigation. Tirupathi Rao *et al.* (2012) measured the drug efficacy for non-clinical and short term drug administration practices, and the effectiveness of the drug in trinomial experimental cases. Isabella Bordi *et al.* (2013) studied the modifying therapies through mechanistic model for the erratic behavior of the disease course observed on data set containing the time series of relapses and remissions of disease among MS patients.

Quality Control tools in Disease Management

Knapp R. G.*et al.* (1983) outlined procedures for evaluation of healthcare data generated by quality control and aduit systems. Some univariate SQC charts are discussed in this work. Gentleman *et al.* (1992) identified the need of quality control to ensure the satisfactory performance of HIV-1 ELISA in day to day screening or diagnosis. The statistical concepts are discussed in HIV testing. Oniki *et al.* (1995) measured blood glucose

of the patients in the laboratory from those who received enteral or patenteral nutrition. They constructed the statistical quality control charts, as a continuous quality improvement technique. George A. Green *et al.* (1997) evaluated the precision performance of the assay using different control charts and quantitative quality control procedures developed to assure analytical quality required for an ELISA of hepatitis B surface antigen.

Benneyan *et al.* (2003) overviewed statistical process control (SPC) and discussed healthcare application of several problems including Flash sterilization rate, Laboratory turnaround time, Surgical site infections, Appointment access satisfaction and Infectious waste monitoring through control charts. David J. Biau *et al.* (2007) used CUSUM chart and discussed quality control of surgical and interventional procedures. They carried out a systematic literature search of Medline. The study deals with the data regarding the design of the study, the specialty, the performance criterion, the unit under control, the methodology and the model of the CUSUM used.

1.3 MOTIVATION AND OBJECTIVE OF THE STUDY

Observing the literature, it is evident that the modeling aspects of neurological functions and the related disease patterns are categorized as Mathematical or Classical; Statistical or Empirical; Computational or Measurable; and probabilistic or stochastic. The classical models demonstrate the use of mathematics in deterministic environment which have number of limitations to apply them in realistic situation. However they can contribute the theoretical and scientific methods for understanding the functions of neuro systems. Statistical modeling is mostly concentrated on identification of patterns in historical data sets. The considerable applications are in clinical trials through the valid diagnostic methods such as MRI, CT scans, EEG etc. These models have limitations that they can't be used for understanding the pathological issues of the diseases. On the other hand computational models deal with estimating the future scenario of disease through several simulation techniques. Even though this modeling is considered to be relatively better than the statistical modeling, it has notable limitations on model validity due to the miss matching of disease related assumptions and transforming them to computational models. Among all these models stochastic models are considered to be more appropriate as they are based on genetical and pathological related assumptions in the environment of uncertainty. So probabilistic modeling for studying the disease related issues is the suitable option.

The pioneering works of Neuronal models were based on Hodgkin and Huxley (1952), developed mathematical formulism for the neural excitability process. Chistina Wolfson (1984), Confavreux *et al.* (1989) proposed stochastic survival models by describing transition state of prognostic factors. The works of David Greenhalgh (1988), Lawrence Joseph *et al.* (1990), Albert (1994) have proposed the concepts of Markov process in MS measurements. Yakovlen (1998, 2000) proposed branching process for modeling the brain cell differentiation. Boucher *et al.* (1999), Koen Van Leemput *et al.* (2001) developed stochastic models for generation of oligodendrocytes and automate segmentation of MS lesions. Lecca *et al.* (2004) developed lymphocyte recruitment model for MS extravasations.

Rachel (2004, 2007) proposed stationary HMM for MS data. Ollivier *et al.* (2005) developed stochastic models based on branching processes for generation and death of oligodendrocytes. Rachel MacKay Altman *et al.* (2005, 2007) developed HMM for lesion count of MS for RRMS stage. Mounira *et al.* (2006) developed stochastic model for detecting MS lesions from MRI. Phenyo E. Lekone *et al.* (2006) developed a stochastic discrete time susceptible-exposed-infectious-recovered (SEIR) model for infectious diseases.

Xiobai Li (2006) developed biological related (M/M/∞) queueing model for lesion counts of RRMS. Petiot *et al.* (2007) analyzed the markov modeling of MS disability. Antti Saatinen *et al.* (2008) developed a model of neuron through stochastic differential equations and Brownian motion. Rasoul Khayati *et al.* (2008) developed a model for automatic segmentation of MS lesion through MRI. Stephanie Bricq *et al.* (2008) used HMCM for brain segmentation of MS lesions with MRI. Douglas S. Goodin (2009, 2010) developed mathematical models for MS pathogenesis based on genetic susceptibility.

Broome *et al.* (2011) developed a mathematical model for cell death in MS due to Bio chemical system theory. Tirupathi Rao *et al.* (2012) developed a bivariate stochastic model for growth and loss of MS causing cells and oligodendrocytes. Henry C. Tuckwell (2013) modeled the neural anatomy with linear stochastic partial differential equations. Regarding the reported literature work on optimization models for disease management procedures; the works of Martin *et al.* (1993) developed the model strategy for vaccination to measles epidemic. Alexander Zorin *et al.* (2000) used Kiefer-Wolfowitz procedures for modeling the oligodendrocytes generation. Urszula Ledzewicz *et al.* (2000) formulated chemotherapy models. Hem Raj Josh (2002) explored drug treatment strategies with Runge-Kutta schemes. Mark S. Freedman *et al.* (2004), Graeme A. Forster *et al.* (2007), Juan Luis Ruiz-Pena *et al.*

(2008), Matthew W. Tanner *et al.* (2008), Panos M. Pardalos *et al.* (2009), Martial L. Ndeffo *et al.* (2010), Vicente Pico–Ramirez *et al.* (2010) developed procedures for treatment of diseases of neuro and MS related. Byung-Jun Yoon (2011) proposed an algorithm, for effective drug administration.

Elsa Hansen *et al.* (2011) derived policies for isolation and vaccination for treating a disease. Using optimality control and stochastic programming techniques a multi objective genetic algorithm for multiple drug scheduling was described by Algoul *et al.* (2011). Tirupathi Rao *et al.* (2011, 2012) developed a stochastic optimization model for glucose regulatory system and optimal energy release in type-2 diabetic patients. Ludwig Kuznia (2012) studied the mixed integer programming procedures for decision making with chance constraints. Khalid Hattaf *et al.* (2012) modeled the optimization of cell mediated immune response with delay differential equations. Tirupathi Rao *et al.* (2013) have developed optimization programming problems to minimize the severity of MS.

Based on the information above mentioned, there is little evidence on stochastic modeling of multiple sclerosis by considering evidence in development of stochastic models on growth and loss processes of protective and harming mechanism of myelin sheath. In order to cover this gap in the mentioned research area, we have developed bivariate linear birth and death processes of MS causing cells and oligodendrocytes. The developed stochastic model has been used for deriving various statistical measures in the format of bivariate moments. These measures will explain the behavior of the model.

The derived statistical measures and the disease related issues namely average number of MS causing cells, average number of oligodendrocytes, variances of both has been considered for developing an optimization programming problems. The objectives of the problems are to minimize the intensity of multiple sclerosis, to maximize the size of oligodendrocytes, maximize joint effect of both MS causing cells and oligodendrocytes and Minimize the variability of both MS causing cells and oligodendrocytes with the suitable subjective to the constraints.

The study aims to explore the decision parameters for all the four programming problems and conduct the rational analysis on the model behavior. The other objective of the study is to construct quality assurance tools by developing the threshold limits for natural tolerance (control limits) and specification limits. This study will help to explore the healthy threshold limits on the wanted cells like oligodendrocytes and also assess the risk prone limits

through stipulated assumptions in the earlier models. These tools shall make use of MS health management and optimal drug administrations.

1.4 ORGANIZATION OF THESIS

This thesis is organized in 5 chapters. In chapter-I, brief overview is presented on Immune System, Central Nervous System,Multiple Sclerosis, Pathogensis and Modeling of MS, Quantification of MS. The review of research literature is presented in 4 categories namely the mathematical and stochastic modeling; the optimization modeling MS and related disease treatments; Statistical and data modeling issues; the quality assurance methods in healthcare. The literature review also focused on extracting the reported research work in stochastic programming of optimal drug administrations and other optimization issues related to multiple sclerosis. The review of literature further covers the information on quality assurance on health monitoring with reference to multiple sclerosis. We have also presented the motivational factors for selecting this study. This chapter ends with presentation on organization of thesis.

Chapter –II deals with bivariate stochastic modeling of multiple sclerosis includes assumptions and postulates related to MS in the context of Poisson processes. This chapter is divided in to two sections. The first section of the chapter is on stochastic model based on Bivariate Poisson process using the birth and death processes. The anatomy of the disease and its spread was modelled through suitable biological issues and disease structures. The formulation of the model was based on the postulates MS formation and its growth. Model construction was carried out by considering the Stochasticity as the basic frame work. This study will help to understand the intensity/severity of MS by measuring the growth and loss factors through stochastic processes, differential equations and statistical relations. Numerical illustrations were presented to analyze the model behavior. In the second section of the chapter –II, a model for Multiple Sclerosis during treatment was developed. As multiple sclerosis has resulting effect of infections and inflammations, the severity of the problem can be minimized by the suitable treatment to get rid of infections and inflammations. The usual drug treatment is in spells (for short duration). It will act as control device of growth and loss of both multiple sclerosis and oligodendrocytes during infection time. A linear convex combination is considered to measure the overall phenomena of both multiple sclerosis and oligodendrocytes. In this chapter, an attempt is made to speak the behavior of the disease by

counting the expected overall phenomena. Numerical illustrations were presented to analyze the model behavior.

Chapter-III deals with formulation of optimization programming problems with several objectives. This chapter has two sections. The first section deals with ordinary environment whereas; the second section deals with the treatment environment. This chapter concludes with summary presentations of the optimization models. Multi objective nonlinear programming problems were formulated. The values of decision parameters of the process are derived. The broad spectrum of this chapter having 4 optimization programming problemsis,

1. Minimization of severity of MS 2. Maximization of size of oligodendrocytes 3. Maximization of joint effect of MS and oligodendrocytes 4. Minimization of variance of joint effect of MS and oligodendrocytes. All the optimization problems are supported with suitable constraints. Numerical illustrations are presented to understand model behavior and to explore the values of decision parameters.

Chapter IV deals with development of health assurance devices through quality control and specification limits for optimal health management of MS disease. The control and specification limits were constructed by considering the derived statistical relations in chapter-II. The devices namely Upper Specification Limit (USL), Lower Specification Limit (LSL), Upper Control limit (UCL) and Lower Control Limit (LCL) are computed based on theoretical derivations of chapter-II. The control limits are developed through sampling distributions and data sets. A hypothetical data is considered for studying the status of the quality assurance through Mean (Average) and Standard Deviations (Root Mean square deviation. The control limits for assessment of quality standards are fixed with USL and LSL. The analysis is carried out with control limits where natural tolerance or 3σ limits are considered. The analysis is also extended to develop specification limits with required level of significance. Quality devices are derived through the control and specification limits for both standard and volatility measures. Variance of number of MS causing cells and variance of number of oligodendrocytes will provide the allowable and observed fluctuations on the health variations. These will provide the measures of volatility in health standards.

Chapter-V deals with summary and conclusions in which brief information on the output of each chapter is presented. This chapter also provides the scope of the future work and bibliography.

CHAPTER-2

STOCHASTIC MODEL FOR MULTIPLE SCLEROSIS

2.1 INTRODUCTION

Multiple sclerosis is a disease caused by the loss of white material, membrane on axon of a nerve cell. Myelin sheath is formulated by the proteins and oligodendrocytes. It acts as insulation to axon and protects the axon from volatile exposure and cross connectivity with other axons belong to other nerve cells. In simple sense myelin sheath acts as a protective material around the axon and avoids short circuit electronic impulses. The effectiveness of signal impulses depends on thickness of myelin sheath around the axon. Due to various ill health related reasons like immunity deficiency, exposure to infection, having inflammations, influence of bacteria and virus there will be significant loss to myelin sheath. This sort of development on the loss of white material layer is referred as multiple sclerosis. The protective immune system will act as the defense mechanism and compensate the loss of myelin due to multiple sclerosis with oligodendrocytes so as the recovery process also happens simultaneously.

Observing the phenomena, multiple sclerosis is a harming device whereas oligodendrocytes is the helping device for the myelin sheath. In this chapter, we have proposed a bivariate stochastic model for studying the growth and loss of MS causing and oligodendrocytes by considering the joint stochastic processes of them. Due to variations in physiological activities of an individual, the construction and destruction of myelin sheath is influenced by both the processes. Prevailing uncertainty conditions on health status, stochastic modeling is the appropriate method for understanding the behavior of MS. In this chapter, bivariate stochastic models are developed based on the growth and loss processes of both oligodendrocytes and multiple sclerosis. Two cases namely 1).when the patient is not in drugs treatment and 2).when the patient is in treatment with drugs.

Notations

λ_1= Growth rate of MS causing cells per unit time

λ_2= Growth rate of oligodendrocytes per unit time

μ_1= Loss rate of MS causing cells per unit time

μ_2= Loss rate of oligodendrocytes per unit time

I_0=Initial size of MS causing cells at a point of time t

J_0=Initial size of oligodendrocytes at a point of time t

K_0=Coefficient of initiation for correlating the variables MS and oligodendrocytes cells

t=Time of observation

2.2 STOCHASTIC MODEL

In this section, we have proposed a stochastic model based on Bivariate Poisson processes using birth and death processes. The anatomy of the disease and its spread was modeled through suitable biological issues and disease structure. The formulation of the model was based on the postulates of MS formation and its growth, influenced by natural and individual physiological responses. Model construction was carried out by considering the Stochasticity as the basic frame work because of the formulation and expansion of MS is influenced by numerous uncertainty reasons. This study shall understand the intensity/severity of MS behavior by observing the growth and loss factors through stochastic processes, differential equations and statistical measures. The model is developed for multiple sclerosis with the following assumptions. Let us consider the events occurred in non-overlapping intervals of time and statistically independent.

- Infinitesimal interval of time is denoted by Δt.
- The number of MS causing cells at time 't' is 'i'.
- The number of oligodendrocytes at time 't' is 'j'.
- The growth process of MS causing cells is Poisson with parameter λ_1.
- The growth process of oligodendrocytes is also Poisson with parameter λ_2.
- The loss process of MS causing cells is Poisson with parameter μ_1.
- The growth process of oligodendrocytes is Poisson with parameter μ_2.

Along with these assumptions, the postulates of the model are

1. The probability of growth of one MS causing cell during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $i\lambda_1\Delta t + o(\Delta t)$.

2. The probability of growth of one oligodendrocyte during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $j\lambda_2\Delta t + o(\Delta t)$.

3. The probability of loss of one MS causing cell during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $i\mu_1\Delta t + o(\Delta t)$.

4. The probability of loss of one oligodendrocyte during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $j\mu_2\Delta t + o(\Delta t)$.

5. The probability of no growth in MS causing cells during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $1 - (i\lambda_1\Delta t + o(\Delta t))$

6. The probability of no growth in oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $1 - (j\lambda_2\Delta t + o(\Delta t))$

7. The probability of no loss to MS causing cells during (t, t+ Δt) given that there exists 'i' cells during (0,t) is 1-($i\mu_1\Delta t + o(\Delta t)$)

8. The probability of no loss to oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $1 - (j\mu_2\Delta t + o(\Delta t))$

9. The probability of happing of more than one events during Δt time is $o(\Delta t)^2$.

10. Let $p_{ij}(t)$ be the joint probability of 'i' MS causing cells and 'j' oligodendrocytes in the myelin sheath during time 't', then

$p_{ij}(t+\Delta t) = p_{i,j}(t)$*[p(No growth of MS causing cells in Δt)
*p(No death of MS causing cells in Δt)
*p(No growth of oligodendrocytes in Δt)
*p(No death of oligodendrocytes Δt)]
$+p_{i-1,j}(t)$*[p(One growth of MS causing cell in Δt)
*p(No loss of MS causing cell in Δt)
*p(No growth of oligodendrocytes in Δt)
*p(No loss of oligodendrocytes in Δt)]
$+p_{i+1,j}(t)$*[p(No growth of MS causing cell in Δt)
*p(One loss of MS causing cell in Δt)
*p(No growth of oligodendrocytes in Δt)

*p(No loss of oligodendrocytes in Δt)]

$+p_{i,\,j-1}(t)$*[p(No growth of MS causing cell in Δt)

*p(No loss of MS causing cell in Δt)

*p(One growth of oligodendrocyte in Δt)

*p(No loss of oligodendrocyte in Δt)]

$+p_{i,\,j+1}(t)$*[p(No growth of MS causing cell in Δt)

*p(No loss of MS causing cell in Δt)

*p(No growth of oligodendrocyte in Δt)

*p(One loss of oligodendrocyte in Δt)]

$+ p_{i\pm k\,,j\pm k}(t)$*[p(Happening k (k≥2) births/deaths among MS causing cells / oligodendrocytes during Δt)]

2.2.1 Difference differential equations of the Model

By considering the assumptions and postulates, the difference differential equations can be formulated as below:

$$p_{i,j}(t+\Delta t) = p_{i,j}(t)\begin{Bmatrix}\left[1-\left(i\lambda_1\Delta t+o(\Delta t)\right)\right]\left[1-\left(i\mu_1\Delta t+o(\Delta t)\right)\right]\\ \left[1-\left(j\lambda_2\Delta t+o(\Delta t)\right)\right]\left[1-\left(j\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{i-1,j}(t)\begin{Bmatrix}\left[(i-1)\lambda_1\Delta t+o(\Delta t)\right]\left[1-\left((i-1)\mu_1\Delta t+o(\Delta t)\right)\right]\\ \left[1-\left(j\lambda_2\Delta t+o(\Delta t)\right)\right]\left[1-\left(j\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{i+1,j}(t)\begin{Bmatrix}\left[1-\left((i+1)\lambda_1\Delta t+o(\Delta t)\right)\right]\left[(i+1)\mu_1\Delta t+o(\Delta t)\right]\\ \left[1-\left(j\lambda_2\Delta t+o(\Delta t)\right)\right]\left[1-\left(j\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{i,j-1}(t)\begin{Bmatrix}\left[1-\left(i\lambda_1\Delta t+o(\Delta t)\right)\right]\left[1-\left(i\mu_1\Delta t+o(\Delta t)\right)\right]\\ \left[(j-1)\lambda_2\Delta t+o(\Delta t)\right]\left[1-\left((j-1)\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{i,j+1}(t)\begin{Bmatrix}\left[1-\left(i\lambda_1\Delta t+o(\Delta t)\right)\right]\left[1-\left(i\mu_1\Delta t+o(\Delta t)\right)\right]\\ \left[1-\left((j+1)\lambda_2\Delta t+o(\Delta t)\right)\right]\left[(j+1)\mu_2\Delta t+o(\Delta t)\right]\end{Bmatrix}+o(\Delta t)^2$$

$$= p_{i,j}(t) - p_{i,j}(t)\left[i(\lambda_1+\mu_1) - j(\lambda_2+\mu_2)\right]\Delta t$$

$$+\left[p_{i-1,j}(t)(i-1)\lambda_1 + p_{i+1,j}(t)(i+1)\mu_1\right]\Delta t$$

$$+\left[p_{i,j-1}(t)(j-1)\lambda_2 + p_{i,j+1}(t)(j+1)\mu_2\right]\Delta t + o(\Delta t)^2$$

$$\therefore p_{i,j}(t+\Delta t) - p_{i,j}(t) = -p_{i,j}(t)\left[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)\right]\Delta t$$

$$+\left[p_{i+1,j}(t)(i+1)\mu_1 + p_{i-1,j}(t)(i-1)\lambda_1\right]\Delta t$$

$$+\left[p_{i,j-1}(t)(j-1)\lambda_2 + p_{i,j+1}(t)(j+1)\mu_2\right]\Delta t + o(\Delta t)^2$$

Taking on both sides limit as $\Delta t \to 0$, we get

$$\lim_{\Delta t\to 0}\left[\frac{p_{i,j}(t+\Delta t) - p_{i,j}(t)}{\Delta t}\right] = -\lim_{\Delta t\to 0} p_{i,j}(t)\left[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)\right]$$

$$+\lim_{\Delta t\to 0}\left[p_{i+1,j}(t)(i+1)\mu_1 + p_{i-1,j}(t)(i-1)\lambda_1\right]$$

$$+\lim_{\Delta t\to 0}\left[p_{i,j-1}(t)(j-1)\lambda_2 + p_{i,j+1}(t)(j+1)\mu_2\right]$$

$$+\lim_{\Delta t\to 0}\frac{o(\Delta t)^2}{\Delta t}$$

$$p'_{i,j}(t) = -p_{i,j}(t)\left[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)\right]$$

$$+p_{i+1,j}(t)(i+1)\mu_1 + p_{i-1,j}(t)(i-1))\lambda_1$$

$$+p_{i,j-1}(t)(j-1)\lambda_2 + p_{i,j+1}(t)(j+1)\mu_2; \quad i,j \geq 1 \qquad (2.2.1)$$

$p_{0,0}(t+\Delta t) = p_{0,0}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{1,0}(t)$*[p(No growth of MS causing cells in Δt)

*p(One death of MS causing cell in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{0,1}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(One death of oligodendrocyte in Δt)]

$+ p_{1,1}(t)$*[p(No growth of MS causing cells in Δt)

*p(One death of MS causing cell in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(One death of oligodendrocyte in Δt)]

This implies that,

$$p_{0,0}(t+\Delta t) = p_{0,0}(t)\begin{Bmatrix}\left[1-\left(0\lambda_1\Delta t + o(\Delta t)\right)\right]*\left[1-\left(0\mu_1\Delta t + o(\Delta t)\right)\right]*\\ \left[1-\left(0\lambda_2\Delta t + o(\Delta t)\right)\right]*\left[1-\left(0\mu_2\Delta t + o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{1,0}(t)\begin{Bmatrix}\left[1-\left(\lambda_1\Delta t + o(\Delta t)\right)\right]*\left[\mu_1\Delta t + o(\Delta t)\right]*\\ \left[1-\left(0\lambda_2\Delta t + o(\Delta t)\right)\right]*\left[1-\left(0\mu_2\Delta t + o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{1,1}(t)\begin{Bmatrix}\left[1-\left(\lambda_1\Delta t + o(\Delta t)\right)\right]*\left[\mu_1\Delta t + o(\Delta t)\right]*\\ \left[1-(\lambda_2\Delta t + o(\Delta t)\right]*\left[\mu_2\Delta t + o(\Delta t)\right]\end{Bmatrix}$$

$$+ p_{0,1}(t)\begin{Bmatrix}\left[1-\left(0\lambda_1\Delta t + o(\Delta t)\right)\right]*\left[1-(0\mu_1\Delta t + o(\Delta t)\right]*\\ \left[1-(\lambda_2\Delta t + o(\Delta t)\right]*\left[\mu_2\Delta t + o(\Delta t)\right]\end{Bmatrix}$$

$$= p_{0,0}(t) + p_{1,0}(t)\mu_1\Delta t + p_{0,1}(t)\mu_2\Delta t + p_{1,1}(t)\left[(\mu_1\Delta t)\mu_2\Delta t\right]$$

$$\therefore p_{0,0}(t+\Delta t) = p_{0,0}(t) + \left[p_{1,0}(t)\mu_1 + p_{0,1}(t)\mu_2\right]\Delta t$$

Taking on both sides limit as $\Delta t \to 0$, we get

$$\lim_{\Delta t \to 0}\left[\frac{p_{0,0}(t+\Delta t) - p_{0,0}(t)}{\Delta t}\right] = \lim_{\Delta t \to 0}\left[p_{1,0}(t)\mu_1 + p_{0,1}(t)\mu_2\right]$$

$$p'_{0,0}(t) = p_{1,0}(t)\mu_1 + p_{0,1}(t)\mu_2 \qquad (2.2.2)$$

$p_{0,1}(t+\Delta t) = p_{0,1}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{0,0}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(One growth of oligodendrocyte in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{1,1}(t)$*[p(No growth of MS causing cells in Δt)

*p(One death of MS causing cell in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{0,2}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(One death of oligodendrocyte in Δt)]

This implies that

$$p_{0,1}(t+\Delta t) = p_{0,1}(t)\begin{Bmatrix}\left[1-\left(0\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[1-\left(0\mu_1\Delta t+o(\Delta t)\right)\right]*\\ \left[1-\left(\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[1-\left(\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{0,0}(t)\begin{Bmatrix}\left[1-\left(0\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[1-\left(0\mu_1\Delta t+o(\Delta t)\right)\right]*\\ \left[0\lambda_2\Delta t+o(\Delta t)\right]*\left[1-\left(0\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{1,1}(t)\begin{Bmatrix}\left[1-\left(\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[\mu_1\Delta t+o(\Delta t)\right]*\\ \left[1-\left(\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[1-\left(\mu_2\Delta t+o(\Delta t)\right)\right]\end{Bmatrix}$$

$$+ p_{0,2}(t)\begin{Bmatrix}\left[1-\left(\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[1-\left(\mu_1\Delta t+o(\Delta t)\right)\right]*\\ \left[1-\left(2\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[2\mu_2\Delta t+o(\Delta t)\right]\end{Bmatrix}$$

$$= p_{0,1}(t)\left[1-\mu_2\Delta t-\lambda_2\Delta t\right]+p_{1,1}(t)\left[\mu_1\Delta t\left(1-\mu_2\Delta t-\lambda_2\Delta t\right)\right]$$

$$+ p_{0,2}(t)\left\{\left[1-\mu_1\Delta t-\lambda_1\Delta t\right]2\mu_2\Delta t\right\}$$

$$\therefore p_{0,1}(t+\Delta t)-p_{0,1}(t) = -p_{0,1}(t)\left[\mu_2+\lambda_2\right]\Delta t + p_{1,1}(t)\mu_1\Delta t + 2p_{0,2}(t)\mu_2\Delta t$$

Taking on both sides limit as $\Delta t \to 0$, we get

$$\lim_{\Delta t\to 0}\left[\frac{p_{0,1}(t+\Delta t)-p_{0,1}(t)}{\Delta t}\right] = \lim_{\Delta t\to 0}\left[-p_{0,1}(t)\left(\lambda_2+\mu_2\right)+p_{1,1}(t)\mu_1+2\mu_2 p_{0,2}(t)\right]$$

$$p'_{0,1}(t) = -p_{0,1}(t)\left(\lambda_2+\mu_2\right)+p_{1,1}(t)\mu_1+2\mu_2 p_{0,2}(t) \qquad (2.2.3)$$

$p_{1,0}(t+\Delta t) = p_{1,0}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{0,0}(t)$*[p(One growth of MS causing cell in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$+p_{1,1}(t)$*[p(No growth of MS causing cells in Δt)

*p(No death of MS causing cells in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(One death of oligodendrocyte in Δt)]

$+p_{2,0}(t)$*[p(No growth of MS causing cells in Δt)

*p(One death of MS causing cell in Δt)

*p(No growth of oligodendrocytes in Δt)

*p(No death of oligodendrocytes in Δt)]

$$p_{1,0}(t+\Delta t) = p_{1,0}(t)\left\{\begin{array}{l}\left[1-\left(\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[1-\left(\mu_1\Delta t+o(\Delta t)\right)\right]* \\ \left[1-\left(0\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[1-\left(0\mu_2\Delta t+o(\Delta t)\right)\right]\end{array}\right\}$$

$$+\,p_{0,0}(t)\left\{\begin{array}{l}\left[0\lambda_1\Delta t+o(\Delta t)\right]*\left[1-\left(0\mu_1\Delta t+o(\Delta t)\right)\right]* \\ \left[1-\left(0\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[1-\left(0\mu_2\Delta t+o(\Delta t)\right)\right]\end{array}\right\}$$

$$+\,p_{1,1}(t)\left\{\begin{array}{l}\left[1-\left(\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[1-\left(\mu_1\Delta t+o(\Delta t)\right)\right]* \\ \left[1-\left(\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[\mu_2\Delta t+o(\Delta t)\right]\end{array}\right\}$$

$$+\,p_{2,0}(t)\left\{\begin{array}{l}\left[1-\left(2\lambda_1\Delta t+o(\Delta t)\right)\right]*\left[2\mu_1\Delta t+o(\Delta t)\right]* \\ \left[1-\left(0\lambda_2\Delta t+o(\Delta t)\right)\right]*\left[1-\left(0\mu_2\Delta t+o(\Delta t)\right)\right]\end{array}\right\}$$

$$= p_{1,0}(t)\left[1-\mu_1\Delta t-\lambda_1\Delta t+o(\Delta t)\right]+p_{1,1}(t)\left[\mu_2\Delta t\left(1-\mu_1\Delta t-\lambda_1\Delta t\right)\right]$$

$$+\,p_{2,0}(t)\left(2\mu_1\Delta t\right)$$

$$\therefore\ p_{1,0}(t+\Delta t)-p_{1,0}(t) = -p_{1,0}(t)\left[\mu_1+\lambda_1\right]\Delta t+p_{1,1}(t)\,\mu_2\Delta t+2p_{2,0}(t)\,\mu_1\Delta t$$

Taking on both sides limit as $\Delta t\to 0$, we get

$$\lim_{\Delta t\to 0}\left[\frac{p_{1,0}(t+\Delta t)-p_{1,0}(t)}{\Delta t}\right]=\lim_{\Delta t\to 0}\left[-p_{0,1}(t)\left(\lambda_1+\mu_1\right)+p_{1,1}(t)\,\mu_2+2\mu_1 p_{2,0}(t)\right]$$

$$p'_{1,0}(t) = -p_{1,0}(t)\left(\lambda_1+\mu_1\right)+p_{1,1}(t)\,\mu_2+2\mu_1 p_{2,0}(t) \qquad (2.2.4)$$

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

Let p(x,y;t) be the joint probability generating function of $p_{i,j}(t)$

Where $p(x,y;t)=\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}x^i y^j p_{i,j}(t)$ (2.2.5)

Multiplying the equations (2.2.1) to (2.2.4) both sides with $x^i y^j$ and summing overall i and j, we obtain joint probability generating function of $p_{i,j}(t)$, such that

$$\sum_{i=1}^{\infty}\sum_{j=1}^{\infty} x^i y^j p'_{i,j}(t) + x^0 y^0 p'_{0,0}(t) + x^0 y^1 p'_{0,1}(t) + x^1 y^0 p'_{1,0}(t)$$

$$= -\sum_{i=1}^{\infty}\sum_{j=1}^{\infty}\left[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)\right]x^i y^j p_{i,j}(t)$$

$$+ \sum_{i=1}^{\infty}\sum_{j=1}^{\infty}(i-1)\lambda_1 x^i y^j p_{i-1,j}(t) + \sum_{i=1}^{\infty}\sum_{j=1}^{\infty}(i+1)\mu_1 x^i y^j p_{i+1,j}(t)$$

$$+ \sum_{i=1}^{\infty}\sum_{j=1}^{\infty}(j-1)\lambda_2 x^i y^j p_{i,j-1}(t) + \sum_{i=1}^{\infty}\sum_{j=1}^{\infty}(j+1)\mu_2 x^i y^j p_{i,j+1}(t)$$

$$+ \mu_1 x^0 y^0 p_{1,0}(t) + \mu_2 x^0 y^0 p_{0,1}(t) - (\lambda_2+\mu_2) x^0 y^1 p_{0,1}(t)$$

$$+ \mu_1 x^0 y^1 p_{1,1}(t) + 2\mu_2 x^0 y^1 p_{0,2}(t) - (\lambda_1+\mu_1) x^1 y^0 p_{1,0}(t)$$

$$+ \mu_2 x^1 y^0 p_{1,1}(t) + 2\mu_1 x^1 y^0 p_{2,0}(t)$$

$$\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} x^i y^j p'_{i,j}(t) = -\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}[i(\lambda_1+\mu_1) + j(\lambda_2+\mu_2)]x^i y^j p_{i,j}(t)$$

$$+ \sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(i-1)\lambda_1 x^i y^j p_{i-1,j}(t) + \sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(i+1)\mu_1 x^i y^j p_{i+1,j}(t)$$

$$+ \sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(j-1)\lambda_2 x^i y^j p_{i,j-1}(t) + \sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(j+1)\mu_2 x^i y^j p_{i,j+1}(t)$$

$$\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} x^i y^j p'_{i,j}(t) = -(\lambda_1+\mu_1)\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} i x^i y^j p_{i,j}(t) - (\lambda_2+\mu_2)\sum_{i=0}^{\infty}\sum_{j=0}^{\infty} j x^i y^j p_{i,j}(t)$$

$$+ \lambda_1\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(i-1)x^i y^j p_{i-1,j}(t) + \mu_1\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(i+1)x^i y^j p_{i+1,j}(t)$$

$$+ \lambda_2\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(j-1)x^i y^j p_{i,j-1}(t) + \mu_2\sum_{i=0}^{\infty}\sum_{j=0}^{\infty}(j+1)x^i y^j p_{i,j+1}(t)$$

$$\frac{\partial}{\partial t}p(x,y;t) = -(\lambda_1+\mu_1)x\frac{\partial}{\partial x}p(x,y;t) - (\lambda_2+\mu_2)y\frac{\partial}{\partial y}p(x,y;t)$$

$$+ \lambda_1 x^2\frac{\partial}{\partial x}p(x,y;t) + \mu_1\frac{\partial}{\partial x}p(x,y;t) + \lambda_2 y^2\frac{\partial}{\partial y}p(x,y;t) + \mu_2\frac{\partial}{\partial y}p(x,y;t)$$

$$\frac{\partial}{\partial t}p(x,y;t)=\left[-(\lambda_1+\mu_1)x+\lambda_1x^2+\mu_1\right]\frac{\partial}{\partial x}p(x,y;t)$$
$$+\left[-(\lambda_2+\mu_2)y+\lambda_2y^2+\mu_2\right]\frac{\partial}{\partial y}p(x,y;t) \qquad (2.2.6)$$

We can obtain the characteristics of the model by using the joint cummulant generating function of $p_{i,j}(t)$. Taking $x=e^u$ and $y=e^v$, denoting $k(x,y;t)$ as the cummulant generating function of $p_{i,j}(t)$. we obtain the following:

$$k(x,y;t)=p(x,y;t)|J|$$

$$|J|=\frac{\partial(x,y)}{\partial(u,v)}=\begin{vmatrix}\frac{\partial x}{\partial u} & \frac{\partial y}{\partial u}\\ \frac{\partial x}{\partial v} & \frac{\partial y}{\partial v}\end{vmatrix}$$

$$|J|=\begin{vmatrix}e^u & 0\\ 0 & e^v\end{vmatrix}=e^{u+v}$$

$$p(x,y;t)=k(x,y;t)e^{-(u+v)}$$

Further $\frac{\partial}{\partial x}\left[p(x,y;t)\right]=\frac{\partial}{\partial x}\left[e^{-(u+v)}k(x,y;t)\right]$ and $\frac{\partial}{\partial y}\left[p(x,y;t)\right]=\frac{\partial}{\partial y}\left[e^{-(u+v)}k(x,y;t)\right]$

From the equation (2.2.6)

$$\frac{\partial}{\partial t}\left[k(u,v;t)e^{-(u+v)}\right]=\left[-(\lambda_1+\mu_1)e^u+\lambda_1e^{2u}+\mu_1\right]\frac{\partial}{\partial u}e^{-(u+v)}\left[k(x,y;t)\right]$$
$$+\left[-(\lambda_2+\mu_2)e^v+\lambda_2e^{2v}+\mu_2\right]\frac{\partial}{\partial v}e^{-(u+v)}\left[k(x,y;t)\right]$$

$$\frac{\partial}{\partial t}\left[k(u,v;t)\right]=\left[-(\lambda_1+\mu_1)e^u+\lambda_1e^{2u}+\mu_1\right]e^{-u}\frac{\partial}{\partial u}\left[k(x,y;t)\right]$$
$$+\left[-(\lambda_2+\mu_2)e^v+\lambda_2e^{2v}+\mu_2\right]e^{-v}\frac{\partial}{\partial v}\left[k(x,y;t)\right]$$

$$\frac{\partial}{\partial t}\left[k(u,v;t)\right]=\left[-(\lambda_1+\mu_1)+\lambda_1e^u+\mu_1\right]\frac{\partial}{\partial u}\left[k(x,y;t)\right]$$
$$+\left[-(\lambda_2+\mu_2)+\lambda_2e^v+\mu_2\right]\frac{\partial}{\partial v}\left[k(x,y;t)\right] \qquad (2.2.7)$$

With reference of Bharucha Reid (1997), by the definition of

$$k(u,v;t) = uE\left[X(t)\right] + vE\left[Y(t)\right] + \frac{1}{2}u^2D^2\left[X(t)\right] + \frac{1}{2}v^2D^2\left[Y(t)\right] + uvCov\left\{X(t),Y(t)\right\} \quad (2.2.7.1)$$

$$\begin{aligned}\frac{\partial}{\partial t}k(u,v;t) &= u\frac{\partial}{\partial t}E\left[X(t)\right] + v\frac{\partial}{\partial t}E\left[Y(t)\right] + \frac{1}{2}u^2\frac{\partial}{\partial t}D^2\left[X(t)\right] \\ &\quad + \frac{1}{2}v^2\frac{\partial}{\partial t}D^2\left[Y(t)\right] + uv\frac{\partial}{\partial t}Cov\left\{X(t),Y(t)\right\}\end{aligned} \quad (2.2.7.2)$$

$$\frac{\partial}{\partial u}k(u,v;t) = E\left[X(t)\right] + uD^2\left[X(t)\right] + vCov\left\{X(t),Y(t)\right\} \quad (2.2.7.3)$$

$$\frac{\partial}{\partial v}k(u,v;t) = E\left[Y(t)\right] + vD^2\left[Y(t)\right] + uCov\left\{X(t),Y(t)\right\} \quad (2.2.7.4)$$

Substitute the equations (2.2.7.1), (2.2.7.2), (2.2.7.3.) and (2.2.7.4.) in equation (2.2.7), we have

$$\begin{aligned}&u\frac{\partial}{\partial t}E\left[X(t)\right] + v\frac{\partial}{\partial t}E\left[Y(t)\right] + \frac{1}{2}u^2\frac{\partial}{\partial t}D^2\left[X(t)\right] + \frac{1}{2}v^2\frac{\partial}{\partial t}D^2\left[Y(t)\right] + uv\frac{\partial}{\partial t}Cov\left\{X(t),Y(t)\right\} \\ &= \left[-\left(\lambda_1+\mu_1\right) + \lambda_1e^{u} + \mu_1e^{-u}\right]\left[E\left[X(t)\right] + uD^2\left[X(t)\right] + vCov\{X(t),Y(t)\}\right] \\ &+ \left[-\left(\lambda_2+\mu_2\right) + \lambda_2e^{v} + \mu_2e^{-v}\right]\left[E\left[Y(t)\right] + vD^2\left[Y(t)\right] + uCov\{X(t),Y(t)\}\right]\end{aligned} \quad (2.2.7.5)$$

2.2.2 Differential Equations

Comparing on both sides 'u' coefficients from equation (2.2.7.5.), we have

$$\begin{aligned}\frac{\partial}{\partial t}E\left[X(t)\right] &= \left[-\left(\lambda_1+\mu_1\right) + \lambda_1e^{u} + \mu_1e^{-u}\right]\left[E\left[X(t)\right] + uD^2\left[X(t)\right]\right] \\ &= -\left(\lambda_1+\mu_1\right)D^2\left[X(t)\right] \\ &\quad + \left[\lambda_1\left(1+u+\frac{u^2}{2!}+\ldots\right) + \mu_1\left(1-u+\frac{u^2}{2!}+\ldots\right)\right]\left[E\left[X(t)\right] + uD^2\left[X(t)\right]\right] \\ &= -\left(\lambda_1+\mu_1\right)D^2\left[X(t)\right] + \left(\lambda_1+\mu_1\right)D^2\left[X(t)\right] + \left(\lambda_1-\mu_1\right)E\left[X(t)\right]\end{aligned}$$

$$\frac{\partial}{\partial t}E\left[X(t)\right] = \left[\lambda_1-\mu_1\right]E\left[X(t)\right]$$

$$\therefore \frac{\partial}{\partial t} E\left[X(t)\right] = \frac{\partial}{\partial t} m_{1,0}(t) = \left[\lambda_1 - \mu_1\right] m_{1,0}(t) \tag{2.2.8}$$

Comparing both sides 'v' coefficients from equation (2.2.7.5.)

$$\frac{\partial}{\partial t} E\left[Y(t)\right] = \left[-\left(\lambda_2 + \mu_2\right) + \lambda_2 e^{v} + \mu_2 e^{-v}\right]\left[E\left[Y(t)\right] + vD^2\left[Y(t)\right]\right]$$

$$= -\left(\lambda_2 + \mu_2\right) D^2\left[Y(t)\right]$$

$$+\left[\lambda_2\left(1 + v + \frac{v^2}{2!} + \ldots\right) + \mu_2\left(1 - v + \frac{v^2}{2!} + \ldots\right)\right]\left[E\left[Y(t)\right] + vD^2\left[Y(t)\right]\right]$$

$$= -\left(\lambda_2 + \mu_2\right) D^2\left[Y(t)\right] + \left[\lambda_2 + \mu_2\right] D^2\left[Y(t)\right] + \left[\lambda_2 - \mu_2\right] E\left[Y(t)\right]$$

$$\frac{\partial}{\partial t} E\left[Y(t)\right] = \left[\lambda_2 - \mu_2\right] m_{0,1}(t)$$

$$\frac{\partial}{\partial t} E\left[Y(t)\right] = \frac{\partial}{\partial t} m_{0,1}(t) = \left[\lambda_2 - \mu_2\right] m_{0,1}(t) \tag{2.2.9}$$

Comparing both sides 'u^2' coefficients from equation (2.2.7.5)

$$\frac{1}{2}\frac{\partial}{\partial t} D^2\left[X(t)\right] = \left[\lambda_1 e^{u} + \mu_1 e^{-u}\right]\left[E\left[X(t)\right] + uD^2\left[X(t)\right]\right]$$

$$= \left[\lambda_1\left(1 + u + \frac{u^2}{2!} + \ldots\right) + \mu_1\left(1 - u + \frac{u^2}{2!} + \ldots\right)\right]\left[E\left[X(t)\right] + uD^2\left[X(t)\right]\right]$$

$$= \left[\lambda_1 - \mu_1\right] D^2\left[X(t)\right] + \left(\frac{\lambda_1}{2} + \frac{\mu_1}{2}\right) E\left[X(t)\right]$$

$$\frac{\partial}{\partial t} D^2\left[X(t)\right] = \left[\lambda_1 + \mu_1\right] E\left[X(t)\right] + 2\left[\lambda_1 - \mu_1\right] D^2\left[X(t)\right]$$

$$\frac{\partial}{\partial t} D^2\left[X(t)\right] = \frac{\partial}{\partial t} m_{2,0}(t) = \left[\lambda_1 + \mu_1\right] m_{1,0}(t) + 2\left[\lambda_1 - \mu_1\right] m_{2,0}(t) \tag{2.2.10}$$

Comparing both sides 'v^2' coefficients from equation (2.2.7.5)

$$\frac{1}{2}\frac{\partial}{\partial t} D^2\left[Y(t)\right] = \left[\lambda_2 e^{v} + \mu_2 e^{-v}\right]\left[E\left[Y(t)\right] + vD^2\left[Y(t)\right]\right]$$

$$= \left[\lambda_2 \left(1 + u + \frac{u^2}{2!} + \ldots \right) + \mu_2 \left(1 - u + \frac{u^2}{2!} + \ldots \right) \right] \left[E\left[Y(t) \right] + vD^2\left[Y(t) \right] \right]$$

$$= \left[\lambda_2 - \mu_2 \right] D^2\left[Y(t) \right] + \left(\frac{\lambda_2}{2} + \frac{\mu_2}{2} \right) E\left[Y(t) \right]$$

$$\frac{\partial}{\partial t} D^2\left[Y(t) \right] = \left[\lambda_2 + \mu_2 \right] E\left[Y(t) \right] + 2\left[\lambda_2 - \mu_2 \right] D^2\left[Y(t) \right]$$

$$\frac{\partial}{\partial t} D^2\left[Y(t) \right] = \frac{\partial}{\partial t} m_{0,2}(t) = \left[\lambda_2 + \mu_2 \right] m_{0,1}(t) + 2\left[\lambda_2 - \mu_2 \right] m_{0,2}(t) \tag{2.2.11}$$

Comparing both sides 'uv' coefficients from equation (2.2.7.5)

$$\frac{\partial}{\partial t} Cov\left\{ X(t), Y(t) \right\} = \left[\lambda_1 e^u + \mu_1 e^u \right] vCov\left\{ X(t), Y(t) \right\} + \left[\lambda_2 e^v + \mu_1 e^v \right] uCov\left\{ X(t), Y(t) \right\}$$

$$= \left[\lambda_1 - \mu_1 \right] Cov\left\{ X(t), Y(t) \right\} + \left[\lambda_2 - \mu_1 \right] Cov\left\{ X(t), Y(t) \right\}$$

$$\frac{\partial}{\partial t} Cov\left\{ X(t), Y(t) \right\} = \left\{ \left[\lambda_1 - \mu_1 \right] + \left[\lambda_2 - \mu_1 \right] \right\} Cov\left\{ X(t), Y(t) \right\}$$

$$\frac{\partial}{\partial t} Cov\left\{ X(t), Y(t) \right\} = \frac{\partial}{\partial t} m_{1,1}(t) = \left\{ \left[\lambda_1 - \mu_1 \right] + \left[\lambda_2 - \mu_1 \right] \right\} m_{1,1}(t) \tag{2.2.12}$$

2.3 STATISTICAL MEASURES

Let $m_{i,j}(t)$ denote the moments of order (r, s) of MS causing cells and Oligodendrocytes at time 't' . Then the differential equations from (2.2.8) to (2.2.12) are represented as

$$\frac{\partial}{\partial t} m_{1,0}(t) = \left[\lambda_1 - \mu_1 \right] m_{1,0}(t) \tag{2.2.8}$$

$$\frac{\partial}{\partial t} m_{0,1}(t) = \left[\lambda_2 - \mu_2 \right] m_{0,1}(t) \tag{2.2.9}$$

$$\frac{\partial}{\partial t} m_{2,0}(t) = \left[\lambda_1 + \mu_1 \right] m_{1,0}(t) + 2\left[\lambda_1 - \mu_1 \right] m_{2,0}(t) \tag{2.2.10}$$

$$\frac{\partial}{\partial t} m_{0,2}(t) = \left[\lambda_2 + \mu_2 \right] m_{0,1}(t) + 2\left[\lambda_2 - \mu_2 \right] m_{0,2}(t) \tag{2.2.11}$$

$$\frac{\partial}{\partial t} m_{1,1}(t) = \left\{ \left[\lambda_1 - \mu_1 \right] + \left[\lambda_2 - \mu_1 \right] \right\} m_{1,1}(t) \tag{2.2.12}$$

Solving the equation (2.2.8),

$$\frac{\partial}{\partial t} m_{1,0}(t) = [\lambda_1 - \mu_1] m_{1,0}(t)$$

Taking both sides integration, we have

$$\int \frac{\frac{\partial}{\partial t} m_{1,0}(t)}{m_{1,0}(t)} dt = \int [\lambda_1 - \mu_1] dt$$

$$\log m_{1,0}(t) = [\lambda_1 - \mu_1] t + c_1$$

The initial condition is when t=0 then $m_{1,0}(t)=I_0$

Therefore $c_1 = \log(I_0)$

Substituting the c_1 in the above equation we get

$$m_{1,0}(t) = e^{[\lambda_1 - \mu_1]t} I_0 \qquad (2.3.1)$$

Solving the equation (2.2.9)

$$\frac{\partial}{\partial t} m_{0,1}(t) = [\lambda_2 - \mu_2] m_{0,1}(t)$$

Taking both sides integration, we have

$$\int \frac{\frac{\partial}{\partial t} m_{0,1}(t)}{m_{0,1}(t)} dt = \int [\lambda_2 - \mu_2] dt$$

$$\log m_{0,1}(t) = [\lambda_2 - \mu_2] t + c_2$$

The initial condition is when t=0 then $m_{0,1}(t)=J_0$

Therefore $c_2 = \log(J_0)$

Substituting the c_1 in the above equation we get

$$m_{0,1}(t) = e^{[\lambda_2 - \mu_2]t} J_0 \qquad (2.3.2)$$

Solve the equation (2.2.10)

$$\frac{\partial}{\partial t} m_{2,0}(t) = [\lambda_1 + \mu_1] m_{1,0}(t) + 2[\lambda_1 - \mu_1] m_{2,0}(t)$$

$$\Rightarrow \frac{\partial}{\partial t} m_{2,0}(t) = I_0 [\lambda_1 + \mu_1] e^{[\lambda_1 - \mu_1]t} + 2[\lambda_1 - \mu_1] m_{2,0}(t)$$

$$\Rightarrow \frac{\partial}{\partial t} m_{2,0}(t) - 2[\lambda_1 - \mu_1] m_{2,0}(t) = I_0 [\lambda_1 + \mu_1] e^{[\lambda_1 - \mu_1]t}$$

This is the first order differential equation of the form is $\frac{dy}{dt} + Py = Q$

The solution is of the above differential equation is $ye^{I.F} = \int Qe^{I.F}\, dt + c_3$

Where $y = m_{2,0}(t)$, $P = -2[\lambda_1 - \mu_1]$ and $Q = I_0 [\lambda_1 + \mu_1] e^{[\lambda_1 - \mu_1]t}$

Here $I.F = \int -2[\lambda_1 - \mu_1]\, dt = -2[\lambda_1 - \mu_1]$

$$\therefore m_{2,0}(t) e^{-2[\lambda_1 - \mu_1]t} = \int I_0 [\lambda_1 + \mu_1] e^{[\lambda_1 - \mu_1]t} e^{-2[\lambda_1 - \mu_1]t}\, dt + c_3$$

$$= I_0 [\lambda_1 + \mu_1] \int e^{-[\lambda_1 - \mu_1]t}\, dt + c_3$$

$$m_{2,0}(t) e^{-2[\lambda_1 - \mu_1]t} = -I_0 \left[\frac{\lambda_1 + \mu_1}{\lambda_1 - \mu_1}\right] e^{-[\lambda_1 - \mu_1]t} + c_3$$

The initial condition is when t=0 then $m_{0,2}(t)=0$

$$-I_0 \left[\frac{\lambda_1 + \mu_1}{\lambda_1 - \mu_1}\right] e^{-[\lambda_1 - \mu_1]0} + c_3 = 0$$

$$c_3 = I_0 \left[\frac{\lambda_1 + \mu_1}{\lambda_1 - \mu_1}\right]$$

Substituting the c_3 in the above equation we get

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

$$= I_0 \left[\frac{\lambda_1 + \mu_1}{\lambda_1 - \mu_1}\right] \left[e^{2[\lambda_1 - \mu_1]t} - e^{[\lambda_1 - \mu_1]t}\right]$$

$$\therefore m_{2,0}(t) = I_0\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]e^{[\lambda_1-\mu_1]t}\left[e^{[\lambda_1-\mu_1]t}-1\right] \tag{2.3.4}$$

Solving the equations (2.2.11)

$$\frac{\partial}{\partial t}m_{0,2}(t) = [\lambda_2+\mu_2]m_{0,1}(t) + 2[\lambda_2-\mu_2]m_{0,2}(t)$$

$$\Rightarrow \frac{\partial}{\partial t}m_{0,2}(t) = J_0[\lambda_2+\mu_2]e^{[\lambda_2-\mu_2]t} + 2[\lambda_2-\mu_2]m_{0,2}(t)$$

$$\Rightarrow \frac{\partial}{\partial t}m_{0,2}(t) - 2[\lambda_2-\mu_2]m_{0,2}(t) = J_0[\lambda_2+\mu_2]e^{[\lambda_2-\mu_2]t}$$

This is the first order differential equation of the form is $\frac{dy}{dt}+Py=Q$

The solution is of the above differential equation is $ye^{I.F} = \int Qe^{I.F}dt + c_4$

Where $y = m_{0,2}(t)$, $P = -2[\lambda_2-\mu_2]$ and $Q = J_0[\lambda_2+\mu_2]e^{[\lambda_2-\mu_2]t}$

Here $I.F = \int -2[\lambda_2-\mu_2]dt = -2[\lambda_2-\mu_2]$

$$\therefore m_{0,2}(t)e^{-2[\lambda_2-\mu_2]t} = \int J_0[\lambda_2+\mu_2]e^{[\lambda_2-\mu_2]t}e^{-2[\lambda_2-\mu_2]t}dt + c_4$$

$$= J_0[\lambda_2+\mu_2]\int e^{-[\lambda_2-\mu_2]t}dt + c_4$$

$$m_{0,2}(t)e^{-2[\lambda_2-\mu_2]t} = -J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{-[\lambda_2-\mu_2]t} + c_4$$

The initial condition is when t=0 then $m_{2,0}(t)=0$

$$-J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{-[\lambda_2-\mu_2]0} + c_4 = 0$$

$$c_4 = J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]$$

Substituting the c_4 in the above equation we get

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

$$= J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]\left[e^{2[\lambda_2-\mu_2]t} - e^{[\lambda_2-\mu_2]t}\right]$$

$$\therefore m_{0,2}(t) = J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{[\lambda_2-\mu_2]t}\left[e^{[\lambda_2-\mu_2]t} - 1\right] \qquad (2.3.5)$$

Solving the equation (2.2.12), we get

$$\frac{\partial}{\partial t}m_{1,1}(t) = \left\{\left[\lambda_1-\mu_1\right]+\left[\lambda_2-\mu_1\right]\right\}m_{1,1}(t)$$

$$\int\frac{\frac{\partial}{\partial t}m_{1,1}(t)}{m_{1,1}(t)}dt = \int\left\{\left[\lambda_1-\mu_1\right]+\left[\lambda_2-\mu_1\right]\right\}dt$$

$$\log m_{1,1}(t) = \{[\lambda_1-\mu_1]+[\lambda_2-\mu_2]\}t + c_5$$

The initial condition is when t=0 then $m_{1,1}$ (t)=K_0

Therefore $c_5 = \log(K_0)$

Substituting the c_5 in the above equation we get

$$m_{1,1}(t) = e^{\{[\lambda_1-\mu_1]+[\lambda_2-\mu_1]\}t}e^{\log(K_0)}$$

$$\therefore m_{1,1}(t) = e^{\{[\lambda_1-\mu_1]+[\lambda_2-\mu_1]\}t}K_0$$

The Coefficient of variation of MS causing cells is $CV_{1,0}$

$$CV_{1,0} = \left(\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]\frac{\left[e^{[\lambda_1-\mu_1]t}-1\right]}{I_0e^{[\lambda_1-\mu_1]t}}\right)^{1/2} X100 \qquad (2.3.6)$$

The Coefficient of variation of oligodendrocytes is $CV_{0,1}$

$$CV_{0,1} = \left(\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]\frac{\left[e^{[\lambda_2-\mu_2]t}-1\right]}{J_0e^{[\lambda_2-\mu_2]t}}\right)^{1/2} X100 \qquad (2.3.7)$$

The correlation coefficient between MS causing cells and Oligodendrocytes is

$$\therefore r = K_0\left[\left(\frac{(\lambda_1-\mu_1)(\lambda_2-\mu_2)}{(\lambda_1+\mu_1)(\lambda_2+\mu_2)}\right)\frac{e^{\{[\lambda_1-\mu_1]+[\lambda_2-\mu_1]\}t}}{I_0 J_0\left(e^{[\lambda_1-\mu_1]t}-1\right)\left(e^{[\lambda_2-\mu_2]t}-1\right)}\right]^{\frac{1}{2}} \quad (2.3.8)$$

In summary, the results from 2.3.1 to 2.3.8 are presented as below.

The Expected number of MS causing cells at time 't' is

$$m_{1,0}(t) = e^{[\lambda_1-\mu_1]t} I_0 \quad (2.3.1)$$

Expected number of oligodendrocytes at time 't' is

$$m_{0,1}(t) = e^{[\lambda_2-\mu_2]t} J_0 \quad (2.3.2)$$

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

$$m_{2,0}(t) = I_0\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]e^{[\lambda_1-\mu_1]t}\left[e^{[\lambda_1-\mu_1]t}-1\right] \quad (2.3.3)$$

The variance of number of oligodendrocytes at time 't' is

$$m_{0,2}(t) = J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{[\lambda_2-\mu_3]t}\left[e^{[\lambda_2-\mu_2]t}-1\right] \quad (2.3.4)$$

Covariance of number of MS causing cells and oligodendrocytes at time 't' is

$$m_{1,1}(t) = e^{\{[\lambda_1-\mu_1]+[\lambda_2-\mu_1]\}t} K_0 \quad (2.3.5)$$

The Coefficient of variation of MS causing cells is

$$CV_{1,0} = \left(\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]\frac{\left[e^{[\lambda_1-\mu_1]t}-1\right]}{I_0 e^{[\lambda_1-\mu_1]t}}\right)^{1/2} X100 \quad (2.3.6)$$

The Coefficient of variation of oligodendrocytes is

$$CV_{0,1} = \left(\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]\frac{\left[e^{[\lambda_2-\mu_2]t}-1\right]}{J_0 e^{[\lambda_2-\mu_2]t}}\right)^{1/2} X100 \quad (2.3.7)$$

The correlation coefficient between MS causing cells and oligodendrocytes is

$$r = K_0\left[\left(\frac{(\lambda_1-\mu_1)(\lambda_2-\mu_2)}{(\lambda_1+\mu_1)(\lambda_2+\mu_2)}\right)\frac{e^{\{[\lambda_1-\mu_1]+[\lambda_2-\mu_1]\}t}}{I_0J_0\left(e^{[\lambda_1-\mu_1]t}-1\right)\left(e^{[\lambda_2-\mu_2]t}-1\right)}\right]^{\frac{1}{2}} \quad (2.3.8)$$

2.4 Numerical Illustrations and Interpretations of Model

From equations (2.3.1) to (2.3.8) the values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ and r are computed respectively for different values of the parameters are presented in tables from 2.4.2 to 2.4.8

Table 2.4.1: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values J_0=15; K_0=1.2; λ_1=2; μ_1=1.2; λ_2=1.4; μ_2=0.8; t=2

I_0	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
10	49.53	49.80	783.18	423.67	19.73	56.50	41.33	0.032
11	54.48	49.80	861.50	423.67	19.73	53.87	41.33	0.031
12	59.44	49.80	939.82	423.67	19.73	51.58	41.33	0.030
13	64.39	49.80	1018.00	423.67	19.73	49.56	41.33	0.029
14	69.34	49.80	1096.00	423.67	19.73	47.75	41.33	0.033

Table 2.4.2: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values I_0=10; K_0=1.2; λ_1=2; μ_1=1.2; λ_2=1.4; μ_2=0.8; t=2

J_0	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
16	49.53	53.12	783.18	451.91	19.73	56.50	40.02	0.033
17	49.53	56.44	783.18	480.16	19.73	56.50	38.82	0.032
18	49.53	59.76	783.18	508.40	19.73	56.50	37.73	0.031
19	49.53	63.08	783.18	536.65	19.73	56.50	36.72	0.030
21	49.53	69.72	783.18	593.14	19.73	56.50	34.93	0.029

From tables 2.4.1 and 2.4.2, it is observed that average number of MS causing cells and average number of oligodendrocytes, variance of MS causing cells and variance of oligodendrocytes are increasing functions of initial sizes of MS causing cells (I_0) and oligodendrocytes (J_0) when all other parameters are constant. It is also observed that the coefficient of variation of MS causing cells, coefficient of variation of oligodendrocytes and correlation coefficient between MS causing cells and oligodendrocytes are decreasing

functions of initial sizes of MS causing cells (I_0) and oligodendrocytes (J_0) when all other parameters are constant.

Table 2.4.3: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $\lambda_1=2$; $\mu_1=1.2$; $\lambda_2=1.4$; $\mu_2=0.8$; t=2

K_0	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
1.3	49.53	49.80	783.18	423.67	21.38	56.50	41.33	0.037
1.4	49.53	49.80	783.18	423.67	23.02	56.50	41.33	0.040
1.5	49.53	49.80	783.18	423.67	24.67	56.50	41.33	0.043
1.6	49.53	49.80	783.18	423.67	26.31	56.50	41.33	0.046
1.7	49.53	49.80	783.18	423.67	27.96	56.50	41.33	0.049

Form table 2.4.3, it is observed that covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are increasing functions of coefficient of initiation for correlating the variables MS and oligodendrocytes cells (K_0) when all other parameters are constant.

Table 2.4.4: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $K_0=1.2$; $\mu_1=1.2$; $\lambda_2=1.4$; $\mu_2=0.8$; t=2

λ_1	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
2.2	73.89	49.80	1605	423.67	29.44	54.22	41.33	0.036
2.4	110.23	49.80	3315	423.67	43.92	52.23	41.33	0.037
2.6	164.45	49.80	6894	423.67	65.52	50.49	41.33	0.038
2.8	245.33	49.80	14430	423.67	97.74	48.97	41.33	0.040
3	365.98	49.80	30400	423.67	145.81	47.64	41.33	0.041

From table 2.4.4, it is observed that the average number of MS causing cells, variance of MS causing cells, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are increasing functions of growth rate of MS causing cells (λ_1) when all other parameters are constant and also observed that coefficient of variation of MS causing cells is decreasing function of growth rate of MS causing cells (λ_1) when all other parameters are constant.

Table 2.4.5: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $K_0=1.2$; $\lambda_1=2$; $\lambda_2=1.4$; $\mu_2=0.8$; t=2

μ_1	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
1.3	40.55	49.80	584.07	423.67	16.16	59.60	41.33	0.032
1.4	33.20	49.80	436.51	423.67	13.23	62.93	41.33	0.031
1.5	27.18	49.80	326.95	423.67	10.83	66.52	41.33	0.029
1.6	22.26	49.80	245.47	423.67	8.87	70.40	41.33	0.027
1.7	18.22	49.80	184.75	423.67	7.26	74.60	41.33	0.026

From table 2.4.5, it is observed that average number of MS causing cells, variance of MS causing cells, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are decreasing functions of death rates of MS causing cells (μ_1). And also it is observed that C.V of MS causing cells is increasing function of death rates of MS causing cells (μ_1) when all other parameters are constant.

Table 2.4.6: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $K_0=1.2$; $\lambda_1=2$; $\mu_1=1.2$; $\mu_2=0.8$; t=2

λ_2	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
1.5	40.55	60.83	584.07	610.62	19.73	59.60	40.62	0.033
1.6	40.55	74.30	584.07	881.08	24.10	59.60	39.95	0.034
1.8	40.55	110.84	584.07	1841.00	35.96	59.60	38.71	0.035
2	40.55	165.35	584.07	3867.00	53.64	59.60	37.61	0.036
2.2	40.55	246.67	584.07	8164.00	80.02	59.60	36.63	0.037

From table 2.4.6, it is observed that the average number of oligodendrocytes, variance of oligodendrocytes, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are increasing functions of growth rates of oligodendrocytes (λ_2). It is also observed that C.V of oligodendrocytes is decreasing function of growth rate of oligodendrocytes (λ_2) when the all other parameters are constant.

Table 2.4.7: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $K_0=1.2$; $\lambda_1=2$; $\mu_1=1.2$; $\lambda_2=1.4$; t=2

μ_2	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
0.9	40.55	40.77	584.07	322.28	13.23	59.60	44.03	0.030
1	40.55	33.38	584.07	245.47	10.83	59.60	46.93	0.029
1.1	40.55	27.33	584.07	187.25	8.87	59.60	50.07	0.027
1.2	40.55	22.38	584.07	143.08	7.26	59.60	53.45	0.025
1.3	40.55	18.32	584.07	109.52	5.94	59.60	57.12	0.024

From table 2.4.7, it is observed that the average number of oligodendrocytes, variance of oligodendrocytes, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are decreasing functions of death rate of oligodendrocytes (μ_2). And also observed that coefficient of variation of oligodendrocytes is increasing function of death rates of oligodendrocytes (μ_2) when the remaining parameters are constant.

Table 2.4.8: Values of $m_{10}(t)$, $m_{01}(t)$, $m_{20}(t)$, $m_{02}(t)$, $m_{11}(t)$, $cv_{1,0}(t)$, $cv_{0,1}(t)$ for varying values of other parameters with values $I_0=10$; $J_0=15$; $K_0=1.2$; $\lambda_1=2$; $\mu_1=1.2$; $\lambda_2=1.4$; $\mu_2=0.8$; t=2

t	$m_{1,0}(t)$	$m_{0,1}(t)$	$m_{2,0}(t)$	$m_{0,2}(t)$	$m_{1,1}(t)$	$CV_{1,0}(t)$	$CV_{0,1}(t)$	r
2	49.53	49.80	783.18	423.67	19.73	56.50	41.33	0.034
3	81.66	90.75	2759	1680.00	59.28	64.32	45.17	0.028
3.1	87.58	96.36	3203	1916.00	67.51	64.62	45.43	0.027
3.5	115.88	122.49	5784	3219.00	113.56	65.63	46.32	0.026
4.1	176.37	175.57	13830	6891.00	247.73	66.69	47.28	0.025

From table 2.4.8, it is observed that the average numbers of MS causing cells, average number of oligodendrocytes, variance of MS causing cells, variance of oligodendrocytes, C. V of MS causing cells, C. V of oligodendrocytes, covariance between MS causing cells and oligodendrocytes are increasing functions of time (t). And also observed that correlation coefficient between MS causing cells and oligodendrocytes is decreasing function of time (t), when the other parameters are constant in normal environment.

2.5 STOCHASTIC MODEL FOR MS DURING TREATMENT

2.5.1 Introduction

As multiple sclerosis is a resulting effect of infections and inflammations, the severity of the problem can be minimized by the suitable treatment to get rid of infections and inflammations. The usual anti biotech treatment is within spells for short duration will act on growth and loss dynamics of both multiple sclerosis and oligodendrocytes. Obviously, we can observe the growth of multiple sclerosis during infection time (in other words when there is no drug presence). Whereas, the growth of oligodendrocytes is observed when the patient is free from infection may be due to the treatment. Hence, there is a possibility of alternative growth and loss processes observed in multiple sclerosis and oligodendrocytes when there are alternative spells of drug treatment.

In order to measure the overall phenomena of both multiple sclerosis causing cells and oligodendrocytes, we consider a linear convex combination Z=a X+(1-a)Y. where X and Y are the variables. X reveal the growth and loss aspects of multiple sclerosis cells and Y reveal the growth and loss aspects of oligodendrocytes. The usual mechanisms also suggest that increasing the severity of one component leads to decrement in another component vice versa. In this section, a model is developed to study the behavior of the disease by computing the overall phenomena.

The following assumptions are considered to develop the model for the said purpose. Let Z=a X+ (1-a) Y be the joint effect of multiple sclerosis causing cells and oligodendrocytes, where $0 \leq a \leq 1$; Z is considered to be a convex combination of multiple sclerosis cells and oligodendrocytes. It will give the total count of both cells. 'a' can be assume that the values of either '0' or '1' as mentioned below

a=0; if the patient is in treatment (during this time the development of oligodendrocytes will be observed).

a=1; if the patient is not in treatment (during this time the development of MS causing cells will be observed).

$$E(Z) = E\left[aX + (1-a)Y\right] = aE(X) + (1-a)E(Y)$$

Expected joint effect of both MS causing cells and oligodendrocytes at time period 't' is

$$E(Z) = a\left(e^{(\lambda_1-\mu_1)t} I_0\right) + (1-a)\left(e^{(\lambda_2-\mu_2)t} J_0\right) \tag{2.5.1}$$

$$\begin{aligned} V(Z) &= V\left[aX + (1-a)Y\right] \\ &= a^2 V(X) + (1-a)^2 V(Y) + 2a(1-a)Cov(X,Y) \end{aligned}$$

$2a(1-a)Cov(X,Y) = 0$ at a=0 and a=1

$$\therefore V(Z) = a^2 V(X) + (1-a)^2 V(Y)$$

Variance of joint effect of both MS causing cell and oligodendrocytes at time period 't' is

$$V(Z) = a^2 I_0\left(\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right)e^{(\lambda_1-\mu_1)t}\left(e^{(\lambda_1-\mu_1)t}-1\right) + (1-a)^2 J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right) \tag{2.5.2}$$

The coefficient of variation is

$$C.V = \frac{\left\{a^2 I_0\left(\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right)e^{(\lambda_1-\mu_1)t}\left(e^{(\lambda_1-\mu_1)t}-1\right) + (1-a)^2 J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)\right\}^{1/2}}{a\left(e^{(\lambda_1-\mu_1)t} I_0\right) + (1-a)\left(e^{(\lambda_2-\mu_2)t} J_0\right)}$$

(2.5.3)

2.5.2 Numerical Illustrations and Interpretations of Model

Table-2.2: From equations (2.5.1) and (2.5.3) the values of E(Z) ,V(Z) and C.V(Z) are computed respectively for different values of the parameters

a	t	I_0	J_0	λ_1	μ_1	λ_2	μ_2	E(Z)	V(Z)	CV(Z)
0	1	20	10	1.5	2.8	2.7	2.5	24.4280	5.4080	0.095
	2							29.8360	14.6740	0.128
	3							36.4420	29.9600	0.150
	3.2							37.9300	34.0030	0.154
	3.4							39.4780	38.4460	0.157
	1	21	10	1.5	2.8	2.7	2.5	24.4280	5.4080	0.095
		22						24.4280	5.4080	0.095
		23						24.4280	5.4080	0.095
		24						24.4280	5.4080	0.095
		25						24.4280	5.4080	0.095
0	1	20	11	1.5	2.8	2.7	2.5	13.4350	2.9750	0.128
			12					14.6570	3.2450	0.123
			13					15.8780	3.5150	0.118
			14					17.1000	3.7860	0.114
			15					18.3210	4.0560	0.110
0	1	20	10	1.6	2.8	2.7	2.5	12.2140	2.7040	0.135
				1.7				12.2140	2.7040	0.135
				1.8				12.2140	2.7040	0.135
				1.9				12.2140	2.7040	0.135
				2				12.2140	2.7040	0.135
0	1	20	10	1.5	2.9	2.7	2.5	12.2140	2.7040	0.135
					3			12.2140	2.7040	0.135
					3.1			12.2140	2.7040	0.135
					3.2			12.2140	2.7040	0.135
					3.3			12.2140	2.7040	0.135
0	1	20	10	1.5	2.8	3	2.5	16.4870	10.6960	0.198
						3.1		18.2210	14.9800	0.212

a	t	I_0	J_0	λ_1	μ_1	λ_2	μ_2	E(Z)	V(Z)	CV(Z)
						3.2		20.1380	20.4140	0.224
						3.3		22.2550	27.2750	0.235
						3.4		24.5960	35.9000	0.244
0	1	20	10	1.5	2.8	2.7	2.51	12.0920	2.5300	0.132
							2.52	11.9720	2.3610	0.128
							2.53	11.8530	2.1960	0.125
							2.54	11.7350	2.0360	0.122
							2.55	11.6180	1.8800	0.118
1	1	20	10	2.4	1.8	1.5	2.5	36.4420	29.96	0.150
	1.1							38.6960	36.17	0.155
	1.2							41.0890	43.33	0.160
	1.3							43.6290	51.55	0.165
	1.4							46.3270	60.98	0.169
1	1	21	10	2.4	1.8	1.5	2.5	38.2640	31.4580	0.147
		22						40.0870	32.9560	0.143
		23						41.9090	34.4540	0.140
		24						43.7310	35.9520	0.137
		25						45.5530	37.4500	0.134
1	1	20	11	2.4	1.8	1.5	2.5	36.4420	29.9600	0.150
			12					36.4420	29.9600	0.150
			13					36.4420	29.9600	0.150
			14					36.4420	29.9600	0.150
			15					36.4420	29.9600	0.150
1	1	20	10	2.5	1.8	1.5	2.5	40.2750	40.8290	0.159
				2.6				44.5110	54.5500	0.166
				2.7				49.1920	71.8010	0.172
				2.8				54.3660	93.4150	0.178
				2.9				60.0830	120.417	0.183
1	1	20	10	2.4	1.81	1.5	2.5	36.0800	29.0080	0.149
					1.82			35.7210	28.0780	0.148
					1.83			35.3650	27.1700	0.147

a	t	I_0	J_0	λ_1	μ_1	λ_2	μ_2	E(Z)	V(Z)	CV(Z)
					1.84			35.0130	26.2840	0.146
					1.85			34.6650	25.4180	0.145
1	1	20	10	2.4	1.8	1.51	2.5	36.4420	29.9600	0.150
						1.52		36.4420	29.9600	0.150
						1.53		36.4420	29.9600	0.150
						1.54		36.4420	29.9600	0.150
						1.55		36.4420	29.9600	0.150
1	1	20	10	2.4	1.8	1.5	2.51	36.4420	29.9600	0.150
							2.52	36.4420	29.9600	0.150
							2.53	36.4420	29.9600	0.150
							2.54	36.4420	29.9600	0.150
							2.55	36.4420	29.9600	0.150

From the table (2.2), it is observed that average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of time 't' under the treatment; the average and variance of joint effect of both MS causing cells and oligodendrocytes are increasing functions and coefficient of variation is decreasing functions of initial sizes of oligodendrocytes under the treatment; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of birth rate of oligodendrocytes under the treatment; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are decreasing functions of death rate of oligodendrocytes under the treatment when all other parameters are constant.

It is observed that during absence treatment, the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of time 't'; the average, variance of joint effect of both MS causing cells and oligodendrocytes are increasing functions of initial sizes of MS causing cells and coefficient of variation is decreasing function of initial sizes of MS causing cells; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of birth rate of MS causing cells; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are decreasing functions of death rate of MS causing cells; when all other parameters are constant.

CHAPTER-3

STOCHASTIC OPTIMIZATION PROGRAMMING PROBLEMS

3.1 INTRODUCTION

In this chapter we have developed optimization programming problems for using them in drug administration procedures. As multiple sclerosis is a disease related to central nervous system it may be badly affected with the bacterial attacks and viral infections. There are numerous reasons that central nervous system to get exposure to infections. Inflammation and loss of immunity are the causing factors, which have significant influence of adverse results with oligodendrocytes and proactive results with multiple sclerosis. It is observed that improved immunity of the body system will act as catalyst to boost the protective mechanisms of central nervous system so as the myelin sheath by generating good number of oligodendrocytes. On the other hand, the hazard levels of multiple sclerosis will deteriorate the CNS.

In the previous chapter the study is focused on modeling the growth and loss processes of both multiple sclerosis and oligodendrocytes using bivariate processes. This study will help to derive the formulae of various statistical measures like average, standard deviation, coefficient of variation and the other related. The growth of oligodendrocytes will improve the thickness of myelin sheath and the electrical signal impulses have effective transmission among the nerve cells. Hence, obviously the healthy size of myelin sheath is the concern of study. This part of the study can be handled with computing the average number of oligodendrocytes.

This chapter deals with set of nonlinear programming problems with multiple objectives where each nonlinear programming problem can be handled separately. The values of decision parameters of bivariate stochastic processes namely λ_1, λ_2, μ_1 and μ_2 are obtained. Here, different stochastic optimization programming problems are developed in two environments such as, (i) when the patients are not in treatment and (ii) when patients are under treatment. The study has explored four stochastic optimization programming problems in general environment i.e. during non- treatment and two optimization problems during treatment. A programming problem is formulated with the objective of maximizing the average number of oligodendrocytes, subject to the constraints that the average number of

MS causing cells should not be exceed certain harmful level and the average number of oligodendrocytes should have at least the minimum wanted size, the variability of MS causing cells should be more than certain limit and the variability of oligodendrocytes less than certain limit. Another optimization programming problem is to minimize the severity of multiple sclerosis subject to the constraints as the above problem. The other set of optimization programming problems consists of first optimization programming problem is on maximizing the overall joint effect of both the MS causing cells and oligodendrocytes, subject to the constraints of minimum required quantity of joint effect of both the MS and oligodendrocytes at fixed minimum variation. Second optimization programming problem is to minimize the variation during treatment subject to the constraints of minimum required joint effect of both the MS causing cells, oligodendrocytes and fixed minimum variation. While framing the optimization programming problems, we have considered the statistical measures derived from the previous chapter. The core objective of this work is to develop the programming problems that can minimize the severity of MS with several feasible constraints.

3.2 STOCHASTIC OPTIMIZATION PROGRAMMING PROBLEMS DURING NON-TREATMENT PERIOD

Notations

λ_1= Growth rate in MS causing cells per unit time

λ_2= Growth rate in oligodendrocytes per unit time

μ_1= Loss rate in MS causing cells per unit time

μ_2= Loss rate in oligodendrocytes per unit time

I_0=Initial size of MS causing cells at a point of time t

J_0=Initial size of oligodendrocytes at a point of time t

t =Time of observation

A= Allowable maximum number of MS cells on average

B= Minimum required number of oligodendrocytes on average

C=Minimum variability in the size MS causing cells

D=Maximum allowable variability in oligodendrocytes

E=Minimum required combined effectiveness of MS causing cells and oligodendrocytes

F= Maximum allowable variability in the combined effectiveness of MS causing cells and oligodendrocytes

g= The coefficient in linear combination of growth of MS causing cells and oligodendrocytes

h= The coefficient in linear combination of loss of MS causing cells and oligodendrocytes

K_1 and K_2 are constants

3.2.1 Optimization Programming Problem for Minimizing the Severity of MS

In this programming problem, the objective function is formulated with loss function through derived statistical measures during non-treatment period. The problem deals with minimization of severity of MS, subject to the constraints of the average number of MS cells should be less than certain limit (A), there should be minimum size in the average number of oligodendrocytes (B), the variance of MS cells should be greater than certain size (C) and the variance of oligodendrocytes should maintain at minimum size (D). The constraints are also formulated with linear combinations of growth rates of both MS causing cells and oligodendrocytes cells; the linear combination of loss rates of both MS causing cells and oligodendrocytes cells. The purpose of the problem is to explore the decision parameters namely λ_1 (growth rate in MS causing cells per unit time); λ_2 (growth rate in oligodendrocytes per unit time); μ_1 (loss rate in MS causing cells per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non-negative.

Problem -1:

From the derived relations in chapter-2, the expected size of the MS causing cells at a point of time 't' is $e^{[\lambda_1-\mu_1]t}I_0$, where I_o is the initial size of MS causing cells and the expected size of the oligodendrocytes at a point of time 't' is $e^{[\lambda_2-\mu_2]t}J_0$, where J_o is the initial size of oligodenrocytes. Here, the average number of MS causing cells is considered as unwanted component and average number of oligodendrocytes considered as wanted component. By using the concept of loss function, the relation between the difference of size in MS causing cells and size in oligodendrocytes is $Z_1= e^{[\lambda_1-\mu_1]t}I_0 - e^{[\lambda_2-\mu_2]t}J_0$.

The objective is to minimize

$$Z_1= e^{[\lambda_1-\mu_1]t}I_0 - e^{[\lambda_2-\mu_2]t}J_0 \qquad (3.2.1.1)$$

The above mentioned objective function is in the influence of the following constraints. Let 'A' be the maximum threshold limit on the average number of MS causing cells. From chapter-2, the average number of MS causing cells at a point of time is E (MS) = $e^{[\lambda_1-\mu_1]t}I_0$. Since E (MS) should not exceed the value of 'A'.

The constraint with 'A' and E (MS) is

$$e^{[\lambda_1-\mu_1]t}I_0 \leq A \tag{3.2.1.2}$$

Let 'B' be the minimum threshold limit on the average number of oligodendrocytes. The expected number of oligodendrocytes at a point of time is equal to $e^{[\lambda_2-\mu_2]t}J_0$. Since the average size of oligodendrocytes should be more than a limit 'B'.

The constraint with 'B' and E(oligodendrocytes) is

$$e^{[\lambda_2-\mu_2]t}J_0 \geq B \tag{3.2.1.3}$$

Let 'C' be the minimum threshold limit on the variance of MS causing cells. The derived relation on variance of MS causing cells at a point of time is V (MS) = $I_0\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]e^{[\lambda_1-\mu_1]t}\left[e^{[\lambda_1-\mu_1]t}-1\right]$. Since, V (MS) should be greater than the value of C.

The constraint with 'C' and V (MS) is

$$I_0\left[\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right]e^{[\lambda_1-\mu_1]t}\left[e^{[\lambda_1-\mu_1]t}-1\right]\geq C \tag{3.2.1.4}$$

Let 'D' be the maximum threshold limit on the variance of oligodendrocytes. The derived relation on variance of oligodendrocytes at a point of time is $J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{[\lambda_2-\mu_2]t}\left[e^{[\lambda_2-\mu_2]t}-1\right]$.

Since V (oligodendrocytes) should be less than the value of D.

The constraint with 'D' and V(oligodendrocytes) is

$$J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{[\lambda_2-\mu_2]t}\left[e^{[\lambda_2-\mu_2]t}-1\right]\leq D \tag{3.2.1.5}$$

Let K_1 be the constant, which is equal to the linear combinations of both growth rates of MS causing cells and oligodendrocytes. Here, we are assuming that the number of MS

causing cells and oligodendrocytes are having the growth such that one is influencing the other. The linear combination of both growth rates of MS causing cells and oligodendrocytes cells is $g\lambda_1 + (1-g)\lambda_2$, where 'g' is the coefficient is convex combination and its limits are 0≤ g ≤ 1. Since, linear combinations of both growth rates should be equal to K_1.

The constraint with K_1 and linear combinations of both growth rates is

$$g\lambda_1 + (1-g)\lambda_2 = k_1 \tag{3.2.1.6}$$

Let K_2 be the constant equal to the linear combinations of both loss rates of MS causing cells and oligodendrocytes. Here, we are assuming that the number of MS causing cells and oligodendrocytes are having the loss such that one is influencing the other. The linear combination of both loss rates of MS causing cells and oligodendrocytes is $h\mu_1 + (1-h)\mu_2$, where 'h' is the coefficient of convex combination and its limits are 0≤ h ≤ 1. Therefore linear combinations of both loss rates should be equal to K_2.

The constraint with K_2 and linear combinations of both loss rates is

$$h\mu_1 + (1-h)\mu_2 = K_2 \tag{3.2.1.7}$$

Further it is assumed that the decision parameters λ_1 (growth rate in MS causing cells per unit time); λ_2 (growth rate in oligodendrocytes per unit time); μ_1 (loss rate in MS causing cells per unit time) and μ_2 (loss rate in oligodendrocytes per unit time) are non-negative. In summary, the optimization programming problem is

To minimize $(Z_1) = e^{[\lambda_1-\mu_1]t} I_0 - e^{[\lambda_2-\mu_2]t} J_0$

Subject to the constraints: $e^{[\lambda_1-\mu_1]t} I_0 \le A;$

$$e^{[\lambda_2-\mu_2]t} J_0 \ge B;$$

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

$$J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right] e^{[\lambda_2-\mu_2]t}\left[e^{[\lambda_2-\mu_2]t} - 1\right] \le D;$$

$$g\lambda_1 + (1-g)\lambda_2 = K_1;$$

$h\mu_1 + (1-h)\mu_2 = K_2$ and $\lambda_1, \lambda_2, \mu_1$and $\mu_2 \ge 0$. (3.2.1)

3.2.2 Optimization Programming Problem for Maximizing the Size of Oligodendrocytes

In this programming problem, the objective function is formulated with an objective of maximizing the average size of oligodendrocytes derived through the relation of chapter-2 under the assumption that the patient is not in treatment. The subjective constraints are designed with the average number of MS causing cells should be less than certain limit (A), the average size of oligodendrocytes should be more than some wanted levels (B), the variance of MS causing cells should be greater than certain size (C) and the variance of oligodendrocytes should maintain at minimum size (D). Further the constraints are formulated with linear combinations of growth rates of both MS causing cells and oligodendrocytes; the linear combination of loss rates of both MS causing cells and oligodendrocytes. The purpose of the problem is to explore the decision parameters as in the previous problem.

Problem -2:

The expected size of the MS causing cells at a point of time 't' is $e^{[\lambda_1-\mu_1]t}I_0$, where Io is the initial size of MS causing cells. The expected size of oligodendrocytes at a point of time 't' is $e^{[\lambda_2-\mu_2]t}J_0$, where Jo is the initial size of oligodendrocytes. Here the average number of MS cells considered to be unwanted level of objective and average number of oligodendrocytes considered to be wanted level of objective. Notion of resulting positive benefit, the relation between the difference of oligodendrocytes and MS causing cells is

$$Z_2 = e^{[\lambda_2-\mu_2]t}J_0 - e^{[\lambda_1-\mu_1]t}I_0$$

Z_2 is the objective function to maximize the resulting size. The objective function is in the influence of the same constraints as in the previous problem along with decision parameters. In summary, the optimization programming problem is

To maximize $(Z_2) = e^{[\lambda_2-\mu_2]t}J_0 - e^{[\lambda_1-\mu_1]t}I_0$

Subject to the constraints: $e^{[\lambda_1-\mu_1]t}I_0 \le A$;

$$e^{[\lambda_2-\mu_2]t}J_0 \ge B;$$

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

$$J_0\left[\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right]e^{[\lambda_2-\mu_2]t}\left[e^{[\lambda_2-\mu_2]t}-1\right]\leq D;$$

$$g\lambda_1+(1-g)\lambda_2=K_1;$$

$$h\mu_1+(1-h)\mu_2=K_2;\ \text{and } \lambda_1,\ \lambda_2,\ \mu_1,\ \mu_2\geq 0. \qquad (3.2.2)$$

3.2.3 Numerical Illustrations and Sensitivity Analysis

The non-linear programming problems 3.2.1 and 3.2.2 are solved with a mathematical software LINGO 13 and the results were presented in table 3.1 and table 3.2. For computing the objective function and decision parameters, the hypothetical varying values of I_0, J_0, A, B, C, D, K1 and K2 are assumed.

Table 3.2.3.1: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I₀' at fixed values of other parameters are J₀=4620; A=5600; B=2700; C=1200; D=1000; K1=220; K2=220; g=0.3 and h=0.3.

I_0	Z	λ_1	μ_1	λ_2	μ_2
2360	-3870.78	733.1373	733.3333	0.08401	0
2370	-3864.02	733.1373	733.3333	0.08401	0
2375	-3860.64	733.1373	733.3333	0.08401	0
2380	-3857.26	733.1373	733.3333	0.08401	0
2385	-3853.89	733.1373	733.3333	0.08401	0

Table 3.2.3.2: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I₀' at fixed values of other parameters are I₀=2370; A=5600; B=2700; C=1200; D=1000; t=2;K1=220; K2=220; g=0.3 and h=0.3.

J_0	Z	λ_1	μ_1	λ_2	μ_2
4615	-3859.44	733.1371	733.3333	0.08409	0
4620	-3864.02	733.1373	733.3333	0.08401	0
4625	-3868.6	733.1375	733.3333	0.08394	0
4630	-3873.18	733.1376	733.3333	0.08387	0
4635	-3877.77	733.1378	733.3333	0.08380	0

From the tables 3.2.3.1and 3.2.3.2, it is observed that the objective function Z is increasing function of I_0 (Initial size of MS causing cells at a point of time t) when all the other parameters are constant. The objective function Z, growth rate of oligodendrocytes are decreasing functions of J_0. The growth rate of MS causing cell is an increasing function of J_0 (Initial size of oligodendrocytes at a point of time t) when all other parameters are constant.

Table 3.2.3.3: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=1200; J_0=1800; A=6600; B=1700; D=1200; t=2;K1=300; K2=320; g=0.1 and h=0.3.

C	Z	λ_1	μ_1	λ_2	μ_2
1000	-1796.265	386.1037	388.9899	290.4329	290.4329
1001	-1796.262	386.1043	388.99	290.4329	290.4329
1002	-1796.258	386.1049	388.9902	290.4328	290.4328
1003	-1796.255	386.1054	388.9903	290.4327	290.4327
1005	-1796.249	386.1066	388.9906	290.4326	290.4326

Table 3.2.3.4: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=800; J_0=1800; A=3600; B=1700; C=1200; t=2; K1=200; K2=200; g=0.3 and h=0.3.

D	Z	λ_1	μ_1	λ_2	μ_2
1100	-2221.924	666.251	666.6667	0.17812	0
1110	-2228.999	666.2486	666.6667	0.17917	0
1120	-2236.039	666.2462	666.6667	0.18021	0
1130	-2243.046	666.2438	666.6667	0.18124	0
1140	-2250.02	666.2414	666.6667	0.1823	0

From the tables 3.2.3.3 and 3.2.3.4, it is observed that the objective function, growth and loss rates of MS causing cells are increasing functions of 'C'. Growth and loss rate of oligodendrocytes are decreasing functions of C, when other parameters are constant. The objective function Z, growth rates of MS causing cells are decreasing functions and growth rates of oligodendrocytes is increasing function of D, when all other parameters are constant.

Table 3.2.3.5: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=2370; J_0=4620; A=5600; B=2700; C=1200; D=1000; K1=220; K2=220; g=0.3 and h=0.3.

T	Z	λ_1	μ_1	λ_2	μ_2
1.9	-3864.021	733.127	733.3333	0.08844	0
2	-3864.021	733.1373	733.3333	0.08401	0
2.1	-3544.514	733.185	733.3333	0.06359	0
2.12	-3544.506	733.1864	733.3333	0.06299	0
2.13	-3544.501	733.1871	733.3333	0.06269	0

From the table 3.2.3.5, the objective function, growth rate of MS causing cells are increasing functions and growth rate of oligodendrocytes are decreasing functions of 't'(time of observation) when all other parameters are constant in non-treatment environment.

Table 3.2.3.6: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are J_0=1800; A=6600; B=1700; C=1000; D=1200; K1=300; K2=320; g=0.1 and h=0.3.

I_0	Z	λ_1	μ_1	λ_2	μ_2
1200	1796.265	386.104	388.990	290.4329	290.4329
1210	1796.260	386.099	388.989	290.4335	290.4335
1220	1796.256	386.094	388.987	290.4340	290.4340
1230	1796.251	386.090	388.986	290.4345	290.4345
1240	1796.247	386.085	388.985	290.4350	290.4350

From the table 3.2.3.6, it is observed that the objective function, growth and loss rate of MS causing cells are decreasing functions, growth and loss rate of oligodendrocytes are increasing functions of I_0 (Initial size of MS causing cells at a point of time) when all other parameters are constant.

Table 3.2.3.7: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=1200; A=6600; B=1700; C=1000; D=1200; t=2;K1=300; K2=320; g=0.1 and h=0.3.

J_0	Z	λ_1	μ_1	λ_2	μ_2
1810	1806.27	386.104	388.990	290.433	290.4329
1820	1816.27	386.104	388.990	290.433	290.4329
1830	1826.27	386.104	388.990	290.433	290.4329
1840	1836.27	386.104	388.990	290.433	290.4329
1850	1846.27	386.104	388.990	290.433	290.4329

Table 3.2.3.8: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=1200; J_0=1800; A=6600; B=1700; D=1200; t=2;K1=300; K2=320; g=0.1 and h=0.3.

C	Z	λ_1	μ_1	λ_2	μ_2
1010	1796.23	386.110	388.991	290.4323	290.4323
1020	1796.20	386.115	388.993	290.4317	290.4317
1030	1796.17	386.121	388.994	290.4310	290.4310
1040	1796.14	386.126	388.996	290.4304	290.4304
1050	1796.11	386.132	388.997	290.4298	290.4298

From the tables 3.2.3.7 and 3.2.3.8, it is observed that the objective function Z is increasing function of J_0 (Initial size of oligodendrocytes at a point of time t) when all other parameters are constant. The objective function Z, growth and loss rate of oligodendrocytes

are decreasing functions of 'C', growth and loss rate of MS cells are increasing functions of C(Minimum variability in the size MS causing cells) when all other parameters are constant.

Table 3.2.3.9: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=1510; J_0=1900; A=2300; B=1270; C=1200; t=2;K1=205; K2=205; g=0.2 and h=0.2.

D	Z	λ_1	μ_1	λ_2	μ_2
1100	2298.36	1024.312	1025	0.17196	0
1101	2299.22	1024.312	1025	0.17206	0
1102	2300.08	1024.311	1025	0.17216	0
1103	2300.94	1024.311	1025	0.17227	0
1105	2302.66	1024.310	1025	0.17247	0

Table 3.2.3.10: Values of Z, λ_1, λ_2, $\mu_1$and μ_2 for varying values of 'I_0' at fixed values of other parameters are I_0=1200; J_0=1800; A=6600; B=1700; C=1000; D=1200; K1=300; K2=320; g=0.3 and h=0.3.

t	Z	λ_1	μ_1	λ_2	μ_2
1.1	1793.77	383.543	388.326	290.717	290.717
1.12	1793.87	383.640	388.351	290.707	290.707
1.14	1793.96	383.734	383.734	290.696	290.696
2.12	1794.05	383.825	388.399	290.686	290.686
2.13	1794.09	383.869	388.411	290.681	290.681

From the tables 3.2.3.9 and 3.2.3.10, it is observed that the objective function, growth rates of oligodendrocytes are increasing functions and growth rates of MS cells are decreasing function of D when all other parameters are constant. And also it is observed that the objective function, growth rates of MS causing cells are increasing functions and loss rate of MS causing cells, growth and loss rates of oligodendrocytes are decreasing functions of t when other all parameters are constant.

3.3 STOCHASTIC OPTIMIZATION PROGRAMMING PROBLEMS DURING TREATMENT PERIOD

3.3.1 Introduction

Treatment of MS is mostly on short term basis as health fluctuations due to infections and inflammations are of short duration. As the viral infections are the factors of myelin sheath. The effective growth of oligodendrocytes may be sullen due to this development. The

damage to myelin sheath will be more rigorous and growth of MS becomes obvious. In order to minimize the severity of MS, the immunity system of the body comes to the rescue, but the intensity of infections may create a demand of external use of antibiotic drugs. The drug consumption for the improvement of health conditions is a common and conventional approach but it equally gives adverse effects on health and immune systems. Therefore either over dose or under dose on infection makes the body either drug resistance or drug over complications. And hence the optimal drug administration is the need of the hour by keeping the general health of the patient at wanted levels of health without harming the protective mechanisms.

In this section we propose an optimization programming problem for effective drug administration with the objectives of maximizing the overall growth of oligodendrocytes and minimize the overall expansion of MS during the treatment periods. Resulting to these, the objective is considered to be maximizing the overall performance of drug. Another important criteria that is to be observed during the treatment period is the volatility of drug effectiveness should be at minimum fluctuations. The other programming problem is developed with an objective of minimizing the overall variability of disease intensity. We have also formulated the subject to the constraints by maintaining the wanted and unwanted levels of disease causing cells and disease defense cells. This part of the problem can be used for extracting the decision parameters namely growth and loss rates of both MS and oligodendrocytes.

3.3.2 Optimization Programming Problem for Maximizing the overall Combined Effectiveness of MS and Oligodendrocytes

In this optimization programming problem, the objective function is formulated with derived statistical measures during treatment period. The problem deals with maximization of positive joint effect of both MS causing cells and oligodendrocytes, subject to the constraints on overall joint effect of both MS causing cells and oligodendrocytes should be more than certain limit (E), the variance should be less than certain minimum size (F) The purpose of the problem is to explore the decision parameters namely λ_2 (growth rate in oligodendrocytes per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non-negative.

Problem -3:

The overall joint effect of both MS causing cells and oligodendrocytes under treatment is $a\left(e^{(\lambda_1-\mu_1)t}I_0\right)+(1-a)\left(e^{(\lambda_2-\mu_2)t}J_0\right)$, where Io is the initial size of MS causing calls and Jo is the initial size of oligodendrocytes. Under the treatment the value of a=0; which implies the overall joint effect of both MS causing cells and oligodendrocytes under treatment is $e^{(\lambda_2-\mu_2)t}J_0$. Here, the objective function is maximizing the overall joint effect of both MS causing cells and oligodendrocytes, denoted by

$$Z_3 = e^{(\lambda_2-\mu_2)t}J_0$$

The objective function is in the influence of the following constraints. Let 'E' be the minimum threshold limit that the overall joint effect of both MS causing cells and oligodendrocytes. The overall joint effect of both MS causing cells and oligodendrocytes under treatment is $e^{(\lambda_2-\mu_2)t}J_0$. Hence expectation of joint effect of both MS causing cells and oligodendrocytes should exceed the value of 'E'.

Therefore the constraint with 'E' and expectation of joint effect of both MS and oligodendrocytes is

$$e^{(\lambda_2-\mu_2)t}J_0 \geq E$$

Let 'F' be the maximum threshold limit of the variance. The variance is $a^2 I_0\left(\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right)e^{(\lambda_1-\mu_1)t}\left(e^{(\lambda_1-\mu_1)t}-1\right)+(1-a)^2 J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$ Since a=0, the variance is $J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$. Variance value should not exceed the value of 'F'.

The constraint with 'F' and variance is

$$J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)\leq F$$

The problem decision parameters namely λ_2 is growth rate in oligodendrocytes per unit time and μ_2 is loss rate in oligodendrocytes per unit time. The decision parameters are non-negative. Summarize the above problem, the optimization programming problem is

To maximize (Z_3)= $e^{(\lambda_2-\mu_2)t}J_0$

Subject to the constraints

$$e^{(\lambda_2-\mu_2)t}J_0 \geq E;$$

$$J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)\leq F;$$

λ_2 and $\mu_2 \geq 0$. (3.3.1)

3.3.3 Optimization programming problem for minimization of volatility

In this optimization programming problem, the objective function is formulated with derived statistical measures during treatment period. The problem deals with minimization of variance of joint effect of both MS causing cells and oligodendrocytes, subject to the constraints on overall joint effect of both MS causing cells and oligodendrocytes should be more than certain limit (E), the variance should be less than certain minimum size (F) The purpose of the problem is to explore the decision parameters namely λ_2 (growth rate in oligodendrocytes per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non-negative.

Problem -4:

The variance of joint effect of both MS causing cells and oligodendrocytes under treatment is $a^2 I_0\left(\frac{\lambda_1+\mu_1}{\lambda_1-\mu_1}\right)e^{(\lambda_1-\mu_1)t}\left(e^{(\lambda_1-\mu_1)t}-1\right)+(1-a)^2 J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$, where Io is the initial size of MS causing calls and Jo is the initial size of oligodendrocytes. Under the treatment the value of a=0 then the variance of joint effect of both MS causing cells and oligodendrocytes under treatment is $J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$. Here, the objective is to minimize the variance of joint effect of MS causing cells and oligodendrocytes, denoted as

$$Z_4 = J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$$

The objective function is in the influence of the same constraints as in the previous problem along with decision parameters. In summary, the optimization programming problem is

To minimize $Z_4 = J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right)$

Subject to the constraints

$e^{(\lambda_2-\mu_2)t}J_0 \geq E;$

$J_0\left(\frac{\lambda_2+\mu_2}{\lambda_2-\mu_2}\right)e^{(\lambda_2-\mu_2)t}\left(e^{(\lambda_2-\mu_2)t}-1\right) \leq F;$

And λ_2 and $\mu_2 \geq 0$. (3.3.2)

The resulting non-linear programming problems 3.3.1 and 3.3.2 are solved with mathematical software LINGO 13 and presented in tables 3.3 and 3.4

3.3.4 Numerical Illustrations and Analysis

Table-3.3: Values of Z, λ_2 and μ_2 for varying values of J_0, E, F and t

J_0	E	F	t	Z	λ_2	μ_2
2500	1800	1260	2	3420.83	0.1568	0
2510				3431.61	0.1564	0
2520				3442.38	0.1560	0
2530				3453.16	0.1555	0
2540				3463.92	0.1551	0
2500	1800	1270	2	3426.58	0.1576	0
		1280		3432.32	0.1585	0
		1290		3438.04	0.1593	0
		1300		3443.74	0.1601	0
		1310		3449.43	0.1610	0
122	75	50	1.1	160.10	0.247	0
			1.2	160.10	0.226	0
			1.3	160.10	0.209	0
			1.4	160.10	0.194	0
			1.5	160.10	0.181	0

From the table (3.3), it is observed that the objective function is increasing function and growth rate of oligodendrocytes are decreasing functions of J_0 (initial size of oligodendrocytes) when other parameters are constant; the objective function is decreasing function and growth rate of oligodendrocytes are increasing functions of F(Maximum allowable variability in the effectiveness of both MS causing cells and oligodendrocytes) when other parameters are constant; the growth rate of oligodendrocytes is decreasing function of 't' when all other parameters are constant.

Table-3. 4: Values of Z, λ_2 and μ_2 for varying values of J_0, E, F and t

J_0	E	F	t	Z	λ_2	μ_2
122	160	50	1	49.84	0.271153	0
123				48.13	0.26299	0
124				46.45	0.254892	0
125				44.8	0.24686	0
126				43.17	0.238892	0
122	155	53	1	41.93	0.239404	0
	156			43.48	0.245835	0
	157			45.04	0.252225	0
	158			46.62	0.258574	0
	159			48.22	0.264883	0
122	155	53	1.1	41.93	0.21764	0
			1.2	41.93	0.199503	0
			1.3	41.93	0.184157	0
			1.4	41.93	0.171003	0
			1.5	41.93	0.159603	0

From the table (3.4), it is observed that the objective function and growth rate of oligodendrocytes are decreasing functions of J_0 (initial size of oligodendrocytes) when other parameters are constant; the objective function and growth rate of oligodendrocytes are increasing functions of E(Minimum required effectiveness of both MS causing cells and oligodendrocytes) when other parameters are constant; the growth rate of oligodendrocytes are decreasing function of t (time of observations) when all other parameters are constant.

CHAPTER-4

QUALITY ANALYSIS THROUGH OPTIMAL CONTROL AND SPECIFICATION LIMITS

4.1 INTRODUCTION

In chapter-II, the study is focused on development of stochastic models to understand the dynamics of growth and loss rates of MS related issues. In chapter-III, the study is focused on development of optimization programming problems with objectives of minimizing the disease intensity and maximizing the effectiveness of defense mechanism. The feasible constraints are framed on the average and variance of MS causing cells and oligodendrocytes. There is significant evidence in literature on medical Quality assurance tools through statistical control charts. Knapp *et al.* (1983) outlined the procedures for interpreting evaluation of healthcare data generated by quality control and audit systems. Oniki *et al.* (1995) constructed statistical quality control charts for monitoring the blood glucose levels. Benneyan *et al.* (2003) overviewed statistical process control (SPC) in healthcare applications. David J. Biau *et al.* (2007) reviewed CUSUM charts in quality control of surgical and interventional procedures. However there is a little evidence on development of quality assurance and control limits to monitor the health status of MS disease.

In this chapter the study is focused on development of quality control and specification limits for optimal health management of MS disease. In order to construct the control and specification limits, we have considered the derived statistical relations in chapter-II. The developed probability functions and derived statistical measures were considered for getting standard and precision. These are further used to understand the shift in quality of standard and the range of its volatility. As the quality assurance has to be analyzed at feasible standards and significant precisions, we have considered the control chart approach for means and standard deviations. The devices namely Upper Control Limit (UCL) and Lower Control Limit (LCL), Upper Specification Limit (USL) and Lower Specification Limit (LSL) are computed based on theoretical derivations of chapter-II. Whereas the control limits are derived through sampling distributions and data sets. Here, a hypothetical data is considered (generated through simulation techniques) for studying the status of the quality assurance. Mean (Average) and Standard Deviations (Root Mean square deviation) were

obtained through the data sets. The control limits for assessment of quality standards are fixed with UCL, LCL, USL and LSL. Therefore, the quality analysis is carried out through valid techniques namely sampling distributions (through numerical/data sets) and quality specification limits (through theoretical concepts). These devices will act as guiding principles for healthcare takers for designing the quality specifications and health care decision support systems. The analysis is carried out with control limits at required level of significance by considering the natural tolerance.

4.2 CONTROL AND SPECIFICATION LIMITS FOR STANDARD ANDVOLATILITY MEASURES OF MS CAUSING CELLS AND OLIGODENDROCYTES

In this section, the study is focused on development of quality devices through the specification limits for both standard and volatility measures. The values like average number of MS causing cells and the average number of oligodendrocytes will provide the relevant information on desired levels of standards. Similarly, variance of number of MS causing cells and variance of number of oligodendrocytes will provide the fluctuations in the health variations. Hence, we can derive the quality guiding devices namely control charts for standards (means) and control charts for volatility (standard deviations). The derived relations of chapter-II mentioned below are considered.

The Expected number of MS causing cells at time 't' is

$$m_{1,0}(t) = e^{[\lambda_1 - \mu_1]t} I_0$$

Expected number of oligodendrocytes at time 't' is

$$m_{0,1}(t) = e^{[\lambda_2 - \mu_2]t} J_0$$

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

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

The variance of number of oligodendrocytes at time 't' is

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

Where λ_1 is growth rate of MS causing cells per unit time; λ_2 is growth rate of oligodendrocytes per unit time; μ_1 is loss rate of MS causing cells per unit time; μ_2 is loss rate of oligodendrocytes per unit time; I_0 is initial size of MS causing cells at a point of time t; J_0 is initial size of oligodendrocytes at a point of time t and t is time of observation.

4.2.1 Control and Specification Limits for Standards (means) chart

Here we have developed control chart for means useful for evaluating the health standards of both MS spreading intensity and oligodendrocytes expansion.

4.2.1.1 Control and Specification Limits for Mean –Chart of MS Causing Cells

Let 'X' be a number of MS causing cells, then the expected number of MS causing cells at time period't' is $e^{[\lambda_1-\mu_1]t}I_0$. Where I_0 is initial size of MS causing cells. Let a_1, a_2,…. a_k be the average number of MS causing cells at different time points 1,2,……..,k respectively. Then $a_1 = e^{[\lambda_{11}-\mu_{11}]t_1}I_0, a_2 = e^{[\lambda_{12}-\mu_{12}]t_2}I_0, ..., a_k = e^{[\lambda_{1k}-\mu_{1k}]t_k}I_0$; it implies that

$$E(\bar{a}) = E\left(\frac{1}{k}\sum_{i=1}^{k}a_i\right) = \frac{1}{k}E\left(\sum_{i=1}^{k}a_i\right) = \frac{1}{k}\sum_{i=1}^{k}E(a_i) = \frac{1}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}I_0 = \frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i} \qquad (4.2.1.1.1)$$

$$E(\bar{a})^2 = E\left(\frac{1}{k}\sum_{i=1}^{k}a_i\right)^2 = \frac{1}{k^2}E\left(\sum_{i=1}^{k}a_i\right)^2 = \frac{1}{k^2}E\left(\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)^2$$

$$= \frac{I_0^2}{k^2}E\left(\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2 = \frac{I_0^2}{k^2}\left\{\sum_{i=1}^{k}E\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2 + \sum_{i\neq j=1}\sum E\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}.e^{[\lambda_{1i}-\mu_{1i}]t_j}\right)\right\}$$

$$= \frac{I_0^2}{k^2}\sum_{i=1}^{k}\left\{I_0\left[\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right]e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)^2\right\}$$

$$\therefore E(\bar{a})^2 = \frac{I_0^3}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right]e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}$$

As $V(\bar{a}) = E(\bar{a})^2 - \left[E(\bar{a})\right]^2$, Substitute $E(\bar{a})$ and $E(\bar{a})^2$ in $V(\bar{a})$, we have

$$V(\bar{a}) = \frac{I_0^3}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right]e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\} - \left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2 \qquad (4.2.1.1.2)$$

$$S.E(\bar{a}) = \left[\frac{I_0^{\,3}}{k^2} \sum_{i=1}^{k} \left\{ \left[\frac{\lambda_{1i} + \mu_{1i}}{\lambda_{1i} - \mu_{1i}} \right] e^{[\lambda_{1i} - \mu_{1i}]t_i} \left(e^{[\lambda_{1i} - \mu_{1i}]t_i} - 1 \right) + \left(e^{2[\lambda_{1i} - \mu_{1i}]t_i} I_0 \right) \right\} - \left(\frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \right)^2 \right]^{1/2}$$

(4.2.1.1.2)

Therefore the control limits for mean chart of MS causing cells are

$$E(\bar{a}) \pm 3S.E(\bar{a})$$

$$= \frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \pm 3 \left[\frac{I_0^{\,3}}{k^2} \sum_{i=1}^{k} \left\{ \left[\frac{\lambda_{1i} + \mu_{1i}}{\lambda_{1i} - \mu_{1i}} \right] e^{[\lambda_{1i} - \mu_{1i}]t_i} \left(e^{[\lambda_{1i} - \mu_{1i}]t_i} - 1 \right) + \left(e^{2[\lambda_{1i} - \mu_{1i}]t_i} I_0 \right) \right\} - \left(\frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \right)^2 \right]^{1/2}$$

Which implies

$$UCL_{\bar{X}} = \frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} + 3 \left[\frac{I_0^{\,3}}{k^2} \sum_{i=1}^{k} \left\{ \left[\frac{\lambda_{1i} + \mu_{1i}}{\lambda_{1i} - \mu_{1i}} \right] e^{[\lambda_{1i} - \mu_{1i}]t_i} \left(e^{[\lambda_{1i} - \mu_{1i}]t_i} - 1 \right) + \left(e^{2[\lambda_{1i} - \mu_{1i}]t_i} I_0 \right) \right\} - \left(\frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \right)^2 \right]^{1/2}$$

(4.2.2.1.4)

$$LCL_{\bar{X}} = \frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} - 3 \left[\frac{I_0^{\,3}}{k^2} \sum_{i=1}^{k} \left\{ \left[\frac{\lambda_{1i} + \mu_{1i}}{\lambda_{1i} - \mu_{1i}} \right] e^{[\lambda_{1i} - \mu_{1i}]t_i} \left(e^{[\lambda_{1i} - \mu_{1i}]t_i} - 1 \right) + \left(e^{2[\lambda_{1i} - \mu_{1i}]t_i} I_0 \right) \right\} - \left(\frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \right)^2 \right]^{1/2}$$

(4.2.1.1.5)

Similarly the specification limits for mean chart of MS causing cells are $E(\bar{a}) \pm (Z_{\alpha/2}) S.E(\bar{a})$ at 5% level of significance the value of ($Z_{\alpha/2}$) from the normal distribution is 1.96. Therefore the specification limits are

$$E(\bar{a}) \pm 1.96 S.E(\bar{a})$$

$$= \frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \pm 1.96 \left[\frac{I_0^{\,3}}{k^2} \sum_{i=1}^{k} \left\{ \left[\frac{\lambda_{1i} + \mu_{1i}}{\lambda_{1i} - \mu_{1i}} \right] e^{[\lambda_{1i} - \mu_{1i}]t_i} \left(e^{[\lambda_{1i} - \mu_{1i}]t_i} - 1 \right) + \left(e^{2[\lambda_{1i} - \mu_{1i}]t_i} I_0 \right) \right\} - \left(\frac{I_0}{k} \sum_{i=1}^{k} e^{[\lambda_{1i} - \mu_{1i}]t_i} \right)^2 \right]^{1/2}$$

Which implies

$$USL_{\bar{X}} = \frac{I_0}{k}\sum_{i=1}^{k} e^{[\lambda_{1i}-\mu_{1i}]t_i}$$

$$+1.96\left[\frac{I_0^3}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right]e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2}$$

(4.2.1.1.6)

$$LSL_{\bar{X}} = \frac{I_0}{k}\sum_{i=1}^{k} e^{[\lambda_{1i}-\mu_{1i}]t_i}$$

$$-1.96\left[\frac{I_0^3}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right]e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2}$$

(4.2.1.1.7)

4.2.1.2 Control and Specification Limits for Standard (Mean) of Oligodendrocytes

Let 'Y' be number of oligodendrocytes, then expected number of oligodendrocytes at time period 't' is $e^{[\lambda_2-\mu_2]t}J_0$. Where, J_0 is the initial size of oligodendrocytes. Let b_1, b_2… b_k be the average numbers of oligodendrocytes at different time points 1, 2,..., k respectively. Then $b_1 = e^{[\lambda_{21}-\mu_{21}]t_1}J_0, b_2 = e^{[\lambda_{22}-\mu_{22}]t_2}J_0, \ldots, b_k = e^{[\lambda_{2k}-\mu_{2k}]t_k}J_0$.

$$E\left(\bar{b}\right) = E\left(\frac{1}{k}\sum_{i=1}^{k}b_i\right) = \frac{1}{k}E\left(\sum_{i=1}^{k}b_i\right) = \frac{1}{k}\sum_{i=1}^{k}E\left(b_i\right) = \frac{1}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}J_0 = \frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}$$

(4.2.1.2.1)

$$E\left(\bar{b}\right)^2 = E\left(\frac{1}{k}\sum_{i=1}^{k}b_i\right)^2 = \frac{1}{k^2}E\left(\sum_{i=1}^{k}b_i\right)^2 = \frac{1}{k^2}E\left(\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)^2 = \frac{J_0^2}{k^2}E\left(\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2$$

$$= \frac{J_0^2}{k^2}\left\{\sum_{i=1}^{k}E\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2 + \sum_{i\neq j=1}\sum E\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}e^{[\lambda_{2i}-\mu_{2i}]t_j}\right)\right\}$$

$$\therefore E\left(\bar{b}\right)^2 = \frac{J_0^3}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}$$

As $V\left(\bar{b}\right) = E\left(\bar{b}\right)^2 - \left[E\left(\bar{b}\right)\right]^2$, substitute $E\left(\bar{b}\right)$ and $E\left(\bar{b}\right)^2$ in $V(\bar{b})$, we have

$$V(\bar{b}) = \frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2$$

(4.2.1.2.2)

$$S.E(\bar{b}) = \left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

(4.2.1.2.3)

Therefore the control limits for mean chart of oligodendrocytes are

$$E(\bar{b})\pm 3S.E(\bar{b})$$

$$=\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\pm 3\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

Which implies

$$UCL_{\bar{y}} = \frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i} + 3\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

(4.2.1.2.4)

$$LCL_{\bar{y}} = \frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i} - 3\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

(4.2.1.2.5)

Similarly the specification limits for mean chart of oligodendrocytes are $E(\bar{b})\pm(Z_{\alpha/2})S.E(\bar{b})$. At 5% level of significance the value of ($Z_{\alpha/2}$) from the normal distribution is 1.96. Specification limits are

$$E(\bar{b})\pm 1.96S.E(\bar{b}) =$$

$$=\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}$$

$$\pm 1.96\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

Which implies

$$USL_{\bar{y}} = \frac{J_0}{k}\sum_{i=1}^{k} e^{[\lambda_{2i}-\mu_{2i}]t_i} + 1.96\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2} \quad (4.2.1.2.6)$$

$$LSL_{\bar{y}} = \frac{J_0}{k}\sum_{i=1}^{k} e^{[\lambda_{2i}-\mu_{2i}]t_i} - 1.96\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2} \quad (4.2.1.2.7)$$

4.2.2 Control and Specification Limits for Volatility Chart

In this section, we develop the control limits for evaluating the variability conditions of disease by constructing the control charts for standard deviations for both MS spreading intensity and Oligodendrocytes expansion.

4.2.2.1 Control and Specification Limits for SD-Charts for MS Causing Cells

The general control limits for 's' chart are $E(s) \pm 3S.E(s)$

Therefore control limits for 's' chart are $\sigma_x \pm 3\sigma_x^{\,2}$

From the equation (4.2.1.1.2),

$$\sigma_x^{\,2} = \left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2$$

The control limits for Volatility of MS causing cells are

$$UCL_{\sigma x} = \left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2} + 3\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right] \quad (4.2.2.1.1)$$

$$LCL_{\sigma x}=\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2}$$

$$-3\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]$$

(4.2.2.1.2)

The specification limits for 'S' chart of MS causing cells are $E(s)\pm\left(Z_{\alpha/2}\right)S.E(s)$, at 5% level of significance the value of ($Z_{\alpha/2}$) from the normal distribution is 1.96. Specification limits are $E(s)\pm1.96S.E(s)=\sigma_x\pm1.96{\sigma_x}^2$

Which implies

$$USL_{\sigma x}=\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2}$$

$$+1.96\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]$$

(4.2.2.1.3)

$$LSL_{\sigma x}=\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]^{1/2}$$

$$-1.96\left[\left(\frac{I_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left(\frac{\lambda_{1i}+\mu_{1i}}{\lambda_{1i}-\mu_{1i}}\right)e^{[\lambda_{1i}-\mu_{1i}]t_i}\left(e^{[\lambda_{1i}-\mu_{1i}]t_i}-1\right)+\left(e^{2[\lambda_{1i}-\mu_{1i}]t_i}I_0\right)\right\}\right)-\left(\frac{I_0}{k}\sum_{i=1}^{k}e^{[\lambda_{1i}-\mu_{1i}]t_i}\right)^2\right]$$

(4.2.3.1.2)

4.2.2.2 Control and Specification Limits for S.D –Charts for Oligodendrocytes

The general control limits for 'S' chart are $E(s)\pm3S.E(s)$

Therefore 'S' chart limit are $\sigma_y\pm3{\sigma_y}^2$

From the equation (4.2.1.2.2),

$${\sigma_y}^2=\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2$$

The control limits for Volatility of oligodendrocytes are as below

$$UCL_{\sigma y}=\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

$$+3\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]$$

(4.2.2.2.1)

$$LCL_{\sigma y}=\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

$$-3\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]$$

(4.2.2.2.2)

The specification limits for 'S' chart of oligodendrocytes are $E(s)\pm(Z_{\alpha/2})S.E(s)$. At 5% level of significance the value of ($Z_{\alpha/2}$) from the normal distribution is 1.96. Specification limits are $E(s)\pm 1.96S.E(s)=\sigma_y\pm 1.96\sigma_y^{\,2}$

Which implies that

$$USL_{\sigma y}=\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

$$+1.96\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]$$

(4.2.2.2.3)

$$LSL_{\sigma y}=\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]^{1/2}$$

$$-1.96\left[\frac{J_0^{\,3}}{k^2}\sum_{i=1}^{k}\left\{\left[\frac{\lambda_{2i}+\mu_{2i}}{\lambda_{2i}-\mu_{2i}}\right]e^{[\lambda_{2i}-\mu_{2i}]t_i}\left(e^{[\lambda_{2i}-\mu_{2i}]t_i}-1\right)+\left(e^{2[\lambda_{2i}-\mu_{2i}]t_i}J_0\right)\right\}-\left(\frac{J_0}{k}\sum_{i=1}^{k}e^{[\lambda_{2i}-\mu_{2i}]t_i}\right)^2\right]$$

(4.2.2.2.4)

4.3 NUMERICAL ILLUSTRATIONS AND ANALYSIS

In this section, an attempt is made for understanding the evaluation protocols of health status with numerical illustrations. The numerical data sets are obtained by simulation techniques by using the software Mathcad 7.0 version. Sections from 4.3.1.1 to 4.3.1.6 deals with the construction and interpretation of control charts, specification charts related MS causing cells. Whereas the sections from 4.3.2.1 to 4.3.2.6 deals with construction and interpretation of control charts and specification limits related to oligodendrocytes.

Table-4.1: The expected number of MS causing cells $E(a_i)$ at different time periods

λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	T	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$
1.9	0.3	1	7.92	1.45	0.52	2	10.28	1.7	1.73	3	1.46	2.45	1.9	4	14.44	2.39	2.4	5	1.52
2.6	0.26	1	16.61	1.32	1.35	2	1.51	1.9	1.23	3	11.94	2.46	1.92	4	13.87	2.37	2.1	5	6.17
1.7	0.31	1	6.42	1.68	0.91	2	7.46	2.15	*1.6*	3	8.33	2.1	2.2	4	1.07	2.4	2.05	5	9.21
2.7	0.6	1	13.07	1.86	1.89	2	1.51	2.02	1.5	3	7.61	2.64	2.19	4	9.68	2.48	2.5	5	1.45
1.88	0.18	1	8.76	1.13	0.16	2	11.13	1.99	2.01	3	1.51	2.61	2.31	4	5.31	2	2.01	5	1.52
1.81	0.2	1	5.00	0.9	0.2	2	4.06	2.5	1.8	3	13.07	2.56	2.29	4	4.71	2.42	2.1	5	7.93
2.2	0.17	1	12.18	0.92	0.35	2	5.00	1.6	0.82	3	16.61	2.58	2.12	4	10.07	1.85	1.86	5	1.52
1.9	2.1	1	1.31	1.1	0.18	2	10.07	1.5	0.8	3	13.07	2.88	2.54	4	6.23	1.83	1.43	5	11.82
2.17	1.83	6	12.31	2.5	2.24	7	9.88	2.29	2.12	8	6.23	2.81	2.76	9	2.51	3.3	3.2	10	4.35
2.21	1.9	6	10.28	2.46	2.26	7	6.49	2.32	2.12	8	7.93	2.83	2.66	9	7.39	3.4	3.21	10	10.70
2.22	1.89	6	11.59	2.69	2.51	7	5.64	2.38	2.2	8	6.75	2.61	2.51	9	3.94	3.1	2.99	10	4.81
1.6	1.62	6	1.42	2.7	2.71	7	1.49	2.15	1.9	8	11.82	2.92	2.93	9	1.46	3.42	3.44	10	1.31
1.87	1.63	6	6.75	1.95	1.95	7	1.60	2.09	2.1	8	1.48	2.85	2.87	9	1.34	2.96	2.8	10	7.93
1.92	1.61	6	10.28	1.97	1.87	7	3.22	2.33	2.12	8	8.59	2.87	2.65	9	11.59	2.81	2.77	10	2.39
2.1	2.13	6	1.34	2.21	1.97	7	8.59	2.08	2.13	8	1.07	2.79	2.6	9	8.85	3.32	3.2	10	5.31
2.2	2.24	6	1.26	2.25	2.06	7	6.05	2.35	2.15	8	7.93	2.12	2.14	9	9.68	3.18	3.12	10	2.92
3.2	3.12	11	3.86	2.61	2.46	12	9.68	2.51	2.38	13	8.67	2.25	2.12	14	9.88	1.55	1.45	15	7.17
3.35	3.21	11	7.46	2.52	2.49	12	2.29	2.58	2.47	13	6.69	2.12	2.13	14	1.39	1.58	1.46	15	9.68

λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$	λ_{1i}	μ_{1i}	t	$E(a_i)$
3.19	3.2	11	1.43	2.49	2.4	12	4.71	2.55	2.42	13	8.67	2.15	2.12	14	2.44	1.54	1.42	15	9.68
3.23	3.1	11	6.69	2.7	2.59	12	5.99	2.62	2.47	13	11.25	2.28	2.17	14	7.46	1.5	1.39	15	8.33
3.4	3.28	11	5.99	2.6	2.62	12	1.26	2.57	2.48	13	5.16	2.23	2.15	14	4.90	1.47	1.5	15	1.02
3.49	3.29	11	14.44	2.54	2.5	12	2.59	2.5	2.53	13	1.08	2.21	2.23	14	1.21	1.52	1.41	15	8.33
3.33	3.21	11	5.99	2.59	2.45	12	8.59	2.48	2.37	13	6.69	2.24	2.19	14	3.22	1.62	1.54	15	5.31
3.31	3.25	11	3.10	2.56	2.44	12	6.75	2.45	2.3	13	11.25	2.6	2.5	14	6.49	1.58	1.49	15	6.17

Table 4.2: Summarized values of table 4.1

S.No	t_1=1	t_2=2	t_3=3	t_4=4	t_5=5	t_6=6	t_7=7	t_8=8	t_9=9	t_{10}=10	t_{11}=11	t_{12}=12	t_{13}=13	t_{14}=14	t_{15}=15
1	7.92	10.28	1.46	14.44	1.52	12.31	9.88	6.23	2.51	4.35	3.86	9.68	8.67	9.88	7.17
2	16.61	1.51	11.94	13.87	6.17	10.28	6.49	7.93	7.39	10.70	7.46	2.29	6.69	1.39	9.68
3	6.42	7.46	8.33	1.07	9.21	11.59	5.64	6.75	3.94	4.81	1.43	4.71	8.67	2.44	9.68
4	13.07	1.51	7.61	9.68	1.45	1.42	1.49	11.82	1.46	1.31	6.69	5.99	11.25	7.46	8.33
5	8.76	11.13	1.51	5.31	1.52	6.75	1.60	1.48	1.34	7.93	5.99	1.26	5.16	4.90	1.02
6	5.00	4.06	13.07	4.71	7.93	10.28	3.22	8.59	11.59	2.39	14.44	2.59	1.08	1.21	8.33
7	12.18	5.00	16.61	10.07	1.52	1.34	8.59	1.07	8.85	5.31	5.99	8.59	6.69	3.22	5.31
8	1.31	10.07	13.07	6.23	11.82	1.26	6.05	7.93	9.68	2.92	3.10	6.75	11.25	6.49	6.17
Means	8.91	6.38	9.20	8.17	5.14	6.90	5.37	6.47	5.84	4.96	6.12	5.23	7.43	4.62	6.96
S.D	4.89	3.92	5.54	4.66	4.19	4.88	3.08	3.62	4.02	3.08	3.92	3.06	3.35	3.12	2.86

4.3.1.1 Control Charts for Standard of MS Causing Cells (control limits are through natural tolerance/data sets)

Here, the sample observations are considered from the data in tables (4.1) and (4.2). The control limits are calculated by using the concept of natural tolerance.From the table 4.2, the calculated means at various time points of MS causing cells are 8.91, 6.38, 9.2, 8.17, 5.14, 6.9, 5.37, 6.47, 5.84, 4.96, 6.12, 5.23, 7.43, 4.62, and 6.96

n= sample size=8; Overall mean $E(\bar{X})$=6.51; Overall standard deviation (S.D)=3.97

Control limits of mean chart is $E(\bar{X}) \pm 3S.E(\bar{X})$, which provides

The Upper control limit (UCL) = $UCL_{\bar{x}}$ = 10.72

The lower control limit (LCL) = $LCL_{\bar{x}}$ = 2.31

Central limit (CL) = $CL_{\bar{x}}$ = 6.51

Table:-4.2.1

t_i	Means	UCL	LCL	CL
1	8.91	10.72	2.31	6.51
2	6.38	10.72	2.31	6.51
3	9.20	10.72	2.31	6.51
4	8.17	10.72	2.31	6.51
5	5.14	10.72	2.31	6.51
6	6.90	10.72	2.31	6.51
7	5.37	10.72	2.31	6.51
8	6.47	10.72	2.31	6.51
9	5.84	10.72	2.31	6.51
10	4.96	10.72	2.31	6.51
11	6.12	10.72	2.31	6.51
12	5.23	10.72	2.31	6.51
13	7.43	10.72	2.31	6.51
14	4.62	10.72	2.31	6.51
15	6.96	10.72	2.31	6.51

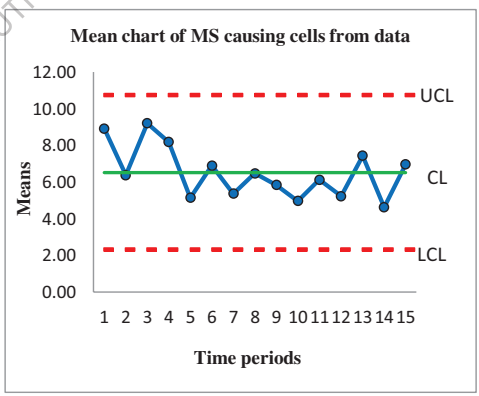

Figure 4.2.1

From the table 4.2.1 and figure 4.2.1, it is observed that the process of standard (average number) of MS causing cells is under control.

4.3.1.2 Control Chart for Standards of MS Causing cells (control limits are through theoretical devices)

Here the sample observations are obtained from Table 4.1 and 4.2. The control limits are calculated by the formula $UCL_{\bar{X}}$ (4.2.2.1.4) and $LCL_{\bar{X}}$ (4.2.2.1.5)

Let us consider, I_0= 1.6, k=1, 2,.., 15, t_i=1,2,…, 15; i=1,2,…,15

λ_{1i}=2.09, 1.35, 1.91, 2.54, 2.22, 2.01, 2.34, 2.19, 2.93, 2.1, 3.31, 2.52, 2.49, 2.26 and 1.4

μ_{1i}=2.1, 0.9, 1.89, 2.51, 2.2, 1.96, 2.2, 2.18, 3.1, 2.31, 3.29, 2.51, 2.48, 2.28 and 1.52

The derived control limits for MS causing cells from (4.2.2.1.4) and (4.2.2.1.5) are

$UCL_{\bar{X}}$ =10.63;

$LCL_{\bar{X}}$ =-7.09, since number of MS causing cells≥0, then $LCL_{\bar{X}}$ =0 and $CL_{\bar{X}}$ =6.51

Table:-4.2.2

t_i	Mean	UCL	LCL	CL
1	8.91	10.63	0	6.51
2	6.38	10.63	0	6.51
3	9.20	10.63	0	6.51
4	8.17	10.63	0	6.51
5	5.14	10.63	0	6.51
6	6.90	10.63	0	6.51
7	5.37	10.63	0	6.51
8	6.47	10.63	0	6.51
9	5.84	10.63	0	6.51
10	4.96	10.63	0	6.51
11	6.12	10.63	0	6.51
12	5.23	10.63	0	6.51
13	7.43	10.63	0	6.51
14	4.62	10.63	0	6.51
15	6.96	10.63	0	6.51

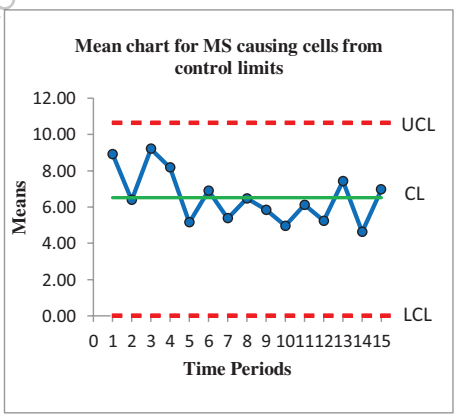

Figure 4.2.2

From the table 4.2.2 and figure 4.2.2, it is observed that the process of standard (average) of MS causing cells is under control.

4.3.1.3 Specification Chart (specification limits at 5% level of significance)

Here the sample data source is from the tables 4.1 and 4.2. However specification limits are computed by getting mean and standard error from the data sets.

Let us consider I_0= 1.6, k=1, 2,.., 15, t_i=1,2,…, 15; i=1,2,…,15

λ_{1i}=2.09, 1.35, 1.91, 2.54, 2.22, 2.01, 2.34, 2.19, 2.93, 2.1, 3.31, 2.52, 2.49, 2.26 and 1.4

μ_{1i}=2.1, 0.9, 1.89, 2.51, 2.2, 1.96, 2.2, 2.18, 3.1, 2.31, 3.29, 2.51, 2.48, 2.28 and 1.52

The computed specification limits of MS causing cells at 5% level of significance are from the relations $USL_{\bar{X}}$ (4.2.2.16) and $LSL_{\bar{X}}$ (4.2.2.17)

$USL_{\bar{X}}$ =7.56 and $LSL_{\bar{X}}$ =-4.02, since number of MS causing cells≥0, then $LSL_{\bar{X}}$ =0 and $CL_{\bar{X}}$ =6.51

Table:-4.2.3

t_i	Mean	USL	LSL	CL
1	8.91	7.56	0	6.51
2	6.38	7.56	0	6.51
3	9.20	7.56	0	6.51
4	8.17	7.56	0	6.51
5	5.14	7.56	0	6.51
6	6.90	7.56	0	6.51
7	5.37	7.56	0	6.51
8	6.47	7.56	0	6.51
9	5.84	7.56	0	6.51
10	4.96	7.56	0	6.51
11	6.12	7.56	0	6.51
12	5.23	7.56	0	6.51
13	7.43	7.56	0	6.51
14	4.62	7.56	0	6.51
15	6.96	7.56	0	6.51

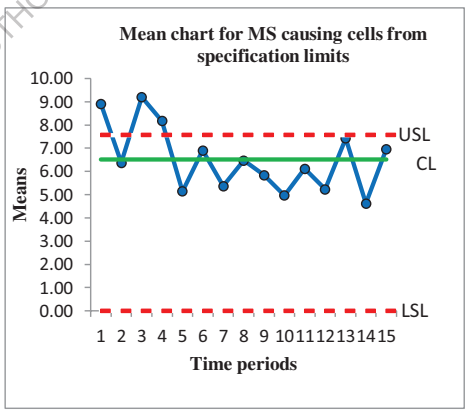

Figure 4.2.3

From the table 4.2.3 and figure 4.2.3, it is observed that the process quality standard (mean) of MS causing cells is out of control in mean chart of specification limits at 5% level of significance.

4.3.1.4 Control Charts for Volatility of MS Causing Cells (control limits are through process capability from the data sets)

Here, the sample data is considered as in the Table 4.1 and 4.2. The control limits are constructed using natural tolerance procedure. i.e., Mean and S.D are obtained through data sets.From the table 4.1, the calculated standard deviations (S.D) at various time points of MS causing sells are 4.89, 3.92, 5.54, 4.66, 4.19, 4.88, 3.08, 3.62, 4.02, 3.08, 3.92, 3.06, 3.35, 3.12 and 2.86

Sample size (n)=8; $E(S) = \bar{s} = 3.88$ and variance (s^2)=15.74

Therefore control limits for 'S' chart are 3.88±15.74(0.5)

The upper control limit (UCL) =3.88+15.74(0.5)=11.75

The lower control limit (LCL) =3.88-15.74(0.5)= -3.99, since $\sigma_x \geq 0$ then LCL=0

Central limit (CL)=3.88

Table:-4.2.4

t_i	S.D	UCL	LCL	CL
1	4.89	11.75	0	3.88
2	3.92	11.75	0	3.88
3	5.54	11.75	0	3.88
4	4.66	11.75	0	3.88
5	4.19	11.75	0	3.88
6	4.88	11.75	0	3.88
7	3.08	11.75	0	3.88
8	3.62	11.75	0	3.88
9	4.02	11.75	0	3.88
10	3.08	11.75	0	3.88
11	3.92	11.75	0	3.88
12	3.06	11.75	0	3.88
13	3.35	11.75	0	3.88
14	3.12	11.75	0	3.88
15	2.86	11.75	0	3.88

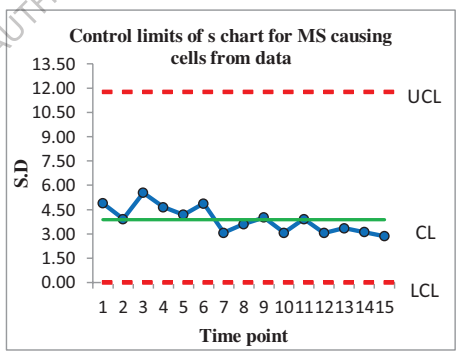

Figure 4.2.4

From the table 4.2.4 and figure 4.2.4, it is observed that the process quality on Volatility of MS causing cells is under control.

4.3.1.5 Control chart for volatility of MS causing cells (control limits are obtained through theoretical devices)

Here, the sample data mentioned in Table 4.1 and 4.2 are considered for computing S.D's of each sample. For computing UCL and LCL, we have consider (4.2.3.1.1) and (4.2.3.1.2). Let us consider I_0=1.6, k=1,2,..,15, t_i=1,2,…, 15; i=1,2,…,15

λ_{1i}=2.09, 1.35, 1.91, 2.54, 2.22, 2.01, 2.34, 2.19, 2.93, 2.1, 3.31, 2.52, 2.49, 2.26 and 1.4

μ_{1i}=2.1, 0.9, 1.89, 2.51, 2.2, 1.96, 2.2, 2.18, 3.1, 2.31, 3.29, 2.51, 2.48, 2.28 and 1.52

The control limits for volatility of MS causing cells obtained from (4.2.3.1.1) and (4.2.3.1.2)

$UCL_{\sigma x} = 16.04$

$LCL_{\sigma x} = -23.21$, since $\sigma_x \geq 0$ that implies $LCL\sigma_x = 0$, $CL_{\sigma x} = 3.88$

Table:-4.2.5

t_i	S.D	$UCL\sigma_x$	$LCL\sigma_x$	$CL\sigma_x$
1	4.89	29.12	0	3.88
2	3.92	29.12	0	3.88
3	5.54	29.12	0	3.88
4	4.66	29.12	0	3.88
5	4.19	29.12	0	3.88
6	4.88	29.12	0	3.88
7	3.08	29.12	0	3.88
8	3.62	29.12	0	3.88
9	4.02	29.12	0	3.88
10	3.08	29.12	0	3.88
11	3.92	29.12	0	3.88
12	3.06	29.12	0	3.88
13	3.35	29.12	0	3.88
14	3.12	29.12	0	3.88
15	2.86	29.12	0	3.88

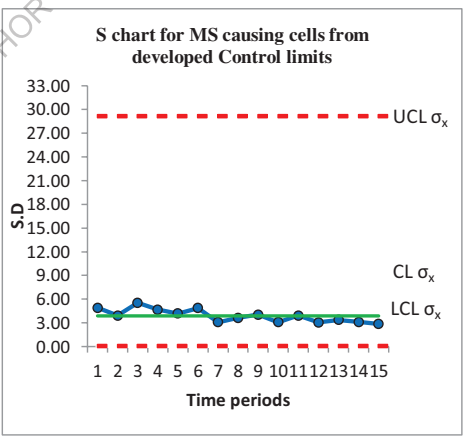

Figure 4.2.5

From the table 4.2.5 and figure 4.2.5, it is observed that the quality process on volatility of MS causing cells is under control.

4.3.1.6 Specification Chart on Volatility of MS Causing Cells with S.D (specification limits through theoretical devices)

Here, the data is from tables 4.1 and 4.2, whereas specification limits are obtained through (4.2.3.1.3) and (4.2.3.1.4). Let us consider I_0=1.6, i, k=1,2,..,15, t_i=1,2,…, 15;

λ_{1i}=2.09, 1.35, 1.91, 2.54, 2.22, 2.01, 2.34, 2.19, 2.93, 2.1, 3.31, 2.52, 2.49, 2.26 and 1.4

μ_{1i}=2.1, 0.9, 1.89, 2.51, 2.2, 1.96, 2.2, 2.18, 3.1, 2.31, 3.29, 2.51, 2.48, 2.28 and 1.52

The specification limits for volatility of MS causing cells obtained from the relations (4.2.3.1.3) and (4.2.3.1.4)

$USL_{\sigma x}$ = 11.5

$LSL_{\sigma x}$ =-14.14, since $\sigma_x \geq 0$, then LSL σ_x =0 and CL σ_x =3.88

Table:-4.2.6

t_i	S.D	USLσ_x	LSLσ_x	CLσ_x
1	4.89	20.05	0	3.88
2	3.92	20.05	0	3.88
3	5.54	20.05	0	3.88
4	4.66	20.05	0	3.88
5	4.19	20.05	0	3.88
6	4.88	20.05	0	3.88
7	3.08	20.05	0	3.88
8	3.62	20.05	0	3.88
9	4.02	20.05	0	3.88
10	3.08	20.05	0	3.88
11	3.92	20.05	0	3.88
12	3.06	20.05	0	3.88
13	3.35	20.05	0	3.88
14	3.12	20.05	0	3.88
15	2.86	20.05	0	3.88

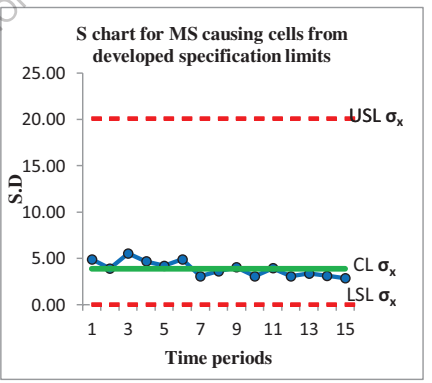

Figure 4.2.6

From the table 4.2.6 and figure 4.2.6, it is observed that the process quality on volatility of MS causing cells is under specification limits at 5% level of significance.

Table-4.3: The expected number of oligodendrocytes $E(b_i)$ at different time periods

λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$
2.5	1.2	1	5.14	1.6	1.7	2	1.15	2.31	1.8	3	6.47	2.26	1.9	4	5.91	2.45	2.12	5	7.29
2.47	1.3	1	4.51	2.35	1.5	2	7.66	2.32	1.78	3	7.07	2.16	1.85	4	4.84	2.49	2.22	5	5.40
2.4	1.15	1	4.89	2.24	1.6	2	5.04	2.3	1.82	3	5.91	2.1	1.86	4	3.66	2.6	2.62	5	1.27
2.61	1.2	1	5.73	2.41	1.68	2	6.03	2.28	1.66	3	8.99	2.55	2.1	4	8.47	2.58	2.26	5	6.93
2.53	2.55	1	1.37	2.46	1.56	2	8.47	2.26	1.69	3	7.74	2.4	2	4	6.93	2.54	2.21	5	7.29
2.63	1.86	1	3.02	1.96	1.57	2	3.05	2.26	1.8	3	5.57	2.42	2.43	4	1.35	2.59	2.25	5	7.66
2.66	1.96	1	2.82	1.95	1.58	2	2.93	2.38	1.78	3	8.47	2.36	2.1	4	3.96	2.57	2.22	5	8.06
2.59	1.6	1	3.77	2.45	1.66	2	6.80	2.15	1.62	3	6.87	2.6	2.3	4	4.65	2.4	2.18	5	4.21
1.56	1.32	6	5.91	2.34	2.12	7	6.53	3.1	2.87	8	8.82	1.6	1.42	9	7.07	2.66	2.5	10	6.93
1.42	1.26	6	3.66	2.36	2.1	7	8.64	2.8	2.6	8	6.93	1.82	1.63	9	7.74	2.67	2.49	10	8.47
1.41	1.25	6	3.66	2.35	2.2	7	4.00	3.52	3.3	8	8.14	1.87	1.75	9	4.12	2.48	2.33	10	6.27
1.96	1.71	6	6.27	2.42	2.22	7	5.68	3.5	3.29	8	7.51	1.84	1.68	9	5.91	2.47	2.34	10	5.14
1.98	1.7	6	7.51	2.45	2.26	7	5.29	3.48	3.31	8	5.46	1.95	1.96	9	1.28	2.64	2.46	10	8.47
1.92	1.72	6	4.65	2.42	2.19	7	7.00	3.62	3.4	8	8.14	1.9	1.74	9	5.91	2.56	2.4	10	6.93
1.94	1.96	6	1.24	2.33	2.18	7	4.00	3.53	3.38	8	4.65	1.89	1.75	9	4.94	2.59	2.5	10	3.44
1.85	1.68	6	3.88	2.48	2.51	7	1.14	3.56	3.35	8	7.51	2.1	1.92	9	7.07	2.77	2.6	10	7.66
3.18	3.1	11	3.38	3.26	3.19	12	3.24	2.99	2.86	13	7.59	2.72	2.73	14	1.22	2.5	2.39	15	7.29
λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$	λ_{2i}	μ_{2i}	t	$E(b_i)$
3.1	2.95	11	7.29	3.31	3.21	12	4.65	3.1	2.96	13	8.64	2.85	2.74	14	6.53	2.41	2.31	15	6.27

3.15	3.17	11	1.12	3.34	3.2	12	7.51	2.86	2.75	13	5.85	2.82	2.72	14	5.68	2.56	2.46	15	6.27
3.36	3.2	11	8.14	3.36	3.25	12	5.24	2.88	2.76	13	6.66	2.8	2.68	14	7.51	2.63	2.52	15	7.29
3.29	3.22	11	3.02	3.39	3.26	12	6.66	2.82	2.72	13	5.14	2.82	2.71	14	6.53	2.58	2.47	15	7.29
3.35	3.21	11	6.53	3.18	3.11	12	3.24	2.8	2.66	13	8.64	2.92	2.81	14	6.53	2.58	2.48	15	6.27
3.11	3.01	11	4.21	3.05	3	12	2.55	2.87	2.74	13	7.59	2.72	2.6	14	7.51	2.45	2.33	15	8.47
3.23	3.12	11	4.70	3.43	3.33	12	4.65	2.89	2.75	13	8.64	2.66	2.55	14	6.53	2.51	2.41	15	6.27

Table 4.4: Summarized values of table 4.3

S.No	t_1=1	t_2=2	t_3=3	t_4=4	t_5=5	t_6=6	t_7=7	t_8=8	t_9=9	t_{10}=10	t_{11}=11	t_{12}=12	t_{13}=13	t_{14}=14	t_{15}=15
1	5.14	1.15	6.47	5.91	7.29	5.91	6.53	8.82	7.07	6.93	3.38	3.24	7.59	1.22	7.29
2	4.51	7.66	7.07	4.84	5.40	3.66	8.64	6.93	7.74	8.47	7.29	4.65	8.64	6.53	6.27
3	4.89	5.04	5.91	3.66	1.27	3.66	4.00	8.14	4.12	6.27	1.12	7.51	5.85	5.68	6.27
4	5.73	6.03	8.99	8.47	6.93	6.27	5.68	7.51	5.91	5.14	8.14	5.24	6.66	7.51	7.29
5	1.37	8.47	7.74	6.93	7.29	7.51	5.29	5.46	1.28	8.47	3.02	6.66	5.14	6.53	7.29
6	3.02	3.05	5.57	1.35	7.66	4.65	7.00	8.14	5.91	6.93	6.53	3.24	8.64	6.53	6.27
7	2.82	2.93	8.47	3.96	8.06	1.24	4.00	4.65	4.94	3.44	4.21	2.55	7.59	7.51	8.47
8	3.77	6.80	6.87	4.65	4.21	3.88	1.14	7.51	7.07	7.66	4.70	4.65	8.64	6.53	6.27
Means	3.91	5.14	7.14	4.97	6.01	4.60	5.29	7.14	5.51	6.67	4.81	4.72	7.34	6.00	6.93
S.D	1.44	2.57	1.20	2.17	2.30	1.95	2.28	1.42	2.08	1.71	2.37	1.73	1.35	2.02	0.80

4.3.2.1 Control Charts for Standard (Mean) of Oligodendrocytes (control limits are through natural tolerance/data sets)

Here, the sample observations are considered from the data in tables (4.3) and (4.4). The control limits are calculated through the concept of natural tolerance. From the table 4.4, the calculated means at various time points are 3.91, 5.14, 7.14, 4.97, 6.01, 4.6, 5.29, 7.14, 5.51, 6.67, 4.81, 4.72, 7.34, 6 and 6.93. Sample size=8; Overall mean $E(\bar{X})$ =5.74; Overall standard deviation (S.D)=2.07

Control limits of mean chart is $E(\bar{Y}) \pm 3S.E(\bar{Y})$

Here, Upper control limit (UCL) = $UCL_{\bar{y}} = 7.94$

Lower control limit (LCL) = $LCL_{\bar{y}} = 3.55$

Central limit (CL) = $CL_{\bar{y}} = 5.74$

Table:-4.4.1

t_i	Means	UCL	LCL	CL
1	3.91	7.94	3.55	5.74
2	5.14	7.94	3.55	5.74
3	7.14	7.94	3.55	5.74
4	4.97	7.94	3.55	5.74
5	6.01	7.94	3.55	5.74
6	4.60	7.94	3.55	5.74
7	5.29	7.94	3.55	5.74
8	7.14	7.94	3.55	5.74
9	5.51	7.94	3.55	5.74
10	6.67	7.94	3.55	5.74
11	4.81	7.94	3.55	5.74
12	4.72	7.94	3.55	5.74
13	7.34	7.94	3.55	5.74
14	6.00	7.94	3.55	5.74
15	6.93	7.94	3.55	5.74

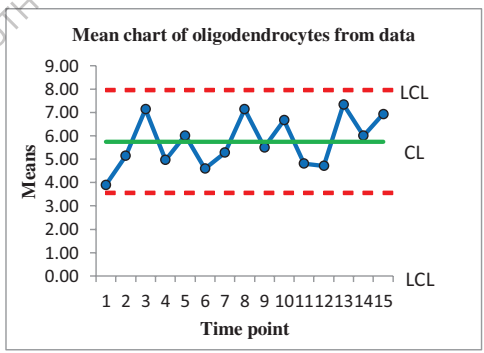

Figure 4.4.1

From the table 4.4.1 and figure 4.4.1, it is observed that average number of oligodendrocytes is under the control in mean chart.

4.3.2.2 Control Chart for Process Standard (Mean) of Oligodendrocytes (control limits are through theoretical devices)

Here the sample observations are obtained from Table (4.3) and (4.4). The control limits are calculated by the formulae $UCL_{\bar{y}}$ and $LCL_{\bar{y}}$.

J_0= 1.4, k=1,2,..,15, t_i=1,2,…, 15; i=1,2,…,15

λ_{2i}=3.68, 1.82, 1.82, 2.33, 2.36, 1.76, 2.39, 3.39, 1.87, 2.61, 3.22, 3.29, 2.9, 2.66 and 2.45

μ_{2i}=2.1, 1, 1.46, 2.1, 2.32, 1.79, 2.35, 3.34, 1.83, 2.59, 3.19, 3.26, 2.89, 2.81 and 2.42

The developed control limits for mean number of oligodendrocytes are from the relations (4.2.2.2.4) and (4.2.2.2.5)

$UCL_{\bar{y}}$=10.76; $LCL_{\bar{y}}$=-5.57, since the number of oligodendrocytes≥0, then $LSL_{\bar{y}}$=0; $CL_{\bar{y}}$ =5.74

Table:-4.4.2

t_i	Means	UCL	LCL	CL
1	3.91	10.76	0	5.74
2	5.14	10.76	0	5.74
3	7.14	10.76	0	5.74
4	4.97	10.76	0	5.74
5	6.01	10.76	0	5.74
6	4.60	10.76	0	5.74
7	5.29	10.76	0	5.74
8	7.14	10.76	0	5.74
9	5.51	10.76	0	5.74
10	6.67	10.76	0	5.74
11	4.81	10.76	0	5.74
12	4.72	10.76	0	5.74
13	7.34	10.76	0	5.74
14	6.00	10.76	0	5.74
15	6.93	10.76	0	5.74

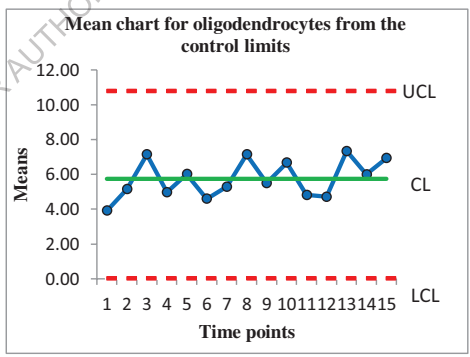

Figure 4.4.2

From the table 4.4.2 and figure 4.4.2, it is observed that average number of oligodendrocytes is under the control limits. It implies that the process quality standard (mean number) of oligodendrocytes is according to process capability of the patient.

4.3.2.3 Specification Chart for Process Quality Standard (mean number) of Oligodendrocytes

Here, the mean and standard error are obtained from the sample data of table 4.3, whereas process quality specification limits for mean number of oligodendrocytes are constructed at 5 % level of significance. For calculating them, we have considered the theoretical relations $USL_{\bar{y}}$ (4.2.2.2.6) and $LSL_{\bar{y}}$ (4.2.2.2.7)

Let us consider J_0= 1.4, k=1,2,..,15, t_i=1,2,…, 15; i=1,2,…,15

λ_{2i}=3.68, 1.82, 1.82, 2.33, 2.36, 1.76, 2.39, 3.39, 1.87, 2.61, 3.22, 3.29, 2.9, 2.66 and 2.45

μ_{2i}=2.1, 1, 1.46, 2.1, 2.32, 1.79, 2.35, 3.34, 1.83, 2.59, 3.19, 3.26, 2.89, 2.81 and 2.42

The computed specification limits for oligodendrocytes are

$USL_{\bar{y}}$ =7.93; $LSL_{\bar{y}}$ =-274, since the number of oligodendrocytes≥0, then $LSL_{\bar{y}}$ =0 and $CL_{\bar{y}}$ =5.74

Table:-4.4.3

t_i	Means	USL	LSL	CL
1	3.91	7.93	0	5.74
2	5.14	7.93	0	5.74
3	7.14	7.93	0	5.74
4	4.97	7.93	0	5.74
5	6.01	7.93	0	5.74
6	4.60	7.93	0	5.74
7	5.29	7.93	0	5.74
8	7.14	7.93	0	5.74
9	5.51	7.93	0	5.74
10	6.67	7.93	0	5.74
11	4.81	7.93	0	5.74
12	4.72	7.93	0	5.74
13	7.34	7.93	0	5.74
14	6.00	7.93	0	5.74
15	6.93	7.93	0	5.74

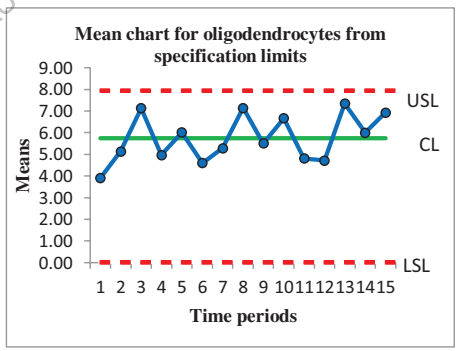

Figure 4.4.3

From the table (4.4.3) and figure (4.4.3), it is observed that average number of oligodendrocytes is under specification limits process standards. Hence, it implies that the

process quality standard (mean number) of oligodendrocytes is meeting the specific quality standard at 5% level of significance.

4.3.2.4 Control Chart for Process Quality Volatility (S.D) of Oligodendrocytes (control limits through natural tolerance)

Here, the sample data for calculating average standard deviation and standard error of standard deviation is obtained from table 4.3. The control limits are calculated through usual process capability or natural tolerance concepts. From the table 4.4 the calculated standard deviations (S.D) at various time points are 1.44, 2.57, 1.2, 2.17, 2.3, 1.95, 2.28, 1.42, 2.08, 1.71, 2.37, 1.73, 1.35, 2.02 and 0.8;

The sample size n=8; $E(S) = \bar{s} = 1.83$; variance (s^2)=4.28

Therefore 'S' chart limits are 1.83±4.28(0.5)

The upper control limit of S.D=UCL σ_y =3.97

The lower control limitof S.D=LCL σ_y =-0.31, since $\sigma_y \geq 0$, thenLCL σ_y =0

Central line =CL σ_y =1.83

Table:-4.4.4

t_i	S.D	UCLσ_y	LCLσ_y	CLσ_y
1	1.44	3.97	0	1.83
2	2.57	3.97	0	1.83
3	1.20	3.97	0	1.83
4	2.17	3.97	0	1.83
5	2.30	3.97	0	1.83
6	1.95	3.97	0	1.83
7	2.28	3.97	0	1.83
8	1.42	3.97	0	1.83
9	2.08	3.97	0	1.83
10	1.71	3.97	0	1.83
11	2.37	3.97	0	1.83
12	1.73	3.97	0	1.83
13	1.35	3.97	0	1.83
14	2.02	3.97	0	1.83
15	0.80	3.97	0	1.83

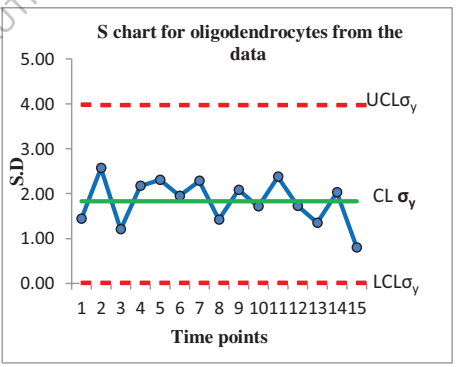

Figure 4.4.4

From the table 4.4.4 and figure 4.4.4, it is observed that standard deviation of number of oligodendrocytes is under the control. Hence, it implies that the process quality volatility (S.D) of oligodendrocytes is under control.

4.3.2.5 Control Chart for Process Quality Volatility (S.D) of Oligodendrocytes(control limits through theoretical relations)

Here, the sample data in table 4.3 is considered for computing mean of S.D and S.E of standard deviation. For computing the control limits, the relations (4.2.3.2.1) and (4.2.3.2.2) are considered. Let us consider J_0= 1.4, k=1,2,..,15, t_i=1,2,…, 15; i=1,2,…,15

λ_{2i}=3.68, 1.82, 1.82, 2.33, 2.36, 1.76, 2.39, 3.39, 1.87, 2.61, 3.22, 3.29, 2.9, 2.66 and 2.45

μ_{2i}=2.1, 1, 1.46, 2.1, 2.32, 1.79, 2.35, 3.34, 1.83, 2.59, 3.19, 3.26, 2.89, 2.81 and 2.42

The computed control limits for volatility of oligodendrocytes are

$UCL_{\sigma y}$ =24.95; $LCL_{\sigma y}$ =-19.51, since $\sigma_y \geq 0$, then LCL σ_y =0and CL σ_y =1.83

Table:-4.4.5

t_i	S.D	UCLσ_y	LCLσ_y	CLσ_y
1	1.44	24.95	0	1.83
2	2.57	24.95	0	1.83
3	1.20	24.95	0	1.83
4	2.17	24.95	0	1.83
5	2.30	24.95	0	1.83
6	1.95	24.95	0	1.83
7	2.28	24.95	0	1.83
8	1.42	24.95	0	1.83
9	2.08	24.95	0	1.83
10	1.71	24.95	0	1.83
11	2.37	24.95	0	1.83
12	1.73	24.95	0	1.83
13	1.35	24.95	0	1.83
14	2.02	24.95	0	1.83
15	0.80	24.95	0	1.83

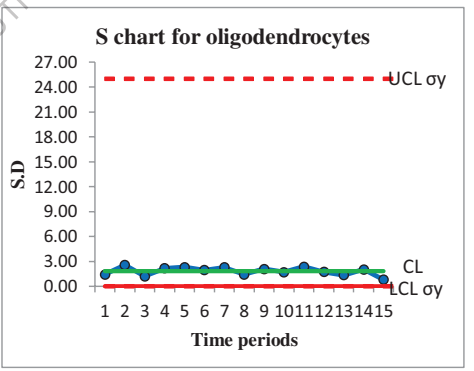

Figure 4.4.5

From the table 4.4.5 and figure 4.4.5, it is observed that standard deviation of oligodendrocytes is under control. Hence, it implies that the process volatility of oligodendrocytes is under control.

4.3.2.6 Specification chart for process quality volatility (S.D) of oligodendrocytes

Here, the average of S.D and S.E of S.D are obtained from the sample data in table 4.3. While computing the USL and LSL of volatility, we have considered the theoretical relations (4.2.3.2.3) and (4.2.3.2.4). Let us consider J_0= 1.4, k=1,2,..,15, t_i=1,2,…, 15; i=1,2,…,15

λ_{2i}=3.68, 1.82, 1.82, 2.33, 2.36, 1.76, 2.39, 3.39, 1.87, 2.61, 3.22, 3.29, 2.9, 2.66 and 2.45

μ_{2i}=2.1, 1, 1.46, 2.1, 2.32, 1.79, 2.35, 3.34, 1.83, 2.59, 3.19, 3.26, 2.89, 2.81 and 2.42

The computed specification limits for volatility of oligodendrocytes are

$USL_{\sigma y}$=17.25; $LSL_{\sigma y}$=-11.8, since $\sigma_y \geq 0$ then LSL σ_y =0 and CL σ_y=1.83

Table:-4.4.6

t_i	S.D	USLσ_y	LSLσ_y	CL σ_y
1	1.44	17.25	0	1.83
2	2.57	17.25	0	1.83
3	1.20	17.25	0	1.83
4	2.17	17.25	0	1.83
5	2.30	17.25	0	1.83
6	1.95	17.25	0	1.83
7	2.28	17.25	0	1.83
8	1.42	17.25	0	1.83
9	2.08	17.25	0	1.83
10	1.71	17.25	0	1.83
11	2.37	17.25	0	1.83
12	1.73	17.25	0	1.83
13	1.35	17.25	0	1.83
14	2.02	17.25	0	1.83
15	0.80	17.25	0	1.83

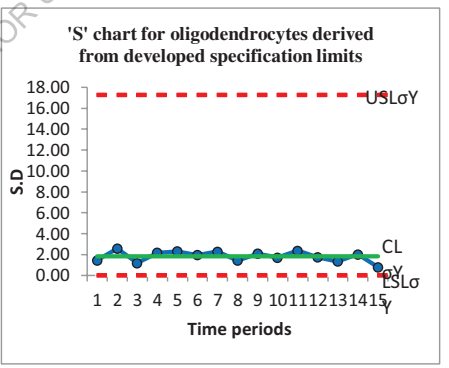

Figure 4.4.6

From the table 4.4.6 and figure 4.4.6, it is observed that standard deviation of oligodendrocytes is under specification limits. Hence, it implies that the process volatility of oligodendrocytes is according to the specifications of the quality of 5% level of significance.

CHAPTER-5

SUMMARY AND CONCLUSIONS

In this chapter, the brief presentation on total activity of thesis is given. This chapter is intended to present the study findings along with the future scope of the work. Multiple sclerosis is a neurological disease which is of more concern due to its complications. People are not much aware of the spread aspects of this disease as it is not much handled clinically. Understanding the severity of this problem through mathematical modeling is the main theme behind the work.

5.1 Summary on Chapter-1

In chapter one, the overview on disease related issues were presented. Brief information on Immune systems of the body and working networks of various subsystems of the immunity were discussed. The concepts on how a human body is self sustainable to handle the hazardous situations when either foreign cells or any pathogen such as a virus, bacteria, fungus etc. invaded to the existing setup. The network with organs, tissue, cells and bio molecules and its actions to defend the body against things that are non self are explained. The types of immunity and their functioning for crisis management during ill health to the body were briefed. The immunity memory issues and their reactions during the needy time were also presented. The leukocytes or WBC acts on three fold with phagocytes, lymphocytes, and auxiliary cells is crucial in working nature of these cells has unique mechanism for defense, detecting and interacting antigens. These are immune stimulating components of foreign substances. Each immune cell is also able to interact with other immune cells to heighten or suppress the immune response. The immune responses depend on lymphocytes primarily B-cells and T-cells were discussed. Being MS is neuro related health problem it absolutely acts with the central nervous system (CNS), which is made up of the brain and spinal cord. These components are responsible for coordinating the senses of the touch, taste, smell, sight, and hearing with appropriate response. The types of cells in CNS namely Neurons and Glia cells for generation of astrocytes, oligodendrocytes and microglia was presented. The information on how impulses creation among nerve cells, actions and reactions related to neurons stimulated by mechanical force, pain, heat, light or chemical reactions, etc. were discussed.

This chapter has provided the brief information on the very meaning, the nature, generation, expansion/spread, and types of Multiple Sclerosis. The symptoms, remedial measures to deal the MS problem were discussed. The volatile and defend materials of neuro related diseases due to the inflammatory episodes in CNS, discolorations in the myelinated white matter of brain, neuronal degeneration and loss of mobility were discussed. The roles of Axon, Myelin, Oligodendrocytes, specialized lipids and proteins were explained. The nature and behaviour of 4 types MS namely Relapsing-remitting MS (RRMS), Secondary progressive MS (SPMS), Progressive Relapsing MS (PRMS) and Primary progressive MS (PPMS) were briefed.

The three types of symptoms of MS primary, secondary and tertiary and their quantification methods were discussed. Laboratory study methods of MS with magnetic resonance imaging (MRI), Cerebrospinal fluid (CSF), were briefed. The conceptual developments on Pathogenesis and mathematical modeling issues were overviewed. The mechanism of central nervous system using with axon of the nerve cell networking between brain and the muscles of different organs were presented. The pioneering works on Neuronal models based on Hodgkin and Huxley formalism described in 1952 were studied. Modeling the neurological activities through mathematical methods in understanding and assessment of the mechanisms in neural functions were discussed. Functioning of the physiological systems and operating mechanisms with subsystems of immunity and body system were discussed. The quantification methods of MS with Magnetic resonance imaging (MRI), Cerebrospinal fluid (CSF), total white blood cell (WBC) count , CSF immunoglobulin (Ig) levels, CSF-specific oligoclonal bands (OCBs), Optical coherence tomography (OCT), rate of thinning of the ganglion cell/inner plexiform (GCIP) layer, etc were discussed in brief. The methodological issues on MS measurement and its formation location in CNS were discussed.

Review on research literature was done as 4 categories namely 1. Mathematical and Stochastic models on MS and related diseases. 2. Optimization models with mathematical and stochastic programming approaches for optimal drug administrations and effective disease control managements. 3. Empirical data set modeling's using statistical techniques for MS disease, neurological and other related diseases. 4. Quality control tools in healthcare management. The total literature covers during the time period from 1952 to 2013 were reviewed. The focus is on Stochastic and Mathematical Modeling on MS and related diseases with the works of Christina Wolf son from 1984 till Henry C. Tuck well of 2013.

The study has another dimension of research reporting on Models for Optimization Methods related to Neurological and other disease management methods which covers the works ranging from Martin *et al.*,1993 to Tirupathi Rao, 2012. In order to understand the data patterns the review is also focused on Statistical and Data Related Models of MS and other disease of the works of Andrej Y. Yakovlev*et al.* (1998)and of Isabella Bordi *et al,* 2013. Research literature related to Quality assurance through modeling of disease management were also presented covering the works of Knapp R. G.*et al.*, 1983 up to of George A. Green *et al.*,1997.

As there is on stochastic modeling of multiple sclerosis, this study has considered the evidence on growth and loss processes of protective and harming mechanism of myelin sheath. The study is developed based on the motivational aspects of modeling neurological functions and the related disease patterns with Mathematical/Classical, Statistical/Empirical, Computational/Measurable and Probabilistic/Stochastic considerations. The Structural conditions, formulation methods and assumptions, Merits and limitations of each of the model were studied. Due the practicability and the validity towards the realistic situations, it is observed that Stochastic Modeling is the suitable alternative among all the mentioned models. They can model genetical and pathological information as natural assumptions with mathematical formulation protocols.

The study aims to explore the decision parameters for all the four programming problems and conduct the rational analysis on the model behavior. The other objective of the study is to construct quality assurance tools by developing the threshold limits for natural tolerance (control limits) and specification limits. This study will help to explore the healthy threshold limits on the wanted cells like oligodendrocytes and also assess the risk prone limits through stipulated assumptions in the earlier models. These tools shall make use of MS health management and optimal drug administrations. This thesis is organized in 5 chapters. In chapter-I, brief overview on the problem, literature review, Modeling and Quantification of MS and motivational factors of the study. Chapter –II deals with Bivariate stochastic modeling of multiple sclerosis with Poisson processes. Chapter-III deals with formulation of multi objective nonlinear programming problems. Chapter IV deals with development of health assurance devices through quality control concept. Chapter-V is with summary and scope of the study.

5.2 Summary on Chapter-2

In Chapter-2, a stochastic model based on Bivariate Poisson processes using birth and death processes for understanding the growth and loss processes of Multiple Sclerosis is discussed. The anatomy of the disease and its spread was modeled through suitable biological issues and disease structure. The formulation of the model was based on the postulates of MS formation and its growth, influenced by natural and individual physiological responses. Model construction was carried out by considering uncertainty assumptions as the basic frame work is on as the formulation and expansion of MS is influenced by numerous uncertainty reasons. A Bivariate stochastic model for studying the growth and loss of MS causing and oligodendrocytes was proposed by considering the joint stochastic processes of them. Multiple sclerosis is the harming device whereas oligodendrocytes is the helping device for the myelin sheath. Further the models are developed with two cases namely 1) when the patient is not in drugs treatment and 2) when the patient is in treatment with drugs.

While developing this model, the growth rates of MS and Oligodendrocytes λ_1 and λ_2; the loss rates of MS and Oligodendrocytes μ_1, μ_2 are considered. The model includes the postulates of The probability of growth of one MS causing 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 one oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $j\lambda_2\Delta t + o(\Delta t)$; The probability of loss of one MS causing cell during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $i\mu_1\Delta t + o(\Delta t)$; The probability of loss of one oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $j\mu_2\Delta t + o(\Delta t)$; The probability of no growth in MS causing cells during (t, t+ Δt) given that there exists 'i' cells during (0,t) is $1 - (i\lambda_1\Delta t + o(\Delta t))$; The probability of no growth in oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $1 - (j\lambda_2\Delta t + o(\Delta t))$; The probability of no loss to MS causing cells during (t, t+ Δt) given that there exists 'i' cells during (0,t) is 1-($i\mu_1\Delta t + o(\Delta t)$); The probability of no loss to oligodendrocytes during (t, t+ Δt) given that there exists 'j' cells during (0,t) is $1 - (j\mu_2\Delta t + o(\Delta t))$; The probability of happing of more than one events during Δt time is $o(\Delta t)^2$; $p_{ij}(t)$ is the joint probability of 'i' MS causing cells and 'j' oligodendrocytes in the myelin sheath during time 't'.

The difference differential equations of the Model were developed in section 2.2.1; Differential equations are derived in the section 2.2.2; to joint moments were presented in the relations differential equations for joint moments were presented in the relations 2.2.8 to

2.2.12. The derived formulae for various statistical measures were presented as below. The Expected number of MS causing cells at time 't' is in (2.3.1);Expected number of oligodendrocytes at time 't' is in (2.3.2); The variance of number of MS causing cells at time 't' is in (2.3.3); The variance of number of oligodendrocytes at time 't' is in (2.3.4); Covariance of number of MS causing cells and oligodendrocytes at time 't' is in (2.3.5); The Coefficient of variation of MS causing cells is in (2.3.6); The Coefficient of variation of oligodendrocytes is in (2.3.7) and The correlation coefficient between MS causing cells and oligodendrocytes is in (2.3.8).

From tables 2.4.1 and 2.4.2, it is observed that average number of MS causing cells and average number of oligodendrocytes, variance of MS causing cells and variance of oligodendrocytes are increasing functions of initial sizes of MS causing cells(I_0) and oligodendrocytes (J_0) when all other parameters are constant. It is also observed that the coefficient of variation of MS causing cells, coefficient of variation of oligodendrocytes and correlation coefficient between MS causing cells and oligodendrocytes are decreasing functions of initial sizes of MS causing cells (I_0) and oligodendrocytes (J_0) when all other parameters are constant. Form table 2.4.3, it is observed that covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are increasing functions of coefficient of initiation for correlating the variables MS and oligodendrocytes cells (K_0) when all other parameters are constant.

From table 2.4.4, it is observed that the average number of MS causing cells, variance of MS causing cells, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are increasing functions of growth rate of MS causing cells (λ_1) when all other parameters are constant and also observed that coefficient of variation of MS causing cells is decreasing function of growth rate of MS causing cells (λ_1) when all other parameters are constant. From table 2.4.5, it is observed that average number of MS causing cells, variance of MS causing cells, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are decreasing functions of death rates of MS causing cells (μ_1) when all other parameters are constant. And also it is observed that coefficient of variation of MS causing cells is increasing function of death rates of MS causing cells (μ_1) when all other parameters are constant. From table 2.4.6, it is observed that the average number of oligodendrocytes, variance of oligodendrocytes, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and

oligodendrocytes are increasing functions of growth rates of oligodendrocytes (λ_2) when all other parameters are constant. It is also observed that coefficient of variation of oligodendrocytes is decreasing function of growth rate of oligodendrocytes (λ_2) when the remaining parameters are constant. From table 2.4.7, it is observed that the average number of oligodendrocytes, variance of oligodendrocytes, covariance between MS causing cells and oligodendrocytes, correlation coefficient between MS causing cells and oligodendrocytes are decreasing functions of death rate of oligodendrocytes (μ_2) when the remaining parameters are constant. And also observed that coefficient of variation of oligodendrocytes is increasing function of death rates of oligodendrocytes(μ_2)when the remaining parameters are constant. From table 2.4.8, it is observed that the average numbers of MS causing cells, average number of oligodendrocytes, variance of MS causing cells, variance of oligodendrocytes, coefficient of variation of MS causing cells, coefficient of variation of oligodendrocytes, covariance between MS causing cells and oligodendrocytes are increasing functions of time (t) when all other parameters are constant. And also observed that correlation coefficient between MS causing cells and oligodendrocytes is decreasing function of time (t), when the other parameters are constant in normal environment.

Another stochastic model for MS during treatment was developed and presented in the section 2.5. As multiple sclerosis is a resulting effect of infections and inflammations, the severity of the problem can be minimized by the suitable treatment to get rid of infections and inflammations. The usual anti biotech treatment is within spells (for short duration) will act on growth and loss dynamics of both multiple sclerosis and oligodendrocytes. Obviously, we can observe the growth of multiple sclerosis during infection time (in other words when there is no drug presence). Whereas, the growth of oligodendrocytes is observed when the patient is free from infection may be due to the treatment. Hence, there is a possibility of alternative growth and loss processes observed in multiple sclerosis and oligodendrocytes when there are alternative spells of drug treatment. In order to measure the overall phenomena of both multiple sclerosis causing cells and oligodendrocytes, we consider a linear convex combination Z=a X+(1-a)Y. where X and Y are the variables. X reveal the growth and loss aspects of multiple sclerosis cells and Y reveal the growth and loss aspects of oligodendrocytes. The usual mechanisms also suggest that increasing the severity of one component leads to decrement in another component vice versa. In this section, a model is developed to study the behavior of the disease by computing the overall phenomena.

While studying the joint effect, the following assumptions are considered in model development. Let Z=a X+ (1-a) Y be the joint effect of multiple sclerosis causing cells and oligodendrocytes, where $0 \leq a \leq 1$; Z is considered to be a convex combination of multiple sclerosis cells and oligodendrocytes. It will give the total count of both cells. 'a' can be assumed that the values of either '0' or '1' as a=0; if the patient is in treatment (during this time the development of oligodendrocytes will be observed). a=1; if the patient is not in treatment (during this time the development of MS causing cells will be observed). The Expected joint effect of both MS causing cell and oligodendrocytes at time period 't' is presented in (2.5.1); Variance of joint effect of both MS causing cell and oligodendrocytes at time period 't' is presented in (2.5.2); The coefficient of variation is presented in (2.5.3).

A numerical illustration was presented for understanding the behaviour of the model. From the table (2.1) it is observed that average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of time 't' under the treatment; the average and variance of joint effect of both MS causing cells and oligodendrocytes are increasing functions and coefficient of variation is decreasing functions of initial sizes of oligodendrocytes under the treatment; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of birth rate of oligodendrocytes under the treatment; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are decreasing functions of death rate of oligodendrocytes under the treatment when all other parameters are constant.

It is observed that during absence treatment, the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of time 't'; the average, variance of joint effect of both MS causing cells and oligodendrocytes are increasing functions of initial sizes of MS causing cells and coefficient of variation is decreasing function of initial sizes of MS causing cells; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are increasing functions of birth rate of MS causing cells; the average, variance and coefficient of variation of joint effect of both MS causing cells and oligodendrocytes are decreasing functions of death rate of MS causing cells; when all other parameters are constant.

5.3 Summary on Chapter-3

In chapter-3, some optimization programming problems were developed for using them in drug administration procedures. As multiple sclerosis is a disease related to central nervous system it may badly affect the neurological health with the bacterial attacks and viral infections. There are numerous reasons that central nervous system to get exposure to infections. This chapter deals with the development of set of nonlinear programming problems with multiple objectives where each nonlinear programming problem can be handled separately. The values of decision parameters of bivariate stochastic processes namely λ_1, λ_2, μ_1 and μ_2 are obtained. Here, different stochastic optimization programming problems are developed in two environments such as, (i) when the patients are not in treatment and (ii) when patients are under treatment. The study has explored four stochastic optimization programming problems in general environment i.e. during non- treatment and two optimization problems during treatment. A programming problem is formulated with the objective of the maximizing the average number of oligodendrocytes, subject to the constraints that the average number of MS causing cells should not be exceed certain harmful level and the average number of oligodendrocytes should have at least the minimum wanted size, the variability of MS causing cells should be more than certain limit and the variability of oligodendrocytes less than certain limit. Another optimization programming problem is to minimize the severity of multiple sclerosis subject to the constraints as the above problem. The other set of optimization programming problems consists again of two types. The first optimization programming problem is on maximizing the overall joint effect of both the MS causing cells and oligodendrocytes, subject to the constraints of minimum required quantity of joint effect of both the MS and oligodendrocytes at fixed minimum variation. Second optimization programming problem is to minimize the variation during treatment subject to the constraints of minimum required joint effect of both the MS causing cells, oligodendrocytes and fixed minimum variation. While framing the optimization programming problems, we have considered the statistical measures derived from the previous chapter. The core objective of this work is to develop the programming problems that can minimize the severity of MS with several feasible constraints.

Development of stochastic optimization programming problems during non-treatment period is discussed in section 3.2. Optimization programming problem for minimizing the severity of MS was presented in section 3.2.1. In this programming problem, the objective function is formulated with loss function through derived statistical measures during non-

treatment period. The problem deals with minimization of severity of MS, subject to the constraints of the average number of MS cells should be less than certain limit (A), there should be minimum size in the average number of oligodendrocytes (B), the variance of MS cells should be greater than certain size (C) and the variance of oligodendrocytes should maintain at minimum size (D). The constraints are also formulated with linear combinations of growth rates of both MS causing cells and oligodendrocytes cells; the linear combination of loss rates of both MS causing cells and oligodendrocytes cells. The purpose of the problem is to explore the decision parameters namely λ_1 (growth rate in MS causing cells per unit time); λ_2 (growth rate in oligodendrocytes per unit time); μ_1 (loss rate in MS causing cells per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non- negative.

Optimization programming problem for maximizing the size of oligodendrocytes is discussed in 3.2.3.In this programming problem, the objective function is formulated with an objective of maximizing the average size of oligodendrocytes derived through the relation of chapter-2 under the assumption of the patient is not in treatment. The subjective constraints are designed with the average number of MS causing cells should be less than certain limit (A), the average size of oligodendrocytes should be more than some wanted levels (B), the variance of MS causing cells should be greater than certain size (C) and the variance of oligodendrocytes should maintain at minimum size (D). Further the constraints are formulated with linear combinations of growth rates of both MS causing cells and oligodendrocytes; the linear combination of loss rates of both MS causing cells and oligodendrocytes. The purpose of the problem is to explore the decision parameters as in the previous problem.

Numerical Illustrations and Sensitivity Analysis were presented in 3.2.3.The non-linear programming problems 3.2.1 and 3.2.2 are solved with mathematical software LINGO 13 and the results were presented in table 3.1 and table 3.2. From the tables 3.2.3.1and 3.2.3.2, it is observed that the objective function Z is increasing function of I_0 (Initial size of MS causing cells at a point of time t) when all the other parameters are constant. The objective function Z, growth rate of oligodendrocytes are decreasing functions of Initial size of oligodendrocytes at a point of time t. The growth rate of MS causing cell is an increasing function of Initial size of oligodendrocytes at a point of time t when all other parameters are constant.

From the tables 3.2.3.3 and 3.2.3.4, it is observed that the objective function, growth and loss rates of MS causing cells are increasing functions of 'C'. Growth and loss rate of oligodendrocytes are decreasing functions of C(Minimum variability in the size MS causing cells) when other parameters are constant. The objective function Z, growth rates of MS causing cells are decreasing functions and growth rates of oligodendrocytes is increasing function of D(Maximum allowable variability in the size oligodendrocytes) when all other parameters are constant. From the table 3.2.3.5, the objective function, growth rate of MS causing cells are increasing functions and growth rate of oligodendrocytes are decreasing functions of 't'(time of observation) when all other parameters are constant in non-treatment environment. From the table 3.2.3.6, it is observed that the objective function, growth and loss rate of MS causing cells are decreasing functions, growth and loss rate of oligodendrocytes are increasing functions of I_0 (Initial size of MS causing cells at a point of time) when all other parameters are constant. From the tables 3.2.3.7 and 3.2.3.8, it is observed that the objective function Z is increasing function of J_0 (Initial size of oligodendrocytes at a point of time t) when all other parameters are constant. The objective function Z, growth and loss rate of oligodendrocytes are decreasing functions of 'C', growth and loss rate of MS causing cells are increasing functions of C(Minimum variability in the size MS causing cells) when all other parameters are constant. From the tables 3.2.3.9 and 3.2.3.10, it is observed that the objective function, growth rates of oligodendrocytes are increasing functions and growth rates of MS causing cells are decreasing function of D(Maximum allowable variability in the size oligodendrocytes) when all other parameters are constant; the objective function, growth rates of MS causing cells are increasing functions and loss rate of MS causing cells, growth and loss rates of oligodendrocytes are decreasing functions of t(time of observation) when other all parameters are constant.

Another part of this section deals with stochastic optimization programming problems during treatment period. Here optimization programming problem was developed for effective drug administration with the objectives of maximizing the overall growth of oligodendrocytes and minimize the overall expansion of MS during the treatment periods. Resulting to these, the objective is considered to be maximizing the overall performance of drug. Another important criteria that is to be observed during the treatment period is the volatility of drug effectiveness which should be at minimum fluctuations. The other programming problem is developed with an objective of minimize the overall variability of disease intensity. We have also formulated the subject to the constraints by maintaining the

wanted and unwanted levels of disease causing cells and disease defense cells. This part of the problem can be used for extracting the decision parameters namely growth and loss rates of both MS and oligodendrocytes.

Optimization programming problem for maximizing the overall combined effectiveness of MS and oligodendrocytes is presented in 3.3.2. In this optimization programming problem, the objective function is formulated with derived statistical measures during treatment period. The problem deals with maximization of positive joint effect of both MS causing cells and oligodendrocytes, subject to the constraints on overall joint effect of both MS causing cells and oligodendrocytes should be more than certain limit (E), the variance should be less than certain minimum size (F) The purpose of the problem is to explore the decision parameters namely λ_2 (growth rate in oligodendrocytes per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non-negative.

Optimization programming problem for minimization of volatility was presented in section 3.3.3. In this optimization programming problem, the objective function is formulated with derived statistical measures during treatment period. The problem deals with minimization of variance of joint effect of both MS causing cells and oligodendrocytes, subject to the constraints on overall joint effect of both MS causing cells and oligodendrocytes should be more than certain limit (E), the variance should be less than certain minimum size (F) The purpose of the problem is to explore the decision parameters namely λ_2 (growth rate in oligodendrocytes per unit time) and μ_2 (loss rate in oligodendrocytes per unit time). The decision parameters are non- negative.

Numerical Illustrations and Analysis were given in the section 3.3.4. From the table (3.1), it is observed that the objective function is increasing function and growth rate of oligodendrocytes are decreasing functions of J_0 (initial size of oligodendrocytes) when other parameters are constant; the objective function is decreasing function and growth rate of oligodendrocytes are increasing functions of F(Maximum allowable variability in the effectiveness of both MS causing cells and oligodendrocytes) when other parameters are constant; the growth rate of oligodendrocytes is decreasing function of t (time of observations) when all other parameters are constant. From the table (3.2), it is observed that the objective function and growth rate of oligodendrocytes are decreasing functions of J_0 (initial size of oligodendrocytes) when other parameters are constant; the objective function

and growth rate of oligodendrocytes are increasing functions of E(Minimum required effectiveness of both MS causing cells and oligodendrocytes) when other parameters are constant; the growth rate of oligodendrocytes are decreasing function of t (time of observations) when all other parameters are constant.

5.4 Summary and Conclusion on chapter-4

In this chapter the study is focused on development of quality control and specification limits for optimal health management of MS disease. In order to construct the control and specification limits, we have considered the derived statistical relations in chapter-II. The developed probability functions and derived statistical measures were considered for getting standard and precision. These are further used to understand the shift in quality of standard and the range of its volatility. As the quality assurance has to be analyzed at feasible standards and significant precisions, we have considered the control chart approach for means and standard deviations. The control limits are derived through sampling distributions and data sets through a hypothetical data (generated through simulation techniques) for studying the status of the quality assurance. Mean (Average) and Standard Deviations (Root Mean square deviation) were obtained through the data sets. The control limits for assessment of quality standards are fixed with UCL, LCL, USL and LSL. Therefore, the quality analysis is carried out through valid techniques namely sampling distributions (through numerical/data sets) and quality specification limits (through theoretical concepts). These devices will act as guiding principles for healthcare takers for designing the quality specifications and health care decision support systems. The analysis is carried out with control limits at required level of significance by considering the natural tolerance.

Control and specification limits for standard and volatility measures of MS causing cells were presented in section 4.2. In this section, the study is focused on development of quality devices through the specification limits for both standard and volatility measures. The values like average number of MS causing cells and the average number of oligodendrocytes will provide the relevant information on desired levels of standards. Similarly, variance of number of MS causing cells and variance of number of oligodendrocytes will provide the fluctuations in the health variations. Hence, we can derive the quality guiding devices namely control charts for standards (means) and control charts for volatility (standard deviations).Control and Specification Limits for Standards (means) chart

were given in section 4.2.1. Control chart for means useful for evaluating the health standards of both MS spreading intensity and oligodendrocytes expansion were developed. Control and Specification Limits for Standard (Mean) of Oligodendrocytes were given in section 4.2.1.2. Control and Specification Limits for Volatility Chart were presented in section 4.2.2. In this section, we develop the control limits for evaluating the variability conditions of disease by constructing the control charts for standard deviations for both MS spreading intensity and Oligodendrocytes expansion.

Numerical Illustrations and Analysis were presented in section 4.3. In this section, an attempt is made for understanding the evaluation protocols of health status with numerical illustrations. The numerical data sets are obtained by simulation techniques by using the software Mathcad 7.0 version. Sections from 4.3.1.1 to 4.3.1.6 deals with the construction and interpretation of control charts, specification charts related MS causing cells. Whereas the sections from 4.3.2.1 to 4.3.2.6 deals with construction and interpretation of control charts and specification limits related to oligodendrocytes. From the table 4.2.1 and figure 4.2.1, it is observed that the process of standard (average number) of MS causing cells is under control. From the table 4.2.2 and figure 4.2.2, it is observed that the process of standard (average) of MS causing cells is under control. From the table 4.2.3 and figure 4.2.3, it is observed that the process quality standard (mean) of MS causing cells is under specification at 5% level of significance and control chart it is observed that average number of MS causing cells is out of control in mean chart of specification limits at 5% level of significance. From the table 4.2.4 and figure 4.2.4, it is observed that the process quality on Volatility of MS causing cells is under control. From the table 4.2.5 and figure 4.2.5, it is observed that the quality process on volatility of MS causing cells is under control. From the table 4.2.6 and figure 4.2.6, it is observed that the process quality on volatility of MS causing cells is under specification limits at 5% level of significance.

From the table 4.4.1 and figure 4.4.1, it is observed that average number of oligodendrocytes is under the control in mean chart. Which implies that the process quality standard of oligodendrocytes is meeting its natural tolerance so as the standard of process is under control. From the table 4.4.2 and figure 4.4.2, it is observed that average number of oligodendrocytes is under the control limits. It implies that the process quality standard (mean number) of oligodendrocytes is according to process capability of the patient. From the table (4.4.3) and figure (4.4.3), it is observed that average number of oligodendrocytes is under specification limits process standards. Hence, it implies that the process quality standard

(mean number) of oligodendrocytes is meeting the specific quality standard at 5% level of significance. From the table 4.4.4 and figure 4.4.4, it is observed that standard deviation of number of oligodendrocytes is under the control. Hence, it implies that the process quality volatility (S.D) of oligodendrocytes is under control. From the table 4.4.5 and figure 4.4.5, it is observed that standard deviation of oligodendrocytes is under control. Hence, it implies that the process volatility of oligodendrocytes is under control. From the table 4.4.6 and figure 4.4.6, it is observed that standard deviation of oligodendrocytes is under specification limits. Hence, it implies that the process volatility of oligodendrocytes is according to the specifications of the quality of 5% level of significance.

5.5 Scope of the Future Research

This study is categorized as theory oriented model development of Multiple sclerosis. In fact there is very limited research work has been reported in the area of Mathematical modeling of this disease. Much work on development of Mathematical biology regarding this disease will help the health care industry for proper utilization of mathematical tools. Understanding the biological predictions with a notion of mathematics, particularly for MS requires efficient theoretical model developers, Computing experts, Software developers and statistical data interpreters. Once a basic frame work on mathematical lines is formulated, the concepts of stochasticity will be applied to the problem for better understanding of Biology. Ours is a remarkable work on modeling the pathogenesis of Multiple sclerosis using stochastic processes. Estimation of parameters with Maximum likelihood procedures has good scope for pursuing this problem for inferential aspects. More stochastic Models may be generated by proper synchronization of Biological issues as Mathematical assumptions. The developed stochastic models may be refined with other suitable assumptions where ever non Poisson situations are prevailed. Development of probability distributions, derivation of statistical measures will help to convert them as optimization programming problems. This is another broad area of research for handling healthcare management problems. Development of Quality assurance tools with these studies is a considerable research area for assessment and evaluation of health standards. This study may be considered as the initial step of development of Medical decision support systems. Further, these derived mathematical formulae can be used for the development of computing software devices and hence it may convert as user friendly desk top decision making automations.

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