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TIME LAG MODEL ON THE CONCENTRATION AND SECRETION CONTROL IN MALE REPRODUCTIVE HORMONES

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Abstract
This study explored the time lag model on testosterone secretion control in male reproductive hormones. It revealed a lag in velocity and frequency on the luteinizing hormone-releasing hormone or LHRH (R) thereby leaving a time lag in its position and wavelength. Time delays are potent sources of instability in population growth systems and human beings since they are ubiquitous in ecological systems. Time lag can be explained by the rule that an otherwise stable equilibrium will generally become unstable if a time delay exceeds the dominant time scale of a system. This study considered a negative feedback function of frequency in the form of a travelling wave in the negative x-direction to explain the inhibition of the Luteinizing hormone (L). The study also showcased that the time lag or delay in the secretion of testosterone (T) led to its decay or extinction completely. The system also displayed a stable and significant effect of time lag of testosterone concentration and secretion in male reproductive hormones. The study recommended that clinical routine checkups should be adhered to by men and plans for the treatment should be effective.

Keywords: Time lag model, reproductive hormones in males, frequency function

Introduction

The natural appliance for time lag is age structure, while in physiology, time lags arise from the delay caused by the finite time taken to spread of message through nerves or hormones, or when populations are distributed over space. The hypothalamus monitors and causes the release of hormones from the pituitary gland, which stimulates the release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) into the blood (Bouman et al., 2005). Testosterone is the most important sex hormone in men, and it controls fertility, muscle mass, fat distribution, and red blood cell production. When levels of testosterone drop below the normal, healthy levels, they can lead to conditions like hypogonadism or infertility. Hormones are chemical substances produced by glands in the endocrine system. Hormonal imbalances can affect many bodily functions and can occur naturally at certain points in life, or when the endocrine glands are not functioning properly (Nedresky & Singh, 2021).

Prostate cancer can develop with the aid of androgens or male sex hormones, hypogonadism, radiation or chemotherapy, pituitary tumours, diseases, and genetic conditions. Human Reproductive Hormones (HRHs) are responsible for driving sexual development (puberty), controlling the menstrual cycle, and maintaining the uterus lining. Oestrogen and testosterone are the main reproductive hormones. When the reproductive hormones do not work as they should, fertility problems can occur. The pituitary gland produces, stores and stimulates other reproductive hormones such as HcG, Prolactin, LH and FSH, which are instrumental in sexuality and fertility (Gorter et al., 2012). Male reproductive hormones help maintain the male reproductive system and make sperm. They also help discharge sperm within the female reproductive tract during sex. Testosterone is a sex hormone that regulates many functions in the body, including sex drive, bone mass, fat distribution, muscle mass and strength, and the production of red blood cells and sperm. It is also the primary male hormone responsible for regulating sex differentiation, producing male sex characteristics, spermatogenesis, and fertility. Considering these hormones and their functions, it is necessary to support fertility as stated in the predator-prey model through in vitro fertility (Nkuturum, 2016; Nkuturum, 2017). HRH disparity is becoming a heightened issue of concern to medical officers

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and the right-thinking individuals. Imbalances in hormones can cause side effects throughout the body, including decreased sex drive, erectile dysfunction, loss of muscle mass, thinning hair and reduced hair growth. A mathematical model of human reproductive hormones was developed using a delay differential equation. This model explained the problems identified with the endocrine glands, such as lack of periodicity, instability, lag in the length of interruption preserving the stability, and bifurcation in the stable limit cycle. LH and FSH are important messenger hormones that act on the testicles to produce testosterone and sperm. Testosterone is metabolized into other sex hormones, such as oestradiol and dihydrotestosterone (DHT), which have important roles in bone health and other bodily functions (Murphy et al., 1994).

It had been observed that men have a testosterone level of 2.4-12ng/ml of blood, luteinizing hormone is 5-25miu/ml and follicle-stimulating hormone of 5- 20miu/ml while women have only 0.2-0.8 ng/ml of testosterone. There are many negative feedback pathways in biological systems which can be a result factor in time lags in male hormones. This includes Temperature regulation, Blood pressure regulation, Blood sugar regulation, Thyroid regulation, Photosynthesis in response to increased carbon dioxide and Predator/prey population dynamic. In men, 90 per cent of the total concentration comes primarily from the testis with the rest coming from other parts of the endocrine system which is the reason why women also produce it. Any regular imbalance in testosterone levels can cause dramatic personality changes. It is now well-recognized that blood testosterone levels can fluctuate. In this work, we shall discuss the physiology of testosterone and construct and analyze our model explaining the periodicity of testosterone concentration both analytically and numerically. The model presented here is consistent with actual physiological facts established (Cartwright & Hussain,1986).

Smith (1980) proposed a simple model based on some accepted, experimental facts involving luteinizing hormone-releasing hormone or LHRH (R), luteinizing hormone or LH (L) and testosterone (T). Cartwright and Hussain proposed another model where delays in all R, L and T were incorporated. Murray (1989) proposed yet another model incorporating delay only in T production and he calculated the critical delay for which the steady state becomes unstable by growing oscillation and expected a limit cycle periodic solution to be generated. In their model, they have incorporated delay in all R, L and T. Since both LHRH, and LH productions are inhibited by testosterone (Chatterjee 1979; Gower 1975) they considered two negative feedback functions of the form $\frac{A}{K+T^m}$ in their model.

Assumptions:
However, it can be inferred that the study assumes a delay in male reproductive hormones in the model.

The study assumes that the negative feedback delay in the secretion of male hormones has a travelling wave movement in the negative x-direction describing amplitude (A_1), wavelength (λ), position (x), velocity (v) and frequency as the term $\frac{A_1 \sin \frac{2\pi}{\lambda}(x-vt)}{K+T^m}$.

The study also assumes that the mathematical model and assumptions are in line with previous works done by Yen and Jaffe (1970), Chatterjee 1979, Gower 1975 and Das and Roy (1994), with some variations in constants and parameters used in the analytic solution.

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Description of parameters	
R(t)	Luteinizing hormone-releasing hormone
L(t)	Luteinizing hormone
T(t)	Testosterone
$\frac{dR}{dt}$	Rate of change in Luteinizing hormone-releasing hormone w.r.t. t
$\frac{dL}{dt}$	Rate of change in Luteinizing hormone w.r.t. t
$\frac{dT}{dt}$	Rate of change in Testosterone hormone w.r.t. t
$\tau_1, \tau_2, \tau_3, \tau_4$	Time lags
α, β, γ	Delay rates in the bloodstream
T	Time
K, i, m	Are positive constants (i = 1, 2, ….), $K > 0, m > 1$
A_1, A_2	Amplitude of open loop gain of feedback in the negative x-direction a function of frequency
T^m	The gain of feedback path for testosterone, a function of frequency
μ, λ	Rates of production of L(t) and T(t
$sin\frac{2\pi}{\lambda}(x - vt)$	The open loop gain of feedback in the negative x-direction is a function of frequency
v	velocity in the open loop gain of feedback in the negative x-direction
λ	Wavelength in the open loop gain of feedback in the negative x-direction
x	Position of the hormone in the open loop gain of feedback in the negative x-direction
$2\pi x$	The perimeter of the open loop gain of feedback in the negative x-direction

Table 1 shows dependent, and independent variables and parameter description

Materials and methods

The formulated mathematical model with negative feedback regulation of testosterone concentration and secretion was considered and that Luteinizing hormone-releasing hormone (R) is secreted from the hypothalamus and it reaches the pituitary after a time τ_2 and stimulates the release of Luteinizing hormone-releasing hormone (L). L reaches the testis and stimulates the development of Leading cells, leading to about a twenty-fold rise in plasma testosterone level after a time τ_4. Testosterone (T) has a negative feedback effect on R at the hypothalamic level after a time lag τ_1 and on L at the anterior pituitary after a time lag τ_3 as shown in figure 1 below.

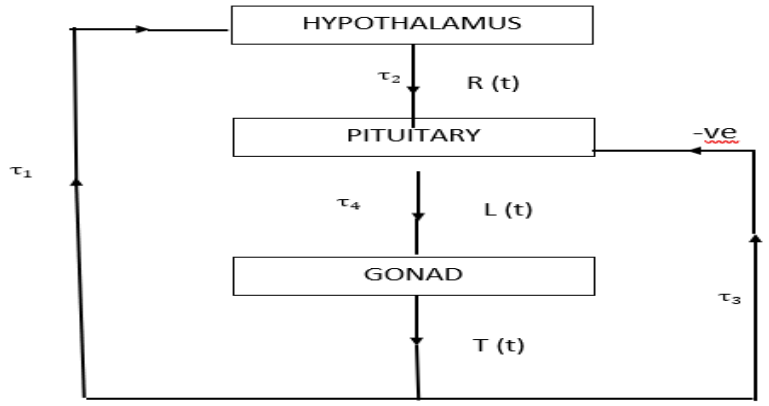

Fig. 1: a flow chart on the negative feedback model involving three hormones luteinizing hormone releasing hormone r(t), luteinizing hormone l(t) and testosterone t(t).

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Thus, the model equations are as follows:

$$\frac{dR}{dt} = -\alpha R + \frac{A_1 \sin\frac{2\pi}{\lambda}(x - vt)}{K + T^m(t - \tau_1)} \quad (1)$$

$$\frac{dL}{dt} = -\beta L + \mu R(t - \tau_2) + \frac{A_2 \sin\frac{2\pi}{\lambda}(x - vt)}{K + T^m(t - \tau_3)} \quad (2)$$

$$\frac{dT}{dt} = -\gamma T + \delta L(t - \tau_4) \quad (3)$$

where μ and δ are the respective rates of production of L(t) and T(t), and α, β and γ are the decay rates in the bloodstream. It is assumed that each of these hormones is cleared from the bloodstream according to the first order kinetics. Thus, $\tau_i \geq 0$ (for $i = 1, 2, 3, 4$) and K > 0, m > 1, $A_1 > 0$ and $A_2 > 0$ respectively. The system of equations (1 -3) is a nonlinear system of delay differential equations with initial conditions given as $R(0) = R_0$, $L(0) = L_0$, $T(0) = T_0$. From equation (1)

$$\left(R' + \alpha R\right)e^{\alpha t} = \frac{A_1 \sin\frac{2\pi}{\lambda}(x - vt)}{K} e^{\alpha t} \quad (4)$$

Using Integrating Factor $e^{\alpha dt} = e^{\alpha t}$

$$\frac{d\left(\mathrm{R}e^{\alpha t}\right)}{dt} = \frac{A_1 \sin\frac{2\pi}{\lambda}(x - vt)}{K} e^{\alpha t} \quad (5)$$

Upon integration by parts, we have

$$R(t) = \frac{A_1}{K}\frac{\alpha}{v^2 + \alpha^2}\sin\frac{2\pi}{\lambda}(x - vt) + \frac{A_1}{K}\frac{v}{\alpha^2 + v^2}\cos\frac{2\pi}{\lambda}(x - vt) + Qe^{-\alpha t} - \frac{A_1}{K}\frac{\alpha e^{-\alpha t}}{v^2 + \alpha^2}\sin\frac{2\pi x}{\lambda} - \frac{A_1}{K}\frac{\alpha e^{-\alpha t}}{v^2 + \alpha^2}\cos\frac{2\pi x}{\lambda} \quad (6)$$

Similarly, equation (2) yields

$$\left(L' + \beta L\right)e^{\beta t} = \frac{A_2 \sin\frac{2\pi}{\lambda}(x - vt)}{K} \quad (7)$$

Upon integration gives

$$L(t) = \frac{A_2}{K}\frac{\beta}{v^2 + \beta^2}\sin\frac{2\pi}{\lambda}(x - vt) + \frac{A_2}{K}\frac{v}{\beta^2 + v^2}\cos\frac{2\pi}{\lambda}(x - vt) + Pe^{-\beta t} - \frac{A_2}{K}\frac{\beta e^{-\beta t}}{v^2 + \beta^2}\sin\frac{2\pi x}{\lambda} - \frac{A_2}{K}\frac{\beta e^{-\beta t}}{v^2 + \beta^2}\cos\frac{2\pi x}{\lambda} \quad (8)$$

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Finally, equation (3) under the initial condition becomes $T(t) = 0$ (9)

This depicts that the testosterone secretion under time lag amounts to decay. Hence, the solutions to the time lags model on the concentration and secretion control in male reproductive hormones obtained in equations (6), (8) and (9) indicated that there is time lags in the Luteinizing hormone-releasing hormone R(t) and Luteinizing hormone L(t) are functions of frequency and position but slowed down with an exponential time decay while the Testosterone T(t) goes extinction completely as a result of time delay. The solutions to the model equations indicated a steady-state solution implying that the hormone secretion had negative exponential decay with time, evidence of the fact that male reproductive hormones' boundless decay is a serious issue of concern that requires medications or treatment strategy to be employed.

Model analysis

However, the systems of non-linear equations were analysed qualitatively to obtain the steady state solution, existence and uniqueness of the steady state.

Steady-state solution of a dynamical system of the model

The steady states of the system of equations were obtained by equating the derivatives to zero and resolving them analytically. The two possible steady states solutions were given as $E^*(0,0,\ 0)$ and $E^*\left(\frac{\delta}{\alpha(1+z')}, \gamma z, \frac{y(t-\tau_4)}{\gamma}\right)$ which represent time lag in Luteinizing hormone-releasing hormone R(t), Luteinizing hormone L(t) and Testosterone T(t) respectively. The E^* are the positive solutions of equations (1 – 3).

Existence and uniqueness of the steady state

To verify this, the equations were equated to zero as seen below:

$$0 = -\alpha x(t) + \frac{\delta}{1+z^{m(t-\tau_1)}} \quad (10)$$

$$0 = -\beta y(t) + x(t-\tau_2) + \frac{\delta}{1+z^{m(t-\tau_3)}} \quad (11)$$

$$0 = -\gamma z(t) + y(t-\tau_4) \quad (12)$$

Solving for x from equation (10) yields,

$$x(t) = \frac{\delta}{\alpha+\alpha z^{m(t-\tau_1)}} \quad (13)$$

From (12) $z(t) = \frac{y(t-\tau_4)}{\gamma}$ and (14)

$$y = z\frac{(t-\tau_4)}{\gamma}$$

$$Q = \frac{(t-\tau_4)}{\gamma}$$

$$y = Qz \quad (15)$$

Similarly, equation (11) gives

$$\alpha\beta\gamma z^{(m+1)} + \alpha\beta\gamma z - (\alpha+1)\delta = 0 \quad (16)$$

Putting $a = \alpha\beta\gamma = b$, $q = z$, for $m = 1$, $c = (\alpha+1)\delta$ giving a quadratic equation of the form $aq^2 + bq - c = 0 \Rightarrow \Rightarrow z = q = \frac{-\alpha\beta\gamma+\sqrt{(\alpha\beta\gamma)^2+4\alpha^2\beta\gamma\delta+4\alpha\beta\gamma\delta}}{2\alpha\beta\gamma}$ or

$$q = \frac{-\alpha\beta\gamma-\sqrt{(\alpha\beta\gamma)^2+4\alpha^2\beta\gamma\delta+4\alpha\beta\gamma\delta}}{2\alpha\beta\gamma} \quad (17)$$

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Equation (17) showed the existence and uniqueness of the solution which has only one positive root and it is in line with (Nkuturum & Onwubuya, 2022; Das & Roy, 1993). Thus, the existence and uniqueness of the steady state are confirmed by Descartes's rule of sign. Descartes' rule of sign states that to determine the number of real zeros (positive and negative roots) of a polynomial function, the number of positive real zeros in a polynomial function f(x) is the same or less than by an even number as the number of changes in the sign of the coefficients.

Stability of the steady state

To examine the stability of steady state, $E^*(x^*, y^*, z^*)$ is linearised by letting: $= x' - x^*$, $y = y' - y^*$ and $z = z' - z^*$ which gives

$$\dot{x} = -\alpha x - \frac{\delta z^{*m-1}}{(1+z^{*m})^2} z(t-\tau_1) \tag{18}$$

$$\dot{y} = -\beta y + x(t-\tau_2) + \frac{\delta m \dot{z}^{m-1}}{(1+\dot{z}^m)^2} z(t-\tau_3) \tag{19}$$

$$\dot{z} = -\gamma z + y(t-\tau_4) \tag{20}$$

Thus, (18 – 20) yields the variation matrix as below:

$$\begin{bmatrix} -\alpha-\lambda & 0 & -\frac{\delta m z^{m-1}}{(1+z^m)^2} e^{-\lambda\tau_1} \\ e^{-\lambda\tau_2} & -\beta-\lambda & -\frac{\delta m z^{m-1}}{(1+z^m)^2} e^{-\lambda\tau_3} \\ 0 & e^{-\lambda\tau_4} & -\gamma-\lambda \end{bmatrix} \tag{21}$$

Equ (22) becomes the characteristic equation

$$\lambda^3 + A\lambda^2 + \left(B + \delta e^{-\lambda T_2}\right)\lambda + C + \alpha\delta e^{-\lambda T_2} + \delta e^{-\lambda T_1} = 0, \tag{22}$$

where;

$$A = \alpha + \beta + \gamma > 0,\ T_1 = \tau_1 + \tau_2 + \tau_4 > 0$$
$$B = \alpha\beta + \beta r + r\alpha > 0,\ T_2 = r_3 + r_4 > 0 \tag{23}$$

$$C = \alpha\beta r > 0\ , \qquad \delta = \frac{\delta m z^{m-1}}{(1+z^m)^2} > 0$$

To determine the nature of the stability, we need the sign of the real parts of the roots of equation (22) above; Let

$$D(\lambda, \tau_i) = \lambda^3 + A\lambda^2 + \left(B + \delta e^{-\lambda(\tau_1+\tau_4)}\right)\lambda + C + \alpha\delta e^{-\lambda(\tau_3+\tau_4)} + \delta e^{-\lambda(\tau_1+\tau_2+\tau_4)} = 0, \tag{24}$$

$$For\ \tau_1 = \tau_2 = \tau_3 = \tau_4 = 0,$$

$$D(\lambda, 0) = \lambda^3 + A\lambda^2 + (B + \delta)\lambda + C + (\alpha+1)\delta = 0 \tag{25}$$

Routh Hurwitz condition for necessary and sufficient conditions for locally asymptotic stability of the steady state is that:

$$A(B+\delta) - [C + (\alpha+1)\delta] > 0$$

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$$\Rightarrow \quad (\alpha+\beta)\,(\gamma+\beta)(\gamma+\alpha)+\ \delta(\beta+\gamma)\,)>\delta \tag{26}$$

∴ D(λ, 0) has roots of the real parts all negative provided (26) holds.

Similarly, put λ = μ+iv, then (22) is equivalent to separate real and imaginary parts (Das & Roy 1993) as

$$\mu^3-3\mu v^2+A\mu^2-Av^2+B\mu+C+\delta\mu e^{-\mu T_2}\cos vT_2$$

$$+\delta v e^{-\mu T_2}\sin vT_2+\ \alpha\delta\, e^{-\mu T_2}\ \cos vT_2\ +\delta e^{-\mu T_1}\ \cos vT_1=0 \tag{27}$$

$$-v^3+3\mu^2 v+2A\mu v+Bv-\delta\mu e^{-\mu T_2}\sin vT_2$$

$$+\delta v e^{-\mu T_2}\cos vT_2-\alpha\delta e^{-\mu T_2}\sin vT_2-\delta e^{-\mu T_1}\ \sin vT_1=0 \tag{28}$$

Discussion

The model equations, 1,2 and 3 respectively presented here incorporated negative feedback inhibiting Luteinizing Hormone (L) secretion by testosterone to make the model more realistic. This negative feedback was identified to be a form of travelling wave in the negative x-direction is a function of frequency. Here we have determined that the exact solution of the system has a region in the parametric plane for oscillation in which there was a decline in the frequency and time of oscillation as in equations 6 and 8 while 9 showed a complete decay as a result of the time lag in secretion of testosterone respectively. The essential requirement for the control system is that it should be **stable.** It means that the output of the system should follow the input. If the input is finite, the output also needs to be finite to satisfy the stability condition. Thus, the system is locally asymptotically stable, for $\tau_i \geq 0$. By continuity and for sufficiently small $\tau_i > 0$, all eigenvalues of (15) have negative real parts, provided one can guarantee that no eigenvalue with positive real part bifurcates from infinity (which could happen since it is a retarded system). For stability analysis, we require the Nyquist criterion. For this, the system (1)–(3) is considered and the space of real-valued continuous functions defined on (τ_i, ∞) satisfies the initial conditions.

Conclusion

In the delay model, a model for time lag on the concentration and secretion control in male reproductive hormones was developed. The model equations were subdivided into three male hormonal delayed differential equations. The researcher has analytically studied this model and derived conditions of local asymptotic stability, steady-state solution, and the existence and uniqueness of the model. The mathematical model and assumptions were given with conditions for the existence of uniqueness of the model solution with exact solutions of the dependent variables. This study can be extended to female reproductive hormones and numerical analysis of mathematical models on oxidative stress and human reproduction.

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