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Mathematical model for Oxytocin alleviates the neuroendocrine in healthy men

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Abstract: - Maximum Likelihood Estimation is by far the most popular method of parameter estimation and is an indispensable tool for many statistical modeling techniques, in particular in non-linear modeling with non-normal data. The purpose of this paper is to provide a good conceptual explanation of the method with illustrative examples. In application part by using normal distribution the likelihood functions for inflammatory hormone levels in response to endotoxin and plasma concentration oxytocin, ACTH, cortisol, and procalcitonin are obtained. These functions show a clear picture for all the above parameters when LPS+Oxytocin is administered to the inflammatory cases and compared with the medical conclusion.

Keywords: *Normal distribution, density function, oxytocin.* ***Mathematical subject classification:*** *$60G_{XX}$, $62H_{XX}$, $62P_{XX}$.*

1.Mathematical model:

I. INTRODUCTION

In the psychological sciences, uncover general laws and principles that govern the behavior under investigation. As these principles are not directly observable, they are formulated in terms of hypotheses. In mathematical modeling, such hypotheses about the structure and inner working of the behavioral process of interest are stated in terms of mathematical functions called models. The goal of modeling is to deduce the form of the underlying process by testing the viability of such models. Once a model is specified with its parameters, data have been collected with specific norms. There are two generally accepted methods of parameter estimation. They are least-squares estimation (LSE) and maximum likelihood estimation (MLE). The former is well known to us as many of the familiar concepts such as linear regression, the sum of squares error, the proportion variance accounted[2] , and the root mean squared deviation are tied to the method. On the other hand, MLE is not widely recognized among modelers in psychology[3], though it is, by far, the most commonly used method of parameter estimation[7]. LSE might be useful for obtaining a descriptive measure for the purpose of summarizing observed data[9], but MLE is more suitable for statistical inference such as model comparison LSE has no basis for constructing confidence intervals or testing hypotheses.

1.2.Maximum Likelihood Estimation

The likelihood Function

Let $X_1,\ldots\ldots X_n$ be an i.i.d sample with probability density function (p.d.f) $f(x_i;\theta)$, where θ is a $(k\times1)$ vector of parameters that characterize $f(x_i;\theta)$[8]. For example, if $X_i\sim N(\mu,\sigma^2)$ then $f(x_i,\theta) = (2\pi\sigma^2)^{-1/2}\exp(-\frac{1}{2\sigma^2}(x_i -\mu)^2)$ and $\theta = (\mu,\sigma^2)'$. Then joint density of the sample is, by independence, equal to the product of the marginal densities

$$f(x_1,\ldots\ldots x_n;\theta) = f(x_1;\theta)\ldots\ldots f(x_n;\theta) = \prod_{i=1}^{n} f(x_i,\theta).$$

The joint density is an n dimensional function of the data $x_1\ldots\ldots,x_n$ given the parameter vector θ. The joint density satisfies

$$f(x_1,\ldots\ldots\ldots x_n;\theta) \geq 0$$
$$\int\ldots\ldots\int f(x_1\ldots\ldots\ldots\ldots x_n;\theta) = 1.$$

The likelihood function is defined as the joint density treated as a functions of the parameters θ :

$$L(\theta/x_1,\ldots\ldots\ldots,x_n) = f(x_{1,\ldots\ldots\ldots} x_n;\theta) = \prod_{i=1}^{n} f(x_i,\theta).$$

Notice that the likelihood function is a k dimensional function of θ given the data $x_1,\ldots..x_n$. It is important to keep in mind that the likelihood function, being a function of θ and not the data, is not a proper p.d.f .It is always positive but

$$\int\ldots\ldots\int L(\theta/x_1\ldots\ldots..x_n)d\theta_1\ldots\ldots\ldots d\theta_k \neq 1.$$

To simplify notation, let the vector $X = (x_1,\ldots\ldots..x_n)$ denote the observed sample. Then the joint p.d.f and likelihood function may be expressed as $f(X;\theta)$ and $L(\theta/X)$.

Example 1 Bernoulli Sampling

Let X_i ~ Bernoulli(θ). That is, $X_i = 1$ with probability θ and $X_i = 0$ with probability $1 - \theta$ where $0 \leq \theta \leq 1$. The p.d.f for X_i is x_i

$$f(x_i;\theta) = \theta^{x_i}(1-\theta)^{1-x_i},\ x_i = 0,1$$

Let $X_1,\ldots..X_n$ be an iid sample with X_i~Bernoulli(θ).The joint density/ likelihood function is given by

$$f(x;\theta) = L(\theta/x) = \prod_{i=1}^{n} \theta^{x_i}(1-\theta)^{1-x_i} = \theta^{\sum_{i=1}^{n} x_i}(1-\theta)^{n-\sum_{i=1}^{n} x_i}$$

For a given value of θ and observed sample x, f(x,θ) gives the probability of observing the sample. For example, suppose n=5 and x = (0,…..,0). Now some values of θ are more likely to have generated this sample than others. In particular, it is more likely that θ is close to zero than one. To see this, note that the likelihood function for this sample is

$$L(\theta/(0,\ldots\ldots,0)) = (1-\theta)^5$$

The likelihood function has a clear maximum at θ = 0. That is, θ = 0 is the value of θ that makes the observed sample x = (0,……,0) most likely (highest probability)

Similarly, suppose x = (1,……..,1). Then the likelihood function is

$$L(\theta/(1,\ldots\ldots,1)) = \theta^5$$

Now the likelihood function has a maximum at θ = 1.

Example 2 Normal Sampling

Let $X_{1,}\ldots\ldots\ldots,X_n$ be an iid sample with X_i~$N(\mu,\sigma^2)$. The pdf for X_i is

$f(x_i;\theta) = (2\pi\sigma^2)^{-1/2}\exp\left(-\frac{1}{2\sigma^2}(x_i-\mu)^2\right)$, $-\infty < \mu < \infty, \sigma^2 > 0, -\infty < x < \infty$

so that $\theta = (\mu,\sigma^2)'$. The likelihood function is given by

$$L(\theta/x) = \sum_{i=1}^{n}(2\pi\sigma^2)^{-1/2}\exp\left(-\frac{1}{2\sigma^2}(x_i-\mu)^2\right),$$

$$= (2\pi\sigma^2)^{-n/2}\exp\left(-\frac{1}{2\sigma^2}\sum_{i=1}^{n}(x_i-\mu)^2\right)$$

Suppose $\sigma^2 = 1$. Then

$$L(\theta/x) = L(\mu/x) = (2\pi)^{-n/2}\exp\left(-\frac{1}{2}\sum_{i=1}^{n}(x_i-\mu)^2\right)$$

Now

$$\sum_{i=1}^{n}(x_i-\mu)^2 = \sum_{i=1}^{n}(x_i-\bar{x}+\bar{x}-\mu)^2$$

$$= \sum_{i=1}^{n}[(x_i-\bar{x})^2 + 2(x_i-\bar{x})(x-\bar{\mu}) + (\bar{x}-\mu)^2]$$

$$= \sum_{i=1}^{n}(x_i-\bar{x})^2 + n(\bar{x}-\mu)^2$$

So that

$$L(\mu/x) = (2\pi)^{-n/2}\exp\left(-\frac{1}{2}[\sum_{i=1}^{n}(x_i-\bar{x})^2 + n(\bar{x}-\mu)^2]\right)$$

Since both $(x_i-\bar{x})^2$ and $(\bar{x}-\mu)^2$ are positive it is clear that L(μ/x) is maximized at $\mu = \bar{x}$.

II. APPLICATION

Oxytocin is a hormone and neurotransmitter found to have anti- inflammatory functions in rodents. Ten healthy men received , in a randomized, placebo controlled crossover design, placebo, oxytocin, LPS, and LPS+oxytocin. Oxytocin treatment resultedin a transient or prolonged reduction of endotoxin-induced increase in plasma ACTH, Cortisol, prolactionin.Oxytocin decreases the neuroendocrine and cytokine activation caused by bacterial endotoxin in men. Possibly due to the pathway. Oxytocin –deficient mice exhibit increased stress response associated with a significant hyperactivation of the HPA axis[6]. Here we present a randomized, placebo-controlled, crossover trial, conducted to test the effect of continuous intravenous oxytocin infusion on LPS-induced systemic inflammation in 10 healthy men. In addition, we investigated whether oxytocin directly affects the LPS-induced cytokine release from peripheral blood mononuclear cells (PBMCs) of healthy human donors in vitro.

2.1.Hormone and cytokine measurement.

Blood samples were immediately cooled and centrifuged for 10 min at 3.000 rpm, 4°C, and plasma aliquots were immediately frozen at -20°C. Plasma oxytocin and ACTH were measured using commercial RIA kits Procalcitonin (PCT) was measured using the BRAHMS Procalcitonin Sensitive LIA kit[5]. All samples taken over the 4 study days for each individual subject were analyzed at the same time and in duplicates.

Cell isolation and culture. PBMCs were isolated from acid citrate dextrose buffy coats of healthy donors. CD14_ monocytes were obtained by magnetic cell sorting using anti-CD14-conjugated magnetic microbeads CD14_ monocytes (2 ± 106) or PBMCs (106 cells/ml) were cultured in human serum albumin-containing X-Vivo 10 medium in 12-well plates for 2, 4, and 24 h. Different concentrations of oxytocin (Sigma) or vehicle control (0.1% water) were added to the cells 30 min before adding LPS.

2.2. Hormone Response

Administration of oxytocin elevated within 10 min plasma oxytocin levels (P = 0.021), which reached peak values at time point 60 min (P <0.001) (Fig. 2.2 *A*). Circulating oxytocin then began to decline 10 min after the infusion was stopped, but remained significantly elevated until time point 120 min (P < 0.001) (Fig. 2.2.*A*). Plasma concentrations of ACTH (Fig. 2.2.*B*) and cortisol (Fig. 2.2.*C*) remained unchanged during oxytocin treatment, but increased after the LPS bolus (P = 0.027 for ACTH at 120 min and P = 0.043 for cortisol at 90 min when comparing LPS vs. placebo). A significantly reduced increase in plasma ACTH was observed at time point 120 min: 36.1 ± 5.9 pg/ml in the LPS ± oxytocin group vs.69.6 ± 14.8 pg/ml in the LPS group (P = 0.019) (Fig. 2.2.*B*). The LPS-induced increase in plasma cortisol was also alleviated in the LPS ±oxytocin group at time points 90 min (P = 0.03) and 120 min (P = 0.01) (Fig. 2.2.*C*).

To further evaluate the impact of oxytocin on the severity of endotoxinemia, measured the plasma concentrations of PCT, a diagnostic and prognostic biomarker in sepsis [10] Oxytocin significantly reduced the LPS-induced increase in PCT, which presented significant differences at the 240th min (0.178 ± 0.05 ng/ml on LPS days compared with 0.072 ± 0.01 ng/ml on LPS ± oxytocin days, P = 0.043), at the 300th min (P = 0.033), and at the 360th min (P = 0.035) (Fig. 2.3). Consideration the possibility that repeated injections of endotoxin itself may result in an altered immune response, inducing resistance or tolerance in humans. Therefore, the subjects received the four treatments in a randomized order. In addition, we compared the changes in plasma ACTH, cortisol, and PCT between volunteers randomized to receive LPS before the application of LPS ± oxytocin (n = 5) and volunteers randomized to receive LPS ±oxytocin before the administration of LPS (n = 5). Results were similar to those obtained from all volunteers being treated with LPS vs. all volunteers having received LPS ±oxytocin.

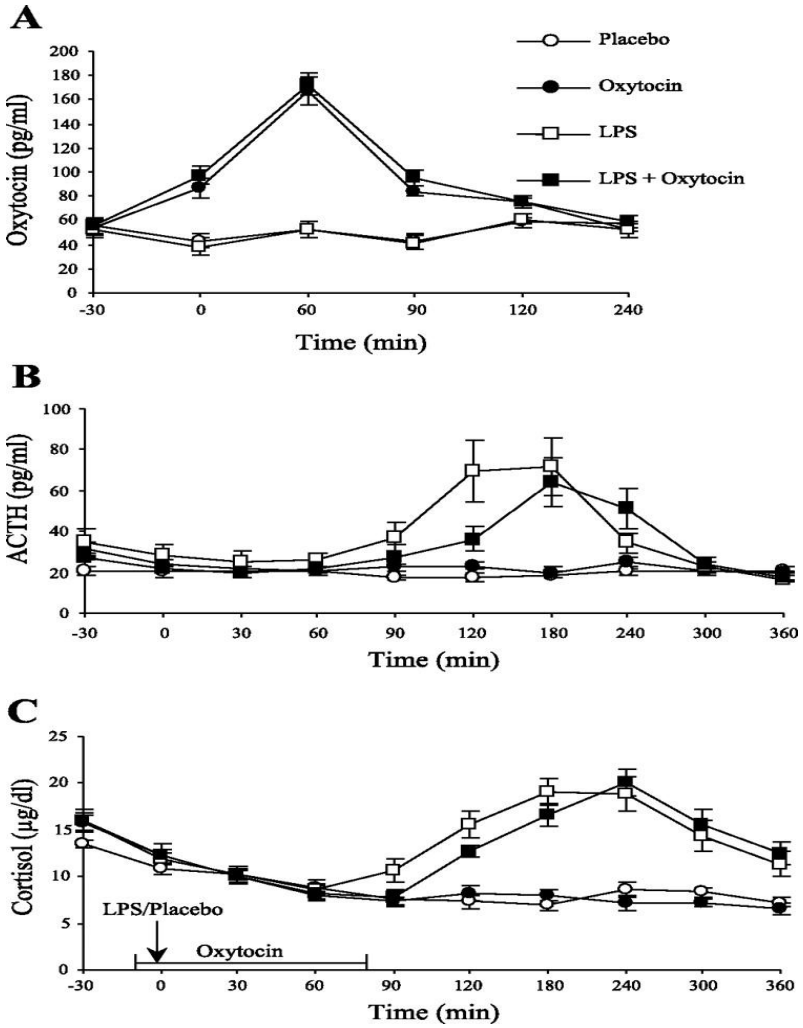


Figure 2.2. Hormone levels in response to endotoxin and oxytocin. Plasma concentrations are shown of oxytocin (A), ACTH (B),and cortisol (C) in response to placebo, oxytocin (1pmol kg $^{-1}$ min^{-1} during 90 min. 1=-10 to 80 min). LPS (2ng/kg iv. i =0 h), and LPS+oxytocin values are means ± SE.

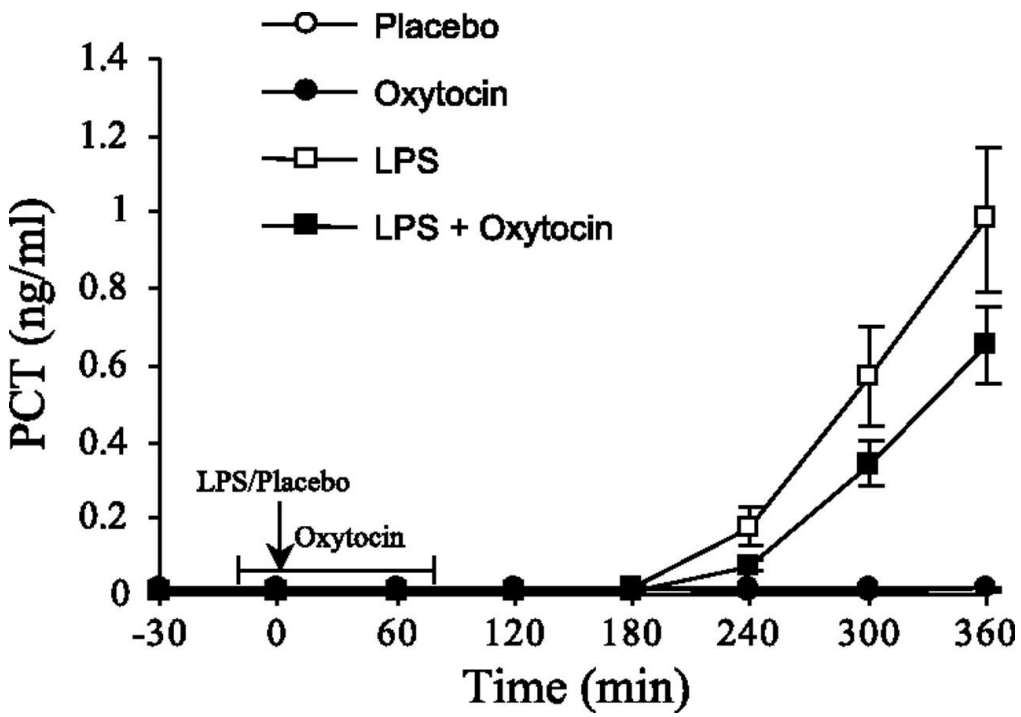
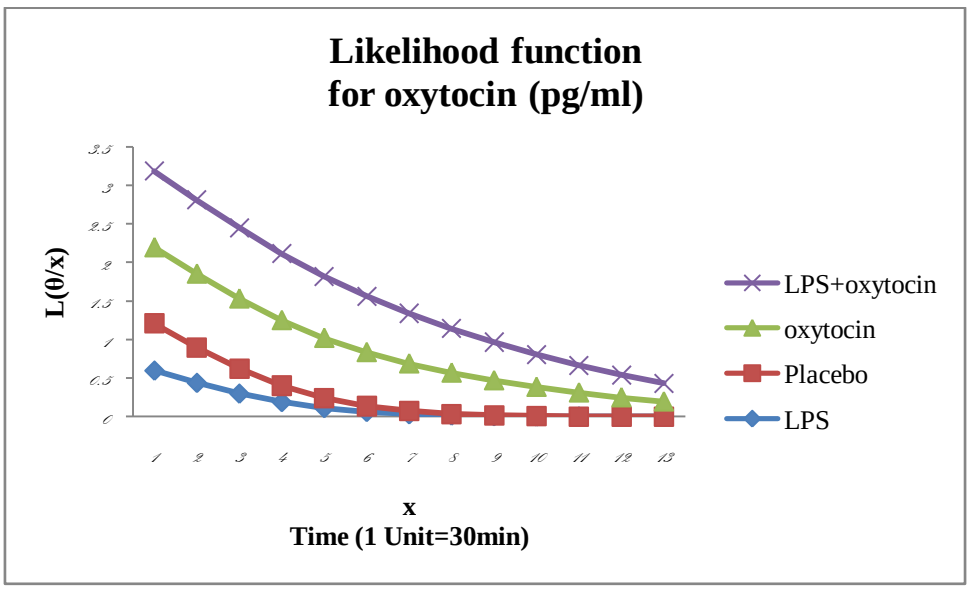


Figure 2.3.Procalcitonin (PCT) levels in response to endotoxin and oxytocin. Plasma PCT concentrations are shown after placebo or LPS administration (2ng/kg iv. i=0 h), in the presence or absence of oxytocin infusion (t= -10 to 80 min). Values are means ± SE.

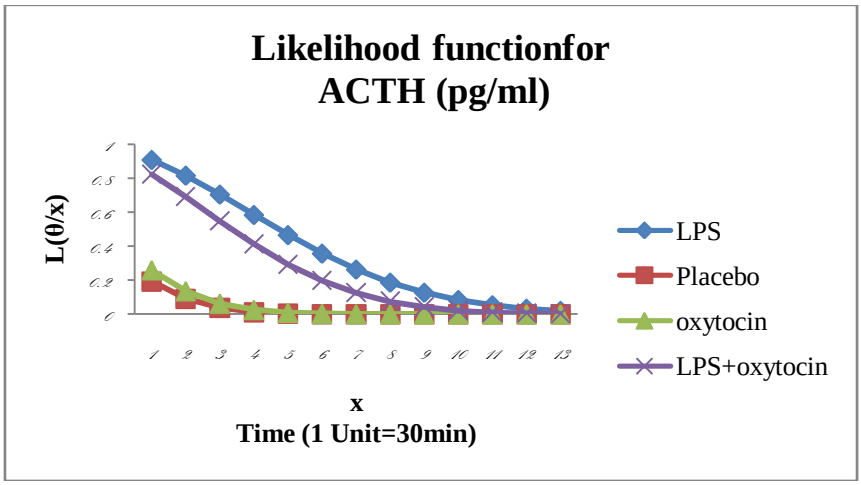
First, the study population included only healthy men, and we have no data on the role of oxytocin on the LPS-induced endocrine and cytokine activation in women[1]. Second, as this is the first study coadministrating LPS and oxytocin in humans, we took care to use the smallest oxytocin dose needed to achieve elevated oxytocin concentrations during the first 120 min after LPS administration. Nevertheless, the achieved maximal concentrations of 160–180 pg/ml are clearly supraphysiological. Third, LPS administration is only an experimental and self-limiting model of infection and inflammation. In summary, this study demonstrates that pharmacological doses of oxytocin attenuate the endocrine and cytokine activation following bacterial endotoxin administration in humans. Oxytocin appears to modulate innate host defense mechanisms, thereby eventually reducing an LPS-induced overshooting immune response.

Mathematical Results

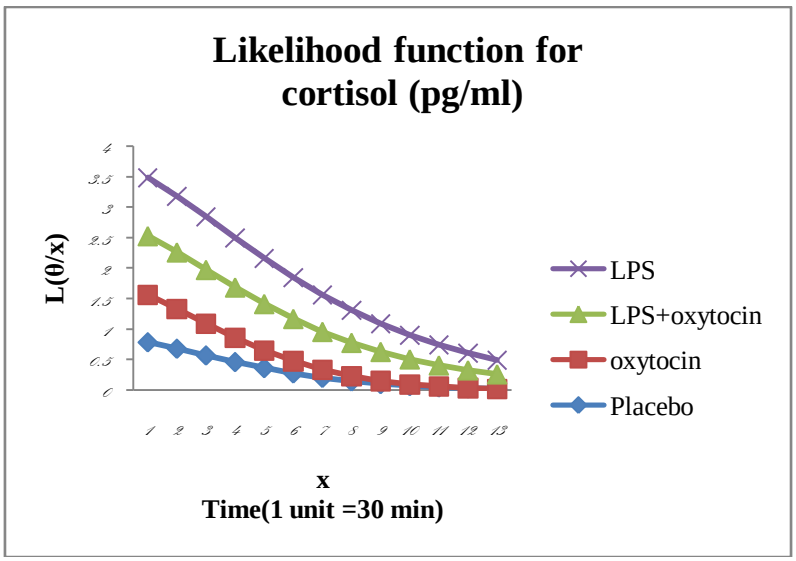
A.



B.



C.



D.

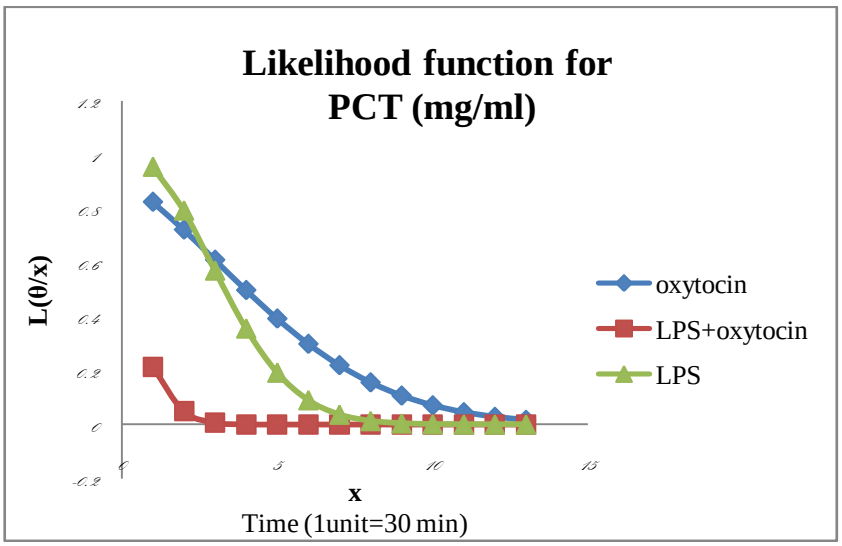


Figure (3.1)

The figure (3.1),A. indicates that the likelyhood function for oxytocin (pg/ml) is suddenly decreased when LPS+oxytocin is administered. In both the cases the curves are continuous and decreased monotonically with the time axis. Similarly we have obtained the curves for the likelyhood functions for all other categories like ACTH, Cortisol, PCT (if we compare LPS administration cases).

These results can be compared with the medical conclusions. This study demonstrates that pharmacological doses of oxytocin attenuate the endocrine and cytokine activation following endotoxin administration in humans. Oxytocin appears to modulate innate host defense mechanism, thereby eventually reducing an LPS induced overshooting immune response.

CONCLUSION

Maximum Likelihood Estimation is by far the most popular method of parameter estimation and is an indispensable tool for many statistical modeling techniques, in particular in non-linear modeling with non-normal data[4]. The purpose of this paper is to provide a good conceptual explanation of the method with illustrative examples. In application part by using normal distribution the likelihood functions for inflammatory hormone levels in response to endotoxin and plasma concentration oxytocin, ACTH, cortisol, and procalcitonin[10] are obtained. These functions show a clear picture for all the above parameters when LPS+Oxytocin is administered to the inflammatory cases and compared with the medical conclusion. This study demonstrates that pharcological doses of oxytocin attenuate the endocrine and cytokine activation following endotoxin administration in humans. Oxytocin appears to modulate innate host defense mechanism, thereby eventually reducing an LPS induced overshooting immune response. The figure (3.1),A. indicates that the likelyhood function for oxytocin (pg/ml) is suddenly decreased when LPS+oxytocin is administered. In both the cases the curves are continuous and decreased monotonically with the time axis. Similarly we have obtained the curves for the likelyhood functions for all other categories like ACTH, Cortisol, PCT (if we compare LPS administration cases).

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