MATHEMATICAL MODEL FOR ADMINISTRATION OF OXYTOCIN REDUCES BASAL AND LIPOPOLYSACCHARIDE-INDUCED GHRELIN LEVELS IN HEALTHY MEN

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ABSTRACT

Phase type distributions constitute a convenient class of models for service times. Increasing hazard rate and decreasing hazard rate curves are obtained in two different phases respectively for the following application. In application part by using exponential distribution the hazard rate for hormone levels in plasma grelin concentrations, the changes in grelin as percent of basal values. oxytocin, LPS induced grelin concentrations during the whole study period. FFA and glucose levels in response to endotoxin and oxytocin are obtained. These functions show a clear picture for all the above parameters when LPS+Oxytocin is administered to all cases and compared with the medical conclusions.

Keywords: Exponential distribution, hazard model, Oxytocin.

Mathematical Subject Classification: $60G_{XX}$, $62H_{XX}$, $62P_{XX}$.

1. MATHEMATICAL MODEL:

1.1. INTRODUCTION

Phase-type distributions constitute a very versatile class of distributions. Since their introduction by Neuts [12] in 1975, phase-type (PH) distributions have been used in a wide range of stochastic modelling applications in areas as diverse as telecommunications, finance, teletraffic modelling, biostatistics, queueing theory, drug kinetics, reliability theory, and survival analysis. PH distributions have enjoyed such popularity defined on the nonnegative real numbers that lead to models which are algorithmically tractable. Their formulation also allows the Markov structure of Stochastic models to be retained when they replace the familiar exponential distribution.

Erlang [7], was the first person to extend the exponential distribution with his "method of stages". He defined a nonnegative random variable as the time taken to move through a fixed number of stages (or states), spending an exponential amount of time with a fixed rate in each one. Nowadays the refer to distributions defined in this manner as Erlang distributions. Generalized Erlang's method of stages by defining a PH random variable as the time spent in the transient states of a finite-state continuous-time Markov chain with one absorbing state, until absorption. In Stochastic modelling and queueing theory relied on random variables of interest and service times being modelled by the exponential or Erlang distributions, and point and interarrival processes by the Poisson or Erlang renewal processes. PH distributions constitute a much more useful class of distributions for a number of reasons.

Definition.

If T is an absolutely continuous non-negative random variable, its hazard rate function

h(t), $t \geq 0$, is defined by $h(t) = \frac{f(t)}{S(t)}$, $t \geq 0$,

where f(t) is the density of T and S(t) is the survival function:

$S(t) = \int_t^{\infty} f(u)du = P\{T > t\}$.

Note that $P\{T \leq t + \Delta / T\} \approx h(t) . \Delta$

If T is a discrete non-negative random variable that takes values $t_1 < t_2 < \ldots\ldots$ with corresponding probabilities $\{p_i , i \geq 1\}$, then its hazard-sequence $\{h(t_i)\}$ is defined by

$$h(t_i) = \frac{p_i}{\sum_{j \geq i} p_j} = \frac{p_i}{S(t_i-)}, \quad i \geq 1.$$

Note that $P\{T = t_i / T > t_{i-1}\} = h(t_i)$.

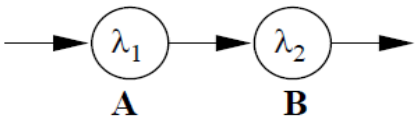
- The hazard rate is a dynamic characteristic of a distribution.
- The hazard rate is a more precise "fingerprint" of a distribution than the cumulative distribution function, the survival function, or density.
- The hazard rate provides a tool for comparing the tail of the distribution.

1.2.Phase-type distributions constitute a convenient class of models for service times:

- dense;
- structurally informative;
- meta theorem: homogeneous unpaced human service/task durations are exponential.

It is convenient to utilize the concept of hazard rate via phase-type distribution. Small number of

Assume that the service time has the representation:



A-Initial time phase

B-After 360 min time phase

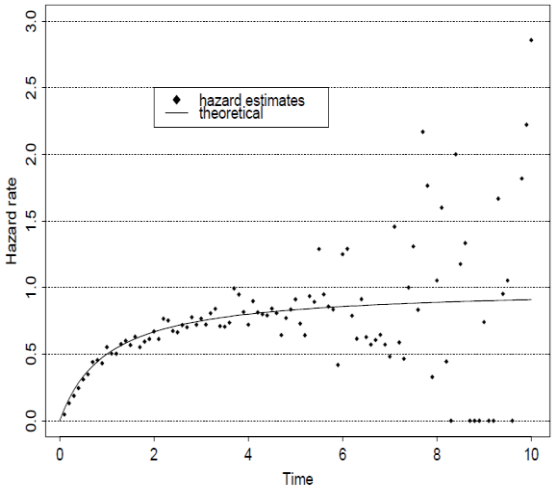
For arbitrary $\lambda_{1,2} > 0$, $\lambda_1 \neq \lambda_2$. Then it can be shown that

$$P_A(t) = \frac{e^{-\lambda_1 t}}{\frac{\lambda_2}{\lambda_2-\lambda_1}e^{-\lambda_1 t} - \frac{\lambda_1}{\lambda_2-\lambda_1}e^{-\lambda_2 t}} \to (1-\frac{\lambda_1}{\lambda_2})^+, \text{ as } t \to \infty;$$

$$P_B(t) = \frac{\lambda_1(e^{-\lambda_1 t} - e^{-\lambda_2 t})}{\lambda_2 e^{-\lambda_1 t} - \lambda_1 e^{-\lambda_2 t}} \to (1 \wedge \frac{\lambda_1}{\lambda_2}), \text{ as } t \to \infty.$$

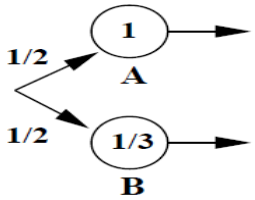
The hazard rate $h(t) = \lambda_2 P_B(t) \to \lambda_1 \wedge \lambda_2$, as $t \to \infty$, converges to the minimum of the two rates[1].

Fig.1.1 Example of increasing hazard rate



1.3 Decreasing hazard rate.

There may be several types of customers, each with an exponential service time. For example, consider the two-phase case with rates 1 and 1/3 respectively:



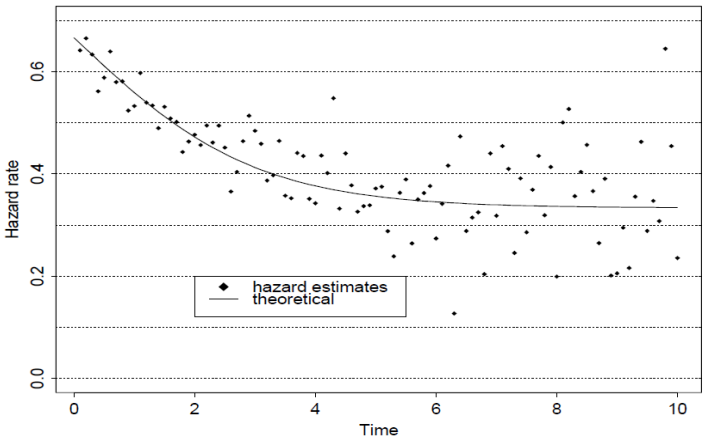
$$P_A(t) = \frac{e^{-2t/3}}{1+e^{-2t/3}}$$

$$P_B(t) = \frac{1}{1+e^{-2t/3}}$$

$$\text{Hazard rate} = P_A(t) + \frac{1}{3}P_B(t)$$

In figure 1.2 the hazard rate near zero is close to 2/3: the average of the two rates of the individual phases[5]. If the service has not been completed for a long time, the probability $P_B(t)$ the phase with the longest expectation (rate1/3) had been chosen" converges to one[10]. Hence, the hazard rate converges to 1/3.

Fig 1.2 Example of decreasing hazard rate



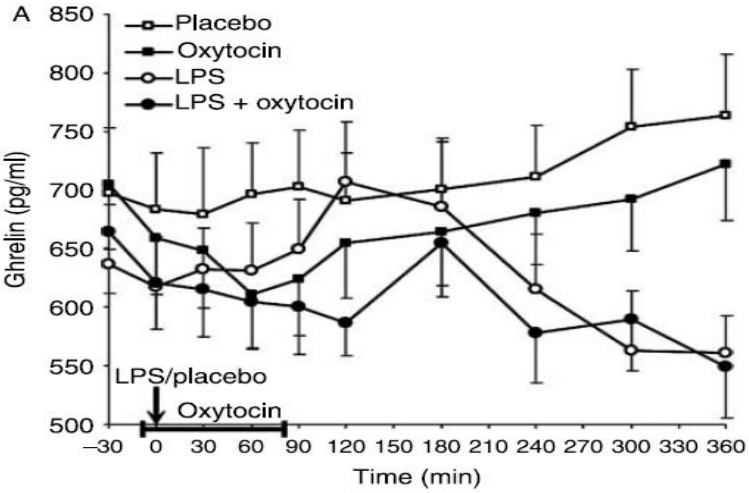
2.Application

The interaction between the nervous and endocrine systems is crucial in coordinating physiological processes and the response to stressors [2]. During the last decade, a new neuroendocrine axis has been established: the gut–brain axis [12].Gut–brain signaling consists of bidirectional cross-talks between the hypothalamic nuclei and neuroendocrine cells of the gut, partially mediated by afferent and efferent nerval components [3]. This axis controls energy homeostasis and was recently found to be involved in the modulation of stress responses [12]. The most important member of the gut–brain axis is ghrelin, a hormone that promotes appetite and growth [10]. Ghrelin immunoreactivity is mainly found in the neuroendocrine cells of the gastric mucosa, and to a lesser extent in the hypothalamus [9]. In the hypothalamus, ghrelin is expressed in neurons that lie upstream to neuropeptide Y (NPY) and proopiomelanocortin neurons, suggesting local effects in the regulation of food intake and energy expenditure . A recent study has showed that intraventricular administration of ghrelin increases the c-fos activity of oxytocin (OXT)-secreting neurons . OXT is involved in social bonding, has important reproductive functions, and is a classical stress hormone. Plasma
OXT displays a distinct circadian rhythm and changes during stress response, parturition and lactation, as well as upon pharmacological use of OXT [14]. OXT infusion in men decreases the NPY response to ghrelin, but an eventual modification of ghrelin levels has not been tested [4]. OXT and ghrelin are hormones with partial but not classical neurotransmitter properties. Both increase in response to stressors, thereby exerting anti-inflammatory and anxiolytic effects[6].

These peptides have opposing effects on appetite regulation, OXT being an anorexigenic hormone, while ghrelin an orexigenic one. The mechanisms underlying the appetite- promoting effects of ghrelin have been investigated in detail. The mechanisms underlying the anorexigenic effect of OXT remain unknown, and could also involve components of the gut–brain axis. Aimed to test whether alterations in circulating OXT modify ghrelin levels under physiological conditions and in response to stressors. This was investigated in a randomized placebo-controlled cross-over study where OXT was intravenously administered under two conditions: during fasting and in response to endotoxemic stress in healthy men.

Result

OXT infusion lasted 90 min and lead to significantly elevated plasma concentrations of OXT during the first 2 h [3] . In accordance with previous findings plasma ghrelin increased during fasting (placebo sessions) and changed biphasically after LPS administration with a rapid surge at 2 h followed by a continuous decline



afterwards (Fig.2.1A).

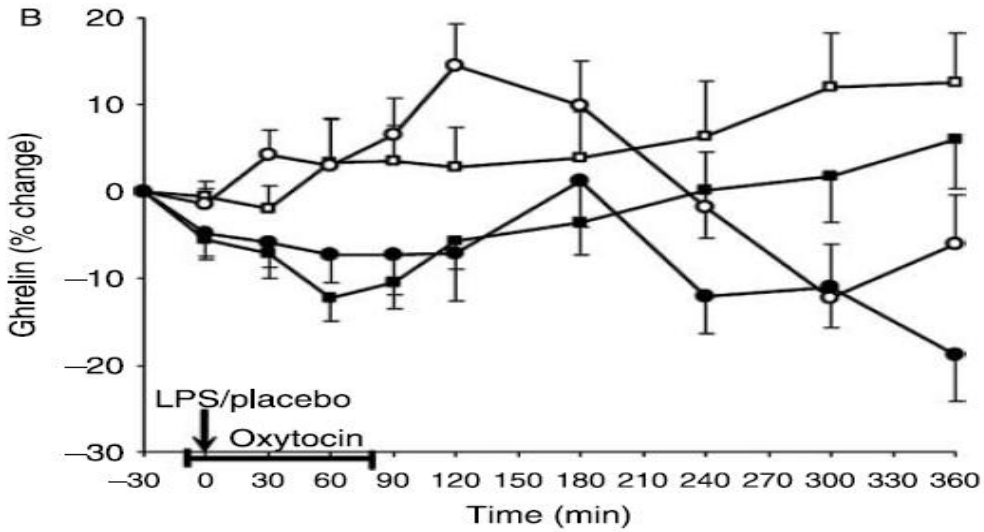


Figure 2.1 Plasma ghrelin concentrations in the 4 study days.(A) The changes in plasma ghrelin concentrations and (B) the changes in ghrelin as percent of basal values. LPS (2 ng/kg i.v.,t=0 min) induces a rapid surge in plasma ghrelin levels at t=120 min followed by a continuous decline afterwards. Oxytocin (continuous i.v. infusion of 1 pmol/kg per min between t=-10 and 80 min) decreased both basal as well as LPS-induced ghrelin concentrations during the whole-study period. Graphs show mean±S.E.M. of absolute values as well mean±S.E.M. of changes (in percent) when compared with baseline (t=-30 min).

Administration of OXT abolished the physiological increase in plasma ghrelin during fasting. Post hoc statistics identified significant changes at 60 min and at 90 min. Furthermore, OXT

significantly modified the profile of changes in ghrelin following LPS administration, leading to reduced plasma ghrelin levels 2 h following LPS administration. At time point 3 h, when plasma OXT reached baseline levels, a reduced and shifted LPS-induced ghrelin peak is observed (Fig.2.1A). The effects of OXT on ghrelin levels were also evaluated using the changes in ghrelin expressed as percent increase over basal values
Fig(2.1B).

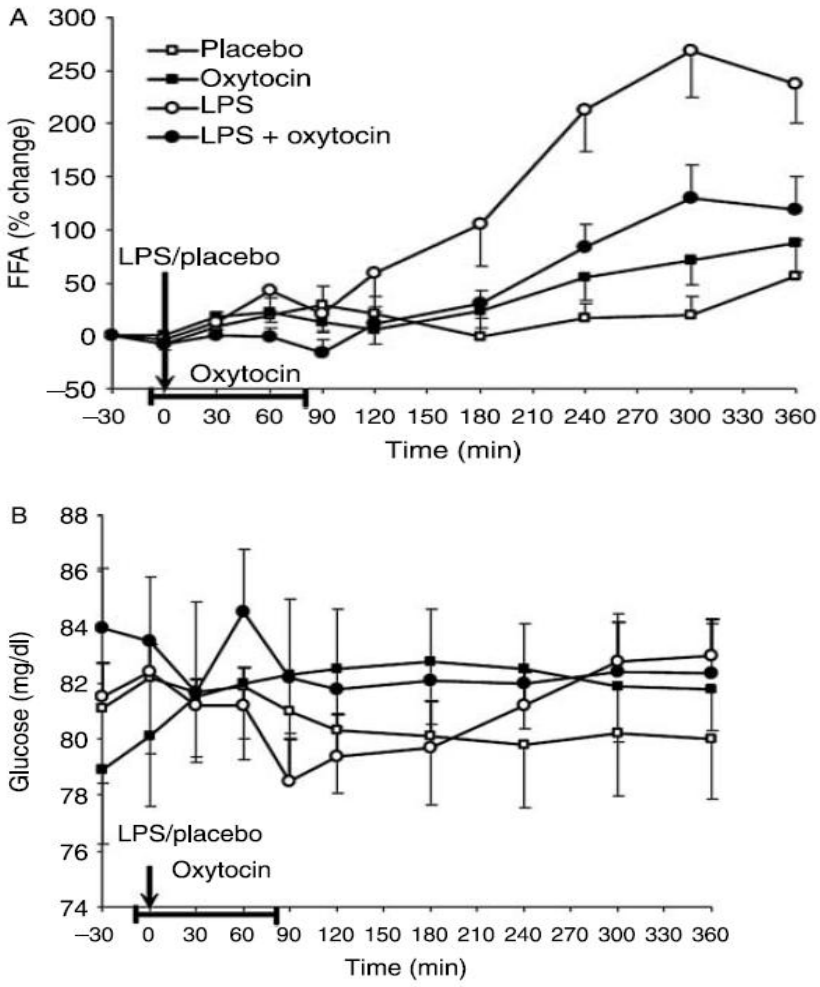


Figure 2.2 FFA and glucose levels in response to endotoxin and oxytocin. Plasma concentrations of (A) FFA (as percent change over the basal values) and glucose (B) in response to placebo, oxytocin (1 pmol/kg per min i.v. during 90 min, t=-10 min till t=80 min), LPS (2 ng/kg i.v., t=0 min), and LPS+oxytocin. Data are presented as mean ± S.E.M.

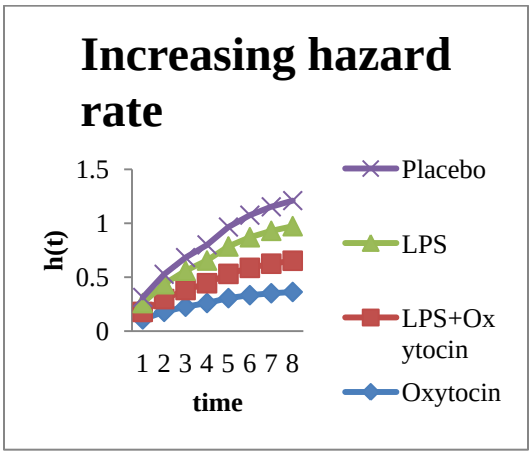
Plasma FFA levels continuously increased during fasting in the placebo days, and were further elevated in response to LPS (Fig. 2.1A). OXT increased the surge in FFA during fasting with a significant rise at time point 5 h (Fig.2. 2A). The administration of OXT reduced the FFA increase in response to LPS with post hoc tests showing significant changes at time points: 1 h, 4 h, 5 h and 6 h (Fig. 2.2A). There were no statistically significant changes in plasma glucose concentrations between placebo and LPS days (Fig. 2.2B). OXT induced a small but significant elevation of plasma glucose under basal conditions as well as after LPS administration, while post hoc tests revealed no significant changes at specific time points Fig(2.2B).

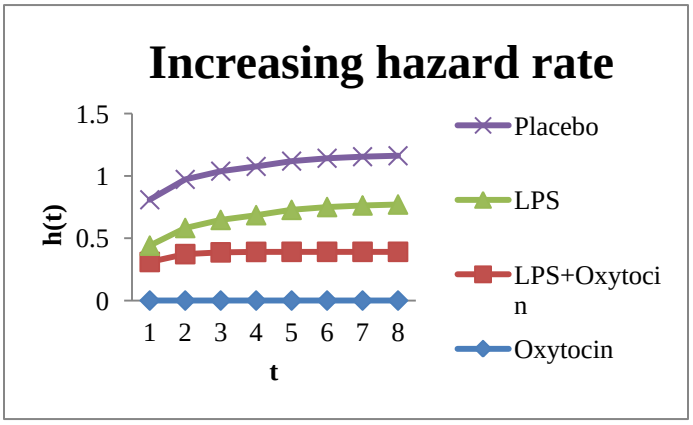
Here, show that increases in systemic OXT lead to reductions in circulating ghrelin levels both during fasting and in response to LPS (Fig. 2.1). The peripheral administration of OXT increases plasma glucose and FFA levels (Fig.2.2).

In summary, the study presents that i.v. administration of OXT reduces both basal and stress-induced systemic levels of ghrelin. The cross-talk between OXT and ghrelin might be of high importance in the regulation of energy homeostasis and stress responses

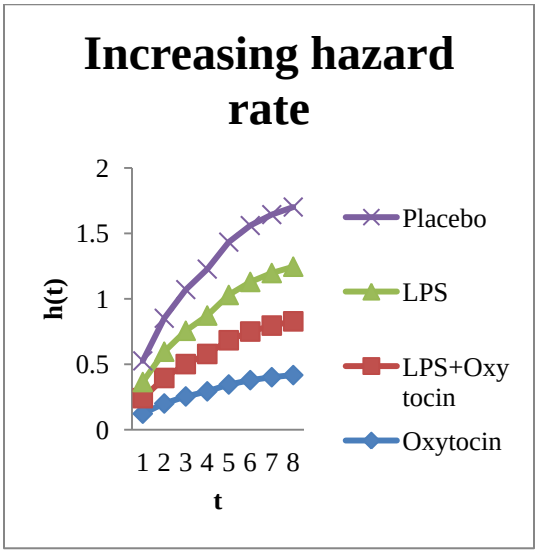
3. Mathematical result:

A. **B.**





C. **D.**



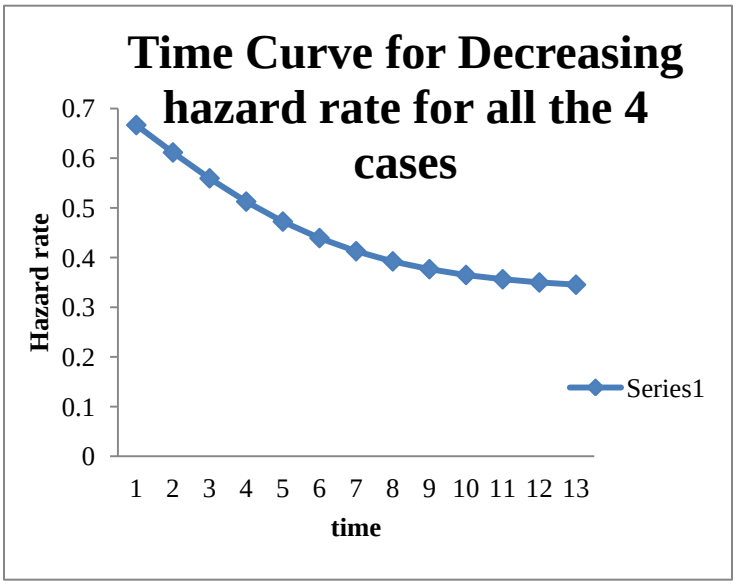


Fig 3.1 A,B,C indicates that the hazard rate function increased LPS+Oxytocin administered. In all the first three cases like grelin (pg/ml), FFA(%change),glucose(mg/dl) the curves are increased with the time axis under phase1.In Fig (D) grelin(%change) the curve is decreased with the time axis under phase2.

These results can be compared with the medical conclusions. This study presents of grelin. The cross-talk between OXT and grelin might be of high importance in the regulation of energy homeostasis and stress responses.

Conclusion

In application part by using exponential distribution the hazard rate functions for hormone levels in response to plasma concentrations grelin(pg/ml), grelin(%change) and FFA, glucose levels are obtained. These functions show a clear picture for all the above parameters when LPS+Oxytocin is administered to this cases and compared with the medical conclusions. The cross-talk between OXT and grelin might be of high importance in the regulation of energy homeostasis and stress responses. Fig 3.1 A,B,C indicates that the hazard rate function increased when LPS+Oxytocin is administered. In all the first three cases like grelin(pg/ml), FFA(%change),glucose(mg/dl) the curves are increased with the time axis. In Fig (D) grelin(%change) the curve is decreased with the time axis.

In medical conclusion show that systemic administration of OXT reduces plasma ghrelin concentrations under fasting conditions and also following endotoxemic stress in healthy men. During fasting, OXT increased both plasma glucose and FFA levels.

During endotoxemia, OXT increased plasma glucose, but decreased the LPS-induced surge in FFA. Ghrelin increases the c-fos immunoreactivity of OXT neurons, which are hypothesized to mediate some of the central effects of ghrelin. OXT infusion decreases the NPY changes in response to ghrelin in men. Nonetheless, the impact of OXT on ghrelin levels has not been studied.

References.

1.Aven, T., Jensen, U.“*Stochastic Models in Reliability*”, Springer-Verlag, 1999. (Section 2.2 is relevant, about Basci Notions of Aging.)

2.Charmandari E, Tsigos C & Chrousos G 2005 Endocrinology of the stress response. Annual Review of Physiology 67 259–284.

3.Clodi M, Vila G, Geyeregger R, Riedl M, Stulnig TM, Struck J, Luger TA &
Luger A 2008 Oxytocin alleviates the neuroendocrine and cytokine response to bacterial endotoxin in healthy men. American Journal of Physiology. Endocrinology and Metabolism 295 E686–E691.

4.Coiro V, Saccani-Jotti G, Rubino P, Manfredi G, Vacca P, Volta E &Chiodera P 2008 Oxytocin inhibits the stimulatory effect of ghrelin on neuropeptide Y levels in humans. Journal of Neural Transmission 115 1265–1267.

5. Daley, D.J., Vere-Jones, D."*An Introduction to the Theory of Point Processes*", Springer-Verlag, 1988. (See Sections 4.6,13.2).

6.Dixit VD, Schaffer EM, Pyle RS, Collins GD, Sakthivel SK, Palaniappan R, Lillard JW Jr & Taub DD 2004 Ghrelin inhibits leptin- and activationinduced proinflammatory cytokine expression by human monocytes and T cells. Journal of Clinical Investigation 114 57–66.

7.Erlang, A. K. Solution of some problems in the theory of probabilities of significance in automatic telephone exchanges. The Post Office Electrical Engineer's Journal 1917-18, 10, 189-197.

8. Hosoda H & Kangawa K 2008 The autonomic nervous system regulates gastric ghrelin secretion in rats. Regulatory Peptides 146 12–18.

9. Lakshmi.S, & Gayathri.M. "Mathematical model for Mean Residual life time of the secretion of the hormone Oxytocin". IJMS.Vol.13,No.1-2, January-June2014, pp.19-27.

11. Lakshmi.S, & Gayathri.M. "Mathematical model for Oxytocin alleviates the neuroendocrine in healthy Men". IOSR-JEN.Version 3.Volume 4,October 2014,Issue10,Verrsion 3,p-ISSN;2278-8719.

12. Last, G., Brandt, A."*Marked Point Processes on the Real Line: The Dynamic Approach*", Springer-Verlag, 1995.(See Appendix A5, Section 1.2, Section 1.6).

11. Murphy KG, Dhillo WS & Bloom SR 2006 Gut peptides in the regulation of food intake and energy homeostasis. Endocrine Reviews 27 719–727.

13. Neuts, M. F. Probability distributions of phase-type. In Liber Amicorum Prof. Emeritus H. Florin, Department of Mathematics, University of Louvain, Belgium; 1975; 173-206.

14.Windle RJ, Forsling MR & Guzek JW 1992 Daily rhythms in the hormone content of the neurohypophysial system and release of oxytocin and vasopressin in the male rat: effect of constant light. Journal of Endocrinology 133 283–290.