CHAPTER 3

REVIEW OF LITERATURE

A complete overview of Literature survey of Mathematical modelling of biological systems is provided in this chapter. This thesis, Mathematical modelling has been used to explore or analyze the effect of stress on the performance of biological organ. The simulations derived here outlines these biological system should improve their research and to help the medical experts in this field. A Mathematical model is an abridged representation or imitation of the real life problem and hence can be used to comprehend biological systems, a mission that can be unnerving given the difficulty of the system. The application of mathematical models to survival function data has led to a better thoughtful and forecast of the outcomes of the stress related diseases. These models have also been used in constraint estimation, hypothesis development and expectations from clinical data to assist policy decisions that affect human biological organs.

Many mathematical models have been developed for the simulation of various engineering systems such as mechanical, electrical and etc. Assuming different hypothetical situations several models have been derived to promote the theory for applicability in practical situations. But little progress has been made in constructing.

Mathematical models to simulate various biological organ systems. Here the authors have developed Mathematical models to study the effects of stress in terms gonadotropin releasing hormone using stochastic models. The critique of relevant literature begins with review of biology and mathematical models discussed in this thesis. Here a brief outline of some chosen papers are given in a series by which they have developed to meet the real life situations.

Keenan D M. et al. (2000) had developed and implemented a bio mathematical statement of how reciprocal connectivity drives stress-adaptive homeostasis in the corticotropic (hypothalamo-pituitary-adrenal) axis. In initial analyses with this interactive construct, they had tested six specific a priori hypotheses of mechanisms linking circadian (24-h) rhythmicity to pulsatile secretory output. This formulation offers a dynamic framework for later statistical estimation of unobserved in vivo neurohormone secretion and within-axis, dose-responsive interfaces in health and disease. Explication of the core dynamics of the stress-responsive corticotropic axis based on secure physiological precepts had helped to unveil new biomedical hypotheses of stressor-specific system failure **[59].**

Lakshmi (2013) has developed a mathematical model for a feedback of stress responsive hormones cortisol feeds back on hypothalamic in HPA axis due to human stress. The stress-responsive hypothalamo adrenocorticotrophic hormone (ACTH)-adrenal (cortisol) axis is critical in initiating life-sustaining

adaptive reactions to internal (disease) and external (environmental) stressors. This neuroendocrine ensemble exhibits prominent time-dependent dynamics reflected in vividly pulsatile (ultradian) and 24-h rhythmic (circadian) output.

Episodic secretion is driven by hypothalamic neuronal pacemakers, which secrete the pituitary signaling peptides CRH (ACTH-releasing hormone) and AVP (arginine vasopressin). These agonists singly and synergistically stimulate ACTH synthesis and secretion (feed forward), which in turn promotes the time-lagged and dose-responsive biosynthesis of cortisol.

Cortisol feeds back to inhibit CRH/AVP and ACTH production via time-delayed concentration-dependent (integral) and rapid, rate-sensitive (differential) mechanisms. These core physiological linkages mediate a homeostatic (servo control) system governed by nonlinear and time-delayed feed forward and feedback signal interchanges. They postulated that such interactive properties generate the observed complex dynamics of this dynamics **[70].**

A mathematical model, based on a statistical system approach, has been implemented and tested by M. Lo Schiavoa et al., (2011) on the basis of a four-year-long experimental data set, with the aim of analyzing the Performance and clinical outcome of an existing medical ward, and predicting the effects that possible readjustments and/or interventions on the structure may produce on it.

The dynamics of the system was assumed to be connected to a variable called ‘‘atmosphere’’ that refers to the perceived social and organizational climate, as well as the comfort and ease realized in the ward.

The atmosphere is intuitively related to the ‘‘quality’’ that is (or is perceived as being) offered by the service, as it affected the ability to satisfy the patients’ needs, to provide a livable environment for patients and medical staff, and guaranteed more efficient performances and a more complete professional development. Identifying variables, parameters and events that control the atmosphere is therefore of the deepest importance from a social and health-care point of view. The proposed interdisciplinary approach, referring to paradigms of physical and mathematical models integrated with theories and methods typical of social sciences, had chances of gaining the attention of the scientific community in both fields, and higher possibilities of obtaining appreciation and generalization **[117].**

A stochastic failure model for a system subject to a random shock process was studied by Ji Hwan Chaa et al., (2010). It was assumed that a fatal shock results in an immediate system failure, whereas a non-fatal shock may increase the susceptibility of the system to failure. The lifetime distribution of the system and its failure rate function are derived, and the effect of environmental factors on the failure process of the system is also investigated. Lifetimes of systems

operated under different environmental conditions are stochastically compared **[52].**

Keenan, D.M et al., (1998) presented a stochastic approach for a pulse generator. Their context of modelling the male reproductive hormone system was to model the pulse time points by a renewal process. Let $\{S\}_{j\in\mathbb{N}}$ be a sequence of independent and identically distributed random variables with the distribution function F. The pulse time points $\{T_j\}_{j\in\mathbb{N}_0}$ are then modeled by $T_0=0, T_{j+1}=T_j+S_{j+1,} j\in\mathbb{N}_0$. It was required that the pulse time points are feedback-regulated by delayed progesterone and estradiol concentrations. Moreover, regulation of the pulse pattern was desired. The Poisson process was not suitable in this case since it didn't offer any kind of flexibility. That is why the Weibull density is chosen for the survival time between two pulses:

$$\begin{aligned} f(s) &= P\left[s/\lambda(.)\right] \\ &= \gamma.\left(\lambda(s)s\right)^{\gamma-1}\exp\left(\left(\lambda(s)s\right)\right)^{\gamma} \end{aligned}$$

They exerted a sort of stochastic time transformation of a Weibull renewal process, i.e. they transformed the deterministic term $\lambda(s)$ into the stochastic term $\int_{T_{j-1}}^{s}\lambda(r)dr$ and obtained

$$F(S_j)=\int_{T_{j-1}}^{T_{j-1}+S_j} f(s)\,ds \;=1-\exp\left(-\left(\int_{T_{j-1}}^{s}\lambda(r)\,dr\right)^{\gamma}\right)$$

To calculate T_j, first the random variable $U_j \sim U[0,1]$ has to be generated. Then, it has to be equated with $F(S_j)$.It follows: $\int_{T_{j-1}}^{T_j} \lambda(r)\,dr = \left(-ln\left(1-U_j\right)\right)^{\frac{1}{\gamma}}$ The function $\lambda(.)$ describes the pulse intensity, affected by progesterone (negative feedback) and estradiol (positive feedback at high concentration)

$$\lambda(t) = h^{-}\left(P_4\left(t-\tau p_4\right); T_{P_4}{}^{freq}, n_{P_4}{}^{freq}\right) \times \left(1 + \left(h^{+} E_4\left(t-\tau E_4\right); T_{E_2}{}^{freq}, n_{E_2}{}^{freq}\right)\right)\lambda_{\max}$$

Where P4 and E2 denote the progesterone and estradiol concentration in the blood, respectively, τp_4 τE_4 the delays, $T_{E_2}{}^{freq}$, $T_{P_4}{}^{freq}$ the threshold values, $n_{P_4}{}^{freq}$, $n_{E_2}{}^{freq}$ the Hill coefficients, and $\lambda_{\max} \in \mathbb{R}_{+}$ **[60].**

Grossman et al., (1999) developed a related non-linear delay model, in which the assumption that a productively infected cell died by a first order process, was replaced by introducing a delay in the cell death process. Because Grossman et al. Assumed that the delay was given by a gamma function, i.e., the cell moving through a set of n-stages, with death and production of virus only occurring at the last stage, the model also incorporated the feature that production of virus was delayed from the time of initial infection. However, the model also assumed that the rate of loss of the end stage cell that was producing virus was identical to the rate of progression through the stages leading up to death. In the delay models analyzed, the death rate d and the delay parameters

are chosen independently. Grossman et al. allowed a less than perfect drug, and emphasized the effects of drug efficacy on viral dynamics. Their work showed it is possible to interpret the slope of the decay curve by the death rate of productively infected T cells. In fact, a mathematically rigorous analysis of the Grossman model, shows that their model also leads to the conclusion that the slope of the viral decay curve is δ **[47].**

The Duane postulate for reliability growth states that the instantaneous system MTBF at cumulative test time t is $M(t) = \left[\lambda\beta t^{\beta-1}\right]^{-1}$, where $0 < \lambda$ and $0 > \beta$ are parameters. Crow L.H, (1974, 1983, 2004) modeled the Duane postulate stochastically as a non-homogeneous Poisson process (NHPP) with intensity

$$r(t) = \lambda\beta t^{\beta-1},$$

thus allowing for statistical procedures based on this process for reliability growth analyses. This model is applicable to test-fix-test data. This was the grouped data version of the Crow model that addressed the situation where the actual failure times may not be known. In this case the total test period was partitioned into K intervals and the number of failures in each interval was known. It was not required that the intervals be of the same length.

Let the length of the q th interval be L_q , q = 1,…,K. Also, let $T_1 = L_1, T_2 = L_1 + L_2 \ldots$ etc., be the accumulated time through the q^{th} interval. Let N_q

be the total number of failures in the q^{th} interval The Crow. L .H, model failure intensity is estimated by $\hat{r}(T) = \hat{\lambda}\hat{\beta}t^{\hat{\beta}-1}$

Where the values $\hat{\lambda}$ and $\hat{\beta}$ satisfy

$$\hat{\lambda} = \frac{N}{T^{\hat{\beta}}}$$

Where $N = N_1 + N_2 .... + N_q$ is the total number of failures. The achieved or demonstrated MTBF is estimated by $\hat{M}CA = \left[\hat{\lambda}CA\right]^{-1}$ **[25, 26, 28].**

Murray, (2002); Farhy, (2004). Concerning mathematical modelling of hormone dynamics, one considers two general tendencies hormone clearing from the blood which implies decrease of the serum concentration and hormone secretion which contributes new amounts of the hormone into the blood stream. Clearing rate is basically proportional to the hormone concentration while secretion of a hormone is defined by concentration and dynamics of other hormones. Concentration rise in hormones can either stimulate secretion of a given hormone or inhibit it. In this way, positive and negative feedbacks arise between different hormone concentrations of an organism. The loop of interacting hormones is closed and dynamically stable which guarantees homeostasis, i.e. biological self-regulation. To correct the dynamic behaviors of

endocrine systems, exogenous signals can be used, e.g. medication, different kinds of medical treatment, physical activity, special diet, etc., **[36, 94].**

Lazarus (1966) and Lazarus and Cohen (1977) have described the concept of stress which is regarded as a process of transactions between the individual and his environment **[83,112]** and Frankenhaeuser (1971a,1971b) has viewed as hormonal measurements which are seen as tools by which new insights can be gained into the dynamics of above said transactions **[42,43].**

Lakshmi (2001, 2004) has developed a stochastic model which suggest that a person unable to balance the body system due to anger or fear and she has premeditated that the secretion of nor-adrenaline is considered as a response of human stress **[69].** Due to stress, the arrival of catecholamine secretions has been analyzed by the concepts of renewal and modified renewal processes; it is mentioned as the magnitude of stress effect. The secretion of catecholamine and the corresponding time epoch are assumed to be independent. The expected catecholamine secretions in adrenal glands have been obtained by using renewal process **[77].**

A theoretical study has been examined the effect of dopamine on human retinal vessel diameter by using conditional and marginal regression models. The mean values of arterial and venous retinal diameters have been obtained during the administration of dopamine in two consecutive doses. The concept of

cumulative damage models has been discussed to determine the response of the stress on the dopamine levels in cortical areas of brain region **[79].** In nature, the effects of human stress have been deliberated as cumulative and additive. It has been measured in terms of glucocorticoids, particularly ACTH and Corticosterone. Glucocorticoids are involved in the induction of the long-term effects of a single exposure to IMO. The formula for the tail behavior of the corresponding distribution with random products has been developed to find the long-term effects of a single exposure to IMO **(**Lakshmi et al 2007, 2009, 2010) [**75, 77, 79].**

A stochastic model for release of dopamine due to stress is developed by using total down time distribution model. The behavioral effects of the administration of brain derived neurotrophic factor antibody methamphetamine in the nucleus accumbens on the extra cellular levels of dopamine were measured. The mean failure and recoupment distribution have been obtained by using total down time distribution for a repairable system during a given time interval. The reliability function of dopamine has been obtained during the stress produced by the administration of the drug methamphetamine in the nucleus accumbens (Venkatesh and Lakshmi, 2009) **[76].**

Shanthikumar and Sumita (1983, 1984, 1985) have developed a general shock model associated with a correlated pair $\{X_n, Y_n\}_{n=0}^{\infty}$ of renewal sequences, where the system fails when the magnitude of a shock exceeds a pre-specified

threshold level. The $\{X_n\}$ and $\{Y_n\}$ are denoted as the sizes of the shocks and the times between successive shocks respectively. Authors have considered the two models which are depending on the n th X_n shock which is correlated to the length Y_n of the interval since the last shock, or to the length Y_n of the subsequent interval until the next shock and they have obtained the transform results, an exponential limit theorem, and properties of the associated renewal process of the system failure times **[123].**

Some distribution properties of the system failure time in general shock models associated with correlated renewal sequences $\{X_n, Y_n\}_{n=0}^{\infty}$ is studied **[125].** A class of cumulative shock models associated with a bivariate sequence of correlated random variables is analyzed **[124].**

Ganesan et al. (2001) have considered the secretion of catecholamine is taken as one of the stress responses and acted as a tool to evaluate the mean and variance of time to get stress related dysfunction by developing suitable stochastic models. Authors have studied the inter arrival time between the successive stress responses are correlated and also they were concluded the results that the more of inter correlation between the successive inter arrival time of stress response that much of fluctuations invaded with regard to the expected duration of getting stress related dysfunction. They have also introduced the alertness factor of the stress affected persons and they have

suggested a person who is in position to regulate the stimulus input and he is able to control both physiological arousal and psychological involvement at an optimum level over a wide range of stimulus conditions **[71].**

Two devices are subjected to common shocks arriving according to two identical counting processes. The $\bar{P}_k$ is denoted as the probability of surviving k shocks for the first device and the $\bar{Q}_k$ is denoted as the probability of surviving k shocks for the second device. The conditions on the discrete distributions $\{\bar{P}_k, k=1,2.....\}$ and $\{\bar{Q}_k, k=1,2.....\}$ in order to obtain the failure rate order, the likelihood ratio order and the mean residual order between the random lifetimes of the two devices are found (Franco Pellerey, 1993) **[40].**

Bhattacharyya (1987) discussed accelerated life testing with reciprocal linear regression model. They explained that a material fails when its accumulated fatigue exceeds a critical amount $w>0$ and assumed fatigue growth take place over time according to a Weiner process with drift $\mu>0$ Actually the inverse Gaussian model conforms to the structure of an exponential family and the methodology of optimum statistical inferences including test of hypotheses is well developed **[10].**