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A MATHEMATICAL MDDI MODEL FOR DIFFERENTIAL ORDERLINESS OF THE GH RELEASE PROCESS IN HUMAN AND ANIMALS

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Abstract: In this paper, we introduce the minimum dynamic discrimination information (MDDI) approach to probability modeling our results lead to MDDI characterizations of many well-known life time models and to the development of application part. Male and female specific modes of episodic growth hormone release are presumptively imposed by sex-steroid hormones are vividly distinguished contractively viva, a regularity statistic approximate entropy (ApEn), in both the rat and human. We here investigate the orderliness of the growth hormone release process by the MDDI model relative to the exponential distribution which are monotonically concave downward functions.

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

Keywords: ApEn, GH, MDDI.

1. INTRODUCTION

Laplace's principal of insufficient reason says to distribute probability uniformly in the absence of any constraint on the probabilities. The maximum entropy (ME) principle extends this to the production of probability models close to uniform which are least sensitive to Information other than that explicitly taken into account via some moment constraints (Jaynes, (1982)). The minimum discrimination information (MDI) or minimum cross entropy principle is a generalization of the ME principle for the development of models close to any given distribution. Recently, a maximum dynamic entropy (MDE) procedure for developing life time models has been proposed. The ME and MDI procedures (i.e, those based on the Corresponding principles) use the calculus of variations, while the MDE procedure uses differential inequalities and hazard ordering. In this paper, we used the minimum dynamic discrimination information (MDDI), or dynamic minimum cross-entropy, approach to probability modeling. In this procedure, models a derived using simple residual moment inequalities, differential residual moment inequalities.

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2. MEAN RESIDUAL LIFE CONSTRAINTS

Consider a set of distribution $\Omega_F = \{F\}$, where F has PDF f and is absolutely continuous with respect to reference distribution G that has PDF g. The MDDI model in Ω_F relative to G is F^*, with PDF f^* such that $K(f^* : g, t) \le K(f : g; t)$ for all $t \ge 0$. That is , among all the residual PDFs $f(x; t)$ induced by all member of Ω_F, the MDDI model $F^* \pounds \Omega_F$ is that whose residual PDF $f^*(x; t)$ retains its MDI property for all $t \ge 0$. The following theorem gives the properties of the MDDI distributions in classes of distributions with mean residual life inequality constraints.

Theorem 2.1: Let $\Omega_F = \{F : \mu_F(t) \le q(t)\}$ be a compact set of distributions, where F is absolutely continuous with respect to a reference distribution G. Let $F^* \in \Omega_F$ be such that $\mu_F(t) = q(t)$. If $\log(f^*(x)/g(x))$ is decreasing and concave then F^* is the MDDI distribution relative to G. The same result holds, with

$$\Omega_F = \{F : \mu_F(t) \ge q(t)\}, \text{ if } \log(f^*(x)/g(x)) \text{ is increasing and convex.}$$

Proof: We will prove the case in which $\mu_F(t) \le q(t)$.

First note that

$$K(f : g; t) = \int_t^\alpha (f(x;t) \log f(x;t))\, dx / g(x;t)$$

$$= \int_t^\alpha (f(x;t) \log f*(x;t))\, dx / g(x;t) + \int_t^\alpha (f(x;t) \log f(x;t))\, dx / f*(x;t)$$

$$\ge \int_t^\alpha (f(x;t) \log f*(x;t))\, dx / g(x;t). \qquad (1)$$

Where the inequality is due to the fact that the second integral in (1) equals $K(f : f^*; t) \ge t$. This gives

$$K(f : g; t) - K(f^* : g; t)$$

$$\ge \int_t^\alpha (f(x;t) \log f*(x;t))\, dx / g(x;t) - \int_t^\alpha (f*(x;t) \log f*(x;t))\, dx / g(x;t)$$

$$= \int_t^\alpha (f(x;t) \log f*(x))\, dx / g(x) - \int_t^\alpha (f*(x;t) \log f*(x))\, dx / g(x)$$

Since $\log(f^*(x)/g(x))$ is decreasing and concave and $\mu_F(t) \le q(t) = \mu F^*(t)$, the last inequality Follows from Theorem 3.A.13 of shaked and shantikumar (1994). The proof for $\mu_F(t) \ge q(t)$ is Similar. When G has a uniform PDF over $\{x : 0 < x < b\}$, the residual model life PDF $g(x; t)$ is also Uniform over $\{x : t < x < b\}$ and the MDDI model reduces to the MDE model. The MDE model in a set of distributions $\mu_F = \{F\}$ is the distribution with PDF $f^*(x)$ such that $H(f; t) \le H(f^*; t)$, for all $t \ge 0$.

Corollary 2.1.1: Let $\Omega_F = \{F : \mu_F(t) \leq q(t)\}$ be a compact set of absolutely continuous Distributions. Let $F^* \in \Omega_F$ be such that $\mu_{F^*}(t) = q(t)$ if $f^*(x)$ is increasing and log convex. Then F^* is the MDE distribution. The same results holds, with $\Omega_F = \{F : \mu_F(t) \geq q(t)\}$. If $f^*(x)$ is decreasing and log-concave.

3. MDDI MODEL RELATIVE TO THE EXPONENTIAL DISTRIBUTION, WITH MEAN RESIDUAL INEQUALITY CONSTRAINT

For generalized normal combination:

$$f^*(x) = e\text{^}(\beta\text{^}2/2\alpha)/\beta\{(x+\beta)^2/\alpha - 1]e^{-(1/2\alpha)}(x+\beta)^2 \quad \text{with} \quad 0 < \alpha < \beta^2.$$

4. APPLICATION

Although one of the visual differences suggested between male and female rat GH profiles is the reduced apparent orderliness of GH secretion in the female, this intuitive characterization of hormone release profiles cannot be defined readily or completely by conventional methods of neuro hormone pulse analysis. To elucidate distinct characteristics of hormone secretory dynamics further, we consider approximate entropy (ApEn), described below, a measure of serial irregularity that has yielded informative insights in both theoretical mathematical (11, 12, 16, 18) and biological settings. In particular, ApEn evaluates both dominant and subordinate patterns in complex data; notably, pertinent to the above investigation of gender distinctions, this regularity measure will detect changes in underlying episodic behavior not reflected in the mean or variance of hormone concentrations or in peak occurrences or amplitudes (17).

We have recently shown via ApEn that females secrete GH consistently and, highly significantly, more irregularly than males, both in intact rats and humans (13). This strong gender contrast presumably reflects the ability of gonadal steroids to modulate the time structure of growth hormone (GH) secretion on a variety of both peak (pulsatile) and subordinate (nonpul-satile) levels of secretory activity. Sex steroids influence expression of the primary hypothalamic peptidic regulators of GH secretion, GH-releasing hormone (GHRH), and somatostatin (1, 8, 9, 10) and also modulate GH negative feedback (2). However, the role of sex steroids in defining and maintaining these gender distinctions in patterns of GH secretion is poorly understood.

We here investigate whether and the extent to which the orderliness of the GH release process is governed by prepubertal gonadal steroids. To this end, we have analyzed extended serum GH concentration profiles from intact and gonadally suppressed male and female rats. We employed both surgical and chemical (GHRH analog) castration in the two sexes to assess possible gradations in the orderliness of GH secretory activity and to define whether

gender differences persist and are of similar magnitude in the partial versus complete absence of gonadal sex steroid secretion. The effects of these manipulations on growth and other GH-dependent parameters have been reported fully elsewhere (5).

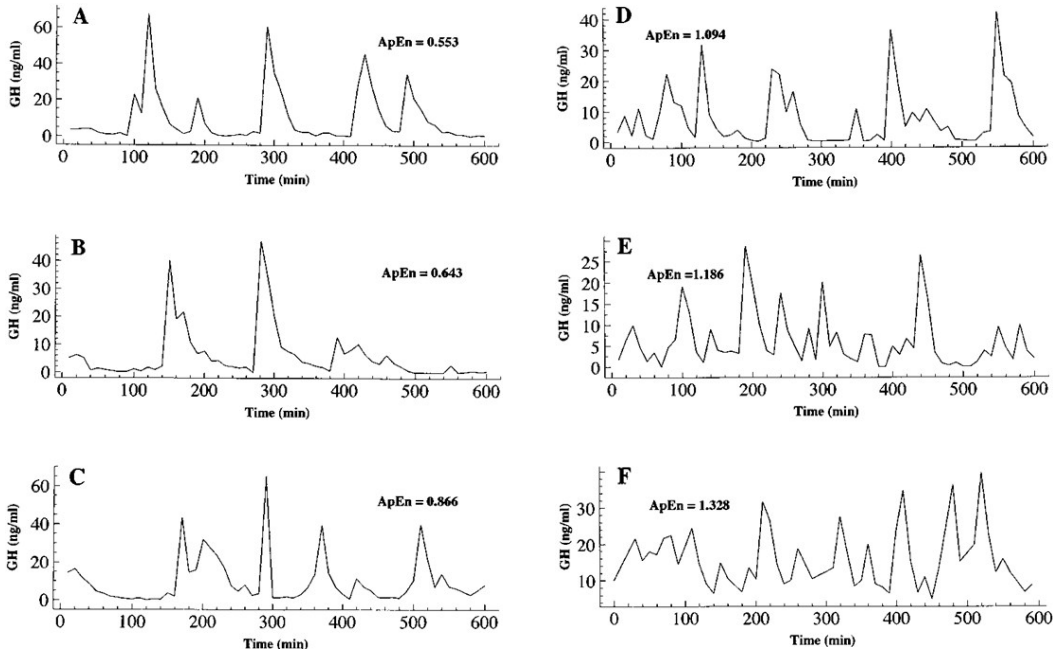


Figure 1: Representative serum GH concentration profiles from (in ascending order of ApEn values and hence increasing irregularity or disorderliness) an intact male (*A*), triptoprelin-treated male (*B*), gonadectomized male (*C*), ovariectomized female (*D*), triptorelin-treated female (*E*), and intact female (*F*) rat sampled for 10 h in the dark. Serum GH concentrations (ng/ml) are standardized via National Institute of Diabetes and Digestive and Kidney Diseases rat pituitary GH-2 standard

4.1 Materials & Methods

Previous studies that included both theoretical analysis (11, 14 , 15) and biological clinical applications, have demonstrated that the input parameters indicated produce good statistical reproducibility for ApEn for time series of the lengths considered here (*n* 5 60 data points). The ApEn application with *m* 5 1 estimates the rate of entropy for a first-order (*m* 5 1)- approximating Markov Chain to the underlying true process (12).

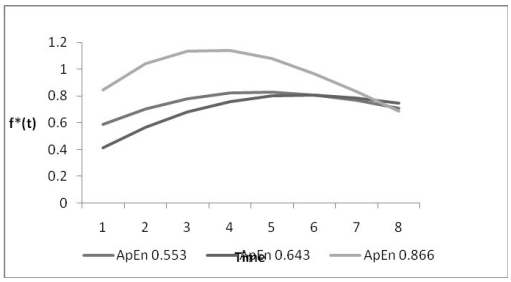
5. DISCUSSION

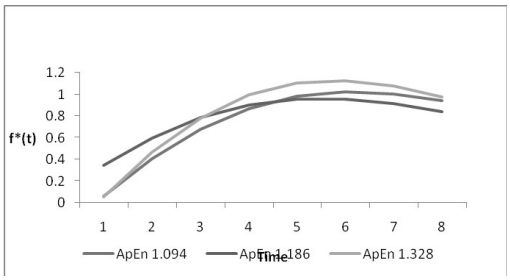
Quantifying the often times visually subtle changes and the inferred complexity of feedback control of neuroendocrine axes in vivo has been very difficult to date. Nonetheless, for the

GH axis, clear determinations of differences in GH release patterns (or temporal differences in exogenous GH treatment schedules) are very important to elucidate mechanisms of GH actions, because distinct GH release patterns evoke remarkably different growth rates and genomic responses (3, 4, 7) and activate separate signal transduction molecules and/or pathways . Therefore, quantifying GH secretory regularity and inferentially gaining insights into the physiological mechanisms that control the orderliness of GH release are important to our overall understanding of GH-regulated growth and GH pattern-dependent differential gene expression.

A recent study showed that ApEn, a regularity statistic, remarkably discriminates between male and female GH secretion patterns with almost complete gender segmentation (13). This finding is confirmed in the current analyses the primary objective of the present study was to go beyond these first-order findings to evaluate whether and how gonadal steroids affect the regularity of GH release.

6. MATHEMATICAL RESULTS





7. CONCLUSION

Here we conclude that the minimum dynamic discrimination information MDDI approach to probability modeling is very useful in analyzing different biological processes in the absence of any constraint on the probabilities. The maximum entropy principle extends this to the production of probability models close to uniform. This entropy principle also extend to the MDDI model to find differential orderliness of the growth hormones release process to illustrate distinguish characteristics of hormone secretary dynamics. We considered approximate entropy (ApEn) for that we used MDDI model relative to the exponential distribution for the generalized normal combination of the functions which show that the functions are monotonic concave downward for different differential orderliness of GH release processes.

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