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A Mathematical Model for the Secretion of Human Corticotrophin Releasing Hormone and Its Relationship with Stress Variables

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Abstract

In this paper, we analyze a dual characterization of life distributions that is based on entropy applied to the past lifetime. Various aspects of this measure of uncertainty are considered, including its connection with the residual entropy. Results on the past entropy is obtained by using the reversed hazard function of X, which is receiving increasing attention in reliability theory and survival analysis. The formula for the past entropy $\bar{H}(t)$ when X is exponentially distributed is obtained and this formula is utilized for our application part. The formula $\bar{H}(t)$ for peripheral administration of CRH is obtained and found that the stress variables increased monotonically upward with respect to time.

Keywords: Residual Lifetime, Reversed Hazard Function, hCRH, oCRH.

Mathematical Subject Classification: Primary 62N05, 60 G_{xx}

I. Mathematical Model

The role of differential entropy as a measure of uncertainty in residual lifetime distributions has attracted increasing attention in recent years. According to Ebrahimi [7], the residual entropy at time t of a random lifetime X is defined as the differential entropy of [X/X>t] (as usual, [X/B] denotes a random variable whose distribution is identical to that of X conditional on B). Formally, for all t>0 the residual entropy of X is given by

$$H(t) = -\int_t^{+\infty} \frac{f(x)}{\bar{F}(t)} \log \frac{f(x)}{\bar{F}(t)} dx$$
$$= \log \bar{F}(t) - \frac{1}{\bar{F}(t)} \int_t^{+\infty} f(x) \log f(x) dx$$
$$= -\frac{1}{\bar{F}(t)} \int_t^{+\infty} f(x) \log r(x) dx, \quad (1.1)$$

Where r(t) = f(t) / $\bar{F}$(t) is the hazard function, or failure rate of X. Given that an item has survived up to time t, H(t) measures the uncertainty about its remaining life.

However, it is reasonable to presume that in many realistic situations uncertainty is not necessarily related to the future but can also refer to the past. For instance, consider a system whose state is observed only at certain preassigned inspection times. If at time t the system is inspected for the first time and it is found to be 'down', then the uncertainty relies on the past, i.e on which instant in (0,t) it has failed. It thus seems natural to introduce a notion of uncertainty that is dual to the residual entropy, in the sense that it refers to past time and not to future time. Without loss of generality, from now on we shall assume that F(0+) > 0.

Let X be a random lifetime and recall that the PDF of [X / X ≤ t] is given by f(x)/F(t), 0< x<t. The differential entropy of [X / X ≤ t] for all t>0 will be called *past entropy* at time t of X, and will be denoted by

$$\bar{H}(t) = -\int_0^t \frac{f(x)}{F(t)} \log \frac{f(x)}{F(t)} dx \quad (1.2)$$

Note that $\bar{H}(t) \in [-\infty, +\infty]$. Given that at time t an item has been found to be failing, $\bar{H}(t)$ measures the uncertainty about its past life.

II. Results on the past entropy

From (1.2) we also have the following expressions for the past entropy:

$$\bar{H}(t) = \log F(t) - \frac{1}{F(t)} \int_0^t f(x) \log f(x) dx$$

$$H(t) = 1 - \frac{1}{F(t)} \int_0^t f(x) \log \tau(x) dx \quad (2.1)$$

Where τ(t) = f(t) / F(t) is the reversed hazard function, or reversed failure rate of X. The function τ(t) is receiving increasing attention in reliability theory and survival analysis (see [3] and [4]). As pointed out by some authors (in particular, see [13]), its role is dual to that of r(t). Indeed, as will appear clear in the following, the role of τ(t) in the analysis of past entropy is analogous to that of r(t) in the analysis of residual entropy as performed by Ebrahimi [7].

Throughout the paper we shall make use of the following relation, which is an immediate consequence of (2.1)

$$\frac{d}{dt} \bar{H}(t) = \tau(t)[1 - \bar{H}(t) - \log \tau(t)] \quad (2.2)$$

For all t<0, $H = H[F(t), \bar{F}(t)] + F(t)\,\bar{H}(t) + \bar{F}(t)H(t)$

If, for instance, X is exponentially distributed with mean $1/\lambda$, then we have

$$\bar{H}(t) = 1 + \log\left(1 - e^{-\lambda t}\right) - \frac{\lambda t e^{-\lambda t}}{1 - e^{-\lambda t}}$$

, t > 0

III. Application

CRH is a Pleuripotent peptide with 41 amino acids that sitmulates ACTH and cortisol secretion. When infused into the brains of animals, CRH inhibits food intake and increases sympathetic outflow [11,10,1]. There are at least two receptors for CRH [6,18,5,12] with several splice variants [12,15]. In the primate brain, CRH receptors are present in many areas of the brain, including the locus coeruleus, amygdale, cerebral cortex, and septum [16,9]. CRH receptors have also been demonstrated in skeletal and cardiac muscle [12], adrenal glands, testes, ovaries, spleen macrophages [20], mast cells [17], sympathetic ganglia [19], and aortic endothelium[8].

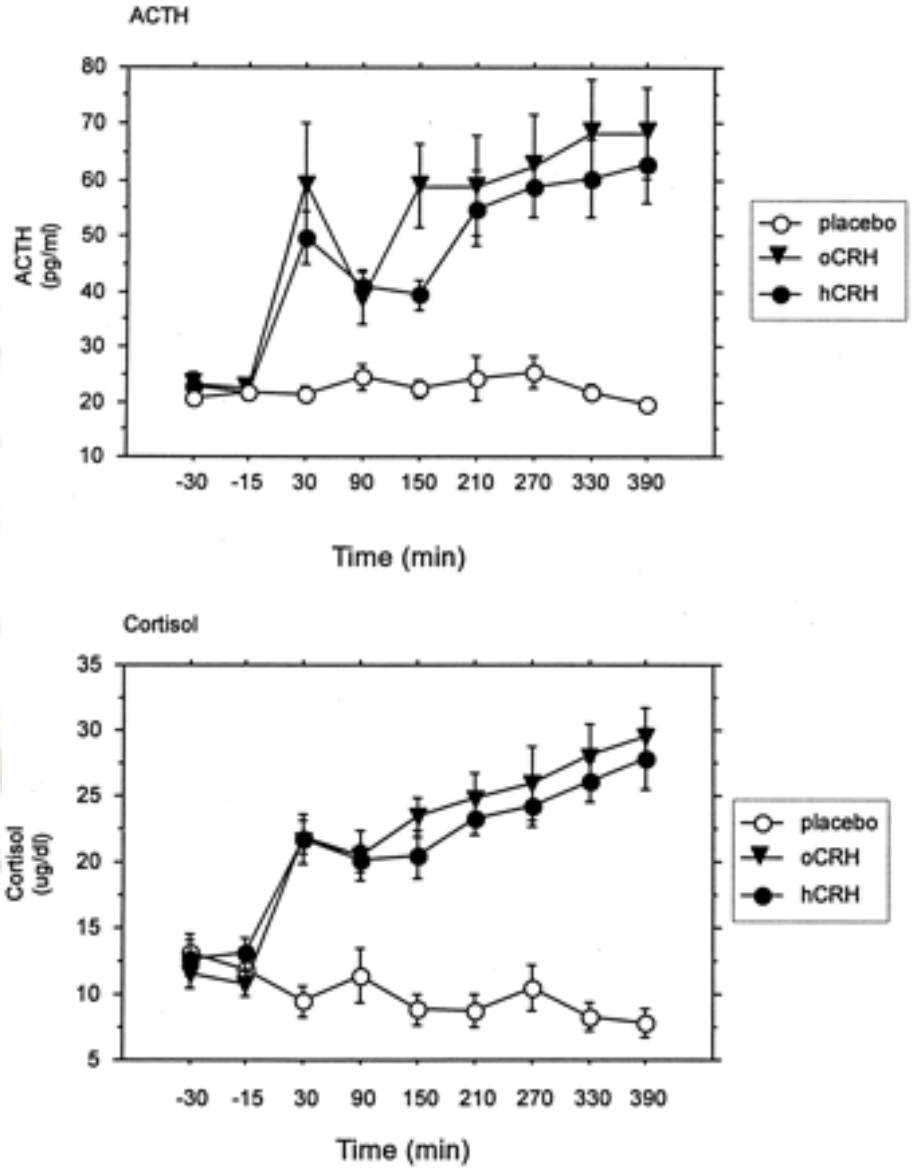

Figure 3.1: *Plasma ACTH and cortisol. Data are presented as the mean ± SEM (n=8). Cortisol and ACTH values were significantly higher in the oCRH and hCRH groups at all doses(P<0.05)*

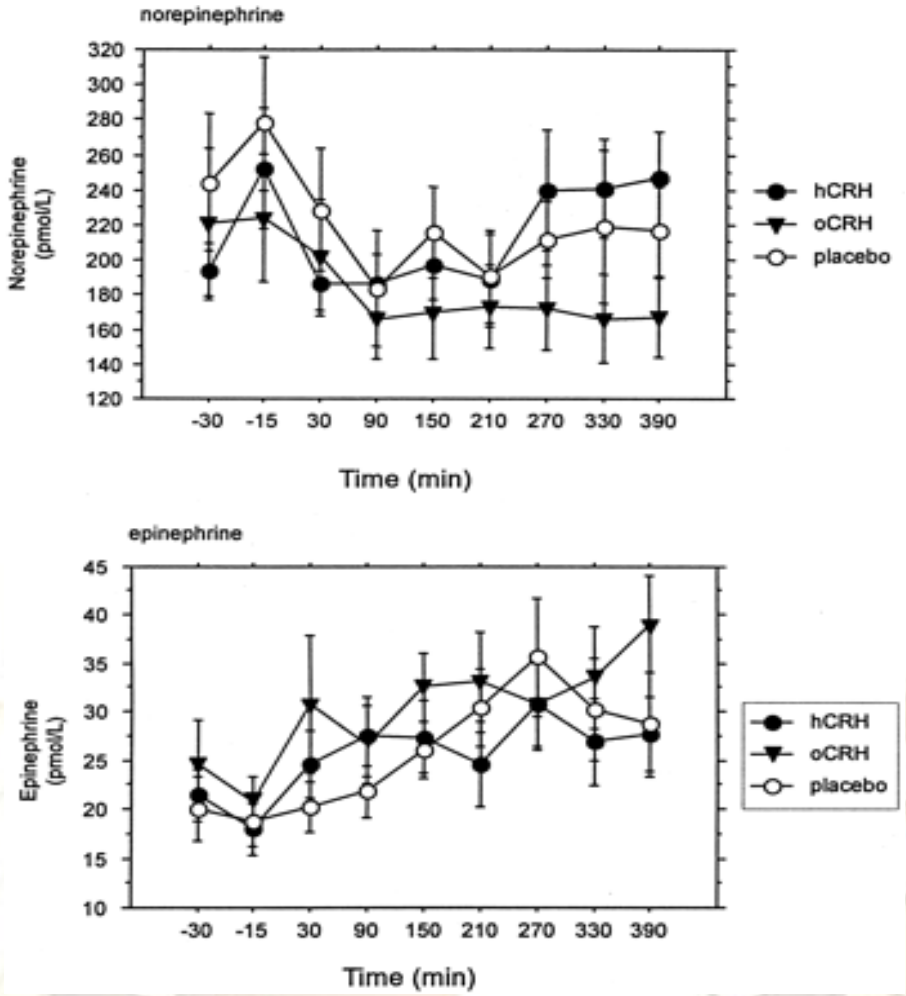

Figure 3.2: *Venous plasma catecholamines. Data are represented as the mean ± SEM (n=7). No differences were observed between the effects of oCRH and hCRH, compared with placebo, on epinephrine (P>0.05). No differences were observed between the effects of oCRH or hCRH, compared with placebo, on norepinephrine (P>0.05), * , Norepinephrine values were significantly different during hCRH and oCRH treatments at 2.0 μkg/kg*min (P<0.05).*

CRH is a potent peptide that is involved in the regulation of a variety of processes, such as ACTH secretion, anxiety disorders, depression, memory and learning, and body weight regulation [2]. Central administration of CRH is also thought to increases thermo genesis in rodents. CRH has been demonstrated to increase brown fat thermo genesis [11], plasma catecholamines [14] and heart rate levels [14] when administered into the brain of rodents. These observations are compatible with central activation of sympathetic outflow by CRH.

CRH receptors are present on sympathetic ganglia [19], and hCRH increases sympathetic tone [11] and plasma catecholamines [14] when administered into the brain of animals. This suggests that hCRH might stimulate the release of catecholamines. This could occur via activation of the SNS or alternately through the release of epinephrine form the adrenal. However, urinary and plasma catecholamines did not change during hCRH infusion compared with levels during placebo infusion.

Plasma norepinephrine was significantly different between oCRH and hCRH at the 2 μg/kg dose. However, it is possible that the rise in cortisol produced by oCRH decreases sympathetic tone, whereas the infusion of hCRH does not produce this effect. Both oCRH and hCRH increased ACTH and cortisol Figure (3.2) also high-light the similarities between the effects of hCRH and oCRH on glucose metabolism; insulin levels probably fall due to prolonged fasting, and glucose probably rises due to increased gluconeogenesis (a known effect of cortisol).

In conclusion, these results demonstrate for the first time that peripheral infusions of oCRH and hCRH increased ACTH and cortisol to an equal extent.

IV. Mathematical Results

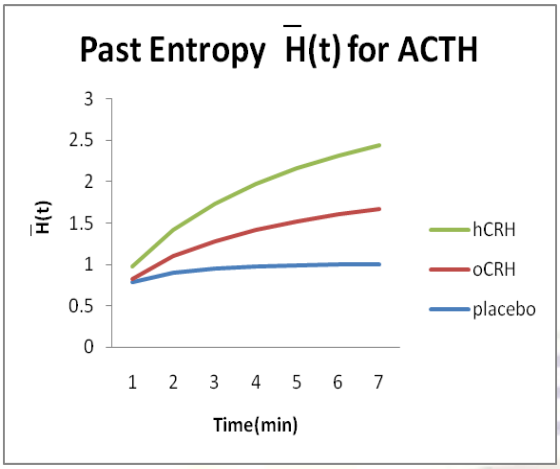

Figure 4.1

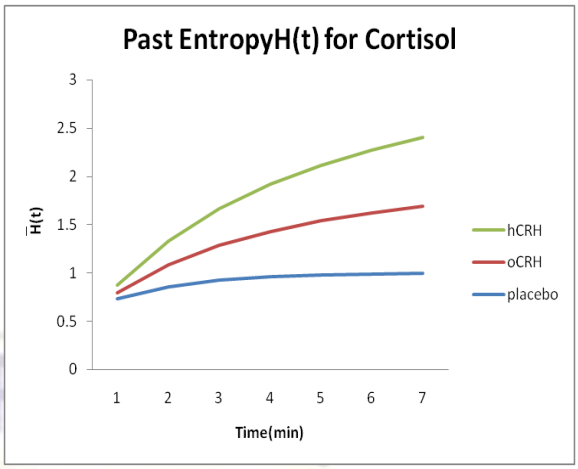

Figure 4.2

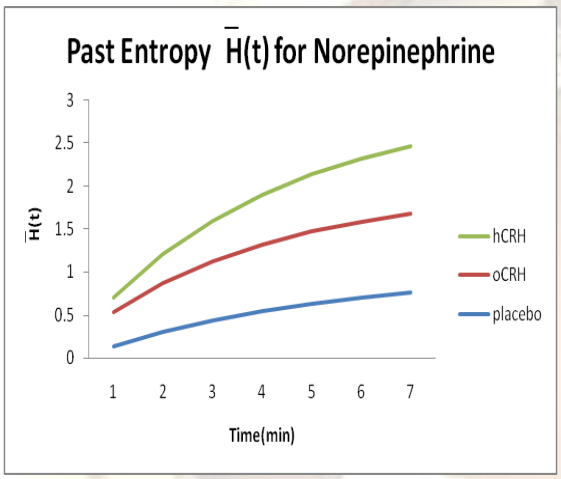

Figure 4.3

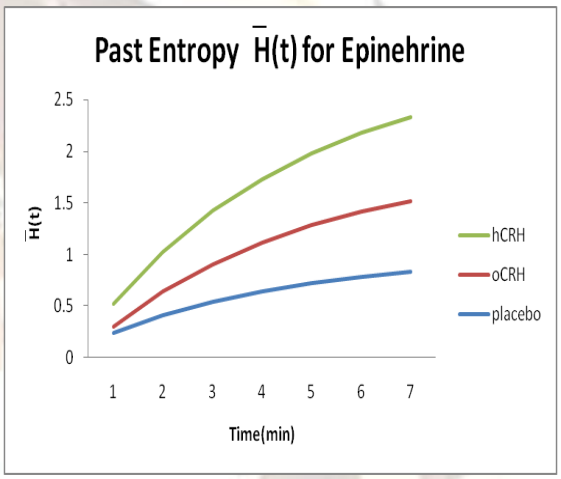

Figure4.4

V. Conclusion

Here, we analyze a dual characterization of life distributions that is based on entropy applied to the past lifetime. Various aspects of this measure of uncertainty are considered, including its connection with the residual entropy. Results on the past entropy is obtained by using the reversed hazard function of X, which is receiving increasing attention in reliability theory and survival analysis. The formula for the past entropy $\bar{H}(t)$ when X is exponentially distributed is obtained and this formula is utilized for our application part.

The past entropy functions of the variables hCRH and oCRH have been obtained and corresponding stress variables ACTH, Cortisol, Norepinephrine and Epinephrine levels are discussed. From figures 4.1, 4.2,4.3 and 4.4 the curves for past entropy are monotonically increasing in the upward direction when $\bar{H}(t)$ increases to the cases of hCRH, oCRH and Placebo.

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