A Mathematical Model Using Gamma Process to Find Pulsatile LH Secretion in Women with Premenstrual Syndrome

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Abstract
The uncertain arrival of shocks can be modeled as a Poisson process. When degradation takes place in very small increments almost continuously over time, a simpler and effective stochastic model of degradation can be derived as a limiting form of the compound poison process. The limiting form is obtained when the rate of damage occurrence approaches infinity in any finite time interval as the size of the increment tends to zero. Such a stochastic process is referred to as a gamma process because the cumulative damage up to time t follows the gamma distribution. The gamma process is suitable to model gradual damage monotonically accumulating over time in a sequence of tiny increments, such as wear, fatigue, degrading health index etc., in the application part the premenstrual syndrome has been proposed to result from excessive exposure to and or withdrawal of brain opioid activity during the luteal phase. The changes in the luteal LH pulse frequency failed to provide evidence that GnRH secretion is impaired, thus challenging the view that the neuroregulation of the menstrual cycle in women with PMS is markedly altered. The mathematical model has been proposed that for women suffering from severe, long term premenstrual symptoms, the symptom free interval associated with the follicular phase is compromised by the feelings of guilt and depression for neglect of families and professional responsibilities.

Keywords: Compound Poisson Process, EF, FSH, GnRH, ML, LH, LL.

2010 AMS Classification: 62H30, 60 E30

I. Mathematical Model
Let the amount of damage in the k-th shock is denoted as $X_k$, which is treated as a positive random variable. The total damage observed up to time $t$ is the sum of the increments $Y(t) = X_1 + X_2 + X_3 + \ldots + X_n$. The number of damage increments in the interval $(0, t)$ need not be a fixed number. The uncertain arrival of shocks can be modeled as a Poisson process, referred to as a compound process [21]. When degradation takes place in very small increments almost continuously over time, a simpler and effective stochastic model of degradation can be derived as a limiting form of the compound Poisson process. The limiting form is obtained when the rate of damage occurrence approaches infinity in any finite time interval as the size of the increment tends to zero. Such a stochastic process is referred to as a gamma process because the cumulative damage up to time $t$ follows the gamma distribution. The gamma process is suitable to model gradual damage monotonically accumulating over time in a sequence of tiny increments, such as wear, fatigue, degrading health index etc.,

A random quantity $X$ has a gamma distribution with shape parameter $V > 0$ and scale parameter $U > 0$ if its probability density function is given by

$$f(x|v, u) = \frac{u^v}{\Gamma(v)} x^{v-1} \exp(-ux)I_{(0,\infty)}(x)$$

$I_A(x) = 1$ for $x \in A$ and $I_A(x) = 0$ for $x \notin A$ and $I(a) = \int_{x=0}^{x=a} z^{a-1} e^{-z} dz$ is the gamma function for $\alpha > 1$. Using moment generating functions it can be proved that the expectation and variance of the process $X(t)$ are given by $E(X(t)) = \frac{vt}{u}$ and $Var(X(t)) = \frac{vt^2}{u^2}$.

Assuming that the expectation and variance are linear in time, i.e., $E(X(t)) = \mu t$, $Var(X(t)) = \sigma^2 t$. Then the parameters of the process $X(t)$ are defined as $v = \frac{\mu^2}{\sigma^2}$ and $u = \frac{\mu}{\sigma^2}$. Where $\mu$ is the average deterioration rate and $\sigma^2$ is the variance of the process. Thus, when the expected deterioration is linear over time, it is convenient to rewrite the probability density function of $X(t)$ as

$$f(x|\mu, \sigma) = \frac{\mu^x}{\sigma^x} \frac{1}{\Gamma(x)} \exp(-\mu x)I_{(0,\infty)}(x)$$

The two parameters expectation and variance are uncertain and assessing both variables for each individual component is very cumbersome. In order to keep the method practical, the standard deviation $\sigma$ may be mixed relative to the mean $\mu$ through the use of a coefficient of variation $v$. 

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Hence, \( \sigma = v \mu \Rightarrow \sigma = \frac{\sigma}{\mu} \). Therefore, the probability density function for \( X(t) \) reduces to \( f_{X(t)}(x) = Ga(x - 1|t/v^2, 1/(\mu v^2)) \).

Let \( X(t) \) denote the deterioration at time \( t, t \geq 0 \). A component is said to fail when its deteriorating resistance, denoted by \( R(t) = r - X(t) \), drops below the stress \( s \). We assume that both the initial resistance \( r \) and the stress to be fixed. Define \( y = r - s \) and let the time at which failure occurs be denoted by the life time. The life time distribution can be rewritten as

\[
F(t) = Pr[T \leq t] = Pr[X(t) \geq y]
\]

\[
\int_{x=y}^{\infty} f_X(t)(x) \, dx = \frac{\Gamma(\mu^2 t^2)}{\sigma^2 \Gamma(\mu^2)} \left[ \frac{y^2}{\sigma^2} \right] - \frac{\Gamma(\mu^2 t^2)}{\sigma^2 \Gamma(\mu^2)} \left[ \frac{y^2}{\sigma^2} - \frac{x^2}{\mu^2} \right].
\]

For computing the probability density function of the time to failure for a stationary gamma process,

\[
F(t) = Pr[X(t) \geq y] \approx \Phi \left( \frac{\mu^2 - y}{\sigma \sqrt{t}} \right)
\]

Where \( \Phi \) is the cumulative distribution function of the standard normal distribution.

The stationarity of the gamma process basically follows from the property that increments are independent and have the same type of distribution as their sum. A random variable \( X \) is infinitely divisible if for any integer \( n \geq 2 \), there are \( n \) independent and identically distributed random variables \( D_i^{(n)} \), \( i = 1, \ldots, n \), such that their sum \( \sum_{i=1}^{n} D_i^{(n)} \) as the same distribution as \( X \). In terms of Laplace transforms, the definition of infinite divisibility can be formulated as: \( e^{-sX} = \prod_{i=1}^{n} E \left( e^{-sD_i^{(n)}} \right) \), \( n \geq 2 \).

In fact every infinitely divisible distribution is a limit of compound Poisson distributions.

An important property of the gamma process is that it is a jump process. The gamma process can be regarded as a compound Poisson process of gamma-distributed increments in which the Poisson rate tends to infinity and increment sizes tend to zero in proportion. Using the technique of Laplace transforms, it can be shown that the gamma process can be reformulated in terms of a limit of a compound Poisson process.

The cumulative distribution function of the total deterioration in time - interval \( (0, n\Delta], n=1, \ldots, \ldots, N-1 \), is the beta distribution in \( \frac{y}{n\Delta} \) with parameters \( n \) and \( N-n-1 \): 

\[
Pr\left\{ \sum_{i=1}^{n} D_i \leq y \right\} \approx \frac{\Gamma \left( \frac{\mu^2}{\sigma^2} \right)}{\Gamma \left( \mu^2 \right)} \left[ \frac{y^2}{\sigma^2} \right] - \frac{\Gamma \left( \frac{\mu^2}{\sigma^2} \right)}{\Gamma \left( \mu^2 \right)} \left[ \frac{y^2}{\sigma^2} - \frac{x^2}{\mu^2} \right].
\]

For \( y \geq 0 \) and 0 otherwise. The beta function coincides with the cumulative distribution function of the \( n^{th} \) order statistic of \( N-1 \) independent and identical distributed random quantities with uniform distribution on \( [0, N-1] \). The beta distribution converges to the gamma distribution with parameters \( n \) and \( \theta \) for \( y \geq 0 \)

\[
P_r \left\{ \sum_{i=1}^{n} D_i \leq y \right\} = \frac{\Gamma \left( \sum_{i=1}^{n} \frac{1}{\theta} \right)}{\Gamma \left( \frac{\mu^2}{\sigma^2} \right)} \left[ \frac{y^2}{\sigma^2} \right] - \frac{\Gamma \left( \sum_{i=1}^{n} \frac{1}{\theta} \right)}{\Gamma \left( \mu^2 \right)} \left[ \frac{y^2}{\sigma^2} - \frac{x^2}{\mu^2} \right].
\]

II. Application

2.1 Introduction

The mechanisms involved in producing the complex of symptoms collectively termed the premenstrual syndrome (PMS) are unknown. The failure to identify gross aberrations in plasma concentrations of the reproductive hormones had led investigators to search for a common link between the dynamic neuroendocrine secretory events that characterize the menstrual cycle and central mechanisms regulating behavior and mood states. It has been proposed that premenstrual symptoms occur in response to the cyclic rise and fall in hypothalamic opioid activity believed to modulate the pulsatile release of gonadotropin – releasing hormone (GnRH) and, in turn, luteinizing hormone (LH), as a result of the characteristic changes in the ovarian production of the estrogen and progesterone [9], [14]. Advocates propose that the withdrawal of high opioid activity prior to menstruation disinhibits opioid – sensitive neurons, resulting in such dysphoric symptoms as irritability, insomnia, food cravings, anxiety, and pain sensitivity [3], [6] & [7]. LH pulse frequency in the mid – luteal (ML) phase has been reported to be faster in PMS patients, despite similar concentrations of P compared to normal volunteers [7]. This finding as well as earlier evidence that LH responsiveness to the opiate antagonist, naloxone, was blunted in PMS patients [6] prompted these investigators to propose that PMS was a central disorder, due to a hypothalamic impairment of the opioid inhibition normally present at this time in the cycle. Differences in LH pulse frequency and amplitude between the patient and control groups in the later study [7] were small, however, and secretory characteristics were within the normal range of variability previously reported for normal, asymptotic women [13]. In addition, these investigators noted that the presence of secondary psychiatric disorders in some of the PMS subjects may have confounded their results.

2.2 Symptom Characteristics during Study:

In both the premenstrual and the premenstrual weeks of the study cycle, the volunteer group demonstrated a lower mean symptom score than the patient group. Mean age and cycle length were similar. Since underlying psychiatric disorders had been ruled out during the diagnostic evaluation, the higher “baseline” scores of the postmenopausal week
more likely reflected the chronic nature and severity of the menstrual health problem. Little is known about how PMS symptom patterns change over time, especially in women who fail to benefit from standard treatment approaches. It has been proposed that for women suffering from severe, long-term premenstrual symptoms, the “symptom-free” interval associated with the follicular phase is compromised by feelings of guilt and depression for neglect of family and professional responsibilities.

![Fig. 2.2.1: Plasma gonadotropin and ovarian steroids during 8–hr rapid-sampling studies in the EF, ML, and LL phases of the menstrual cycle in two subjects with PMS.*=LH pulse. E2 and P values shown are for the beginning and end of the rapid-sampling periods.]

Mean plasma FSH was different in the PMS and control groups mean FSH was higher in the PMS patients in the ML studies.

2.3 Discussion

We studied changes in pulsatile LH secreted in women with PMS to detect peripheral evidence of alterations in the transient increase and withdrawal of endogenous opioid action on GnRH secretion during ovulatory, symptomatic cycles. We chose three different “windows” in the menstrual cycle which have been characterized previously in relation to ovarian steroids, gonadotropin secretion, menstrual symptomatology, and presumed opioid activity. The current view of the hormonal interrelationships in the normal luteal phase is that P in the presence of E2 acts on the hypothalamus to transiently increase opioid activity, thus inhibiting the frequency of pulsatile GnRH secretion and in turn the pulsatile release of LH [19], [2], [8] & [16]. With the fall in E2 and P secretion from the aging corpus luteum, opioid exposure is withdrawn, allowing GnRH pulsatile secretion to increase in the days preceding menses [11]. Thus, assessment of LH pulse frequency in women has been used to infer changes in GnRH secretion and may allow a gross estimation of hypothalamic opioid influence when performed in the presence of a well-defined ovarian steroid milieu. These results provide evidence that the symptoms of PMS can occur in the absence of marked abnormalities in the neuroreproductive axis and challenge the view that opioid inhibition of GnRH secretion is impaired. These findings, however, do not rule out aberrations in other steroid-mediated opioid action external to the hypothalamus that could play a role in the emotional and cognitive symptoms associated with this disorder.

This finding further strengthens evidence from studies of daily hormone measures that the ability to secrete ovulatory levels of ovarian steroids is not compromised in PMS [15]. Moreover, our finding that peripheral plasma P concentrations bear no relationship to PMS symptom severity fails to support the use of ovarian steroids in the treatment of the disorder.

III. Mathematical Results

A useful property of the gamma process with stationary increments is that the gamma density transforms into an exponential density if $t = \frac{\sigma^2}{\mu}$. When the unit-time length is chosen to be $\frac{\sigma^2}{\mu}$, the increments of deterioration are exponentially distributed with mean $\frac{\sigma^2}{\mu}$. The probability of failure in unit time i reduce to a shifted...
Poisson distribution with mean $1 + \frac{\mu}{\sigma^2}$ is given by [18],

$$q_i = \frac{1}{i - 1} \left( \frac{\mu}{\sigma^2} \right)^{i-1} \exp \left\{ -\frac{\mu}{\sigma^2} \right\}, \quad i = 1, 2, 3, \ldots \ldots \ldots$$

A physical explanation for the appearance of the above Poisson distribution is that it represents the probability that exactly $i$ exponentially distributed jumps with mean $\sigma^2 / \mu$ cause the component to fail, that is, cause the cumulative amount of deterioration to exceed $s$. Note that the smaller the unit-time length for which the increments are exponentially distributed, the less uncertain the deterioration process.

**IV. Conclusion**

In both the premenstrual and the premenstrual weeks of the study cycle, the volunteer group demonstrated a lower mean symptom score than the patient group. Mean age and cycle length were similar. Since underlying psychiatric disorders had been ruled out during the diagnostic evaluation, the higher “baseline” scores of the postmenopausal week more likely reflected the chronic nature and severity of the menstrual health problem. Little is known about how PMS symptom patterns change over time, especially in women who fail to benefit from standard treatment approaches. Hence, to find the time interval the Compound Poisson Process is utilized and the corresponding mathematical figures in section 3 have been obtained which show that in all the cases at the end of 15th hour the impairment is vanished for all the variables of the above two subjects taken into consideration.

**REFERENCES**


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