

Quantum Chemical Computational Methods are Essential Tools for Predicting the Vibrational Spectra of Progesterone Treatments in Post Menopausal Women

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ABSTRACT

The problem of generating Trivariate Normal Distributions from univariate ones is drawing the attention of the reliability analyst. Amongst these approaches the characterisation approach and the modelling approach are very appealing. Infact the characterisation approach is of great interest to both theoreticians and applied workers. Here we have used a Trivariate Normal Distribution for application by extending univariate distribution through characterisation approach. In our application part we have considered post-menopausal women. We have concentrated on a 24 hr profile of Melatonin, ACTH, Cortisol, TSH, Prolactin and GH under the treatment with Placebo and with Progesterone. In this respect we have developed a mathematical model which describes the purpose of the present study. The study investigates in post-menopausal women, the effects of a 24-hr profile of progesterone and placebo administration both on sleep architecture and on multiple hormones profile. The protocol allows us to explore the effects of the placebo and progesterone treatment on combined effects of hormones.

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1. Introduction

Melatonin

Melatonin is a form of a hormone produced in the brain that helps regulates your sleep and wake cycles. Melatonin is also very effective in treating jet lag, high blood pressure, tumors, low blood platelets, insomnia caused by withdrawal from drug addiction, or anxiety caused by surgery. Melatonin is also known to cure infertility, to control sleep problems caused by shift work, or to enhance athletic performance. Scientists are also looking at other good uses for melatonin, such as,

- Treating seasonal affective disorder (SAD).
- Helping to control sleep patterns for people who work night shifts.[1]
- Preventing or reducing problems with sleeping and confusion after surgery.

Cortisol

Cortisol is produced from cholesterol in the two adrenal glands located on top of each kidney. It is normally seen in the events such as waking up, exercising and acute stress. Cortisol maintains a systematic approach in body efforts to carry out processes and homeostatis. Cortisol also plays a vital role in human nutrition. It regulates energy by selecting the right type and amount of substrate the body needs to meet the physiological demands placed on it. When chronically elevated, cortisol can have effects on weight, immune function, and chronic disease risk. Cortisol is best known for its involvement in the “fight-or-flight” response and

temporary increase in energy production, at the expense of processes that are not required for immediate survival.[2]

GH

Growth Hormone is a peptide hormone that stimulates growth, development and regeneration. This hormone is made up of amino acids that form a long, single-chain polypeptide. Growth Hormone is organized in the somatotrophic cells, which are found in the anterior pituitary gland. These cells are also responsible for storing and releasing the hormone. Growth Hormone is used widely in medicine to help treat growth disorders in children and Growth Hormone deficiency in adults. Growth Hormone encourages growth and development in children and adolescents. It is also responsible to regulate the body fluids, sugar and fat metabolism and maybe even heart function.[3]

Progesterone

Progesterone is the naturally producing hormone in the body. Women take progesterone by mouth for inducing menstrual periods and it also treats abnormal uterine bleeding associated with hormonal imbalance and severe symptoms of premenstrual syndrome. Progesterone is also used in combination with the hormone Estrogen to “oppose Estrogen” as part of hormone replacement therapy. If Estrogen is given without progesterone, Estrogen increases the risk of uterine cancer. During the reproductive years, the pituitary gland in the brain generates hormones (Follicle-Stimulating Hormone [FSH] and Luteinizing Hormone [LH]) is responsible even for new egg to mature and be released from its ovarian follicle each month.

As the follicle develops, it produces the sex hormones Estrogen and Progesterone, which thicken the lining of the uterus. Progesterone levels becomes high in the next half of the menstrual cycle, and following the release of the egg (ovulation), the ovarian tissue that replaces the follicle proceeds to produce Estrogen and Progesterone. [4]

ACTH

ACTH (Adrenocorticotrophic Hormone) as its name suggests, stimulates the adrenal cortex. More specifically, it stimulates secretion of glucocorticoids such as Cortisol, and has little control over secretion of aldosterone, the other major steroid hormone from the adrenal cortex.

Figure 1. ACTH is secreted from the anterior pituitary in response to corticotropin-releasing hormone from the hypothalamus. corticotropin-releasing hormone is secreted in response to many types of stress, which makes sense in view of the "stress management" functions of glucocorticoids. Additional information on the role of ACTH in regulation of adrenal steroid secretion is presented in the sections on the adrenal gland and glucocorticoids.[1][2]

Within the pituitary gland, ACTH is produced in a process that also generates several other hormones.

Prolactin

Prolactin is a hormone produced by the pituitary gland and its primary role is to help initiate and maintain breast milk production in pregnant and nursing women. Men and non-pregnant women will normally have only small amounts of prolactin in their blood. Prolactin levels do, however, need to be calculated based on the time of day that they are collected. The prolactin levels will vary over a 24-hour period, rising during sleep and peaking in the morning. [3][5]

TSH

The thyroid gland helps to perform many important functions in your body, including metabolism. It is managed by the Thyroid-Stimulating Hormone (TSH). A TSH test counts the amount of TSH in your blood. Any doctor may suggest the test if you are showing symptoms of a thyroid disorder. The results of a TSH test can confirm a diagnosis and help your doctor determine an better treatment plan for a certain condition. A thyroid-stimulating hormone (TSH) test counts the amount of TSH in the blood. TSH is produced by the pituitary gland, which is located at the base of your brain. [5]

2. Methods & Results

Subjects

Postmenopausal women, aged 48–74 yr (mean 57.4 yr), were selected after a careful clinical and biological evaluation. Investigations were performed after natural menopause. Mean age at menopause was 49.4 yr (range, 41–57 yr). The Subjects involved were such that they had never undergone any hormonal therapy. Their body weight was in the normal range for all (body mass index 22.1). In all subjects, Estradiol plasma levels were also normal. FSH plasma levels were under average values. Smokers, shift workers, subjects who had travelled across time zones during the last 2 months, individuals with personal history of drug abuse or with personal or family history of many types of disorders which are highlighted and subjects with current vasomotor symptoms, dieting, or intensive physical exercise were excluded from the study. Each volunteer was examined by one of the authors and had to answer a questionnaire of specific questions concerning her sleep habits. To be included in the study, volunteers had to comply with the following requirements: regular sleep schedules (i.e they sleep from 10

to 12 and 6 to 8), no difficulty to fall asleep, no complaints of awakenings during the sleep period, no snoring, no periodic limb movements, and no daytime fatigue and sleepiness. Written informed consent was obtained from all volunteers.[11][14]

Sleep Analysis

Polygraphic sleep recordings were visually scored at 30-sec intervals, using standardized criteria by the same experienced scorer who was blind to the clinical condition of the subject.

○ Sleep Onset and Morning Awakening :

They are defined as, respectively, the times of the first and last 30-sec intervals scored II, III, IV, or Rapid Eye Movement (REM).

○ The Sleep Period :

It is defined as the time interval separating sleep on set and final awakening.

○ Total Sleep Time :

It is defined as the sleep period minus the total duration of wake after sleep onset (WASO). [12][13]

○ Sleep Latency :

It is defined as the time interval from lights off until sleep onset.

○ Sleep Efficiency :

It is calculated as the total sleep time, expressed as percentage of the time allocated to sleep.

○ Slow-Wave Sleep (SWS) :

It is defined as stages III-IV.

○ A Spectral Analysis was performed on the central electroencephalogram lead. Muscular, ocular, and

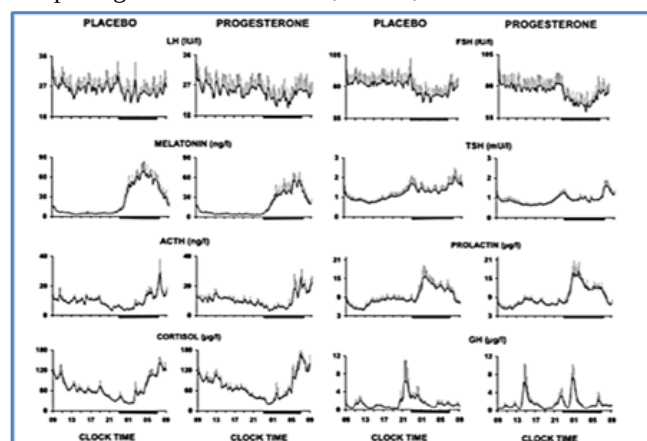


Fig 1. Mean (+ SEM; n = 8, except for Melatonin: n = 6, and for Prolactin: n = 7) 24-hr profiles of Plasma LH, FSH, Melatonin, ACTH, Cortisol, TSH, Prolactin, and GH under Placebo and Progesterone Treatment. Black bars indicate scheduled Sleep Periods.

Classic postmenopausal gonadotropins profiles were observed in both conditions. Mean 24-h LH levels, pulse frequency, duration, and amplitude were similar in both conditions. Each type of values under progesterone correlated positively with corresponding values under placebo for pulse frequency, duration, and amplitude. Mean 24-h FSH levels were slightly but significantly lower under progesterone than under placebo. FSH pulse characteristics were similar in both conditions.

➤ Findings from Placebo and Progesterone Treatment: Reference Fig. 1

○ Melatonin:

Melatonin profiles were obtained in six subjects. In both conditions, classic profiles with stable, low daytime values, an evening circadian rise, and a return to low values in the

morning were observed. The 24-h levels and the timings of onset and offset of the circadian rise in both conditions were not significantly different from each other. However, over the 24 hr period profile, melatonin levels were decreased by more than 40%, compared with placebo ($P \leq 0.03$).

○ ACTH

In both conditions, typical ACTH profiles were observed, with a quiescent period of minimal secretion centred around midnight, followed by an abrupt rise during the second part of the night to reach an early morning maximum, and declining levels during daytime. All variables characterizing ACTH profiles were similar in both conditions. Individual pulse and all type of values under progesterone correlated positively with corresponding values under placebo.

○ Cortisol

In both conditions, typical Cortisol profiles were observed, with a quiescent period of minimal secretion centred around midnight, followed by an abrupt rise during the second part of the night to reach an early morning maximum, and declining levels during daytime. All variables characterizing Cortisol profiles were similar in both conditions. Individual pulse and all type of values under progesterone correlated positively with corresponding values under placebo.

○ TSH

In both conditions, TSH concentrations followed the expected pattern, with relatively constant daytime levels, followed by an early evening circadian rise, a nocturnal decrease, and a transient rebound after final morning awakening. The timings of the onset of the circadian rise and of the peak were similar in both conditions. However, TSH concentrations were 25–30% lower under progesterone than under placebo over the 1500–2300 h and 2300–0700 h periods ($P \leq 0.05$), resulting in a mean 24% decrease over the 24-h period ($P \leq 0.07$). [18]

○ Prolactin

Prolactin profiles were obtained in the subjects. In both conditions, classic profiles, with a major nocturnal curves, were observed. All variables characterizing prolactin profiles were similar in both conditions.

○ GH

Daytime GH secretion was similar in both conditions. In contrast, night time GH secretion was 50% higher under progesterone than under placebo ($P \leq 0.05$). A trend for an increase in IGF-I values was detectable ($P \leq 0.09$). [12][18]

3. Mathematical Model

○ Mathematical Model for Trivariate Normal Distribution

● The Multivariate Normal Distribution

The joint moment-generating function of $X_1, \dots, X_n$ [also called the moment-generating function of the random vector $(X_1, \dots, X_n)$] is defined by

$$M(t_1, \dots, t_n) = E[\exp(t_1 X_1 + \dots + t_n X_n)].$$

Just as in the one-dimensional case, the moment-generating function determines the density uniquely. The random variables $X_1, \dots, X_n$ are said to have the multivariate normal distribution or to be jointly Gaussian (we also say that the random vector $(X_1, \dots, X_n)$ is Gaussian) if

$$M(t_1, \dots, t_n) = \exp(t_1 \mu_1 + \dots + t_n \mu_n) \exp\left(\frac{1}{2} \sum_{i,j=1}^n t_i a_{ij} t_j\right)$$

where the t_i and μ_j are arbitrary real numbers, and the matrix A is symmetric and positive definite. [6]

Let us indicate the notational scheme we will be using. Vectors will be written with an underbar, and are assumed to

be column vectors unless otherwise specified. If $\underline{t}$ is a column vector with components $t_1, \dots, t_n$, then to save space we write $\underline{t} = (t_1, \dots, t_n)'$. The row vector with these components is the transpose of $\underline{t}$, written $\underline{t}'$. The moment-generating function of jointly Gaussian random variables has the form

$$M(t_1, \dots, t_n) = \exp(\underline{t}' \underline{\mu}) \exp\left(\frac{1}{2} \underline{t}' A \underline{t}\right).$$

Theorem

Joint Gaussian random variables arise from non singular linear transformations on independent normal random variables. [7]

Proof. Let $X_1, \dots, X_n$ be independent, with X_i normal $(0, \lambda_i)$, and let $\underline{X} = (X_1, \dots, X_n)'$. Let $\underline{Y} = B\underline{X} + \underline{\mu}$ where B is nonsingular. Then $\underline{Y}$ is Gaussian, as can be seen by computing the moment-generating function of $\underline{Y}$:

$$M_{\underline{Y}}(\underline{t}) = E[\exp(\underline{t}' \underline{Y})] = E[\exp(\underline{t}' B \underline{X})] \exp(\underline{t}' \underline{\mu}).$$

But

$$E[\exp(\underline{u}' \underline{X})] = \prod_{i=1}^n E[\exp(u_i X_i)] = \exp\left(\sum_{i=1}^n \lambda_i u_i^2 / 2\right) = \exp\left(\frac{1}{2} \underline{u}' D \underline{u}\right)$$

where D is a diagonal matrix with λ_i 's down the main diagonal. Set $\underline{u} = B' \underline{t}$, $\underline{u}' = \underline{t}' B$; then

$$M_{\underline{Y}}(\underline{t}) = \exp(\underline{t}' \underline{\mu}) \exp\left(\frac{1}{2} \underline{t}' B D B' \underline{t}\right)$$

and $B D B'$ is symmetric since D is symmetric. Since $\underline{t}' B D B' \underline{t} = \underline{u}' D \underline{u}$, which is greater than 0 except when $\underline{u} = \underline{0}$ (equivalently when $\underline{t} = \underline{0}$ because B is nonsingular), $B D B'$ is positive definite, and consequently $\underline{Y}$ is Gaussian.

Conversely, suppose that the moment-generating function of $\underline{Y}$ is $\exp(\underline{t}' \underline{\mu}) \exp[(1/2) \underline{t}' A \underline{t}]$ where A is symmetric and positive definite. Let L be an orthogonal matrix such that $L' A L = D$, where D is the diagonal matrix of eigenvalues of A . Set $\underline{X} = L(\underline{Y} - \underline{\mu})$, so that $\underline{Y} = \underline{\mu} + L \underline{X}$. The moment-generating function of $\underline{X}$ is

$$E[\exp(\underline{t}' \underline{X})] = \exp(-\underline{t}' \underline{\mu}) E[\exp(\underline{t}' L \underline{Y})]$$

The last term is the moment-generating function of $\underline{Y}$ with $\underline{t}$ replaced by $\underline{t}' L$, or equivalently, $\underline{t}$ replaced by $L \underline{t}$. Thus the moment-generating function of $\underline{X}$ becomes

$$\exp(-\underline{t}' L' \underline{\mu}) \exp(\underline{t}' L' \underline{\mu}) \exp\left(\frac{1}{2} \underline{t}' L' A L \underline{t}\right)$$

$$\exp\left(\frac{1}{2} \underline{t}' D \underline{t}\right) = \exp\left(\frac{1}{2} \sum_{i=1}^n \lambda_i t_i^2\right).$$

Therefore the X_i are independent, with X_i normal $(0, \lambda_i)$. [8]

A Geometric Interpretation:

Assume for simplicity that the random variables X_i have zero mean. If $E(U) = E(V) = 0$ then the covariance of U and V is $E(UV)$, which can be regarded as an inner product. Then $Y_1 - \mu_1, \dots, Y_n - \mu_n$ span an n -dimensional space, and $X_1, \dots, X_n$ is an orthogonal basis for that space. Orthogonality is equivalent to independence. (Orthogonality means that the X_i are uncorrelated, i.e., $E(X_i X_j) = 0$ for $i \neq j$)

Theorem

Let $\underline{Y} = \underline{\mu} + L \underline{X}$ and let A be the symmetric, positive definite matrix appearing in the moment-generating function of the Gaussian random vector $\underline{Y}$. Then $E(Y_i) = \mu_i$ for all i , and furthermore, A is the covariance matrix of the Y_i , in other words, $a_{ij} = \text{Cov}(Y_i, Y_j)$ (and $a_{ii} = \text{Cov}(Y_i, Y_i) = \text{Var } Y_i$). [6][9]

It follows that the means of the Y_i and their covariance matrix determine the moment-generating function, and therefore the density. [8][10]

Proof. Since the X_i have zero mean, we have $E(Y_i) = \mu_i$. Let K be the covariance matrix of the Y_i . Then K can be written in the following peculiar way:

$$K = E \left\{ \begin{bmatrix} Y_1 - \mu_1 \\ \vdots \\ Y_n - \mu_n \end{bmatrix} (Y_1 - \mu_1, \dots, Y_n - \mu_n) \right\}.$$

Note that if a matrix M is n by 1 and a matrix N is 1 by n , then MN is n by n . In this case, the ij entry is $E[(Y_i - \mu_i)(Y_j - \mu_j)] = \text{Cov}(Y_i, Y_j)$. Thus

$$K = E[(Y - \mu)(Y - \mu)'] = E(LXX'L') = LE(XX'L')$$

since expectation is linear. [For example, $E(MX) = ME(X)$ because $E(\sum_j m_{ij}X_j) = \sum_j m_{ij}E(X_j)$.] But $E(XX')$ is the covariance matrix of the X_i , which is D . Therefore $K = LDL' = A$ (because $L'AL = D$).

Finding The Density:

From $\underline{Y} = \mu + L\underline{X}$ we can calculate the density of $\underline{Y}$. The Jacobian of the transformation from $\underline{X}$ to $\underline{Y}$ is $\det L = \pm 1$, and

$$f_{\underline{X}}(x_1, \dots, x_n) = \frac{1}{(\sqrt{2\pi})^n} \frac{1}{\sqrt{\lambda_1 \dots \lambda_n}} \exp\left(-\sum_{i=1}^n x_i^2 / 2\lambda_i\right).$$

We have $\lambda_1 \dots \lambda_n = \det D = \det K$ because $\det L = \det L' = \pm 1$. Thus

$$f_{\underline{X}}(x_1, \dots, x_n) = \frac{1}{(\sqrt{2\pi})^n \sqrt{\det K}} \exp\left(-\frac{1}{2} \underline{x}' D^{-1} \underline{x}\right).$$

But $\underline{y} = \underline{\mu} + L\underline{x}$, $\underline{x} = L'(\underline{y} - \underline{\mu})$, $\underline{x}' D^{-1} \underline{x} = (\underline{y} - \underline{\mu})' L D^{-1} L' (\underline{y} - \underline{\mu})$, and $K = LDL'$, $K^{-1} = LD^{-1}L'$. The density of $\underline{Y}$ is

$$f_{\underline{Y}}(y_1, \dots, y_n) = \frac{1}{(\sqrt{2\pi})^n \sqrt{\det K}} \exp\left[-\frac{1}{2} (\underline{y} - \underline{\mu})' K^{-1} (\underline{y} - \underline{\mu})\right].$$

Individually Gaussian Versus Jointly Gaussian

If $X_1, \dots, X_n$ are jointly Gaussian, then each X_i is normally distributed, but *not conversely*. For example, let X be normal $(0,1)$ and flip an unbiased coin. If the coin shows heads, set $Y = X$, and if tails, set $Y = -X$. Then Y is also normal $(0,1)$ since $P\{Y \leq y\} = 1/2 * P\{X \leq y\} + 1/2 * P\{-X \leq y\} = P\{X \leq y\}$

because $-X$ is also normal $(0,1)$. Thus $FX = FY$. But with probability $1/2$, $X+Y=2X$, and with probability $1/2$, $X+Y=0$. Therefore $P\{X+Y=0\}=1/2$. If X and Y were jointly Gaussian, then $X+Y$ would be normal. We conclude that X and Y are individually Gaussian but not jointly Gaussian. [7]

Theorem

If $X_1, \dots, X_n$ are jointly Gaussian and uncorrelated ($\text{Cov}(X_i, X_j) = 0$ for all $i \neq j$), then the X_i are independent.

Proof. The moment-generating function of $X = (X_1, \dots, X_n)$ is $M_{\underline{X}}(t) = \exp(t'\underline{\mu}) \exp(1/2 t' K t)$

where K is a diagonal matrix with entries $\sigma_1^2, \sigma_2^2, \dots, \sigma_n^2$ down the main diagonal, and 0's elsewhere. Thus

$$M_{\underline{X}}(t) = \prod_{i=1}^n \exp(t_i \mu_i) \exp\left(\frac{1}{2} \sigma_i^2 t_i^2\right)$$

which is the joint moment-generating function of independent random variables $X_1, \dots, X_n$, where X_i is normal (μ_i, σ_i^2) .

Conditional Density

Let $X_1, \dots, X_n$ be jointly Gaussian. We find the conditional density of X_n given $X_1, \dots, X_{n-1}$:

$$f(x_n | x_1, \dots, x_{n-1}) = \frac{f(x_1, \dots, x_n)}{f(x_1, \dots, x_{n-1})}$$

with

$$f(x_1, \dots, x_n) = (2\pi)^{-n/2} (\det K)^{-1/2} \exp\left[-\frac{1}{2} \sum_{i,j=1}^n y_i q_{ij} y_j\right]$$

where $Q = K^{-1} = [q_{ij}]$, $y_i = x_i - \mu_i$. Also,

$$f(x_1, \dots, x_{n-1}) = \int_{-\infty}^{\infty} f(x_1, \dots, x_{n-1}, x_n) dx_n = B(y_1, \dots, y_{n-1}).$$

Now

$$\sum_{i,j=1}^n y_i q_{ij} y_j = \sum_{i,j=1}^{n-1} y_i q_{ij} y_j + y_n \sum_{j=1}^{n-1} q_{nj} y_j + y_n \sum_{i=1}^{n-1} q_{in} y_i + q_{nn} y_n^2.$$

with $C = (1/2)q_{nn}$, $D = \sum_{j=1}^{n-1} q_{nj} y_j = \sum_{i=1}^{n-1} q_{in} y_i$ since $Q = K^{-1}$ is symmetric. The conditional density may now be expressed as [15]

$$\frac{A(y_1, \dots, y_{n-1})}{B(y_1, \dots, y_{n-1})} \exp[-(C y_n^2 + D(y_1, \dots, y_{n-1}) y_n)]$$

We conclude that

given $X_1, \dots, X_{n-1}$, X_n is normal.

The conditional variance of X_n (the same as the conditional variance of $Y_n = X_n - \mu_n$) is [16]

$$\frac{1}{2C} = \frac{1}{q_{nn}} \quad \text{because} \quad \frac{1}{2\sigma^2} = C, \sigma^2 = \frac{1}{2C}.$$

$$\boxed{\text{Var}(X_n | X_1, \dots, X_{n-1}) = \frac{1}{q_{nn}}}$$

and the conditional mean of Y_n is

$$-\frac{D}{2C} = -\frac{1}{q_{nn}} \sum_{j=1}^{n-1} q_{nj} Y_j$$

So the conditional mean of X_n is [17]

$$\boxed{E(X_n | X_1, \dots, X_{n-1}) = \mu_n - \frac{1}{q_{nn}} \sum_{j=1}^{n-1} q_{nj} (X_j - \mu_j)}.$$

$E(Y|X)$ is the best estimate of Y based on X , in the sense that the mean square error is minimized. In the joint Gaussian case, the best estimate of X_n based on $X_1, \dots, X_{n-1}$ is linear, and it follows that the best linear estimate is in fact the best overall estimate. This has important practical applications, since linear systems are usually much easier than nonlinear systems to implement and analyse.

A multivariate normal distribution in three variables. It has probability density function

$$P(x_1, x_2, x_3) = \frac{e^{-w/2}}{2\sqrt{2} \pi^{3/2} \sqrt{1 - (\rho_{12}^2 + \rho_{13}^2 + \rho_{23}^2) + 2\rho_{12}\rho_{13}\rho_{23}}},$$

Where

$$w = x_1^2 (\rho_{23}^2 - 1) + x_2^2 (\rho_{13}^2 - 1) + x_3^2 (\rho_{12}^2 - 1) +$$

$$2[x_1 x_2 (\rho_{12} - \rho_{13} \rho_{23}) + x_1 x_3 (\rho_{13} - \rho_{12} \rho_{23}) + x_2 x_3 (\rho_{23} - \rho_{12} \rho_{13})].$$

The standardized trivariate normal distribution takes unit variances. The quadrant probability in this special case is then given analytically by

$$P(x_1 \leq 0, x_2 \leq 0, x_3 \leq 0)$$

$$= \int_{-\infty}^0 \int_{-\infty}^0 \int_{-\infty}^0 P(x_1, x_2, x_3) dx_1 dx_2 dx_3$$

$$= \frac{1}{8} + \frac{1}{4\pi} (\sin^{-1} \rho_{12} + \sin^{-1} \rho_{13} + \sin^{-1} \rho_{23})$$

4. Mathematical Results

➤ Comparison of Combined Effects on Hormones with Placebo & Progesterone Treatment

For different values of shape and Scale parameters we have the following figures for the application part.

○ Melatonin, GH, TSH

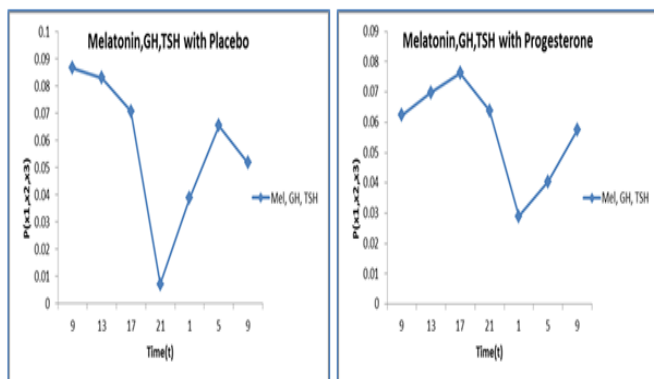


Fig A. The function $P(\text{Melatonin, GH, TSH})$ varying with Time (t).

○ Melatonin, TSH, Prolactin

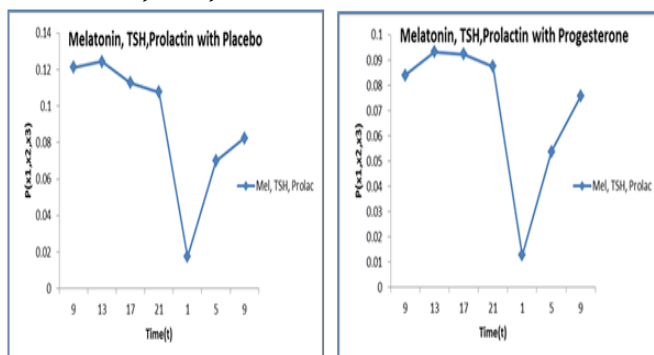


Fig B. The function $P(\text{Melatonin, TSH, Prolactin})$ varying with Time (t).

○ Melatonin, TSH, ACTH

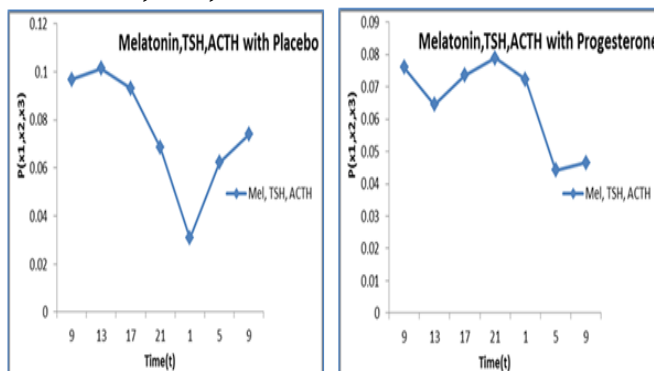


Fig C. The function $P(\text{Melatonin, TSH, ACTH})$ varying with Time (t).

○ Melatonin, GH, ACTH

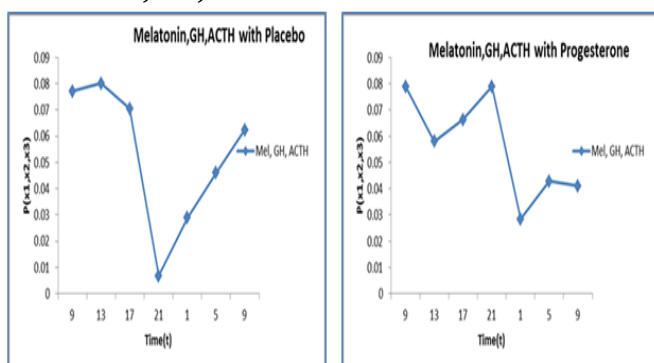


Fig D. The function $P(\text{Melatonin, GH, ACTH})$ varying with Time (t).

○ Melatonin, Prolactin, GH

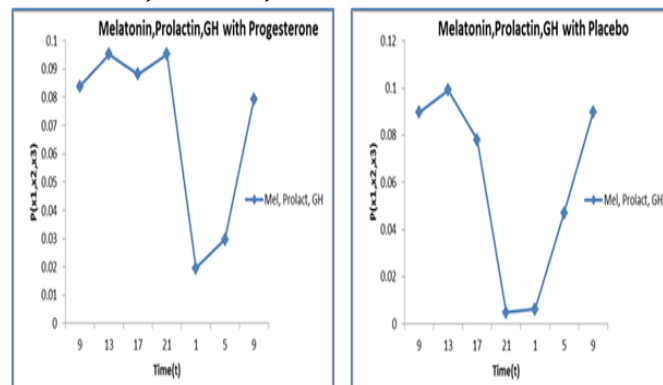


Fig E. The function $P(\text{Melatonin, Prolactin, GH})$ varying with Time (t)

5. Conclusion

➤ Mathematical Conclusion

We have shown the comparison of characterizing hormones with respect to Placebo and Progesterone treatments. The following observations are made:

○ **Figure A :** The function $P(\text{Melatonin, GH, TSH})$ varying with Time (t)

In Both Treatments, Melatonin, GH, TSH concentrations followed the desired way, with relatively constant daytime levels followed by an early nocturnal rise in the concentration levels. The timings in the rise of the nocturnal peak showed a delay of three hours more in the progesterone treatment. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for classic post-menopausal subjects. The Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, GH, TSH shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

○ **Figure B:** The function $P(\text{Melatonin, TSH, Prolactin})$ varying with Time (t)

In Both Treatments, Melatonin, TSH, Prolactin concentrations followed the relative pattern, with relatively constant daytime levels thus showing an major nocturnal elevation in the concentration levels. In both conditions all variables characterising viz.. Melatonin, TSH, Prolactin were found to be more or less similar in both conditions still showing Progesterone treatment more effective than the Placebo one. The timings in the rise of the peak in the progesterone treatment is higher than the placebo one. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for post-menopausal subjects. The Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, TSH, Prolactin shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

○ **Figure C:** The function $P(\text{Melatonin, TSH, ACTH})$ varying with Time (t)

In Both Treatments, Melatonin, TSH, ACTH concentrations followed the relative pattern, with desirably constant daytime levels thus showing an nocturnal elevation in the concentration levels. In Placebo treatment all the variables viz.. Melatonin, TSH, ACTH which are determined by the Function $P(x_1, x_2, x_3)$ showed a decline in the levels of concentrations in the mid-night time with a consequent rise after 1a.m. whereas in case of progesterone treatment the Function $P(x_1, x_2, x_3)$ of all the variables shows a decrease at

mid-night time but with much higher values of the levels of concentrations. In both conditions all variables characterising viz..Melatonin, TSH, ACTH shows Progesterone treatment more effective than the Placebo one. The timings in the rise of the peak in the progesterone treatment is higher than the placebo one. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for post-menopausal subjects. The Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, TSH, ACTH shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

○ **Figure D:** The function $P(\text{Melatonin, GH, ACTH})$ varying with Time (t)

In Placebo Treatment Melatonin, GH, ACTH concentrations followed the desired way, with the Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, GH, ACTH relatively constant during daytime levels followed by an early nocturnal rise in the concentration levels. In Progesterone treatment the Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, GH, ACTH variables shows a fluctuating curve during day times followed by an rise of the nocturnal peak which shows a variation of three hours more in the treatment. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for classic post-menopausal subjects. The Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, GH, ACTH shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

○ **Figure E:** The function $P(\text{Melatonin, Prolactin, GH})$ varying with Time (t)

In Placebo Treatment Melatonin, Prolactin, GH concentrations followed the desired way, with the Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, Prolactin, GH relatively with slight elevation during daytime levels followed by early nocturnal stable curve between 10p.m and 1a.m and then rise in the concentration levels in the mid-night time. In Progesterone treatment the Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, Prolactin, GH variables shows a fluctuating curve during day times followed by an rise of the nocturnal peak which shows a variation of three hours more in the treatment. Thus showing progesterone treatment more effective in the case of combined effects of the hormones in a 24-hr time profile for classic post-menopausal subjects. The Function $P(x_1, x_2, x_3)$ representing the levels of concentrations of Melatonin, Prolactin, GH shows a hike in the Progesterone treatment as compared to the Placebo one thus giving a good conclusion to the medical professionals.

In this direction we have developed a Trivariate Mathematical Normal Distribution Model to analyse a data set of various hormones and compare the combined effects of the hormones in a 24 hr. time profile under Placebo and Progesterone treatments. Here the model concludes that the level of concentrations of respective hormones shows a hike in the Progesterone treatment as compared to the Placebo Treatment. Thus giving a good conclusion to the Medical Professionals.

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