CHAPTER – 9

STOCHASTIC MODELS FOR THE STRESS EFFECTS
DUE TO THE SECRETION OF DHEA AND OTHER
RELATED HORMONES

Introduction

In section 9.1 we discuss two special cases of mixtures of Erlangian distributions with the same scale parameters. Effect of age on serum concentration of the four variables DHEA, DHEA-S, DHEA-FA and Estradiol are taken into account and corresponding fitting of curves by using Generalised Erlang-k distribution is well defined in this section [102]. The mathematical model shows the probability density functions according to age for all the four cases. In section 9.2, we discuss the closure property of Increasing Generalised Failure Rate (IGFR) distributions with respect to mixing operation [107]. Also Log-concave and Log-convex properties of life distributions are studied.

9.1 Generalised Erlang-k Distribution for the connection between the secretions of DHEA, Androgen and Estradiol in women

9.1.1 Notations

\[ f(t) \] - probability density function of Erlang-k distribution.

\[ k \] - independent exponential random variables
9.1.2 Assumptions of the model

- $\alpha$ and $\lambda$ are both positive.
- $\frac{1}{\mu} \leq \mu$ is the common mean for a $E_{k-1,k}$ random variables.
- $\frac{1}{k} \leq c^2 \leq \frac{1}{k-1}$
- $0 \leq p \leq 1$.

9.1.3 Mathematical Model: Gamma Distribution

The density $f(t)$ is given by,

$$f(t) = \frac{\lambda^\alpha t^{\alpha-1}}{\Gamma \alpha} e^{-\lambda t}, t > 0,$$

where the shape parameter $\alpha$ and the scale parameter $\lambda$ are both positive. Here $\Gamma \alpha$ is the complete Gamma function defined by,

$$\Gamma \alpha = \int_0^\infty e^{-t} t^{\alpha-1} dt, \alpha > 0$$

This function has the property $\Gamma \alpha + 1 = \alpha \Gamma \alpha$ for any $\alpha > 0$. The probability distribution function $F(t)$ may be written as,
\[ F(t) = \frac{1}{\Gamma \alpha} \int_{0}^{\infty} e^{-u} u^{\alpha-1} du, t > 0 \]

The later integral is known as the incomplete Gamma function.

If the shape parameter \( \alpha \) is a positive integer \( k \), the Gamma distribution is the well known Erlang – \( k \) (\( E_k \)) distribution with

\[ f(t) = \frac{\lambda^k t^{k-1}}{(k-1)!} e^{-\lambda t} \quad \text{and} \quad F(t) = 1 - \sum_{j=0}^{k-1} \frac{\lambda^j t^j}{j!}, t \geq 0 \]

The Erlang-k distribution has a very useful interpretation. A random variable with an Erlang-k distribution can be represented as the sum of \( k \) independent random variables having a common Exponential distribution.

The mean and the squared co-efficient of variation of the Gamma distribution are given by, \( E(X) = \frac{\alpha}{\lambda} \) and \( c^2_\bar{x} = \frac{1}{\alpha} \)

**9.1.4 Generalised Erlangian distribution**

An Erlang-k (\( E_k \)) distributed random variable can be represented as the sum of \( k \) independent exponentially distributed random variables with the same means[140]. A generalized Erlangian distribution is one built out of a random sum of exponentially distributed components. A particularly convenient distribution arises when these components have the same means. In fact, such a distribution can be used to approximate
arbitrarily closely any distribution having its mass on the positive half axis.

We discuss two special cases of mixtures of Erlangian distributions with the same scale parameters. First, we consider the $E_{k-1,k}$ distribution has the following form:

$$f(t) = p \mu^{k-1} \frac{t^{k-2}}{(k-2)!} e^{-\mu t} + (1-p) \mu^k \frac{t^{k-1}}{(k-1)!} e^{-\mu t}, t \geq 0$$

where $0 \leq p \leq 1$. In words, a random variable having this density is with probability $p$ (respectively $1-p$) distributed as the sum of $k-1$ (respectively $k$) independent exponentials with common mean $\frac{1}{\mu}$. By choosing the parameters $p$ and $\mu$ as,

$$p = \frac{1}{1 + c_x^2 [kc_x^2 - (1 + c_x^2 - k^2 c_x^2)]^{1/2}} \text{ and }$$

$$\mu = \frac{k - p}{E(X)}$$

the associated $E_{k-1,k}$ distribution fits the first two moments of a positive random variable $x$ provided that

$$\frac{1}{k} \leq c_x^2 \leq \frac{1}{k-1}$$
we note that only co-efficient of variation between 0 and 1 can be achieved by mixtures of the \( E_{k-1,k} \) type. Also, it is noteworthy that \( E_{k-1,k} \) density can be shown to have an increasing failure rate.

Next we consider the \( E_{1,k} \) distribution which is defined as a mixture of \( E_1 \) and \( E_k \) distributions with the same scale parameters. The density of the \( E_{1,k} \) distribution has the form

\[
f(t) = p \mu e^{-\mu t} + (1 - p) \mu^k \frac{t^{k-1}}{(k-1)!} e^{-\mu t}, t \geq 0.
\]

where \( 0 \leq p \leq 1 \). By choosing

\[
p = \frac{2kc^2_x + k - 2 - (k^2 + 4 - 4kc^2_x)^{1/2}}{2(k-1)(1+c^2_x)} \quad \text{and} \quad \mu = \frac{p + k(1-p)}{E(X)}
\]

the associated \( E_{1,k} \) distribution fits the first two moments of a positive random variable \( x \) provided that

\[
\frac{1}{k} \leq c^2_x \leq \frac{k^2 + 4}{4k}
\]

9.1.5 Formation of Androgens in peripheral target tissues (intracrinology)

Humans, along with the other primates, are unique among animal species in having adrenals that secrete large amounts of the inactive precursor steroids dehydroepiandrosterone (DHEA) and especially dehydroepiandrosterone sulfate (DHEA-S), which are converted into potent androgens and / or estrogens in peripheral tissues [82, 83, 90, 91, ...]
Figure (9.1.1). In fact, plasma DHEA-S levels in adult women are 10,000 times higher than those of testosterone and 3000 to 30,000 times higher than those of E₂, thus providing a large reservoir of substance for conversion into androgens and/or estrogens in the peripheral intracrine tissues which possess the enzymatic machinery necessary to transform DHEA into active sex steroids.

The major importance of DHEA and DHEAS in human sex steroid physiology is illustrated by the observation that approximately 50% of total androgens in adult men derive from the adrenal precursor steroids [15, 86, 88], while in women, our best estimate of the intracrine formation of estrogens in peripheral tissues is of the order of 75% before menopause and 100% after menopause. In fact in women, the vast majority of androgens are made locally in target tissues throughout life [82] Fig. (9.1.1).
The local synthesis and action of sex steroids in peripheral target tissues has been called intracrinology [81, 82, 92]. Recent and rapid progress in this field has been made possible by elucidation of the structure of most of the tissue-specific genes that encode the steroidogenic enzymes responsible for the transformation of DHEA-S and DHEA into androgens and or estrogens locally in peripheral tissues [89,90,91,92].
9.1.5 Effect of age on serum DHEA, DHEA-S, DHEA-FA and Serum 5-diol in women:

Fig. 9.1.2: (A) Effect of age (20-30 to 70-80 years) on serum concentration of DHEA, (B) DHEA-S, (C) DHEA-FA and (D) androst-5-ene-3β, 17β-diol (5-diol) in women.
All estrogens and almost all androgens are made locally from DHEA in the peripheral tissues which possess the enzymes required to synthesize the physiologically active sex steroids. Local biosynthesis and action of androgens in target tissues eliminates the exposure of other tissues to androgens and thus minimizes the risks of undesirable masculinizing or other androgen–related side effects [16, 125]. The same applies to estrogens, although a reliable parameter of total estrogen secretion (comparable) to the glucuronides identified androgens has yet to be determined. Although a fraction of androgens are aromatized to estrogens, the lack of sufficient information on the identity of the metabolites of estrogens does not permit one to make a sufficiently complete analysis of their metabolism at this time.

In addition to the above–identified major issue about the biological significance of the serum testosterone concentration which does not take into account the large amount of androgens made in peripheral tissues, it should be mentioned that the radioimmunoassays generally used to measure serum sex steroids have questionable specificity [32, 132].

Since serum DHEA, the main source of androgens in women, starts to decrease at the age of 30 years and has already decreased by 60% at
the time of menopause (Fig. 9.1.2), it is reasonable to suggest that a loss of the inhibitory effect of androgens on the cancer – promoting activity of estrogens on the mammary gland accompanies the decreased serum DHEA levels which precede the follow menopause. While the evidence is highly supportive of a counter balancing effect of androgens on the stimulatory effect of estrogens on breast epithelial growth, no replacement of androgens is offered for the multiple conditions causing a decrease of the androgen / estrogen ratio in women.

9.1.6 Result

By using Generalized Erlangian distribution for fitting the curves given in the diagrams A, B, C, D Fig. (9.1.2) is given below.

The curves for the probability density functions of the time variables f(t) of the four variables is well explained in the figures (9.1.3) and (9.1.4). The generalized Erlang-k distribution is fitted for all the four variables DHEA, DHEA-S, DHEA-FA and Serum -5 diol, which shows the sudden decrease of probability density function over the consecutive years of age.
Fig. 9.1.3

Fig. 9.1.4
9.2 Stochastic model for Increasing Generalised Failure Rate for
the Physiological and Psychological effects of compassion and
Anger

9.2.1 Assumptions

- X is a non negative random variable describing the lifetime of a
  component (human system).
- The distribution function $F(x) = p(X \leq x)$.
- The reliability function is $\bar{F}(x) = 1 - F(x)$.
- The density function $f(\cdot)$ is a smooth function on its domain
  $(0, \infty)$.

9.2.2 Notations

$\mathcal{r}(x)$ - failure rate function of x.

$\mathcal{R}(x)$ - Generalised failure rate of x.

9.2.3 Log concavity for continuous distributions

The study of log-concavity and log-convexity are useful in many
areas of Biology, Actuarial science and Engineering. It is often important
to make explicit assumptions on the underlying distributions. However, in some situations there is no closed form expression for the distribution functions, the failure rates, the Mean Residual Life time (MRL), and the variance Residual Life time (VRL) and it is still of interest to study the properties of such functions. Most of the existing results in the literature have dealt with the density functions, distribution functions and their integrals. Some of these results have been related to reliability functions, failure rates, and MRL functions. Yet the log-concave and log-convex properties of the VRL have not been touched. For this reason, we study the log-concavity for the VRL.

**Definition**

A random variable $X$ is said to have a concave distribution if, for any $x_1, x_2$ and any $\lambda \in [0,1]$ the following relation is satisfied for the density $f$:

$$f\left(\lambda x_1 + (1-\lambda)x_2\right) \geq \lambda f(x_1) + (1-\lambda)f(x_2) \quad (9.1)$$

The opposite concept of concave function is for a function to be convex. Hence, $X$ is convexly distributed if the inequality sign in (9.1) is reversed.
Definition

A random variable is said to have a log-concave distribution if for any $x_1, x_2$ and any $\lambda \in [0,1]$, we have

$$f(\lambda x_1 + (1 - \lambda) x_2) \geq f^{\lambda}(x_1) f^{1-\lambda}(x_2) \quad (9.2)$$

Assuming $f$ to be positive, we take a logarithm in (9.2) thus getting

$$\ell n[f(\lambda x_1 + (1 - \lambda) x_2)] \geq \lambda \ell n(f(x_1)) + (1 - \lambda) \ell n(f(x_2)) \quad (9.3)$$

The function $f$ is called a log-convex function if the inequality sign in (9.2) is reversed. It should also be noted that if $f$ is log-concave, then it is a continuous function on its domain and if it is differentiable, then it is continuously differentiable on its domain.

Proposition

If $h(x), x \in D$ is a differentiable function on its domain $D$, $D \subset (0, \infty)$ then the following conditions are equivalent:

a) $h(x)$ is log-concave on $D$.

b) $h^1(x)/h(x)$ is monotone decreasing in $x$.

c) $(\ell n h(x))'' < 0$

Now, let us define the right-hand integral of the reliability function as follows:

$$v(x) = \int_x^\infty F(u) \, du \quad \text{and} \quad V(z) = \int_z^\infty v(u) \, du.$$
Theorem

Suppose that F is a life distribution and its density function f is log-concave on \((0, \infty)\). Then the following hold:

a) \(F(x), \overline{F}(x)\) and \(\nu(x), x > 0\), are log-concave.

b) \(V(x), x > 0\) is log-concave.

9.2.4 Log–concavity for some ageing classes

Here we discuss log-concavity for the main characteristics: failure rate, MRL and VRL. We also discuss log-concavity for the reversed failure rate, Reversed Mean Residual (RMR) and Reversed Variance Residual (RVR). We briefly recall the definitions of the failure rate function \(r(x), x \geq 0\) and the reversed failure rate function \(\overline{r}(x), x \geq 0\) corresponding to a lifetime \(x\), where \(x \sim F = \{F(x), x \geq 0\}\).

\[
 r(x) = -\frac{d}{dx} \ln F(x) = \frac{f(x)}{F(x)} \quad \text{and} \\
 \overline{r}(x) = \frac{d}{dx} \ln F(x) = \frac{f(x)}{F(x)} \quad (9.4)
\]

Proposition

If the density function \(f(x), x \geq 0\) is log-concave, then the following hold:
a) The function \( r(x), x \geq 0 \) is monotone increasing and hence \( F \in IFR \).

b) The function \( \overline{r}(x), x \geq 0 \) is monotone decreasing and hence, \( F \in DRFR \) [25].

9.2.5 Life Distribution with increasing elasticity

The concept of Increasing Generalized Failure Rate (IGFR) was found to be useful in supply chain models, and also in Stochastic models of service systems [4, 116, 152, 157]. We let \( X \) be a random variable representing the life time of a component and denote by \( F \) its distribution; \( \overline{F} = 1 - F \). We further assume that \( F \) has density function \( f \). The failure rate of \( X \) (or \( f \)) is \( f(x) = f(x)/\overline{F}(x), x \geq 0 \). We recall that \( X \) has an increasing failure rate or equivalently \( F \in IFR \) if the function \( r(x), x \geq 0 \) is increasing. The generalized failure rate of \( X \) is defined [52] as,

\[
R(x) = xr(x), x > 0
\]  

**Definition**

A life distribution \( F \) has an increasing generalized failure rate and we write \( F \in IFGR \), if the function \( R(x), x > 0 \) is increasing. Decreasing generalized failure rate (DGFR) distributions can be defined analogously.
If \( x \) is IFR then it is also IGFR. The converse is not generally true: there are many DFR function which are IGFR.

**Closure Property**

In this section, closure properties of IGFR were considered [4]. In particular, the convolution and shifting properties are not preserved. Here, we focus our attention on mixtures of IGFR distributions[4]. We are discussing whether the IGFR distributions closed under mixing.

Let \( X_1 \sim F_1 \) and \( X_2 \sim F_2 \) be random variables representing lifetimes of two independent components. For any \( p \in [0,1] \), we define the functions,

\[
H = pF_1 + (1-p)F_2 \quad \text{and} \quad \overline{H} = p F_1 + (1-p) F_2
\]  

\[ (9.6) \]

It is easy to see that \( H \) is a ‘new’ life distribution with \( \overline{H} \) being its reliability (survival) function [12]. Recall that \( H \) is called a \( p \)-mixture of \( \{F_1, F_2\} \). We can easily extend this definition to a larger set of life distributions. This can also be expressed in terms of densities, assuming they exist [116, 117].

Suppose now that \( R_1(x), R_2(x), x > 0 \) are the generalized failure rate functions associated with \( x_1 \) and \( x_2 \) respectively. This means that \( R_1(x) = x r_1(x) \) and \( R_2(x) = x r_2(x) \), where \( r_1(x) \) and \( r_2(x), x>0 \) are the usual
failure rates of $F_1$ and $F_2$. Then the generalized failure rate function $R(x)$, based on $R_1(x)$ and $R_2(x)$, $x>0$ is defined as follows:

$$R(x) = a(x) R_1(x) + (1-a(x)) R_2(x), \quad x > 0$$  \hspace{1cm} (9.7)

$$a(x) = \frac{p F_1(x)}{p F_1(x) + (1-p) F_2(x)}$$  \hspace{1cm} (9.8)

9.2.6 Effect of Anger on Immune system

In recent years a number of investigators have proposed the DHEA/ Cortisol ratio to be an important biological marker of stress and aging. When individuals are under prolonged stress, a divergence in this ratio results, as cortisol levels continue to rise while DHEA level decreases significantly. The effects of DHEA/ Cortisol imbalance can be severe and may include elevated blood sugar levels, increased bone loss, compromised immune function, decreased skin repair and regeneration, increased fat accumulation and brain cell destruction.

That effective emotional management can have such profound positive effects on the cardiovascular immune, hormonal and autonomic nervous systems may provide a basis for the improved physical health and vitality reported by many individuals who regularly use the HeartMath tools. These effects may also help to explain the health improvements and symptom reduction experienced by individuals suffering from diverse diseases and disorders after using the techniques.
Heart focused sincere, positive feeling states boost the immune system, while negative emotions may suppress the immune response for up to six hours following the emotional experience.

Secretory IgA (Measured from Salivary samples) heart rate and mood were measured in thirty individuals before and after experiencing the emotional states of either care and compassion or anger and frustration. Two methods of inducing the emotional states were compared: Self induction versus external induction via video tapes. Anger produced a significant increase in total mood disturbance and heart rate but not in S-IgA levels. On the other hand, sincere positive feeling states of care and compassion, self-induced via the Freeze –Frame technique[55], produced a significant decrease in total mood disturbance and a significant increase in S-IgA levels. Examining a 6-hour period, it is observed that 5-minute experience of anger produced a significant inhibition of S-IgA from one to five hours after the emotional experience. In contrast, a tendency toward the six hours following a 5-minute experiencing of cares Fig. (9.2.1).
Fig. 9.2.1: This graph shows the impact of one 5-minute episode of recalled anger on the immune antibody IgA over a 6-hour period. The initial slight increase in IgA was followed by a dramatic drop which persisted for six hours. When the subjects used the Freeze-Frame technique and focused on feeling sincere care for five minutes there was a significant increase in IgA, which returned to baseline an hour later and then slowly increased throughout the rest of the day.

Results indicate that self-induction of positive emotional states using Freeze-Frame is more effective in stimulating S-IgA levels than previously used external methods. “The effects of emotions in short-term power spectral analysis of heart rate variability” (Entrainment, Coherence and Autonomic Balance section). It was observed that feelings of appreciation self-generated by the Freeze-Frame Technique shift autonomic nervous system balance towards increased para-sympathetic activity. As salivary secretion is primarily activated by parasympathetic
nerves, autonomic regulation offers a possible mechanism to explain the immediate increase in S-IgA following the experience of positive emotions. The results of this study indicate that the Freeze-Frame Technique may be an effective method to improve mood and minimize the long-term immuno-suppressive effects of negative emotions.

9.2.7 Results

![Graph showing R(x), R1(x), and R2(x)](image)

*Fig. 9.2.2*
Consider the two life times, $x_1 \sim \text{Exp}(\lambda)$ and $x_2 \sim \text{N}(\mu, \sigma)$. Their densities are $f_1(x) = \lambda e^{-\lambda x}$ and $f_2(x) = \frac{1}{\sqrt{2\pi \sigma}} e^{-\frac{(x-\mu)^2}{2\sigma^2}}$. The corresponding $R_1(x)$ and $R_2(x)$ are plotted on the graph and the mixture of two IGFR $R(x)$ is found and it lies between $R_1(x)$ and $R_2(x)$ with bounds which shown in fig.(9.2.2) and (9.2.3). It is an increasing function. Thus the mixture is an Increasing Generalized Failure Rate Function (IGFR).

9.3 Conclusion

In section 9.1, we conclude that since serum DHEA the main source of androgens in women starts to decrease at the age of 30 yrs and has already decreased by 60% at the time of menopause Fig. (9.1.2), it is reasonable to suggest that a loss of the inhibitory effect of androgens on
the mammary gland accompanies the decreased serum DHEA levels which precede and follow menopause. The generalized Erlang-k distribution is fitted for all the four variables which shows the sudden decrease of probability density function over the consecutive years of age [102].

While the evidence is highly supportive of a counterbalancing effect of androgens on the stimulatory effect of estrogens on breast epithelial growth, no replacement of androgens is offered for the multiple conditions causing a decrease of the androgen/estrogen ratio in women.

The purpose of section 9.2 is to extend and systematize known results in Log-concave and Log-convex properties of life distributions. Also to discuss the closure property of Increasing Generalized Failure Rate (IGFR) distributions with respect to mixing operation [107]. The study of Log-concavity and Log-convexity are useful in many areas of Biology, Medicine, Actuarial science and Engineering. It is often important to make explicit assumptions on the underlying distributions, for example, in recent years a number of investigators have proposed the DHEA/cortisol ratio to be an important Biological marker of stress and ageing. The mixture of distribution of this property follows an Increased Generalized Failure Rate Function.
For the two life time distributions one which is Exponential and the other which is Normal, the respective IGFR, $R_1(x)$, $R_2(x)$, $x \geq 0$ are plotted on the graph and the mixture of the two Increased Generalized Failure Rate Function $R(x)$ is found. It lies between $R_1(x)$ and $R_2(x)$ with bounds. It is also an increasing function. Thus the mixture of two Increased Generalized Failure Rate Functions is also an Increasing Generalized Failure Rate Function (IGFR).