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Quantum chemical computational methods for interpreting and predicting the vibrational spectra of menstrual cycle in women

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ABSTRACT

The problem of generating bivariate normal distributions is drawing the attention of the reliability analyst. Amongst those approaches, the characterization approach and the modeling approach are very appealing. In fact characterization approach is of interest to both theoreticians and applied workers. Here we have used a bivariate normal distribution for application from Multivariate normal distribution through characterization approach. In our application we have considered days of Menstrual Cycle with Melatonin hormone as variable combined with LH, Estradiol and Progesterone hormones as variables as women stress effects. In many applications involving functions of random variables one may be interested in only the mean & variance of these functions. Furthermore, one may have available data from which the mean, variance and perhaps correlation coefficients among the variables can be calculated. Here we express the statistics of a function of a several random variables as a function of statistics on its component. In the discussion which follows the joint density is assumed to be a multivariate normal. The mean and variance of four variables have been utilized in the application part. From the clinical point of view menstrual changes due to secretion of hormones Melatonin, LH, Progesterone, Estradiol which are first sign of ovarian function. The curve for moment generating function of the above four variables are obtained here and explained by using a figure in the mathematical results.

Introduction

Recently, it has been discovered that an imbalance of reactive oxygen species, or 'oxidative stress', can have a negative impact on the success of infertility treatments, and furthermore, investigators have begun addressing potential mechanisms of preventing these effects with the use of novel oxygen scavengers such as melatonin. It may be that these agents have a positive effect on pregnancy success rates following IVF treatment. [11]

Melatonin

Melatonin is a hormone made by the Pineal gland, a small gland in the brain. Melatonin helps control our sleep and wake cycles. Very small amount of it are found in foods such as meats, grains, fruits, vegetables. Our body has its own internal clock that controls our natural cycle of waking & sleeping hours. Melatonin levels begin to rise from mid to late evening, remain high for the night and then drop in the early morning hours.[1]

Uses of Melatonin

Melatonin supplements are sometimes used to treat jet lag or sleep problems (insomnia). 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.
- Preventing or reducing problems with sleeping and confusion after surgery.
- Reducing chronic cluster headaches

Melatonin has been identified as a key factor in the regulation of circadian rhythms and the sleep-wake cycle. Long exposure to artificial lighting leads to a reduction in endogenous melatonin exposure. Melatonin is thus associated with sleep disturbances including insomnia, and much of the literature is focused in this area.

Luteinizing Hormone (LH)

This is produced and released in the anterior pituitary gland. This hormone is considered a gonadotrophic hormone because of its role in controlling the function of ovaries in females and testes in males, which are known as the gonads.

Luteinizing hormone is responsible for different functions in men and women. For women, the hormone stimulates the ovaries to produce oestradiol. Two weeks into a woman's cycle, a surge in luteinizing hormone causes the ovaries to release an egg during ovulation. If fertilization occurs, luteinizing hormone will stimulate the corpus luteum, producing progesterone to sustain the pregnancy.

For men, luteinizing hormone stimulates the production of testosterone from Leydig cells in the testes. Testosterone, in turn, stimulates sperm production and helps accentuate male characteristics — like a deep voice or growth of facial hair.

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People who have high levels of luteinizing hormone may experience infertility, because the hormone directly impacts the reproductive system. In women, luteinizing hormone levels that are too high are often connected to polycystic ovary syndrome, which creates inappropriate testosterone levels. Some genetic conditions, like Turner syndrome or Klinefelter's syndrome, can cause high levels of the hormone, as well. People with these conditions are often unable to reproduce.[4]

Estradiol

This is a female sex hormone that is the predominant estrogen throughout a female's reproductive years. This hormone has a significant impact on reproductive and sexual function as well as on other organs, including the bones.

Estradiol acts primarily as a growth hormone for the reproductive structures including the lining of the vagina, the fallopian tubes, the endometrium and the cervical glands. The hormone is also required to maintain oocytes (eggs in the ovary) and triggers a series of events that lead to ovulation. In addition, estradiol works in conjunction with progesterone to prepare the womb lining for implantation. In males, estradiol aids sperm maturation and also helps to maintain a healthy libido.

During the reproductive period (the onset of puberty through to menopause), much of the estradiol is produced by the granulosa cells in the ovaries through aromatization of rostenedione. This rostenedione is produced by the folliculi cells. [1]

Progesterone

This is one of the hormones in our bodies that stimulates and regulates various functions. Progesterone plays a role in maintaining pregnancy. The hormone is produced in the ovaries, the placenta (when a woman gets pregnant) and the adrenal glands. It helps prepare your body for conception and pregnancy and regulates the monthly menstrual cycle. It also plays a role in sexual desire.

During the reproductive years, the pituitary gland in the brain generates hormones (follicle-stimulating hormone [FSH] and luteinizing hormone [LH]) that cause a 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 rise in the second half of the menstrual cycle, and following the release of the egg (ovulation), the ovarian tissue that replaces the follicle (the corpus luteum) continues to produce estrogen and progesterone.[2]

The Role of Progesterone in Women

One of progesterone's most important functions is to cause the endometrium to secrete special proteins during the second half of the menstrual cycle, preparing it to receive and nourish an implanted fertilized egg. If implantation does not occur, estrogen and progesterone levels drop, the endometrium breaks down and menstruation occurs.

If a pregnancy occurs, progesterone is produced in the placenta, and levels remain elevated throughout the pregnancy. The combination of high estrogen and progesterone levels suppress further ovulation during pregnancy. Progesterone also encourages the growth of milk-producing glands in the breast during pregnancy.[3]

High progesterone levels are believed to be partly responsible for symptoms of premenstrual syndrome (PMS), such as breast tenderness, feeling bloated and mood swings. When you skip a period, it could be because of failure to ovulate and subsequent low progesterone levels.

2. Methods & Results

In humans, the only data on cyclical melatonin changes comes from women undergoing ovarian stimulation. Levels of melatonin reach a nadir in the pre ovulatory phase and peak in the luteal phase. This suggests that melatonin has variable effects dependent on the menstrual phase.

It is also well known that shift-workers are more likely than daytime workers to experience circadian disruption and longer menstrual cycles, more menorrhagia and dys-menorrhoea . These results are corroborated by a very large cohort study, which also found that duration of shift work was modestly associated with menstrual cycle irregularity. A Japanese study found that melatonin levels varied significantly between night and day shift workers, while LH and FSH levels did not, suggesting that the menstrual irregularity associated with shift-work could be explained by melatonin fluctuations[11][12]

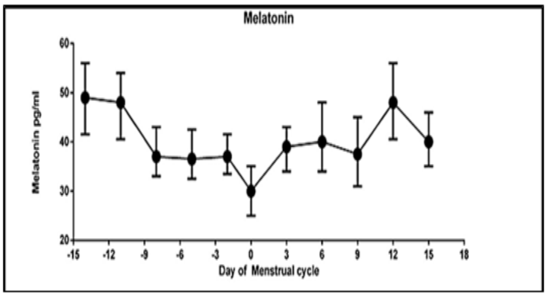

Fig 1. Melatonin : Relative concentrations of Plasma Melatonin treated with respective day of menstrual cycle.

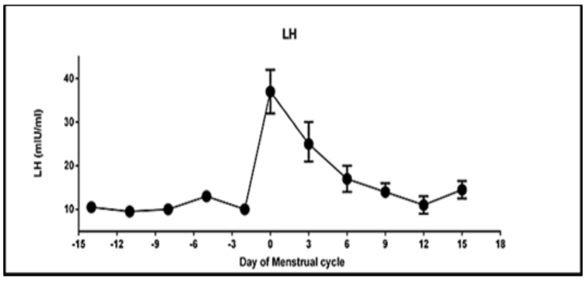

Fig 2 LH . Relative concentrations of LH treated with respective day of menstrual cycle.

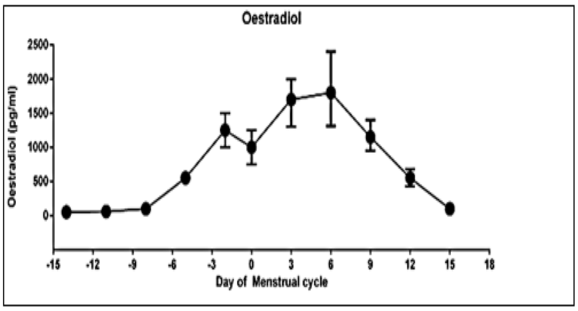

Fig 3.Oestradiol : Relative concentrations of Oestradiol treated with respective day of menstrual cycle.

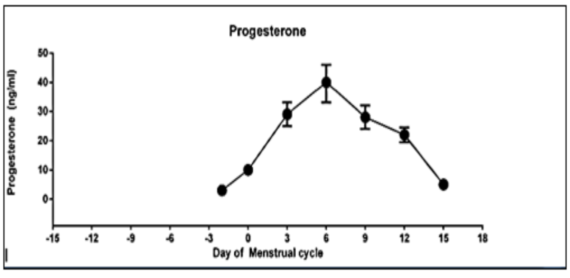

Fig 4. Progesterone : Relative concentrations of Progesterone treated with respective day of menstrual cycle.

The role of Melatonin in Assisted Reproductive Technology:

Oxidative stress occurs at many levels during the treatment of infertility. Interventional studies have begun recently, with an emphasis on oral supplementation of melatonin during the ovarian stimulation phase of the IVF cycle and its effects on gamete and embryo quality. [10]

Effects of Melatonin on Oocyte Quality

• Melatonin is an effective mitigator of mitochondrial DNA damage, likely as a result of an increase in electron transport efficiency within mitochondria, thus preventing the formation of ROS. In some situations melatonin may be even more effective at performing this function than specific mitochondrial antioxidants, and this particular characteristic may have relevance to its use in the treatment of infertility and the improvement of oocyte quality and maturity. [1][2]

3. Mathematical Model

- **The Multivariate Normal Distribution:**

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

$M(t_1,... ,t_n)= E[\exp(t_1X_1 + \cdots + t_nX_n)]$.

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

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

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

Let us indicate the notational scheme we will be using. Vectors will be written with an under bar, and are assumed to be column vectors unless otherwise specified. If $\underline{t}$ is a column vector with components $t_1,... ,t_n$, then to save space we write $\underline{t} =(t_1,... ,t_n)'$. 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.

Proof. Let $X_1,... ,X_n$ be independent, with X_i normal $(0,\lambda_i)$, and let $\underline{X} =(X_1,... ,X_n)'$. Let $\underline{Y} = B\underline{X}+\underline{\mu}$ where B is non singular. 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

$$E[\exp(\underline{u}'\underline{X})]=\prod_{i=1}^{n}E[\exp(u_iX_i)]=\exp\Big(\sum_{i=1}^{n}\lambda_iu_i^2/2\Big)=\exp\Big(\frac{1}{2}\underline{u}'D\underline{u}\Big)$$

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

$$M_{\underline{Y}}(\underline{t})=\exp(\underline{t}'\underline{\mu})\exp(\frac{1}{2}\underline{t}'BDB'\underline{t})$$

and BDB' is symmetric since D is symmetric. Since $\underline{t}'BDB'\underline{t} = \underline{u}'D\underline{u}$, which is greater than 0 except when $\underline{u} = \underline{0}$ (equivalently when $\underline{t} = \underline{0}$ because B is non singular), BDB' 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 $L'AL = D$, 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

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

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

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

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 $Y_1 -\mu_1,... ,Y_n - \mu_n$ span an n-dimensional space, and $X_1,...,X_n$ is an orthogonal basis for that space. Orthogonality is equivalent to independence. (Orthogonality means that the X_i are uncorrelated, i.e., $E(X_iX_j) = 0$ for $I = j$

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 Y. Then $E(Y_i)= \mu_i$ for all i, and furthermore, A is the *covariance matrix* of the Y_i, in other words, $a_{ij} =\mathrm{Cov}(Y_i,Y_j)$ (and $a_{ii} =\mathrm{Cov}(Y_i,Y_i)=\mathrm{Var}\ Y_i$).

It follows that the means of the Y_i and their covariance matrix determine the moment-generating function, and therefore the density. [9][6]

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 is1by n, then MN is n by n. In this case, the ij entry is $E[(Y_i -\mu_i)(Y_j -\mu_j)] = \mathrm{Cov}(Y_i,Y_j)$. Thus

$$K=E[(\underline{Y}-\underline{\mu})(\underline{Y}-\underline{\mu})']=E(L\underline{X}\underline{X}'L')=LE(\underline{X}\underline{X}')L'$$

since expectation is linear. [For example, $E(M\underline{X})= ME(\underline{X})$ because $E(\sum_j m_{ij}X_j) = \sum_j m_{ij}E(X_j)$]. But $E(\underline{X}\underline{X}')$ is the covariance matrix of the X_i, which is D. Therefore $K = LDL' = A$ (because $L'AL= D$). [5][8]

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

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

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

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

But $\underline{y}=\underline{\mu}+L\underline{x}$, $\underline{x}=L'(\underline{y}-\underline{\mu})$, $\underline{x}'D^{-1}\underline{x}=(\underline{y}-\underline{\mu})'LD^{-1}L'(\underline{y}-\underline{\mu})$, and [see the end of (21.4)] $K=LDL'$, $K^{-1}=LD^{-1}L'$. The density of $\underline{Y}$ is

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

Individually Gaussian Versus Jointly Gaussian

If $X_1,\dots,X_n$ are jointly Gaussian, then each Xi 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

$P\{Y \le y\}=1/2 * P\{X \le y\}+ ½ * P\{-X \le y\}= P\{X \le y\}$

[1] 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 (Cov $(X_i,X_j) = 0$ for all i=j), then the X_i are independent.

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

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

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

which is the joint moment-generating function of independent random variables $X_1,\dots,X_n$, where X_i is normal (μ_i,σ^2). [5][6]

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

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

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

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

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

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

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

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

Thus

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

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

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

$E(Y|X)$ 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 analyze. [8][9]

The Bivariate Normal Distribution

Formulas

The general formula for the n - dimensional normal density is

$$f_{\underline{X}}(x_1,\dots,x_n)=\frac{1}{(\sqrt{2\pi})^n}\frac{1}{\sqrt{\det K}}\exp\big[-\frac{1}{2}(\underline{x}-\underline{\mu})'K^{-1}(\underline{x}-\underline{\mu})\big]$$

Where $E(X) = \mu$ and K is the covarient matrix of X. We specialize to the case $n = 2$

$$K=\begin{bmatrix}\sigma_1^2 & \sigma_{12}\\ \sigma_{12} & \sigma_2^2\end{bmatrix}=\begin{bmatrix}\sigma_1^2 & \rho\sigma_1\sigma_2\\ \rho\sigma_1\sigma_2 & \sigma_2^2\end{bmatrix},\quad \sigma_{12}=\mathrm{Cov}(X_1,X_2);$$

$$K^{-1}=\frac{1}{\sigma_1^2\sigma_2^2(1-\rho^2)}\begin{bmatrix}\sigma_2^2 & -\rho\sigma_1\sigma_2\\ -\rho\sigma_1\sigma_2 & \sigma_1^2\end{bmatrix}=\frac{1}{1-\rho^2}\begin{bmatrix}1/\sigma_1^2 & -\rho/\sigma_1\sigma_2\\ -\rho/\sigma_1\sigma_2 & 1/\sigma_2^2\end{bmatrix}$$

Thus the joint density of X_1 and X_2 is

$$\frac{1}{2\pi\sigma_1\sigma_2\sqrt{1-\rho^2}}\exp\Big\{-\frac{1}{2(1-\rho^2)}\Big[\big(\frac{x_1-\mu_1}{\sigma_1}\big)^2-2\rho\big(\frac{x_1-\mu_1}{\sigma_1}\big)\big(\frac{x_2-\mu_2}{\sigma_2}\big)+\big(\frac{x_2-\mu_2}{\sigma_2}\big)^2\Big]\Big\}.$$

The moment-generating function of $\underline{X}$ is

$$M_{\underline{X}}(t_1,t_2)=\exp(\underline{t}'\underline{\mu})\exp\big(\frac{1}{2}\underline{t}'K\underline{t}\big)$$

$$=\exp\Big[t_1\mu_1+t_2\mu_2+\frac{1}{2}\big(\sigma_1^2t_1^2+2\rho\sigma_1\sigma_2t_1t_2+\sigma_2^2t_2^2\big)\Big]$$

If X_1 and X_2 are jointly Gaussian and uncorrelated, then $\rho = 0$, so that $f(x_1, x_2)$ is the product of a function $g(x_1)$ of x_1 alone and a function $h(x_2)$ of x_2 alone. It follows that X_1 and X_2 are independent.

The conditional distribution of X_2 given X_1 is normal, with

$$E(X_2|X_1=x_1)=\mu_2-\frac{q_{21}}{q_{22}}(x_1-\mu_1)$$

$$\frac{q_{21}}{q_{22}}=-\frac{\rho/\sigma_1\sigma_2}{1/\sigma_2^2}=-\frac{\rho\sigma_2}{\sigma_1}.$$

$$E(X_2|X_1=x_1)=\mu_2+\frac{\rho\sigma_2}{\sigma_1}(x_1-\mu_1)$$

$$\mathrm{Var}(X_2|X_1=x_1)=\frac{1}{q_{22}}=\sigma_2^2(1-\rho^2).$$

For $E(X_1|X_2 = x_2)$ and $\mathrm{Var}(X_1|X_2 = x_2)$, interchange μ_1 and μ_2, and interchange σ_1 and σ_2.

4. Mathematical Results

For different values of shape & scale parameters we have following figures for the application part.

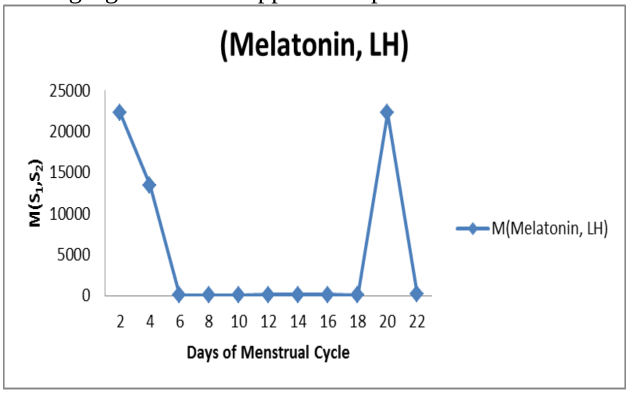

Figure A. Combined effects of Melatonin & LH (M (s_1,s_2)) for Days of Menstrual Cycle.

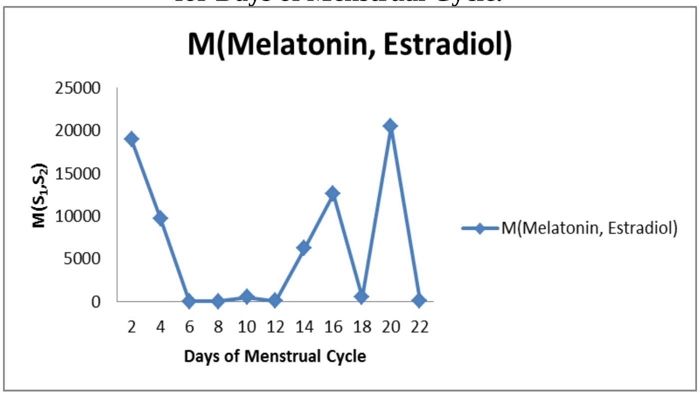

Figure B. Combined effects of Melatonin & Estradiol (M (s_1,s_2)) for Days of Menstrual Cycle.

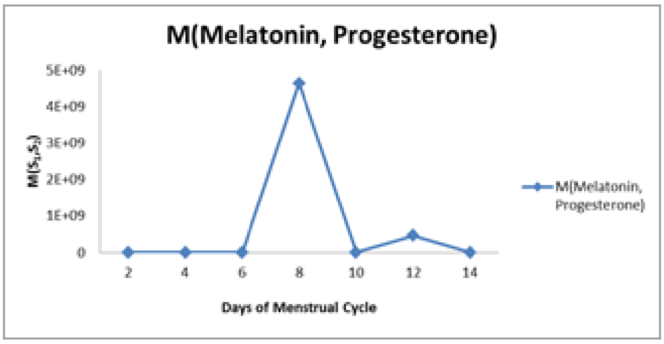

Figure C. Combined effects of Melatonin & Progesterone (M (s_1,s_2)) for Days of Menstrual Cycle.

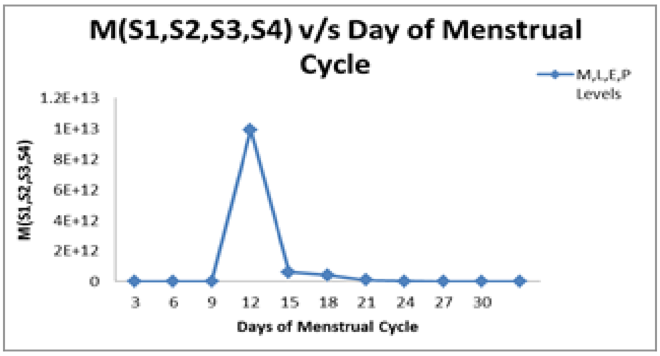

Figure D. Combined effects of Melatonin, LH, Estradiol & Progesterone (M (s_1,s_2 s_3, s_4)) for Days of Menstrual Cycle .

Conclusion

a. Mathematical Conclusion

Fig B shows combined effects of Melatonin and Estradiol for days of Menstrual Cycle. It is clearly seen from Mathematical Graph that the Function in the form of two variables Melatonin and Estradiol has no Effect after completion of the Menstrual Cycle and the Function gradually increases during the ovulation period. At the termination point of the ovulation period there is a decline in the function which again gives a sudden rise during the later stage of the Luteal Phase of the Menstrual Cycle.

Fig A shows combined effects of Melatonin and LH for days of Menstrual Cycle. Mathematical Graph represents that the function of two variables Melatonin and LH has no effect after completion of Menstrual cycle as well as during the ovulation period. Though the function gradually increases during the Luteal Phase of the Menstrual Cycle.

Fig C shows combined effects of Melatonin and Progesterone for days of Menstrual cycle. The graphical representation of the function Mathematically shows that two variables Melatonin and Progesterone has maximum effect during the ovulation period of the Menstrual cycle and the effect gradually goes on decreasing as it attains the Luteal phase of the cycle. During the Luteal phase of the cycle both the variables show minimum effect in the cycle.

Fig D shows combined effects of Melatonin, LH, Estradiol & Progesterone (M (s_1,s_2 s_3, s_4)) for Days of Menstrual Cycle . The graphical representation of the function Mathematically shows that four variables Melatonin, LH, Estradiol & Progesterone attains the highest values during the ovulation period of the Menstrual cycle and the effect gradually becomes negligible during the Luteal phase of the cycle and also before the ovulation period. During the Luteal phase of the cycle all the variables show minimum effect in the cycle

b. Medical Conclusion drawn from Mathematical Model

Medical conclusion suggests that combined effects of Melatonin with different hormones like Estradiol, LH and Progesterone gives us various changes during the days of the Menstrual cycle. Mathematical model in the form of bivariate normal distribution gives a proper distribution function i.e. ($M(S_1,S_2)$ clearly seen in the mathematical graphs) for a given set of values of ρ. From the mathematical model it is clearly seen that combined effects of Melatonin with LH varies with the combined effects of Melatonin with Estradiol and Progesterone. This gives a good conclusion to the medical professionals to measure the level of LH, Estradiol and Progesterone with Melatonin during each day of Menstrual cycle.

Medical conclusion suggests that combined effects of Melatonin, LH, Estradiol & Progesterone (M (s_1,s_2 s_3, s_4)) for Days of Menstrual Cycle gives us highest peak during the ovulation period of the Menstrual cycle. Mathematical model in the form of Four - variate normal distribution gives a proper distribution function i.e. (M (s_1,s_2 s_3, s_4)) clearly seen in the mathematical graphs) for a given set of values of ρ. From the mathematical model it is clearly seen that combined effects of Melatonin, LH, Estradiol & Progesterone is remarkably maximum during ovulation period . This gives a good conclusion to the medical professionals to measure the level of Melatonin, LH, Estradiol and Progesterone during each day of Menstrual cycle thereby giving a negligible secretion during the rest of the cycle.

Infertility treatments are associated with significant levels of reactive oxygen species which have the potential to negatively affect the quality of oocytes and embryos. Melatonin shows promise as an adjunctive therapy in the treatment of infertility. Its unique anti-oxidative characteristics and safety profile make it an ideal potential adjuvant therapy to be further investigated in well designed double blind randomised placebo-controlled trials.

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