

A Delay Differential Equation Mathematical Model for the Control of the Hormonal System of the Hypothalamus, the Pituitary and the Testis in Man

David Greenhalgh⁽¹⁾ and Q.J.A. Khan⁽²⁾

(1) Department of Statistics and Modelling Science, University of Strathclyde, UK,

(2) Department of Mathematics and Statistics, Sultan Qaboos University, Oman

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Talk Structure

- Introduction.
- The Model.
- Equilibria.
- Stability Analysis
 - (i) Positive Equilibrium
 - (ii) Zero Equilibrium.
- Heuristic Discussion.
- Summary.

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1. Introduction.

- Blood testosterone levels fluctuate over the short term (2-3 hours) in humans (Cartwright and Husain, 1986).
- Testosterone production in the testis is influenced by the level of pituitary hormone, luteinizing hormone (LH).
- LH is produced by the gonadotrophs, those pituitary cells which secrete it.
- The production of LH in turn is influenced by the level of the hypothalamic hormone luteinizing hormone release hormone (LHRH), sometimes also called gonadotropin releasing hormone.

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- Several models have been postulated to explain the cyclic release of this set of hormones.
- The first type of model hypothesizes a “neural clock” which forces pulsed secretion of LHRH in waves. However this type of model does not describe the inhibitory effect of gonadal steroids on the LHRH pulse generator and leads to other inconsistencies with the observed biological data.
- The second type of model has no external pulse input. Instead the regular cyclic oscillations in hormones are a natural consequence of feedback oscillations.
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His model was as follows:

$$\frac{dR}{dt} = f(T) - b_1(R),$$

$$\frac{dL}{dt} = g_1(R) - b_2(L), \quad (1)$$

and
$$\frac{dT}{dt} = g_2(L) - b_3(T).$$

Here f is a positive monotonic decreasing function and b_i ($i = 1, 2, 3$) and g_j ($j = 1, 2$) are positive monotonic increasing functions.

$R(t)$ density of LHRH,

$L(t)$ density of LH,

$T(t)$ density of testosterone in the bloodstream at time t .

- Although this model does explain cyclic fluctuations in the levels of the three hormones there is a problem with it as it fails to explain the experimental observations that the concentrations of LH and LHRH in the blood after castration still oscillate.
- Smith (1983) tried to improve this by introducing a time delay τ between the LH concentration and the production of testosterone.
- This time delay is due to delay between stimulation of the testis by LH and the ultimate release of testosterone into the bloodstream and the delay from the transportation time due to the hormone travelling around the body.

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In Smith's improved model in the third equation the term $g_2(L(t))$ is replaced by $g_2(L(t - \tau))$,

$$\frac{dR}{dt} = f(T) - b_1(R),$$

$$\frac{dL}{dt} = g_1(R) - b_2(L), \tag{2}$$

and
$$\frac{dT}{dt} = g_2(L(t - \tau)) - b_3(T).$$

Murray (1989) analyzed this model with

$b_1(R) = b_1R$, $b_2(L) = b_2L$, $b_3(T) = b_3T$, $g_1(R) = g_1R$ and $g_2(L) = g_2L$ where b_1, b_2, b_3, g_1 and g_2 are positive constants.

- By using a linear analysis Murray showed that there is a critical time delay τ_c such that the positive steady state of Smith's model (3) is unstable.
- For certain parameter values limit cycle periodic solutions could occur.
- Ruan and Wei (2001) also considered the general model of Smith (1983) which introduced a time delay, where again f is a general positive monotone decreasing function and b_1, b_2, b_3, g_1 and g_2 are general positive monotone increasing functions.
- They show that for certain parameter values the unique positive steady state of this model is locally asymptotically stable whatever the value of the time delay.

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- However for other parameter values there is a critical time delay such that this unique positive steady state is locally asymptotically stable when the time delay is less than this critical value.
- As the time delay passes through the critical value there is a Hopf bifurcation and the steady state becomes unstable. So the model can explain the regular cyclic fluctuation of these three hormones for certain parameter values.

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- In a previous paper (Khan and Greenhalgh, 2008) we extended Smith's (1983) model in two ways.
- Both models assumed that LHRH release was controlled by a combination of testosterone and luteinizing hormone and luteinizing hormone release hormone was controlled by a combination of LH and testosterone.
- In the first the combination was additive and in the second the combination is multiplicative.
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The equations for the first model were:

$$\frac{dR}{dt} = f_1(T) + f_2(L) - b_1(R),$$

$$\frac{dL}{dt} = g_1(R) + p_2(T) - b_2(L),$$

and
$$\frac{dT}{dt} = a + g_2(L(t - \tau)) - b_3(T)$$

with appropriate initial conditions.

For the second model the equations were

$$\frac{dR}{dt} = f_1(T)f_2(L) - b_1(R),$$

$$\frac{dL}{dt} = g_1(R)p_2(T) - b_2(L),$$

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$$\frac{dT}{dt} = a + g_2(L(t - \tau)) - b_3(T)$$

with appropriate initial conditions.

- Here f_i , $i = 1, 2$ and p_2 are positive monotonic decreasing differentiable functions and b_j ($j = 1, 2, 3$) and g_k ($k = 1, 2$) are positive monotonic increasing differentiable functions.
- We used the time delay as a bifurcation parameter and analyzed necessary and sufficient conditions for Hopf bifurcation to occur.
- We found that usually as the time delay increased through an infinite series of critical values the system passes through alternate regions of stability and instability possibly starting in either region.
- In regions of instability we expect limit cycle behaviour but chaotic behaviour is theoretically possible.
- An interesting consequence is therefore that there exist parameter values for which Hopf bifurcation is possible.

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Cartwright and Husain (1986) postulated another model with differential equations as follows:

$$\frac{dR}{dt} = -d_R R + r_R H \left[2 - \frac{L(t - \tau_A)}{\hat{L}} - \frac{T(t - \tau_B)}{\hat{T}} \right],$$

$$\frac{dL}{dt} = -d_L L + r_L R(t - \tau_C),$$

and
$$\frac{dT}{dt} = -d_T T + r_T L(t - \tau_D - \tau_E).$$

Here d_R, d_L, d_T, r_R, r_L and r_T are all rate constants, $\tau_A, \tau_B, \tau_C, \tau_D$ and τ_E are all time delays. \hat{L} and \hat{T} are constants.

- $H(x)$ is the Heaviside step function:

$$H(x) = \begin{cases} 0, & x < 0, \\ \frac{1}{2}, & x = 0, \\ 1, & x > 0. \end{cases}$$

- This model accounts for the pulsatile release of the three hormones in men.
- It can also explain the cyclic behaviour of LHRH and LH after castration.
- This model is improved by Liu and Yang (1990) and Liu and Deng (1991).

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2. Mathematical Model.

It is important to include as many experimental facts as possible to make the model more realistic.

Our differential equation model which describes the population dynamics of the hypothalamic hormone, R , the pituitary hormone, L , and testosterone, T , is

$$\frac{dR}{dt} = \frac{b_1 R}{(L + T)^a} - b_2 R,$$

$$\frac{dL}{dt} = c_1 \frac{R^a L}{R^a + T^a} - c_2 L, \quad (3)$$

and

$$\frac{dT}{dt} = L(t - \tau)T - b_3 T,$$

with suitable initial conditions.

Here a, b_1, b_2, b_3, c_1 and c_2 are strictly positive constants.

- This model takes into account the fact that LHRH encourages the production of LH which in turn encourages the production of testosterone.
- There is also a time delay between stimulation of the testis by LH and the rise in testosterone level in the bloodstream.
- The rate of removal of all three hormones from the bloodstream is taken to be proportional to their concentration as in Murray (1989).

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- To explain the first differential equation in (3) note that the release of LHRH by the hypothalamus is influenced by the combined effects of LH and testosterone hormones.
- If the concentrations of LH and T are small then LHRH production will be high and vice-versa if the combined concentration of LH and testosterone is high.
- Similarly the secretion of LH will be high if the level of testosterone is small and the concentration of LHRH is high.

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- On the other hand the LH secretion is low if testosterone is high and LHRH concentration is low.
- The parameter value $a = 1$ gives a simple mathematical model including these effects. The two properties above are amplified greatly for higher values of a .
- The model is not well-defined if $L + T = 0$ or $R + T = 0$.
- Various authors (Khan et al., 1986, Meredith et al., 1986 and Ewing and Zirkin, 1983) experimentally proved that secretion of testosterone is stimulated not only by the pituitary hormone LH, but it has an autonomous secretion which comes from the adrenal cortex and is independent of LH. However this value is small so we ignore it.

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- LH stimulates the secretion of androgen and produces a number of Leydig cells. However we have not included the number of Leydig cells as a separate class as Liu and Deng (1991) successfully argued that the proliferation of Leydig cells is small and that they could be regarded as being in a quasi-steady state.
- Our model follows the classical models of Smith (1980, 1983) and Cartwright and Husain (1986) in that it assumes that testosterone concentration inhibits the production of LHRH.
- As in Cartwright and Husain (1986) we are including the experimental facts in our model that both testosterone and luteinizing hormone inhibit LHRH production.

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- As in the models of Smith (1983), Murray (1989) and Cartwright and Husain (1986) we assume that the levels of LH affect the production of testosterone in the testis. This is supported by experimental evidence described by Sharpe (1986).
- As in the models of Smith (1983), Murray (1989) and Cartwright and Husain (1986) as the levels of LH decline then the production of testosterone in the testis also decays.

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Theorem 1

The possible equilibria of the system (3) are:

(i) $E_1 : R = 0, T = 0$ and $L = 0$;

(ii) $E_2 : R = T = 0$ and $L = \bar{L}$ where $\bar{L} > 0$ is any positive constant;

(iii) $E_3 : R = \bar{R}, T = 0$ and $L = (b_1/b_2)^{1/a}$. Here $\bar{R} > 0$ is any positive constant. This equilibrium is possible only for the special values $c_1 = c_2$ and

(iv) $E_4 : R = R^* = \frac{((b_1/b_2)^{1/a} - b_3)}{((c_1/c_2) - 1)^{1/a}}, T = T^* = (b_1/b_2)^{1/a} - b_3$

and $L = L^* = b_3$.

This equilibrium is feasible if and only if $c_1 > c_2$ and $b_1 > b_2 b_3^a$.

- Note that the term $R/(L + T)^a$ on the right hand side of (3) is not defined at E_1 , also the term $R^a/(R^a + T^a)$ is not defined at E_1 or E_2 , but if the former is interpreted as zero, and the latter as any finite value at E_1 and (c_2/c_1) at E_2 these equilibria are possible.
- We are primarily interested in the stability of the system about the equilibrium E_4 which has all three hormones present.
- As E_3 is possible only for special parameter values we do not examine it further.
- It is possible to regard E_3 as a special case of equilibrium E_4 if $c_1 \rightarrow c_2$, $b_1 \rightarrow b_2 b_3^a$.

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- It is possible to regard E_3 as a special case of equilibrium E_4 if $c_1 \rightarrow c_2$, $b_1 \rightarrow b_2 b_3^a$.

- Note that the term $R/(L + T)^a$ on the right hand side of (3) is not defined at E_1 , also the term $R^a/(R^a + T^a)$ is not defined at E_1 or E_2 , but if the former is interpreted as zero, and the latter as any finite value at E_1 and (c_2/c_1) at E_2 these equilibria are possible.
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3. Stability of the Positive Equilibrium

The characteristic equation of the stability matrix of the system linearized about the positive equilibrium E_4 is

$$\omega^3 + pqT^*e^{-\omega\tau} + pq\omega + r\omega T^*e^{-\omega\tau} = 0 \quad (4)$$

$$\text{where } p = \frac{ab_1R^*}{(L^* + T^*)^{a+1}}, \quad q = \frac{c_1L^*aR^{*a-1}T^{*a}}{(R^{*a} + T^{*a})^2}$$

$$\text{and } r = \frac{c_1R^{*a}L^*aT^{*a-1}}{(R^{*a} + T^{*a})^2}.$$

When $\tau = 0$ this reduces to

$$\omega^3 + (pq + rT^*)\omega + pqT^* = 0 \quad (5)$$

and it is straightforward to use the Routh-Hurwitz criteria to show that this equilibrium is unstable. It has one strictly negative real root and two complex roots with strictly positive real parts.

For $\tau \geq 0$ write $\omega = \xi + i\eta$.

If $\xi = 0$, $\eta = \eta^*$ is a purely imaginary root of (4) corresponding to $\tau = \tau^*$ and $u = \eta^{*2}$ then

$$f(u) = u^3 + d_1 u^2 + d_2 u + d_3 = 0 \quad (6)$$

where $d_1 = -2pq$, $d_2 = (pq)^2 - (rT^*)^2$ and $d_3 = -(pqT^*)^2$.

For three positive roots of $f(u) = 0$ we need

$$\Delta = \frac{4}{27}d_2^3 - \frac{1}{27}d_1^2d_2^2 + \frac{4}{27}d_1^3d_3 - \frac{2}{3}d_1d_2d_3 + d_3^2 < 0. \quad (7)$$

Lemma 1

The equation $f(u) = 0$ cannot have three co-incident positive real roots.

Theorem 2

- (i) If $a^a b_2^{a+1} > b_1$ and $\Delta < 0$ then $f(u) = 0$ has three strictly positive distinct real roots;
- (ii) If $a^a b_2^{a+1} > b_1$ and $\Delta = 0$ then $f(u) = 0$ has three strictly positive real roots two of which are repeated;
- (iii) If $a^a b_2^{a+1} \leq b_1$ or $\Delta > 0$ then $f(u) = 0$ has exactly one strictly positive real root.

Corollary 1

The equation $f(u) = 0$ always has at least one simple real root.

The positive real roots u^* of $f(u) = 0$ correspond to critical time delays τ^* at which potential Hopf bifurcation will occur. If u^* is a strictly positive real root of $f(u) = 0$ and $\eta^* = \sqrt{u^*}$ then the equations

$$\sin \alpha = \frac{pq}{\sqrt{(pq)^2 + (\eta^* r)^2}}, \quad (8)$$

$$\cos \alpha = \frac{\eta^* r}{\sqrt{(pq)^2 + (\eta^* r)^2}}, \quad (9)$$

determine $\alpha \in [0, \pi/2)$ uniquely in the range $[0, 2\pi)$.

From (8) and (9)

$$\begin{aligned}\sin(\tau^* \eta^* + \alpha) &= 0, \\ \cos(\tau^* \eta^* + \alpha) &= \frac{(\eta^{*3} - pq\eta^*)}{T^* \sqrt{(pq)^2 + (\eta^* r)^2}}\end{aligned}$$

determine $\alpha + \tau^* \eta^*$ uniquely in the range $[0, 2\pi)$.

$$\tau^* \eta^* + \alpha = \beta_0^*(\eta^*)$$

where $\beta_0^*(\eta^*) = 0$ or π depending on whether or not $\eta^* > \sqrt{pq}$.

Hence $\tau^* \eta^* + \alpha = \beta_0^*(\eta^*) + 2k\pi$ for some integer k so
 $\tau^* = ((\beta_0^*(\eta^*) + 2k\pi - \alpha)/\eta^*)$ for $k \geq 1$ if $\beta_0^*(\eta^*) = 0$ and for
 $k \geq 0$ if $\beta_0^*(\eta^*) = \pi$.

For $\beta_0^*(\eta^*) = 0$, $k \leq 0$ and for $\beta_0^*(\eta^*) = \pi$, $k < 0$ give negative values of τ^* which are infeasible.

The conditions for Hopf bifurcation to occur as τ passes through τ^* are that a complex conjugate pair of eigenvalues cross the imaginary axis as τ passes through τ^* and the crossing is transversal

$$i.e \quad \left. \frac{d\xi}{d\tau} \right|_{\tau=\tau^*} \neq 0. \quad (10)$$

Provided that the corresponding value of u^* is a simple root of $f(u) = 0$ this transversality condition is satisfied.

Hence if u^* corresponds to a simple root of $f(u) = 0$ Hopf bifurcation occurs as τ passes through τ^* .

Therefore for $\tau = 0$ the model (3) is unstable and whenever τ passes through a value $\tau^* = (\beta_0^*(\eta^*) + 2k\pi - \alpha)/\eta^*$ corresponding to $\eta^* = \sqrt{u^*}$, where u^* is a simple root of $f(u) = 0$, Hopf bifurcation occurs.

As $f(u) = 0$ has either one or three positive simple roots there are an infinite number of such values of τ^* separated by $2\pi/\eta^*$.

Hence we expect that as τ increases the model starts off unstable and as τ increases passing through progressively increasing values Hopf bifurcation occurs repeatedly.

In the region where the equilibrium with all three hormones present is unstable we expect limit cycle behaviour as observed biologically and found in simpler simulation models (Murray, 1989), but chaotic behaviour is another possibility.

4. Stability of the Zero Equilibrium.

If R , L and T are all small and strictly positive for $t \geq 0$ then $R \rightarrow \infty$ as $t \rightarrow \infty$ so the equilibrium E_1 is never locally asymptotically stable.

5. Heuristic Discussion of Behaviour.

We shall now discuss the heuristic behaviour of the system when $c_2 > c_1$ or $b_2 b_3^a > b_1$.

If $c_2 > c_1$ or $b_2 b_3^a > b_1$ then the equilibrium with all three hormones present is not possible.

If $c_2 > c_1$ then it is straightforward to show that L and T tend to zero and R tends to infinity as t becomes large.

If $c_1 > c_2$ and $b_2 b_3^a > b_1$ then the potential behaviour is more interesting. Define \hat{L} to be the unique positive root of

$$-\frac{b_1}{L^a} + b_2 = -L + b_3 \quad (11)$$

$\hat{L} < b_3$.

Can show L enters the region $(b_3, (b_1/b_2)^{1/a})$ infinitely often and $L_\infty \leq \hat{L} \leq L^\infty$.

It is tempting to conjecture that $L \rightarrow \hat{L}$ as $t \rightarrow \infty$.

A heuristic argument suggests that $\frac{R^a}{R^a + T^a}$ may approach $\frac{C_2}{C_1}$ as t becomes large.

In this situation it is plausible that L remains constant and T and R exponentially decrease at the same rate $(\hat{L} - b_3)t$, which in some sense corresponds to the possible equilibrium E_2 of Theorem 1 being globally stable.

6. Summary and Conclusions.

In this talk we have discussed a delay-differential equation model to explain the cyclic release of three hormones in the body: the hypothalamic hormone LHRH, pituitary hormone LH and testosterone.

We postulated a new delay differential equation model which improves on previous modelling efforts by taking into account the fact that LHRH encourages the production of LH which in turn encourages the production of testosterone.

We also took into account a time delay between stimulation of the testis by LH and the rise in testosterone level in the bloodstream.

In our model we found that there was a unique equilibrium with all three hormones present.

- This was unstable when the time delay was zero and as the time delay τ increases passing through a progressively infinite series of values Hopf bifurcation occurs repeatedly.
- In regions of instability we expect limit cycle behaviour as observed in practice and discovered in earlier simulation models (Murray, 1989) but chaos is theoretically possible.
- We concluded the talk with a brief heuristic discussion of the likely stability properties of the other equilibria.

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