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Study on the Feedback of Stress Responsive Hormones CRH/AVP in HPA Axis by Residual Life Reliability Function with Hazard Rate Due to Human Stress

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Abstract: ***A study on given that a unit of age‘t’ the remaining life after time t is random. It is well known that the class of distribution with decreasing mean residual life (DMR) contains the class of distribution with increasing hazard rate. If exponential length-biased approximations, bounds and stability results on the distance between residual life reliability functions, with monotone weight functions and exponential counterpart in the class of distribution functions with increasing or decreasing hazard rate functions are established. In the applications part, biologically available cortisol feedback on hypothalamic CRH/AVP and pituitary ACTH outputs by way of both delayed (time-integrated) and rapid (rate-sensitive) inhibitory mechanisms. We incorporate these dynamic relationships in a core biostatistical construct of coupled integral differential equations along with biological variability.***
Keywords: Mean residual hazard rate, DMR, DHR reliability function, CRH/Arginine vasopressin.

I. INTRODUCTION

The stress-responsive hypothalamo-adrenocorticotropic (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 [11, 4].

Episodic secretion is driven by hypothalamic neuronal pacemakers, which secrete the pituitary signaling peptides CRH (ACTH-releasing hormone) and AVP (arginine vasopressin) [9,13]. These agonists singly and synergistically stimulate ACTH synthesis and secretion (feedforward), 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 (servocontrol) system governed by nonlinear and time-delayed feedforward and feed-back signal interchanges. We postulate that such interactive properties generate the observed complex dynamics of this dynamics.

II. CRH/AVP of HYPOTHALAMUS FEEDBACK and PULSE GENERATOR

The interval-averaged blood cortisol concentration (μg/dl) exerts time-delayed (60-80 min) integral feedback, and the rate of change of blood cortisol concentration imposes rapid (5-30 min) rate-sensitive feedback, on CRH/AVP synthesis/secretion (pg/ml per h; Fig.2). The foregoing primary connections do not exclude the existence of other within-axis interactions: e.g., the blood cortisol concentration (μg/dl) might also exert slow (integral) negative feedback on basal ACTH release or the CRH/AVP pulse-firing rate(s). To represent the diversity among individuals, we allow for variations in *in vivo* hormone elimination rates, the degree of CRH/AVP synergism and ACTH priming of cortisol synthesis/secretion, the amplitude and phase of the circadian rhythm, and dose-response parameters.

Conversely, we consider structural mechanisms, such as the pulse shapes for CRH/AVP and ACTH secretion as populationally defined and relatively consistent among subjects. We envision that hypothalamic pulse generators for CRH and AVP drive episodic ACTH release after a slight time delay and poststimulus refractory interval.

For simplification, we consider CRH and AVP as a combined feedforward signal, wherein corticotropic synergy is achieved by

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modifying the joint CRH/AVP dose-response curve (below).

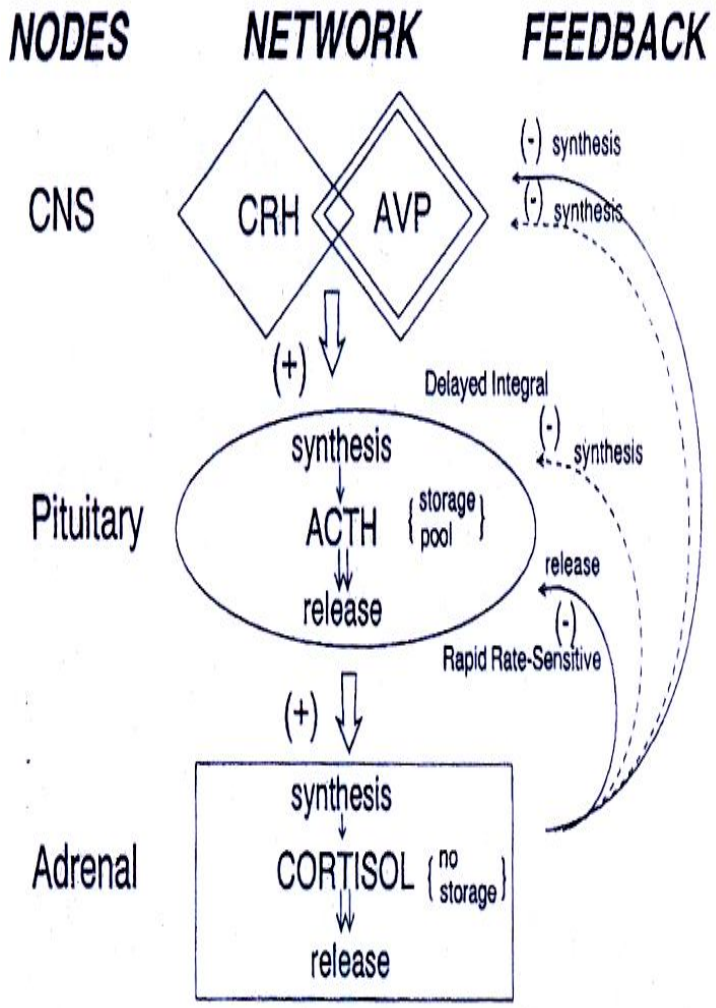

Figure 2. Schematized core model of the interconnected CRH/AVP (hypothalamo)-ACTH (pituitary)-cortisol (adrenal) stress-adaptive axis. Feedforward and feedback interfaces are incorporated via nonlinear dose-response (H) functions, which mediate time-lagged rate-sensitive (differential) and concentration-dependent (integral) internodal signaling. In principle, circadian inputs could modulate any of the foregoing interface functions, time-delays, and/or signaling kinetics.

III. APPLICATION

The present formalism explores the thesis that neuroendocrine ensembles operate homeostatically via organ-specific and time-delayed dose-responsive facilitative or inhibitory interactions. To this end, we embody dynamics of the corticotropic axis via a biomathematical model, wherein relevant dose-response interfaces serve to couple changing hypothalamic-pituitary portal venous CRH/AVP concentrations to time-delayed stimulation of corticotrope ACTH biosynthesis and secretion. In turn, varying systemic blood ACTH concentrations drive nonlinear dose-responsive oscillations in cortisol secretion by steroidogenically responsive adrenal zona-fasciculata cells.

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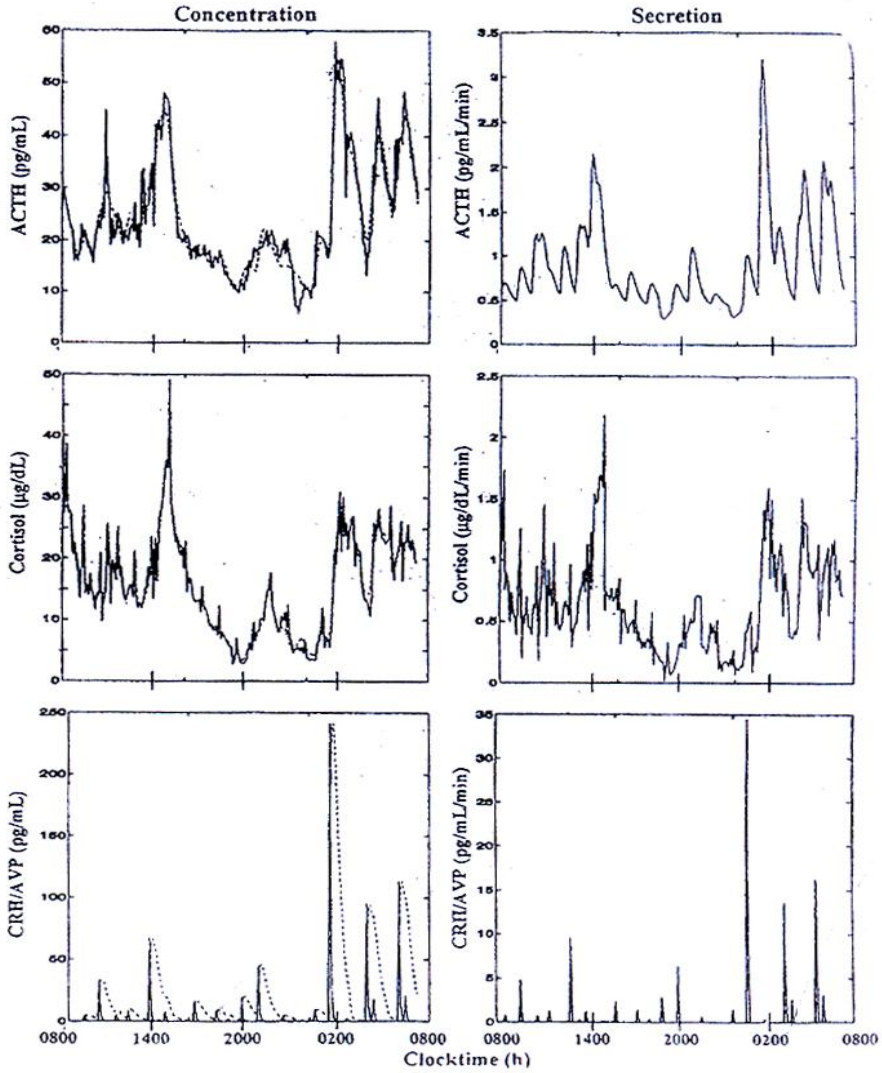

Fig.3. (Left column) Fitted (observed) plasma ACTH (Top) and cortisol (Middle) concentrations and predicted (unobserved) CRH/AVP (Bottom) concentrations in one healthy young male, sampled every 7 min for 24 h. The dotted line in the left bottom subpanel shows the effective CRH/AVP feed-forward signal on ACTH synthesis. (Right column) Corresponding secretion rates are estimated for ACTH (Top), cortisol (Middle) and the conjoint CRH/AVP signal (Bottom).

Biologically available cortisol feedsback on hypothalamic CRH/AVP and pituitary ACTH outputs by way of both delayed (time-integrated) and rapid (rate-sensitive) inhibitory mechanisms. We incorporate these dynamic relationships in a core biostatistical construct of coupled integral differential equations along with biological variability.

We assume that CRH/AVP signaling dictates the pulse times for ACTH after a finite time delay T_A, reflecting hypothalamo-Pituitary portal blood transit, and a poststimulus refractory interval, r_A, when further CRH/AVP inputs are ignored. Thus, there will be two corresponding sets of pulse times: $T^0_{C/V}$, $T^1_{C/V}$, $T^2_{C/V}$ ..... and T^0_A, T^1_A, T^2_A ..... where $T^k_A = [\mathrm{Min}_j\{T^j_{C/V} / T^j_{C/V} \geq T^{k-1}_A + r_A\}] + \tau_A$ with $T^0_{C/V} \leq 0, T^0_A = T^0_{C/V} + \tau_A$.

Let N (t) denote the counting process associated with the ACTH pulse times. Here, we view the pulse times as a Weibull renewal process, where λ a rate parameter (number of pulses/day) parameter is and γ controls the regularity of interpulse interval lengths

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[10]. Then, the conditional probability densities for $T_{C/V}^{k}$ given $T_{C/V}^{k-1}$ are given by:

$$p(s|T_{C/V}^{k-1}) = \gamma \times \lambda^{\gamma}(s - T_{C/V}^{k-1})^{\gamma-1} \exp^{-\lambda^{\gamma}(s-T_{C/V}^{k-1})^{\gamma}}$$

We denote a time-averaged feedback signal at time t with time delay (l_1, l_2) by:

$$\int_{t-l_1}^{t-l_2} Y(r)\,dr = \frac{1}{l_1 - l_2}\int_{t-l_1}^{t-l_2} Y(r)\,dr \ ,$$

where Y(r) is either a hormone concentration or its rate of change at time r.

In what follows, the subscripted numerics 1-7 for the interface (H) functions denote corresponding feedback/feed forward interactions (see Fig.1): viz., ACTH synthesis (Subscript 1,2) and release (subscript 3,4) are each joint functions of time-delayed CRH/AVP feed forward and slow and rapid cortisol feedback signals, respectively.

CRH/AVP synthesis is analogously controlled jointly by respectively rapid and slow cortisol feedback (subscript 6,7). In refs. 7 and 15, we show that the mathematical effect of cascading target-tissue reactions to a signal input is the multiplication of the initial feedback/feed forward signal by a linear combination of exponential functions, denoted by $\Gamma_{C/V}(.)$ and $\Gamma_{A}(.)$ which allows ongoing glandular responses after the signal is with drawn. Let $\psi_{A}(.)$ and $\psi_{C/V}(.)$ represent the normalized rates of secretion per unit mass per unit distribution volume per unit time; these rates are presently modeled as 3-parameter generalized gamma densities

[5,12]. Accordingly, synthesis (S), release ®, accumulation (A), and fractional mass remaining for later secretion (ψ) are given as:

$$S_A(t) = H_{1,2}\left(\int_{T_A^{N(t)}-l_{1,2}}^{T_A^{N(t)}-l_{1,1}} X_{C/V}(s)ds \times \Gamma_{C/V}(t - T_A^{N(t)}), \int_{t-l_{2,2}}^{t-l_{2,1}} X_c(s)ds\right)$$

(ACTH synthesis),

$$R_A(t) = H_{3,4}\left(\int_{T_A^{N(t)}-l_{3,2}}^{T_A^{N(t)}-l_{3,1}} X_{C/V}(s)ds \times \Gamma_{C/V}(t - T_A^{N(t)}), \int_{t-l_{4,2}}^{t-l_{4,1}} \frac{dX_C(s)}{ds}ds\right)$$

(ACTH release).

$$A_A^j = \int_{T_A^{j-1}}^{T_A^j} (1 - R_A(t))S_A(t)dt$$

(Storage of newly synthesized ACTH granules),

$$\psi_A(T_A^{j-1}, T_A^j) = 1 - \int_{T_A^{j-1}}^{T_A^j} \psi_A(s - T_A^{j-1})ds$$

(Fractional mass M_A^{j-1} remaining at time T_A^j)

$$M_A^j = \psi_A(T_A^{j-1}, T_A^j)M_A^{j-1} + A_A^j \qquad \text{(ACTH pulse mass secreted),}$$

$$S_{C/V}(t) = H_{6,7}\left(\int_{t-l_{6,2}}^{t-l_{6,1}} X_C(s)ds, \int_{t-l_{7,2}}^{t-l_{7,1}} \frac{dX_C(s)}{ds}ds\right) \qquad \text{(CRH/AVP synthesis),}$$

$$A_{C/V}^j = \int_{T_{C/V}^{j-1}}^{T_{C/V}^j} S_{C/V}^{(t)}dt \qquad \text{(CRH/AVP mass accumulated),}$$

$$\psi_{C/V}(T_{C/V}^{j-1}, T_{C/V}^j) = 1 - \int_{T_{C/V}^{j-1}}^{T_{C/V}^j} \psi_{C/V}(s - T_{C/V}^{j-1})ds$$

(Proportion of mass remaining for secretion),

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$$M_{C/V}^{j} = \psi_{C/V}(T_{C/V}^{j-1}, T_{C/V}^{j}) M_{C/V}^{j-1} + A_{C/V}^{j}, \quad \text{(CRH/AVP pulse mass secreted)}$$

Based on the above constructions, the corresponding interactively controlled rates of secretion are given as:

$$Z_A(t) = \beta_A + M_A^j \Psi_A(t + T_A^j) + R_A(t) S_A(t) \text{ for } T_A^j \le t < T_A^{j-1}$$

$$Z_C(t) = \beta_C + H_5\left(\int_{t-l_{5,2}}^{t-l_{5,1}} X_A(s) \Gamma_A(t - l_{5,1} - s) ds \right)$$

$$Z_{C/V}(t) = \beta_{C/V} + M_{C/V}^{j} \psi_{C/V}(t - T_{C/V}^{j}) \quad \text{for} \quad T_{C/V}^{j} \le t < T_{C/V}^{j+1}$$

IV. MATHEMATICAL MODEL

The applications of weighted distribution to biased samples in various areas usefulness and including medicine, ecology, reliability, and branching processes can be seen in Patil and Rao (1978), Gupta and Kirmani (1990), Gupta and Keating (1985), Oluyede (1999) and in reference therein [7,1,2,6]. When data is unknowingly sampled from a weighted distribution as opposed to the parent distribution, the survival function, hazard function, and mean residual life function (MRLF) may be under or overestimated depending on the weight function. It is well known that the length of size-biased distribution of an increasing failure rate (IFR) distribution is always IFR. The converse is not true.

Also, if the weight function is monotone increasing and concave, then the weighted distribution of an IFR distribution is an IFR distribution. Similarly the size-biased distribution of a decreasing mean residual (DMRL) distribution has decreasing mean residual life. The residual life at age *t*, is a weighted distribution, with survival function given by

$$\bar{F}_t(x) = \bar{F}(x+t) / \bar{F}(t) \qquad \text{…. (4.1)}$$

for $x \ge 0$. The weight function is $W(x) = f(x+t) / f(x)$, where $f(u) = dF(u)/du$, the hazard function and mean residual life functions are $\lambda_{F_t}(x) = \lambda_F(x+t)$ and $\delta_{F_t}(x) = \delta_F(x+t)$. It is clear that if *F* is IFR (DMRL) distribution, then F_t is IFR (DMRL) distribution, where the hazard function $\lambda_F(x)$ and mean residual life function $\delta_F(x)$ of the distribution function *F* are given by $\lambda_F(x) = f(x)/\bar{F}(x)$, and $\delta_F(x) = \int_x^\infty \bar{F}(u)du / \bar{F}(x)$ respectively. The functions $\lambda_F(x), \delta_F(x),$ and $\bar{F}(x)$ are equivalent [8].

Keilson (1979) suggested a measure of departure from exponentially within the class of completely monotone distributions [3], (mixture of exponential distributions). These measures of departure are given in terms of $\rho = |1 - \mu_2 / 2\mu^2|$, where $\mu_2 = E(X^2)$ and $\mu = E(X)$.

V. SHIFTED EXPONENTIAL DISTRIBUTION

Consider the survival or reliability function given by

$$\bar{F}(x;\theta,\in) = \begin{cases} e^{-(x-\theta)/(1-2\in)^{1/2}} & \text{if } x > \theta, \quad \theta = 1-(1-2\in)^{1/2} \\ 1 & \text{otherwise} \end{cases}$$

Clearly, the first and second moments of *F* are $\mu = 1$ and $\mu_2 = 2(1-\in)$ respectively. Since the failure rate function $\lambda_F(x)$ is increasing, we obtain,

$$L(\in) = \int_0^\infty \left| \bar{F}_t(x) - e^{-(x-\theta)/(1-2\in)^{1/2}} \right| dx$$

$$\le 2\mu \left| 1 - \frac{\mu_2}{2\mu^2} \right|$$

$$= 2\left| 1 - 2(1-\in)/2 \right|.$$

Consequently,

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$$L(\in) = \int_0^{\infty} \left| \bar{F}_t(x) - e^{-(x-\theta)/(1-2\in)^{1/2}} \right| dx \le 2 \in .$$

A. Theorem

If $\bar{F}_t(x)$ is a DHR reliability function, then

$$\int_0^{\infty} \left| \bar{F}_t(x) - (1 + x/(\mu + t))e^{-x/\mu} \right| dx \ge 2 \max\left\{0, \mu e^{-(\in + t)/\mu} - \frac{\mu + t + 1}{\mu + t}\right\}$$

$$= \max\{0, K(\in, \mu, \theta)\} \text{ say}$$

B. Proof

Let $\bar{F}_t(x)$ be a DHR survival function, then there exist $\in \ge \mu$ such that $\bar{F}_t(x) \le (1 + x/(\mu + t))e^{-x/\mu}$ or $\bar{F}_t(x) \ge (1 + x/(\mu + t))e^{-x/u}$ as $x \le \in$ or $x \ge \in$. Now,

$$\int_0^{\infty} \left| \bar{F}_t(x) - \left(1 + \frac{x}{\mu + t}\right) e^{-x/\mu} \right| dx = 2 \int_{\in}^{\infty} \left(\bar{F}_t(x) - (1 + x/(\mu + t))e^{-x/\mu} \right) dx$$

$$\ge 2 \int_{\in}^{\infty} \left(\bar{F}_t(x + t) - \left(1 + \frac{x}{\mu + t}\right) e^{-x/\mu} \right) dx$$

$$= 2S_1(\in + t) - 2 \int_{\in}^{\infty} \left(1 + \frac{x}{\mu + t}\right) e^{-x/\mu} dx$$

$$\ge 2S_0(\in + t) - 2 \int_0^{\infty} \left(1 + \frac{x}{\mu + t}\right) e^{-x/\mu} dx$$

$$\ge 2\left(\mu e^{-(\in + t)/\mu} - \mu - \frac{\mu}{\mu + t} \right)$$

$$= 2\mu \left(e^{-(\in + t)/\mu} - \frac{\mu + t + 1}{\mu + t} \right)$$

The first inequality follows from the fact that $\bar{F}_t(x) \ge \bar{F}(x + t)$ for all $x \ge 0$.

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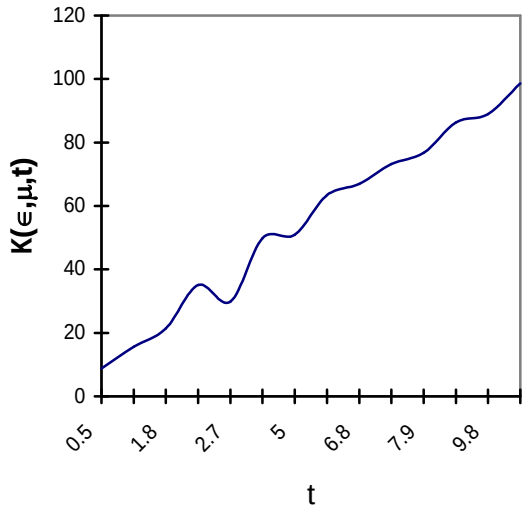
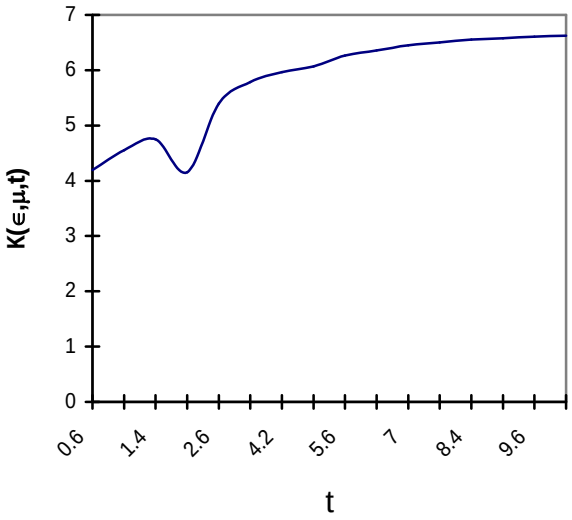
VI. MATHEMATICAL RESULT

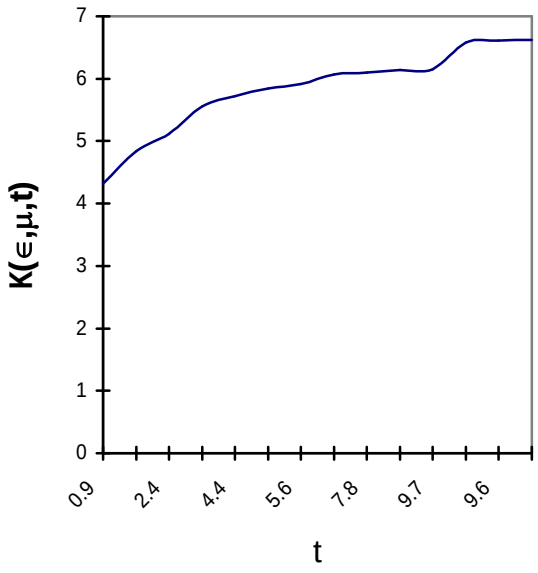
If μ = 3.4381



μ = 3.2528



μ = 3.3236



μ = 3.1656

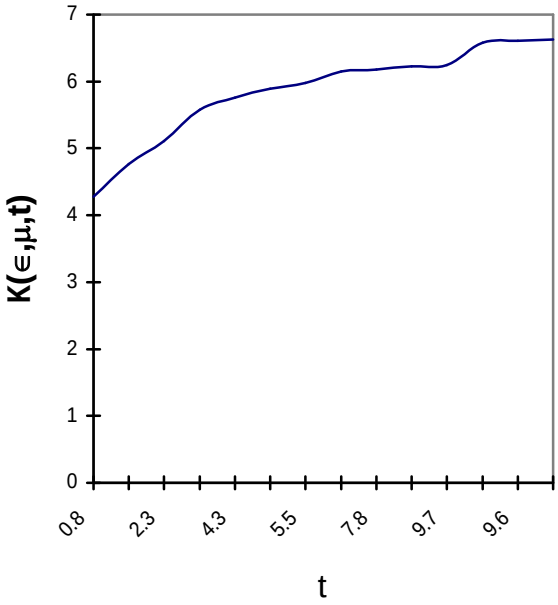


Fig.6

VII. CONCLUSION

In this Paper, exponential-length biased approximation, bounds and stability results on the distance between residual life reliability functions with monotone weight functions and the exponential counterpart in the class of distribution function with increasing or decreasing hazard rate. In the application part figure 3 gives the observed ACTH/Cortisol and predicted conjoint of CRH/AVP. Particularly concentrated on the behavior of CRH/AVP pulse-times based on simultaneous measurements of two of the three signals. It's mean is calculated from the figure and corresponding DHR reliability function for the mean is discuss particularly the function K (∈,μ,θ) is arrived in the figure 6 from the mathematical result.

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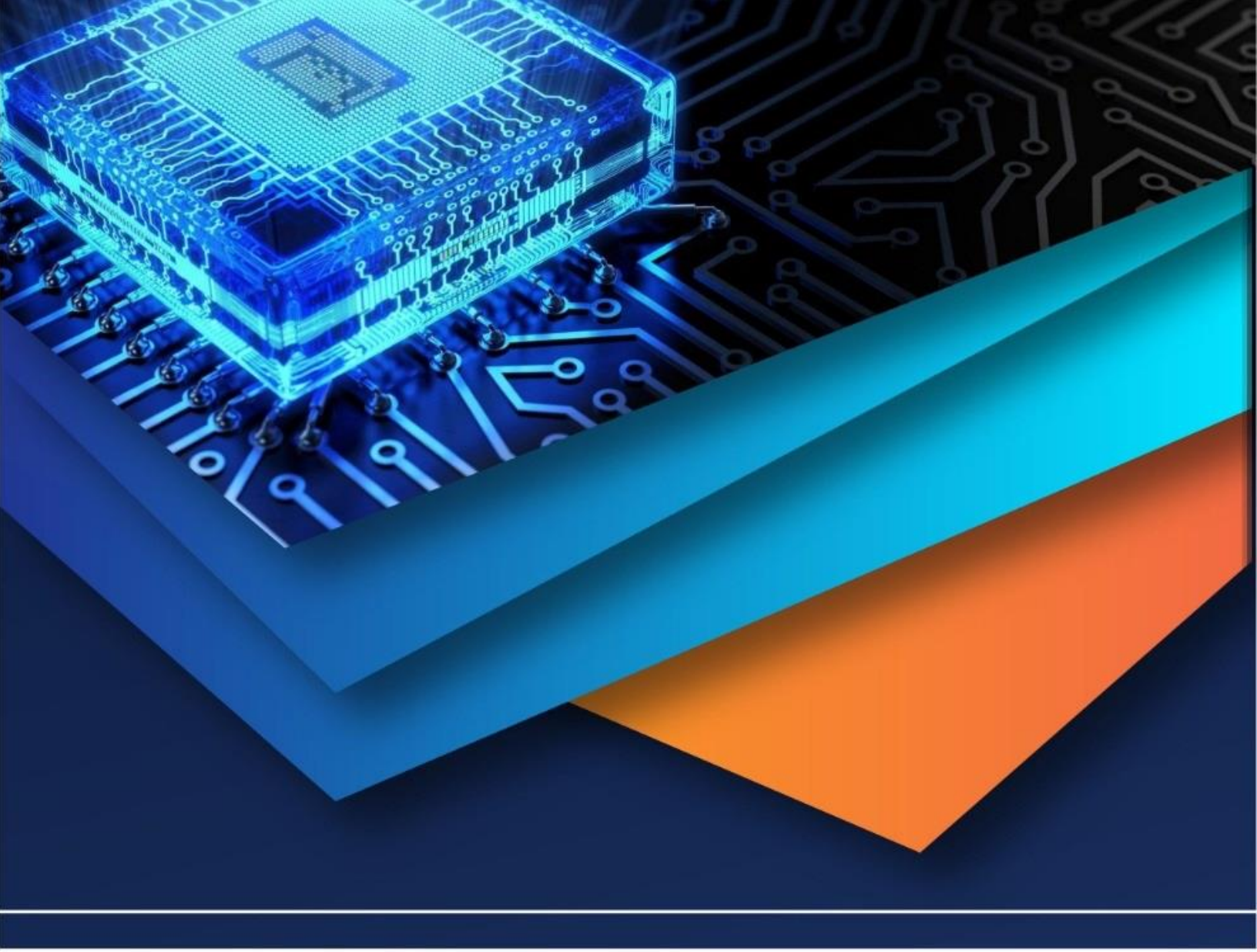
REFERENCES

[1] Gupta, R.C., and S.N.U.A. Kirmani. The Role of Weighted Distributions in Stochastic Modeling. Communications in Statistics, 19(9) (1990), 3147-3162.
[2] Gupta, R.C., and J.P. Keating. Relations for Reliability Measures under Length Biased Sampling. Scandinavian Journal of Statistics, 13(1985).
[3] Kielson. J. Markov Chain Models-Rarity and Exponentiality. Springer-Verlag, New York (1979).
[4] Loudon, A.S.I., Wayne, N.L., Krieg, R.J., Iranmanesh, A., Veldhuis, J., and Menaker, M. Endocrinology, 135 (1994), 712-718.
[5] .Mathier, L., Perreault, L., Bobee, B. and Ashkar, F The use of geometric and Gamma related distributions for frequency analysis of water deficit, stochastic hydrology and Hydraulics 6, (1992) 239 -254.
[6] Oluyede, B.O. On Inequalities and Selection of Experiments for Length-Biased Distributions, Probability in the Engineering and Informational Sciences, 13 (1999), 169-185.
[7] Patil, G.P., and C.R. Rao. Weighted distributions and size-biased sampling with applications to wildlife and human families. Biometrices, 34 (1978), 179-189.
[8] Ross, S.M. Stochastic Processes. Wiley, New York (1983).
[9] Rivier, J., Spiess, J., and Vale, W.W. Proc. Natl. Acad. Sci. USA, 80 (1983), 4851-4855.
[10] Saralees Nadarajah. On the moments of the modified weibull distribution Reliability Engineering and System Safety, Vol. 90, (2005), pp-114-117.
[11] T.F., and Hellman, L. J. Clin. Endocrinol., 33 (1971), 14-22.
[12] Van Noortwijk, J.M. (2009), A survey of the Applications of Gamma Processes in Maintenance, Reliability Engineering and System, Safety, Vol 94, PP.2-21.
[13] Weitzman, E.D., Fukushima, D., Nogeire, C., Roffwarg, H., Gallagher, Vale, W.W., Spiess, J., Rivier, J. Science, 213 (1981), 1394-1397.



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