IJMS, *Vol. 15, Nos. 3-4, (July-December 2016)*

ISSN: 0972-754X

MATHEMATICAL MODEL FOR MEAN RESIDUAL LIFE TIME OF THE SECRETION OF THE HORMONE OXYTOCIN

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Abstract: A linear consecutive -*k*-out-of-*n* : *F* system consist of *n* linearly ordered components such that the system fails if and only if at least *k* consecutive components fail. A linear consecutive -*k*-out-of-*n* : *G* system, on the other hand, consists of *n* linearly ordered components such that the system function if and only if at least *k* consecutive components function. We denote the consecutive -*k*-out-of-*n* : *F* and consecutive -*k*-out-of-*n* : *G* system by (*C*, *k*, *n* : *F*) and (*C*, *k*, *n* : *G*) respectively. Some monotonicity for the mean residual life time function is obtained. This monotonicity is verified for the regulation of the pulsatile secretion of prostaglandin $F_2\alpha$ by the central oxytocin pulse generator.

Mathematical Subject Classification: $60G_{XX}$, $62H_{XX}$, $62P_{XX}$.

Keywords: Consecutive -*k*-out-of-*n* systems, Mean residual lifetime, Stochastic order, Oxytocin, Pulse generator.

1. MEAN RESIDUAL LIFETIME FUNCTION

Let *T* denote the lifetime of the system. Then the residual lifetime of the system given that the system has survived up to time *t* is $(T - t \mid T > t)$. The mean residual lifetime (MRL) function, defined by $m_T(t) = E(T - t \mid T > t)$, plays an important role in reliability and survival analysis. It can be computed from

$$m_T(t) = \frac{1}{R_T(t)} \int_t^\infty R_T(x)\,dx\,. \tag{1.1}$$

'Where $R_T(t) = P\{T > t\}$ is the reliability (or survival) function of *T*.

The MRL function of the (*C*, *k*, *n* : *F*) system is then defined by

$$m_{k|n:F}(t) = E(T_{k|n:F} - t \mid T_{k|n:F} > t)\,.$$

The MRL function of the (*C*, *k*, *n* : *G*) system is defined in a similar way. From the above equation the MRL function of the (*C*, *k*, *n* : *F*) system is given by

$$m_{k\,|\,n\,:\,F}(t) = \frac{\sum_{i=1}^{n} \omega_i R_{i\,:\,n}(t) m_{i\,:\,n}(t)}{\sum_{i=1}^{n} \omega_i R_{i\,:\,n}(t)}\,. \tag{1.2}$$

Where $R_{i:n}$ denotes the reliability function of the i^{th} order statistic and

$$m_{i:n}(t) = E(T_{i:n} - t \,|\, T_{i:n} > t), \tag{1.3}$$

denotes the MRL function of the ith order statistic (or the $(n-i+1)$-out-of-n system). Note that this expression also holds for system with possibly dependent components if they have an exchangeable and absolutely continuous joint distribution. A similar expression can be obtained for the MRL function of the (C, k, n : G) system by using

$$F_{k|n:G}(t) = P\left\{T_{k|n:G} \le t\right\} = \sum_{i=1}^{n} \omega_{n-i+1} F_{i:n}(t). \tag{1.4}$$

Lemma 1.1: For $2k \ge n$ the CDF of the (C, k, n : F) system having i.i.d components with CDF $F(t)$ is given by

$$F_{k|n:F}(t) = (n-k+1)F_{k;k}(t) - (n-k)F_{k+1:k+1}(t). \tag{1.5}$$

Where $F_{k;k}(t)$ denotes the CDF of the parallel system having k i.i.d components with CDF $F(t)$.

Proof: The reliability of the (C, k, n : F) system for $2k \ge n$ is given by

$$R_{n|k:F} = P(L_n^0 < k) = 1 - (n-k+1)q^k + (n-k)q^{k+1}. \tag{1.6}$$

Where $q = P\{X_i = 0\}$ Using the relation

$$P[T_{k|n:F} > t] = P(L_n^0(t) < k).$$

Where $q = P\{T_i \le t\} = F(t)$ the CDF of $T_{k\,|\,n:F}$ for $2k \ge n$ can be written as

$$F_{k|n:F}(t) = (n-k+1)F^k(t) - (n-k)F^{k+1}(t), \tag{1.7}$$

and the proof is complete.

Proposition 1.1: For $2k \ge n$ the MRL function of the (C, k, n : F) system having i.i.d components with CDF $F(t)$ is given by

$$m_{k|n:F}(t) = \frac{(n-k+1)(1-F^k(t)m_{k:k}(t) - (n-k)(1-F^{k+1}(t))m_{k+1:k+1}(t)}{1-(n-k+1)F^k(t) + (n-k)F^{k+1}(t)}. \tag{1.8}$$

Where $m_{k:k}(t)$ denotes the MRL function of the parallel system having k i.i.d components with CDF $F(t)$.

The Proof is immediate from (1) and the proceeding lemma, using the fact that $F_{k:k} = F^k$. Analogously, for $2k \geq n$ the CDF of the $(C, k, n : G)$ system with i.i.d. components with CDF $F(t)$ is given by

$$F_{k|n:G}(t) = (n-k+1)F_{1:k}(t) - (n-k)F_{1:k+1}(t), \tag{1.9}$$

and its MRL function is given by

$$m_{k|n:G}(t) = \frac{(n-k+1)R^k(t)m_{1:k}(t) - (n-k)R^{k+1}(t)m_{1:k+1}(t)}{(n-k+1)R^k(t) - (n-k)R^{k+1}(t)}. \tag{1.10}$$

Where $R(t) = 1 - F(t)$ and $F_{1:k}(t)$ and $m_{1:k}(t)$ respectively denote the CDF and the MRL function of a series system having k i.i.d. components with CDF $F(t)$.

Proposition 1.2: For $2k \geq n$, if $T_{1:k} \geq mrl\ T_{1:k+1}$ or $T_{1:k} \geq hr\ T_{1:k+1}$ then the lifetimes of $(C, k, n : G)$ systems with exchangeable components are respectively *mrl*-increasing or *hr*-increasing in n and respectively *mrl*-better or *hr*-better than the series system with k components, i.e,

$$T_{1:k} \leq mrl \quad T_{k|n:G} \leq mrl \quad T_{k|n+1:G} \quad \text{or respectively,}$$

$$T_{1:k} \leq hr \quad T_{k|n:G} \leq hr \quad T_{k|n+1:G}$$

If the components in a system are i.i.d. with exponential distributions and common reliability function $R(t) = \exp(-\lambda t)$ for $t \geq 0$, where $\lambda > 0$, then $m_{1:k}(t) = 1/(k\lambda)$. Therefore for $k \geq n/2$, $m_{k|n:G} = (n+1)/(k(k+1)\lambda)$ and so $m_{k|n:G}(0) > m_{1:k-1}(0)$ for $n = 6$ and $k = 3$.

Proposition 1.3: If the $(C, k, n : G)$ system has exchangeable components, $2k \geq n$, $T_{1:k}$ is DMRL (Decreasing MRL), and $T_{1:k+1}$ is IMRL (increasing MRL) then $T_{k|n:G}$ is DMRL.

Proposition 1.4: If the $(C, k, n : F)$ system has exchangeable components, $2k \geq n$, $T_{k:k}$ is DMRL, and $T_{k+1:k+1}$ is IMRL then $T_{k|n:F}$ is DMRL

2. APPLICATION

2.1 Hormonal Regulation of Uterine Prostaglandin $F_2\alpha$ Synthesis

Early studies in sheep indicated that $PGF_2\alpha$ synthesis in the endometrium was influenced by the ovarian steroids estradiol-17β (E) and progesterone [9], [10]. It was found that E stimulated endometrial $PGF_2\alpha$ synthesis, but that E-induced $PGF_2\alpha$ production was markedly enhanced by a prior exposure to P. Similar effects of E and P on uterine $PGF_2\alpha$

synthesis were obtained in other species such as the guinea pig and the rat [11] Subsequently it became apparent in the ovine species that *E* and *P* indirectly controlled uterine $PGF_2\alpha$ synthesis *via* the regulation of receptors for oxytocin (*OT*) in the endometrium. We subsequently demonstrated that *OT* infused into the arterial supply of the ovine uterus mimicked the cyclical variation in the effects of mechanical stimulation on $PGF_2\alpha$ secretion from the uterus. Therefore, it seemed likely that the cyclical variation in the ability of *OT* to stimulate the synthesis of endometrial $PGF_2\alpha$ was due to a cyclical variation in the concentration of receptors for *OT* in the endometrium. This proposal was supported by reports that target sites for *OT*, such as the mammary gland and the oviduct, had been shown to bind *OT* with high affinity and that E enhanced the binding of *OT* by the uterus and oviduct in the rat.

A model for the hormonal regulation of endometrial $PGF_2\alpha$ synthesis in the sheep is depicted in Fig. 1. It is proposed that E enhances the formation of *OT* receptors in the endometrium and that during the luteal phase *P*, by blocking the action of *E*, reduces the concentration of *OT* receptors. However *P* eventually catalyzes the destruction of its own receptor so that towards the end of the lutea l phase *E* action is no longer suppressed and thus induces the formation of *OT* receptors. The greatly enhanced synthesis of endometrial $PGF_2\alpha$ by *OT* at the end of the luteal phase most likely results from the priming effect of *P* on lipid precursors in the endometrium during the luteal phase [12].

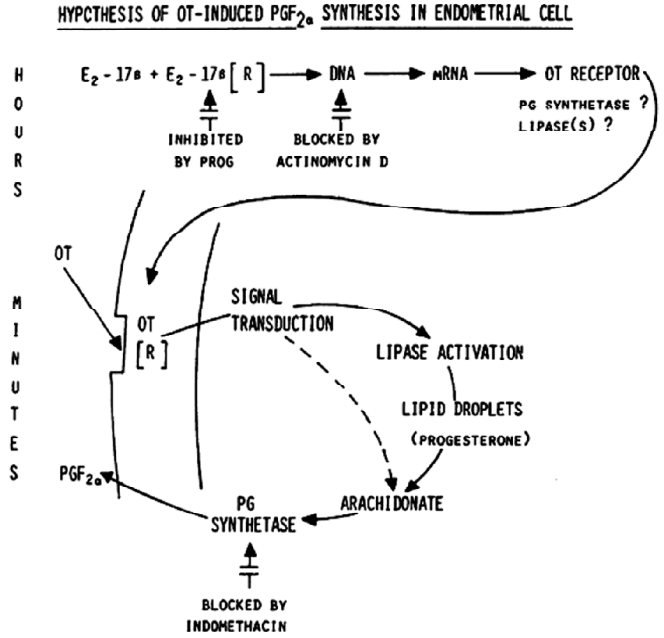

Figure 2.1.1: Model for the Regulation of the Ovine Endometrial *OT* Receptor by *E* and *P*

2.2 Regulation of the Pulsatile Secretion of Prostaglandin $F_2\alpha$ by the Ccentral Oxytocin Pulse Generator

It was established that *E* and *P* indirectly controlled $PGF_2\alpha$ synthesis in the endometrium by regulating the formation of *OT* receptors (see Fig. 2.1.1), the role of circulating levels of *OT* was unclear. Preliminary evidence indicated that, in addition to controlling endometrial *OT* receptors, *E* and *P* might also regulate endogenous circulating levels of *OT* [12]. Indeed, that same year it was reported that peaks of neurophysin I/II carrier proteins, co-secreted with *OT*. To assess the role of circulating levels of *OT* in the regulation of the estrous cycle in sheep. We initially developed a biometric method to measure oxytocic activity in the circulation of conscious sheep in various experimental states[15].

In ovariectomizcd sheep we found that small pulses of intramyometrial pressure (IMP) occurred synchronously in both uterine horns with a mean duration of 5.9 min and a pulse interval of 14.2 min[15]. We also found that low basal levels of *E* (0.05 pg/h) were required to maintain the 20 min frequency of the small pulses of IMP. Subsequently we established that the small pulses of IMP were caused by intennittent small pulses of *OT* secreted by the

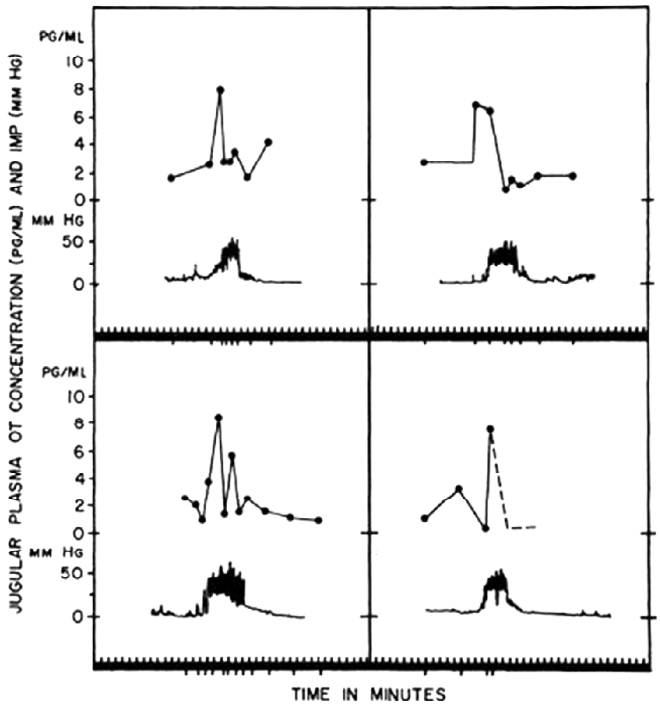

Figure 2.2.1: Oxytocin (*OT*) Concentration in Jugular Venous Plasma Sampled at 1 min Intervals from Conscious Intact Sheep Before During, and After Several Endogenous Small Phases of Intramyometrial Pressure (IMP)[14]

neurohypophysis. This conclusion was based on the finding that the infusion of 0.01 mU *OT* given over one minute into one uterine artery produced an ectopic pulse of IMP only in the adjacent horn, while a one minute infusion of 2.0 mU *OT* into ajugular vein elicited an ectopic pulse of IMP in both uterine horns.

Lastly, peaks of *OT* in jugular plasma (~10 pg/mI) were observed to occur synchronously with pulses of IMP (see Fig. 2.2.1).

2.3 Relative Contribution of the Neurohypophysis to Circulating Levels of *OT* and the Regulation of Its Pulsatile Secretion By *E* and *P*

To distinguish between the relative contributions of the neurohypophysis and the *CL***.** two model systems were employed to exclude the *CL* as a source of *OT*. First, in ovariectomized sheep maintained on low *E* (0.05 mg/h) to preserve the basal frequency of the central *OT* pulse generator high *E* (1.0 mg/h) or *P* (500 mg/h) were infused to determine their effects on the pattern of *OT* release from the neurohypophysis in the absence of the *CL* [13]. Second in intact cycling sheep. the *CL* was removed surgically (lutectomy) during the luteal phase of the cycle to exclude the contribution of *OT* from the *CL*.

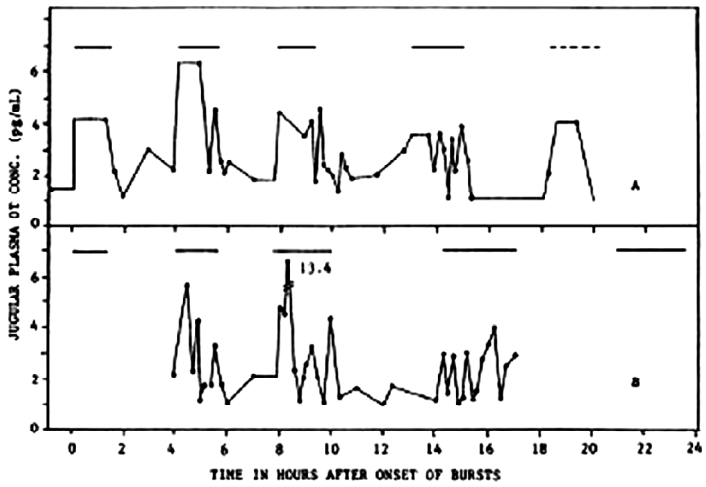

Figure 2.3.1: Jugular Concentration of Oxytocin in Two Ovaricctomized Sheep Maintained on Low Concentration *E* (0.05 mg/h) After the Infusion of High *E* (1.0 mg/h for 12h (A) or **36h (B). Horizontal Lines Mark Bursts of Intramyometrial Pressure [14]**

The concentration of *OT* in peripheral plasma during the first luteolylic pulse of PGF_2a in the intact cycling animal reaches about 200 pg/mI (Fig. 2.3.1) while the levels of *OT* observed during the bursts of IMP induced by hormonal treatment in the ovanectoniized animal is < 20 pg/ml (Fig. 4). Thus, it would appear that, at the onset of luteolysis in the

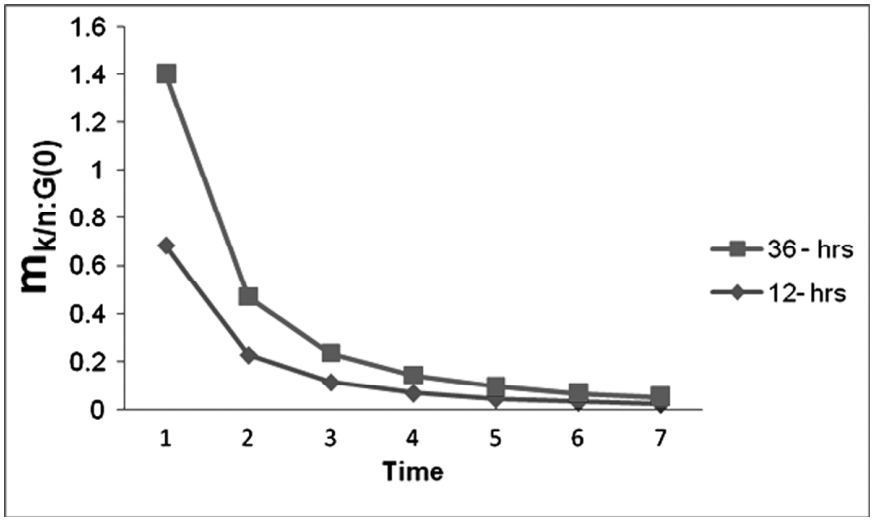

Figure 3.1

intact cycling sheep. the contribution of the neurohypophysis to circulating levels of *OT* is about 10%, whereas the supplemental contribution from the *CL* amounts to 90% of the circulating blood levels of *OT*.

3. MATHEMATICAL RESULT

In the common case of systems with independent exponential components of mean μ, we see that the series systems are also exponential, with mean $\mu_{1:k} = E(T_{1:k}) = \mu / k$ for $k = 1, 2, \ldots, n$ and hence are both IMRL and DMRL. Therefore the $(C, k, n : G)$ systems are DMRL for $k \geq n/2$. This concept is used for our application part.

Hence if

$$m_{k|n:G}(0) = \frac{(n+1)}{k(k+1)}\mu \leq m_{1:k-1}(0) = \frac{1}{(k-1)}\mu,$$

then

$$T_{k|n:G} \leq mrl \quad T_{k-1|n:G}.$$

For $2(k-1) \leq n$. Finally we note that in this case lemma can not be applied to the representation of the $(C, k, n : F)$ systems in terms of the maximal signature since the MRL functions of the parallel systems, from satisfy $\lim_{k\to\infty} m_{k:k}(t) = \mu$ and

$$\mu_{k:k} = m_{k:k}(0) = \sum_{i=0}^{k} (-1)^{i+1} \binom{k}{i} \frac{\mu}{i}.$$

For $k = 1, 2, \ldots, n$ where $\mu_{k:k} = \mathrm{E}(T_{k:k})$ Therefore for $k \geq n/2$.

$$F_{k|n:F}(t) = (n-k+1) \sum_{i=1}^{k} (-1)^{i+1} \binom{k}{i} F_{1:i}(t) - (n-k) \sum_{i=1}^{k+1} (-1)^{i+1} \binom{k+1}{i} F_{1:i}(t)$$

and

$$\mu_{k|n:F} = m_{k|n:F}(0) = (n-k+1) \sum_{i=1}^{k} (-1)^{i+1} \binom{k}{i} \frac{\mu}{i} - (n-k) \sum_{i=1}^{k+1} (-1)^{i+1} \binom{k+1}{i} \frac{\mu}{i}$$

Where $\mu_{k|n:F} = E(T_{k|n:F})$. Hence $\lim_{t \to \infty} m_{k|n:F}(t) = \mu$ for $k \geq n/2$ the consecutive -k-out-of-n.

4. CONCLUSION

A linear consecutive k-out of $n : F$ system consist of n linearly ordered components such that the system fails if and only if atleast k consecutive components fail. A linear consecutive k-out of $n : G$ System. Monotonicity for the mean residual lifetime function is obtained. The monotone residual function for Jugular concentration of oxytocin for low concentration E (0.05 mg/h) after the infusion of high E (1.0 mg/h) for 12 hrs or 36 hrs are obtained. In both the cases the curves are concave upward monotonically decreasing.

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