A Bivariate Mathematical Normal Distribution To Analyze Experimental Conditions from Melatonin Data

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***Abstract*— The problem of generating Bivariate Normal Distribution is drawing the attention of the reliability analyst. Amongst these approaches the modelling approach is very appealing and of great interest. Here we have used the Bivariate Normal Distribution for the application by extending distribution through characterization approach. Melatonin is a sleep hormone that controls sleep wake cycles. Melatonin is presently the most accurate marker of the activity of the human circadian pacemaker. Current methods of analysing the plasma melatonin rhythm can be grouped into three categories: curve fitting methods, differential equation based model, linear differential equations. To determine which method provides the most accurate assessment of circadian phase, we compared the ability to fit the data and the variability of phase estimates for different markers of melatonin phase derived from these methodological categories. We Conclude the results by getting a mathematical curve which is both increasing and decreasing which gives record of complete sleep wake cycles of subjects.**

Keywords*— *Plasma Melatonin, Circadian Phase, Bivariate Normal Distribution

I. INTRODUCTION

Melatonin: Melatonin is a hormone made by the Pineal gland, a small gland in the brain. Melatonin helps control our sleep and wake cycles. Melatonin supplement is very rarely found in food substituents. Our body has its own internal clock that controls our natural cycle of waking & sleeping hours. Melatonin concentrations are increased usually in the mid-night and decreased in the day-time.

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.[1]
- Preventing or reducing problems with sleeping and confusion after surgery.

Circadian phase is a major determinant of the time course and level of sleepiness, good performance, many melatonin hormone concentrations and other conditions gives accurate measurements and plays a important role in the diagonisis and appropriate treatment for circadian rhythm sleep disorders. Since circadian phase of the suprachiasmatic nucleus (SCN), the site of the mammalian circadian pacemaker, cannot be measured directly in humans, outputs of the clock must be used as markers of the circadian system. [1][3]

II. METHODS & RESULTS

Melatonin Analysis Methods

Methods are used for the analysis of the melatonin data : two threshold-based methods, three curve fitting methods, and a physiologically-based model ; these yielded a number of circadian phase markers. Here we provide a description of each marker with abbreviations used throughout the text.

Estimates based on the mean of the 24-hr melatonin profile include the 24hrUpcross, 24hrMidpoint and 24hrDowncross. For each 24-hr segment of data the mean value of the melatonin concentration was computed and used as the threshold. The 24hr Upcross was calculated by linear interpolation as the time at which melatonin concentration crossed this threshold value on the rising portion of the curve. The 24hr Downcross was calculated in a similar fashion on the falling portion of the curve. The 24hr Midpoint was calculated as the average of the 24hr Upcross and 24hr Downcros[8]s times.

"Curve-fitting methods'' refers to methods in which a function was used to fit the entire melatonin profile; this was computed based on the function rather than the data.Curve-fitting methods used Fourier series with either 2 or 3 harmonics, a fundamental plus second harmonic , and a fundamental plus second and third harmonic ; or a skewed bimodal cosine function.. The Upcross and the Downcross were computed as the interpolated values at which half the fit maximum was reached on the rising and falling portion of the curve, respectively. Data were fit using the model converged to a solution and was included in the analysis. Two of the markers fit the model which were used by melatonin synthesis representing the time. In summary, data were available for subjects wherein in each subject, the melatonin profiles were analyzed to generate 17 different circadian phase estimates on each of three 24-hr data segments.

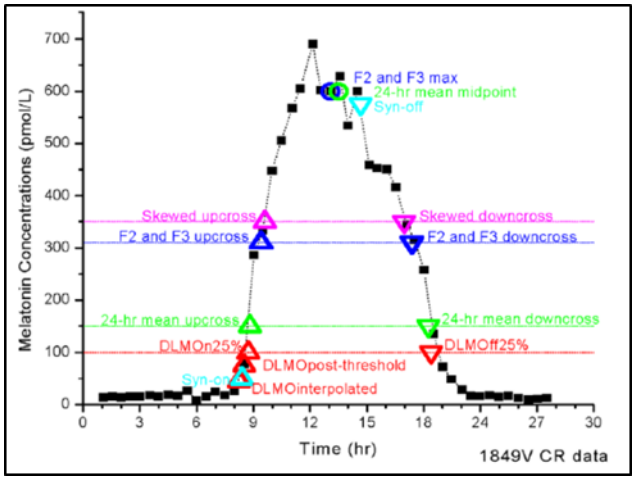

Fig 1. Phase Markers from Six Method Types of Analysing Melatonin Data.

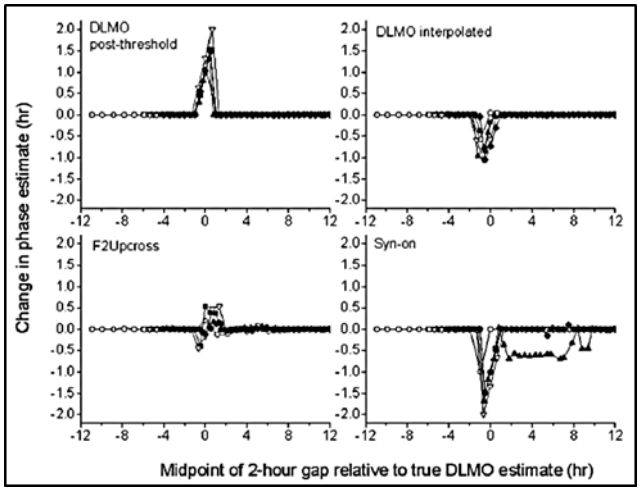

Fig 2. Change in phase estimates (hours) for subjects with 2-hour gaps of data.

Diagram of the phase markers from six methods used to analyse a single melatonin profile (subject 1849v). The upper curve includes the melatonin values, plotted as melatonin concentration . The lower curve includes the various phase markers by method and indicates their position with respect to upper curve. Fourier-based analysis methods F(2) and F(3) have been combined in this diagram because of their similarity.

Results

Not all subjects' data could be fit with all the methods. If the data could not be fit, then there was either no phase assessment produced by the analysis program because the method did not converge to a solution (for curve fitting and differential equation methods)s or the phase assessment using that method was not physiologically possible. The differential equation methods had the most fits and the DLMO based methods had the fewest. There were significantly fewer fits of the data from the older subjects. The data sets that could not be fit by a method had significantly smaller amplitudes than the data sets that could be fit (63.5657.3 (s.d.) vs. 129.7675.5 pmol/L; p,0.001 by t-test), although there was overlap in the range of amplitudes of those that could not and those that could be fit by analysis methods (range 6.4–226.5 vs. 38.2–344.0 pmol/L, respectively).[6][8]

Melatonin concentrations are observed in different subjects to give the idea of the sleep wake cycles for three consecutive days. The concentrations are monitored after every three hours repeatedly for three such days. For healthy subjects the level of melatonin concentrations rise in the mid night where the sleep hormone activates the most. For the weak subjects the level of concentrations of melatonin is not balanced properly. It may rise or fall depending upon the strength of the subjects. Many methods can be applied to get good results which will give more accuracy to the curves. Older subjects also showed imbalanced data values hereby showing distractions in the curves.

The two hour missing data at different values related to melatonin concentrations for five subjects. The data is fitted into different curves plotting melatonin profile. Each curve plots the change in the areas which are estimated for a different method. Data gaps are referenced as the time of midpoint of each gap relative to the DLMO post-threshold computed from the complete data set for each subject. Good changes in the areas are estimated indicating missing data set which is later relative to the estimate from the complete data set, while negative values indicate that the estimate from the missing data set was earlier.

III. MATHEMATICAL MODEL

Let U and V be two independent normal random variables, and consider two new random variables X and Y of the form

$$X = pU + qV,$$

$$Y = rU + sV,$$

Where p, q, r, s are some scalars. Each one of the random variables X and Y is normal, since it is a linear function of independent normal random variables. Here X and Y are linear functions of two random variables, their joint PDF takes a special form, known as the bi-variate normal PDF. The bivariate normal probability density function has various properties which are fitted in the model. In this section, we derive many such properties, both qualitative and analytical, to form a joint probability density function. To keep the discussion simple, we restrict ourselves to the case where X and Y have zero mean.

Note that if X and Y are jointly normal, then any linear combination $Z = s_1X + s_2Y$ has a normal distribution. The reason is that if we have

$X = pU + qV$ and

$Y = rU + sV$

for some independent normal random variables U and V ,then

$Z = s_1(pU + qV) + s_2(rU + sV)$

$=(ps_1 + rs_2)U +(qs_1 + ss_2)V.$

Thus, Z is the sum of the independent normal random variables $(ps_1 + rs_2)U$ and $(qs_1 + ss_2)V$, and is therefore normal.

Here we discuss a vital property which proves that jointly normal random variables have zero correlation and herewith implies independence.

This property can be verified using multivariate transforms, as follows. Assume that U and V are independent zero-mean normal random variables, and that $X = pU + qV$ and $Y = rU + sV$,so that X and Y are jointly normal. We assume that X and Y are not correlated, and we hence show that they are independent. Our first step is to derive a formula for the multivariate transform $M_{X,Y}$ (s_1,s_2) associated with X and Y . Recall that if Z is a zero-mean normal random variable with variance σ_z^2 , the associated transform is

$$\mathbf{E}[e^{sZ}] = M_Z(s) = e^{\sigma_Z^2 s^2/2},$$

Which implies that

$$\mathbf{E}[e^{Z}] = M_Z(1) = e^{\sigma_Z^2/2}.$$

Let us fix some scalars s_1, s_2,and let $Z = s_1X + s_2Y$. The random variable Z is normal, by our earlier discussion, with variance [7]

$$\sigma_Z^2 = s_1^2\sigma_X^2 + s_2^2\sigma_Y^2.$$

This leads to the following formula for the multivariate transform associated with the uncorrelated pair X and Y :

$$\begin{aligned} M_{X,Y}(s_1, s_2) &= \mathbf{E}\left[e^{s_1X+s_2Y}\right] \\ &= \mathbf{E}[e^Z] \\ &= e^{(s_1^2\sigma_X^2+s_2^2\sigma_Y^2)/2}. \end{aligned}$$

Let now $\bar{X}$ and $\bar{Y}$ be independent zero-mean normal random variables with the same variances σ_X^2 and σ_Y^2 as X and Y , respectively. Since $\bar{X}$ and $\bar{Y}$ are independent, they are also uncorrelated, and the receding argument yields [9]

$$M_{\bar{X},\bar{Y}}(s_1, s_2) = e^{(s_1^2\sigma_X^2+s_2^2\sigma_Y^2)/2}.$$

Thus, the two pairs of random variables (X,Y) and $(\bar{X},\bar{Y})$ are associated with the same multivariate transform. Since the multivariate transform completely determines the joint PDF, it follows that the pair (X,Y) has the same joint PDF as the pair $(\bar{X},\bar{Y})$. Since $\bar{X}$ and $\bar{Y}$ are independent, X and Y must also be independent, which establishes our claim. [2][4]

The Conditional Distribution of X Given Y

We now turn to the problem of estimating X, given the value of Y .To avoid uninteresting degenerate cases, we assume that both X and Y have positive variance. Let us define

$$\hat{X} = \rho\frac{\sigma_X}{\sigma_Y}Y, \qquad \tilde{X} = X - \hat{X},$$

where

$$\rho = \frac{\mathbf{E}[XY]}{\sigma_X\sigma_Y}$$

is the correlation coefficient of X and Y .Since X and Y are linear combinations of independent normal random variables U and V , it follows that Y and $\tilde{X}$ are also linear combinations of U and V .In particular, Y and $\tilde{X}$ are jointly normal. Furthermore,

$$\mathbf{E}[Y\tilde{X}] = \mathbf{E}[YX] - \mathbf{E}[Y\hat{X}] = \rho\sigma_X\sigma_Y - \rho\frac{\sigma_X}{\sigma_Y}\sigma_Y^2 = 0.$$

Thus, Y and $\tilde{X}$ are uncorrelated and, therefore, independent. Since $\hat{X}$ is a scalar multiple of Y , it follows that $\hat{X}$ and $\tilde{X}$ are independent. [5]

We have so far decomposed X into a sum of two independent normal random variables, namely,

$$X = \hat{X} + \tilde{X} = \rho\frac{\sigma_X}{\sigma_Y}Y + \tilde{X}.$$

We take conditional expectations of both sides, given Y , to obtain

$$\mathbf{E}[X \mid Y] = \rho\frac{\sigma_X}{\sigma_Y}\mathbf{E}[Y \mid Y] + \mathbf{E}[\tilde{X} \mid Y] = \rho\frac{\sigma_X}{\sigma_Y}Y = \hat{X},$$

where we have made use of the independence of Y and $\tilde{X}$ to set $\mathbf{E}[\tilde{X} \mid Y] = 0.$ We have therefore reached the important conclusion that the conditional expectation $[X \mid Y]$ is a linear function of the random variable Y .

Using the above decomposition, it is now easy to determine the conditional PDF of X. Given a value of Y the random variable $\hat{X} = \rho\sigma_X Y/\sigma_Y$ becomes a known constant, but the normal distribution of the random variable $\tilde{X}$ is unaffected, since $\tilde{X}$ is independent of Y . Therefore, the conditional distribution of X given Y is the same as the unconditional distribution of $\tilde{X}$, shifted by $\hat{X}$. Since $\tilde{X}$ is normal with mean zero and some variance σ^2 , we conclude that the conditional distribution of X is also normal with mean $\hat{X}$ and the same variance σ^2 . The variance of $\tilde{X}$ can be found with the following calculation:

$$\begin{aligned} \sigma_{\tilde{X}}^2 &= \mathbf{E}\left[\left(X - \rho\frac{\sigma_X}{\sigma_Y}Y\right)^2\right] \\ &= \sigma_X^2 - 2\rho\frac{\sigma_X}{\sigma_Y}\rho\sigma_X\sigma_Y + \rho^2\frac{\sigma_X^2}{\sigma_Y^2}\sigma_Y^2 \\ &= (1-\rho^2)\sigma_X^2, \end{aligned}$$

Where we have made use of the property $E[XY]= \rho\sigma X\, \sigma Y$

We summarize our conclusions below. Although our model used the zero-mean value, these conclusions also hold for the non-zero mean case and we state them with this added generality; see the end-of-chapter problems.

The Form of the Bivariate Normal PDF

Having determined the parameters of the PDF of $\tilde{X}$ and of the conditional PDF of X, we can give explicit formulas for these PDFs. We keep assuming that X and Y have zero means and positive variances. Furthermore, to avoid the degenerate where $\tilde{X}$ is identically zero, we assume that $|\rho| < 1$.

We have

$$f_{\tilde{X}}(\tilde{x}) = f_{\tilde{X}|Y}(\tilde{x}\,|\,y) = \frac{1}{\sqrt{2\pi}\sqrt{1-\rho^2}\,\sigma_X} e^{-\tilde{x}^2/2\sigma_{\tilde{X}}^2},$$

and

$$f_{X|Y}(x\,|\,y) = \frac{1}{\sqrt{2\pi}\sqrt{1-\rho^2}\,\sigma_X} e^{-\left(x-\rho\frac{\sigma_X}{\sigma_Y}y\right)^2/2\sigma_{\tilde{X}}^2},$$

where

$$\sigma_{\tilde{X}}^2 = (1-\rho^2)\sigma_X^2.$$

Using also the formula for the PDF of Y,

$$f_Y(y) = \frac{1}{\sqrt{2\pi}\,\sigma_Y} e^{-y^2/2\sigma_Y^2},$$

and the multiplication rule $f_{X,Y}(x, y) = f_Y(y) f_{X|Y}(x \mid y)$, we can obtain the joint PDF of X and Y. This PDF is of the form

$$f_{X,Y}(x, y) = ce^{-q(x,y)},$$

where the normalizing constant is

$$c = \frac{1}{2\pi\sqrt{1-\rho^2}\,\sigma_X\sigma_Y}.$$

The exponent term $q(x, y)$ is a quadratic function of x and y,

$$q(x,y) = \frac{y^2}{2\sigma_Y^2} + \frac{\left(x-\rho\frac{\sigma_X}{\sigma_Y}y\right)^2}{2(1-\rho^2)\sigma_X^2},$$

which after some straightforward algebra simplifies to

$$q(x,y) = \frac{\frac{x^2}{\sigma_X^2} - 2\rho\frac{xy}{\sigma_X\sigma_Y} + \frac{y^2}{\sigma_Y^2}}{2(1-\rho^2)}.$$

An important observation here is that the joint PDF is completely determined by σ_X, σ_Y, and ρ. In the special case where X and Y are uncorrelated ($\rho = 0$), the joint PDF takes the simple form

$$f_{X,Y}(x,y) = \frac{1}{2\pi\sigma_X\sigma_Y} e^{-\frac{x^2}{2\sigma_X^2} - \frac{y^2}{2\sigma_Y^2}},$$

which is just the product of two independent normal PDFs. We can get some insight into the form of this PDF by considering its contours, i.e., sets of points at which the PDF takes a constant value. These contours are described by an equation of the form

$$\frac{x^2}{\sigma_X^2} + \frac{y^2}{\sigma_Y^2} = \text{constant},$$

and are ellipses whose two axes are horizontal and vertical.[9]

IV. MATHEMATICAL RESULTS

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

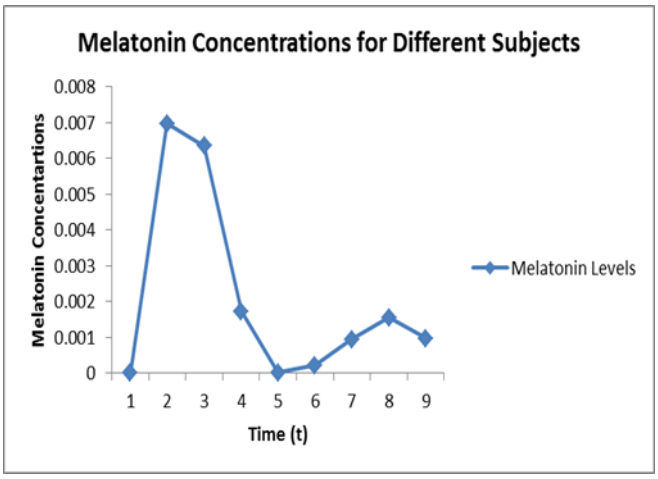

Fig. 3. Effects of Melatonin concentrations studied on different subjetcs for a 3 day cycle

V. CONCLUSION

In this paper, we have shown sleep and wake cycles of different subjects considered with melatonin as hormone. The following observations are made:

i) There is an increase in the Melatonin level in mid-night time of different subjects.

ii) The study even shows that Melatonin levels gradually starts decreasing since morning but this difference is not significant.

In this direction we have developed a Bivariate Normal Distribution Model to analyse the data and fit the experimental curve of the Plasma Melatonin secretions to a monotonic function (both increasing and decreasing). The curve of hormonal values conclude the effects of rise in the level of Melatonin in the mid-night thereby giving a fall at the morning times. The mean levels for Plasma Melatonin gives a study of different subjects for a three days cycle thereby giving a monotonically decreasing curve at morning times and gradually increasing till the mid-night time. It gives mean levels for dark and light period of time where Plasma Melatonin levels can be evaluated from the curve. The overall conclusion from the study is the major subjects that could be correlated with corresponding role of hormone that play particularly an important role.

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