

A Fuzzy Delta Shock Model for the Effect of Thyrotropin Releasing Hormone

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Abstract. The theoretical study of the effect of Thyrotropin Releasing Hormone in Alzheimer's disease patients was investigated. A mathematical model using fuzzy delta shock was developed and used this model to calculate the expected time and variance of systolic blood pressure in the given time interval. The result showed that after Thyrotropin Releasing Hormone treatment, the systolic blood pressure is raised in patients.

Keywords: Thyrotropin Releasing Hormone, Alzheimer's disease, Delta shock model

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1. Introduction

Shock models provide a sensible formulation for modeling certain reliability system in a random environment. Consider a system subjected to shocks occurring randomly in time. Each shock causes damage and the damage accumulates. The system fails when the total accumulated damage exceeds a certain threshold level. In maintenance problems, an optimal replacement policy of the repairable δ – shock system is obtained by Wang and Zhang [13]. Tang and Lam [12] described the system failure by the positive quantity δ , which represent the inter-arrival time of a deterioration system. Bai et al. [1] introduced the latest developments of the single component δ –shock model. The distribution of dual δ –shock and its properties was described by Li et al. [8,9]. The developments of the δ – shock model are mostly based on homogeneous Poisson process. More research results are derived by Li et al. [9] from the perspectives of Probability and Statistics. Li et al. [9] proposed two models according to whether or not the first shock can cause system failure. Chitrakala Rani [4] discussed Maintenance model using shock model and its applications. Thyrotropin-releasing hormone (TRH) is a tripeptide (pGlu-His-Pro-NH₂) hormone that is mainly produced in the paraventricular nucleus of the hypothalamus and represents the most proximal member of the hypothalamic-pituitary-thyroid (HPT) axis [3]. The major known function of TRH is the maintenance of thyroid hormone (TH) homeostasis, via regulation of thyroid-stimulating hormone (TSH) secretion [2]. However, TRH also regulates the release of other hormones, for example, prolactin,

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growth hormone, and insulin [5,6]. TRH is also present in many brain loci out of the hypothalamus and has been found in several non-neuronal tissues of the mammalian body such as the gastrointestinal tract, heart, and reproductive organs. This suggests an additional role for this neuropeptide, well beyond its classical function within the HPT axis [10,11]. Such non classical TRH functions include a role in cardiovascular pathophysiology in experimental models and in humans, as well as in the immune system in general and rodent T-cell-dependent immune responses [14,15]. In particular, mRNA transcripts for HPT axis-related genes were detected in normal human skin and in its constituent cell populations [7]. In this paper, the expected time and variance of systolic blood pressure of Thyrotropin Releasing Hormone in Alzheimer's disease patients was calculated in the given time interval by using fuzzy delta shock model.

2. Fuzzy δ -shock model

In a δ – shock model, the system fails when the time lag between two successive shocks falls into some critical region decided by δ , a positive constant. Such a δ – shock model is different from traditional shock models because system failure only depends on the time lag. Consider a special case of δ – shock model. In this case, the system is subject to external shocks that arrive according to a Poisson process with rate λ . Let X_n ($n = 0, 1, 2, \dots$) represent the time interval between the $(n-1)^{\text{th}}$ shock and n^{th} shock. If $X_n \geq \delta$, the system can recover before the n^{th} shock arrives, and does not fail. If $X_n < \delta$, the system fails. The general setup in shock models is a family $\{A_n, B_n\}$, $n = 0, 1, 2, \dots, \infty$, of two dimensional random variable, where A_n represents the magnitude of the effect on the system from the n^{th} shock. Models are considered depending on whether B_n represents the time interval between the $(n-1)^{\text{th}}$ and n^{th} shock; or the time interval between the n^{th} and $(n+1)^{\text{th}}$ shock. Here we considered the time interval between the $(n-1)^{\text{th}}$ and n^{th} shock.

Let $\{N(t) ; t \geq 0\}$ be the underlying counting process of shock models associates with the sequences $\{B_n\}$, $n = 0, 1, \dots, \infty$. The system is assumed to be new at time $t = 0$. The magnitude X_n of the n^{th} shock is correlated to the time interval, such that $(n-1)^{\text{th}}$ shock does not affect the future events. Suppose that a shock occurs at time $t = 0$, so that the system will fail if $X_n < \delta$. The mean life time and its variance of each component is

$$\mu = E(T) = \frac{1}{\lambda(1 - e^{-\lambda\delta})}, \quad \text{Var}(T) = \frac{2\lambda\delta e^{-\lambda\delta} + 1}{[\lambda(1 - e^{-\lambda\delta})]^2}$$

In most of the times, the parameter used in the δ – shock model is not known precisely. The theory of fuzzy set can be used in solving such problems. The uncertainty existing in the parameter is resolved by assuming that the parameter is a triangular fuzzy number. The alpha cut of fuzzy mean life time is $\bar{E}(T) = [\bar{E}_l(T), \bar{E}_u(T)]$

$$\text{where } \bar{E}_l(T) = \min \left\{ \frac{1}{\bar{\lambda}(1 - e^{-\bar{\lambda}\delta})}, \bar{\lambda} \in \bar{\lambda}[\alpha] \right\}, \quad \bar{E}_u(T) = \max \left\{ \frac{1}{\bar{\lambda}(1 - e^{-\bar{\lambda}\delta})}, \bar{\lambda} \in \bar{\lambda}[\alpha] \right\}$$

The alpha cut of fuzzy variance is $\bar{V}(T) = [\bar{V}_l(T), \bar{V}_u(T)]$

$$\text{where } \bar{V}_l(T) = \min \left\{ \frac{2\bar{\lambda}\delta e^{-\bar{\lambda}\delta} + 1}{[\bar{\lambda}(1 - e^{-\bar{\lambda}\delta})]^2}, \bar{\lambda} \in \bar{\lambda}[\alpha] \right\}, \quad \bar{V}_u(T) = \max \left\{ \frac{2\bar{\lambda}\delta e^{-\bar{\lambda}\delta} + 1}{[\bar{\lambda}(1 - e^{-\bar{\lambda}\delta})]^2}, \bar{\lambda} \in \bar{\lambda}[\alpha] \right\}$$

3. Application

Thyrotropin releasing hormone (TRH) was administered intravenously to 10 patients with Alzheimer’s disease (AD) in a high-dose paradigm, thought to maximize central nervous system effects and potentially produce facilitation of cholinergic function, a known property of the neuropeptide. Acute effects of TRH on behavioral, cognitive and physiologic measures were assessed after patients received 0.3 mg/kg TRH and placebo, the higher TRH dose and placebo being given in a randomized, double-blind fashion. The systolic blood pressure response to the higher TRH dose is depicted in Table: 3.1. Patients showed statistically significant increases in arousal and improvement in effect, as well as a modest improvement in semantic memory, all after receiving the higher TRH dose. Both TRH doses produced transient rises in systolic blood pressure, with no effect on diastolic blood pressure, heart rate or temperature. There were also no significant correlations between peak change in systolic BP and any behavioral or cognitive measures.

Time after infusion	3	5	10	15	20	25	30
Systolic BP(mm/Hg)	144	149	135	132	135	138	137

Table 3.1: The systolic blood pressure response to the higher TRH dose

The scale parameter of exponential distribution for the systolic blood pressure response to the higher TRH doses is 0.007 and the triangular fuzzy number is $\bar{\lambda}=[0.004, 0.007, 0.009]$ and the corresponding α cuts are $\bar{\lambda}[\alpha]=[0.004+0.003\alpha, 0.009-.002\alpha]$. Under the alpha cut zero, the fuzzy expected value for the systolic blood pressure response to the higher TRH doses for various δ values are calculated from $\bar{E}(T) = [\bar{E}_l(T), \bar{E}_u(T)]$ and shown in Table 3.2. Also the fuzzy variances are calculated from $\bar{V}(T) = [\bar{V}_l(T), \bar{V}_u(T)]$ and shown in Table 3.3. The mean and variance for the various δ values are shown in Fig. 3.1, 3.2 and Fig. 3.3, 3.4 respectively.

α	$\delta=2$		$\delta=3$		$\delta=4$		$\delta=5$	
	$\bar{E}_l(T)$	$\bar{E}_u(T)$	$\bar{E}_l(T)$	$\bar{E}_u(T)$	$\bar{E}_l(T)$	$\bar{E}_u(T)$	$\bar{E}_l(T)$	$\bar{E}_u(T)$
0	31375.16	6228.56	20958.58	4171.03	15750.33	3142.30	12625.4 1	2525.10
0.1	27158.08	6513.59	18144.29	4361.47	13637.43	3285.45	10933.3 5	2639.87
0.2	23738.35	6818.71	15861.93	4565.33	11923.77	3438.67	9560.90	2762.70
0.3	20926.86	7145.85	13985.39	4783.88	10514.70	3602.94	8432.32	2894.40
0.4	18587.44	7497.19	12423.82	5018.59	9342.04	3779.33	7493.02	3035.81
0.5	16620.00	7875.16	11110.44	5271.08	8355.70	3969.08	6702.89	3187.91
0.6	14949.63	8282.54	9995.29	5543.20	7518.16	4173.57	6031.92	3351.83
0.7	13519.38	8722.46	9040.38	5837.04	6800.92	4394.37	5457.28	3528.81
0.8	12285.32	9198.48	8216.39	6154.95	6181.97	4633.27	4961.35	3720.28
0.9	11213.13	9714.67	7500.43	6499.73	5644.12	4892.30	4530.37	3927.88
1	10275.67	10275.67	6874.39	6874.39	5173.80	5173.80	4153.47	4153.47

Table 3.2: Mean of Systolic blood Pressure at various δ Values

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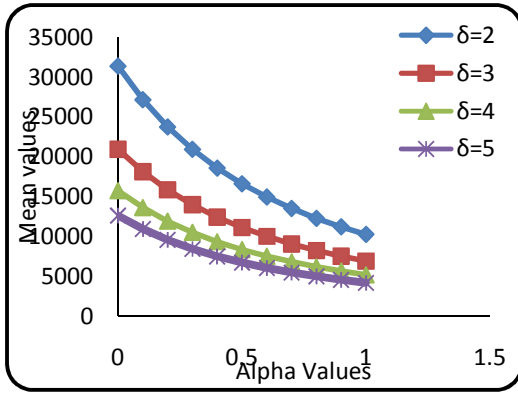


Figure 3.1: Lower α cut for the mean

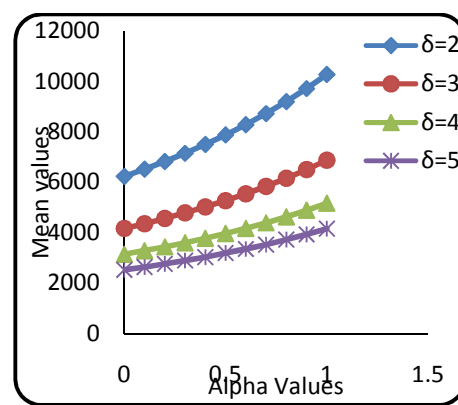


Figure 3.2: upper α cut for the mean

α	$\delta=2$		$\delta=3$		$\delta=4$		$\delta=5$	
	$\bar{V}_l(T)$	$\bar{V}_u(T)$	$\bar{V}_l(T)$	$\bar{V}_u(T)$	$\bar{V}_l(T)$	$\bar{V}_u(T)$	$\bar{V}_l(T)$	$\bar{V}_u(T)$
0	1000026000	40166686	449678757	18311946	255885333	10559900	165650937	6924774
0.1	750139276	43894312	337600215	20000689	192268218	11527859	124569026	7555833
0.2	573782970	48067054	258450118	21890307	147313081	12610525	95520260	8261403
0.3	446433423	52750433	201257746	24010291	114808759	13824696	74503795	9052369
0.4	352605010	58021521	159092521	26395321	90829742	15190118	58989980	9941522
0.5	282234903	63971333	127448861	29086340	72822947	16730101	47332870	10943958
0.6	228616688	70707787	103322688	32131882	59085384	18472264	38434101	12077559
0.7	187179288	78359395	84665538	35589725	48455293	20449481	31544064	13363601
0.8	154743804	87079881	70052213	39528963	40124046	22701051	26140783	14827517
0.9	129059149	97054005	58473044	44032615	33518534	25274183	21854158	16499844
1	108504939	108504939	49200933	49200933	28225865	28225865	18417440	18417440

Table 3.2: Variance of systolic blood pressure at various δ values

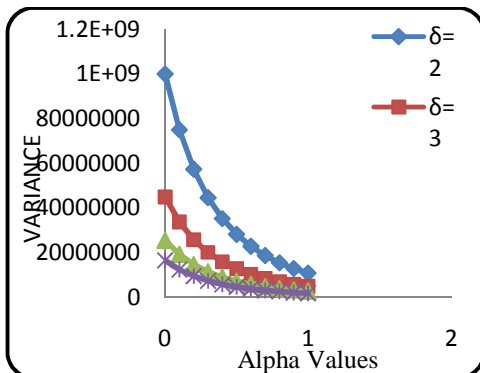


Figure 3.3: Lower α cut for the variance

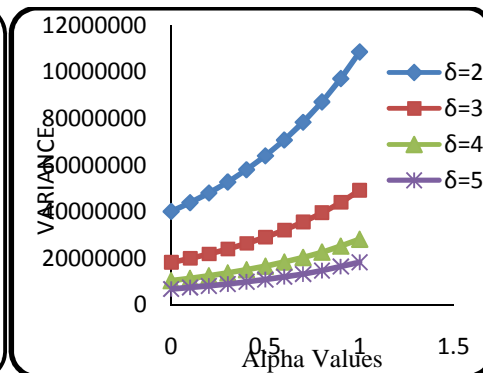


Figure 3.4: Upper α cut for the variance

4. Conclusion

In this study we showed that the fuzzy mean and variance for the systolic blood pressure after TRH treatment is decreased in the lower α cuts and they are increased in the upper α cuts by using fuzzy delta shock model. This study suggests that high – dose TRH can be safely administered to AD patients and is neurobehavioral active. The precise mechanism of the presser effect of TRH is unknown, although it is thought to involve central stimulation of the sympathetic nervous system. Further studies are needed to determine the extent and mechanism of the cognitive and psychobiological properties of this peptide in AD and other neuropsychiatric disorders.

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