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# On the stability of a model of testosterone dynamics

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**Abstract.** We prove the global asymptotic stability of a well-known delayed negative-feedback model of testosterone dynamics, which has been proposed as a model of oscillatory behavior. We establish stability (and hence the impossibility of oscillations) even in the presence of delays of arbitrary length.

## 1. Introduction

The concentration of testosterone in the blood of a healthy human male is known to oscillate periodically with a period of a few hours, in response to similar oscillations in the concentrations of the luteinising hormone (LH) secreted by the pituitary gland, and the luteinising hormone releasing hormone (LHRH), normally secreted by the hypothalamus (see [5, 14]). In his influential textbook *Mathematical Biology* [12], J.D. Murray presents this process as an example of a biological oscillator, and proposes a model to describe it (pp. 244-253 in this edition). To obtain oscillations in an otherwise stable model, he introduces a delay in one of the variables, and by linearizing around the unique equilibrium point, he presents an argument to find conditions for the existence of such oscillations. This section in his book has remained virtually unchanged since the first edition of 1989, up to the recent publication of the third edition in 2002.

The study of delayed models is one of great interest for its relevance in biological applications (consider for instance the delay between the moment a protein is transcribed, and the moment the folded and translated protein gets to act as a transcription factor back in the nucleus). But the introduction of delays often comes at the expense of a higher difficulty in mathematical treatment.

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As a “case study” for a method for proving stability in a class of dynamical systems with delays, we show in this paper that *Murray’s model in fact does not exhibit oscillations.* The biological model itself, while simplified, is still interesting in its own right, and belongs to a commonly recurring class of models of negative feedback proposed (in undelayed form) by Goodwin [8], and illustrated in Goldbeter [7]. In what follows, we first study the linearized system around the unique equilibrium, establishing local stability, and then proceed to show the global stability of the system, borrowing ideas from monotone systems and the theory of control. We also propose an explanation for the confusion in [12].

## 2. The model, and its linearization

The presence of LHRH in the blood is assumed in this simple model to induce the secretion of LH, which induces testosterone to be secreted in the testes. The testosterone in turn causes a negative feedback effect on the secretion of LHRH. Denoting LHRH, LH, and testosterone by $R$, $L$, and $T$ respectively, and assuming first order degradation and a delay $\tau$ in the response of the testes to LH, we arrive to the dynamical system

$$\begin{aligned} \dot{R} &= f(T) - b_1 R \\ \dot{L} &= g_1 R - b_2 L \\ \dot{T} &= g_2 L(t-\tau) - b_3 T \end{aligned} \tag{1}$$

Here, $b_1, b_2, b_3, g_1, g_2$ are positive constants, $\tau \geq 0$ and $f(x) = A/(K+x)$, although other positive, monotone decreasing functions could be employed as well (see Murray, p. 246).

By setting the left hand sides equal to zero, it is straightforward to show that there are as many equilibrium points of (1) as there are solutions of

$$f(T) - \frac{b_1 b_2 b_3 T}{g_1 g_2} = 0 \tag{2}$$

namely for each such solution $T_0$ of (2), one has the equilibrium

$$L_0 = \frac{b_3 T_0}{g_2}, \quad R_0 = \frac{b_3 b_2 T_0}{g_1 g_2}, \quad T_0. \tag{3}$$

By the assumption of positivity and monotonicity of $f$ there always exists a unique solution of (2), thus a unique equilibrium point of (1). Linearizing around that point we obtain the system

$$\begin{aligned} \dot{x} &= f'(T_0) z - b_1 x \\ \dot{y} &= g_1 x - b_2 y \\ \dot{z} &= g_2 y(\cdot - \tau) - b_3 z \end{aligned} \tag{4}$$

The characteristic polynomial of (4), which determines all solutions of (4) of the form $\mathbf{v}(t) = \mathbf{v_0} e^{\lambda t}$, is

$$(\lambda + b_1)(\lambda + b_2)(\lambda + b_3) + d e^{-\lambda\tau} = 0, \ \ d = -f'(T_0) g_1 g_2 > 0. \tag{5}$$

**Proposition 1.** *The linear system (4) is stable, for all values of* $b_1, b_2, b_3, g_1, g_2, \tau$ *and* $f(x) = A/(K + x)$.

*Proof.* For there to be an unstable solution of (4), there must be a solution $\lambda$ of (5) such that Re $\lambda \geq 0$. Assuming that this is the case, we have

$$d \geq |-de^{-\lambda\tau}| = |\lambda + b_1||\lambda + b_2||\lambda + b_3| \geq |b_1||b_2||b_3| = b_1 b_2 b_3 . \quad (6)$$

But on the other hand, using the choice for $f(T)$ above, we have $f'(T_0) = -A/(K + T_0)^2 = -f(T_0)/(K + T_0)$, and

$$d = -f'(T_0)g_1 g_2 = \frac{f(T_0)}{K + T_0} g_1 g_2 = b_1 b_2 b_3 \frac{T_0}{K + T_0} < b_1 b_2 b_3 , \quad (7)$$

which is a contradiction. □

## 3. Global asymptotic stability of the model

Even with the addition of only one simple delay, it is probably best to view (1) as a dynamical system with states in the space $X$ of continuous functions from $[-\tau, 0]$ into the closed positive quadrant $\mathbb{R}^3_+$. The right hand side of (1) defines a function $F : X \to \mathbb{R}^3_+$ in the natural way, and given an initial state $\phi \in X$, the solution of the system is the unique absolutely continuous function $x : [-\tau, \infty) \to \mathbb{R}^3_+$ such that

$$x_{(0)} = \phi \text{ and } \dot{x}(t) = F(x_{(t)}), \ t \geq 0 \quad (8)$$

Here, $x_{(t)}$, or simply $x_t$, is the state defined by $x_t(s) = x(t + s), \ s \in [-\tau, 0]$. The function $\Phi(t, \phi) = x_t$ will be from now on formally identified with system (1). For proofs of the fact that $\Phi$ is well-defined, and more details, the reader is referred to [4,9,15].

**Cutting the Loop** We define a function $G : X \times \mathbb{R}_+ \to \mathbb{R}^3_+$ in a very similar manner to $F$: for $\phi(s) = (R(s), L(s), T(s))$, let

$$G(\phi, w) = (w - b_1 R(0),\ g_1 R(0) - b_2 L(0),\ g_2 L(-\tau) - b_3 T(0)) .$$

Given a piecewise continuous function $u : \mathbb{R}_+ \to \mathbb{R}_+$, called an *input*[1], we define $\Psi(t, \phi, u) = x_t$, where $x : [-\tau, \infty) \to \mathbb{R}^3_+$ is the unique absolutely continuous function such that

$$x_{(0)} = \phi \text{ and } \dot{x}(t) = G(x_t, u(t)), \ t \geq 0. \quad (9)$$

In effect, we are thus cutting the feedback loop induced by $T$ upon $R$, and replacing it with an arbitrary input $u(t)$.

Notation: given $x, y \in \mathbb{R}^3$, let $x \leq y$ denote $x_i \leq y_i$, $i = 1, 2, 3$. For $\phi, \psi \in X$, let $\phi \leq \psi$ denote $\phi(s) \leq \psi(s)$, $\forall s \in [-\tau, 0]$.

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[1] We won't require the more general control–theoretic definition where $u$ is measurable and locally bounded, see [1]

**Theorem 1.** *The dynamical system with input $\Psi(t, \phi, u)$ satisfies the following properties:*

1. *If the input $u(t)$ converges to $w \in \mathbb{R}_+$, then $\Psi(t, \phi, u)$ converges as $t$ tends to $\infty$ towards the constant state*
$$k(w) = \left(\frac{w}{b_1}, \frac{g_1 w}{b_2 b_1}, \frac{g_1 g_2 w}{b_1 b_2 b_3}\right),$$
*for any initial state $\phi \in X$.*
2. *Let $u_1, u_2$ be inputs, and pick any two initial states $\phi, \psi \in X$. If $u_1(t) \le u_2(t)\ \forall t$ and $\phi \le \psi$, then $\Psi(t, \phi, u_1) \le \Psi(t, \psi, u_2)\ \forall t$.*

*Proof.* Suppose that $u(t)$ converges towards $w \in \mathbb{R}_+$. Let $\phi \in X$ be arbitrary. The dynamics of the component $R(t)$ of the solution $x(t)$ is determined by the equation $\dot{R}(t) = u(t) - b_1 R(t)$, and so $R(t)$ converges towards $w/b_1$. Applying a very similar argument to $L(t)$ and $T(t)$ in this order, we obtain the first result.

The proof of the second statement follows by the "Kamke condition" (see [15]): if $w_1 \le w_2,\ \phi \le \psi$, and $\phi(0)_i = \psi(0)_i$ (that is, the $i$th components of $\phi$ and $\psi$ are equal), then $G(\phi, w_1)_i \le G(\psi, w_2)_i$. For instance, if $\phi = (R_1, L_1, T_1),\ \psi = (R_2, L_2, T_2)$, $\phi \le \psi$, and $R_1(0) = R_2(0)$, then $w_1 - b_1 R_1(0) \le w_2 - b_1 R_2(0)$. This can be checked for $L$ and $T$ in the same way. The fact that the Kamke condition implies the desired property follows from the results in [15]; however, in the interest of exposition and since the proof is so short, we provide it next.

Let $x(t)$ be the solution of (9) with input $u_1$ and initial condition $\phi$, and let $G_\epsilon = G + (\epsilon, \epsilon, \epsilon)$, for $\epsilon > 0$. Let $y_\epsilon(t)$ be the solution of $\dot{y}(t) = G_\epsilon(y_t, u_2)$ with initial condition $\psi$. Suppose that at some point $t_1, x(t_1) \not\le y_\epsilon(t_1)$, and so there exists a component $i$ (that is, $R$, $L$ or $T$) and $t_0$ such that $x_{t_0} \le y_{\epsilon t_0},\ x(t_0)_i = y_\epsilon(t_0)_i$ and $\dot{x}(t_0)_i \ge \dot{y}_\epsilon(t_0)_i$. But then

$$\dot{x}(t_0)_i = G(x_{t_0}, u_1(t_0))_i \le G(y_{\epsilon t_0}, u_2(t_0))_i < G_\epsilon(y_{\epsilon t_0}, u_2(t_0))_i = \dot{y}_\epsilon(t_0)_i$$

which is a contradiction. We thus conclude that $x(t) \le y_\epsilon(t),\ \forall t \ge 0$. Now, it can be shown ([9, 15]) that as $\epsilon \to 0$ $y_\epsilon(t)$ converges pointwise to $y(t)$, the solution of (9) with input $u_2$ and initial condition $\psi$, and from here the conclusion follows. □

**Definition 1.** *For an arbitrary continuous function $x : [-\tau, \infty) \to \mathbb{R}^3_+$, we say that $z \in \mathbb{R}^3_+$ is a* lower hyperbound of $x(t)$ *if there is $z_1, z_2, \ldots \to z$ and $t_1 < t_2 < t_3 \ldots \to \infty$ such that for all $t \ge t_i,\ z_i \le x(t)$. If for all $t \ge t_i,\ z_i \ge x(t)$, we say that $z$ is an* upper hyperbound of $x(t)$.

For instance, $z$ is a lower hyperbound of the trajectory $x$ if it bounds from below $x(t)$ for every $t$. Similar definitions are given for inputs $u(t)$. The previous Theorem is the basis for the following result.

**Theorem 2.** *Let $v \in \mathbb{R}_+$ be a lower hyperbound of the input $u(t)$, and let $\phi \in X$ be arbitrary. Then $k(v)$ is a lower hyperbound of the solution $x(t)$ of the system (9). If $v$ is, instead, an upper hyperbound of $u(t)$, then $k(v)$ is an upper hyperbound of $x(t)$.*

*Proof.* Suppose that $v$ is a lower hyperbound of $u(t)$, the other case being similar, and let $v_1, v_2, \ldots \to v$ and $t_1 < t_2 < \ldots \to \infty$ be as above.

For every $i \geq 1$, let $V_i \subset \mathbb{R}^3_+$ be a neighborhood of $k(v_i)$ that is open in $\mathbb{R}^3_+$, and let $y_i \in \mathbb{R}^3_+$ be such that $y_i \leq V_i$ componentwise. Without loss of generality we will assume that $|y_i - k(v_i)| \leq 1/i$. Also, let

$$u_i(t) = \begin{cases} u(t), & 0 \leq t < t_n \\ v_n, & t \geq t_n\,. \end{cases}$$

Let $T_1 < T_2 < \ldots \infty$ be defined by induction as follows: $T_1 = 0$, and if $T_{i-1}$ is defined, let $T_i$ be chosen such that $T_i \geq T_{i-1} + 1$, $T_i \geq t_i$, and for all $t \geq T_i$ : $x_i(t) = \Psi(t, \phi, u_i)$ is contained in $V_i$. By the previous theorem, $x_i(t) \leq x(t) \forall t$, and so $y_i \leq x(t)$, $\forall t \geq T_i$. As $y_i \to k(v)$, the conclusion follows. □

The following simple Lemma is standard in the literature on discrete iterations (and is used in a similar context in [3]); we provide a proof for expository purposes.

**Lemma 1.** *Let $S : \mathbb{R}_+ \to \mathbb{R}_+$ be a continuous, nonincreasing function. Then the discrete system $u_{n+1} = S(u_n)$ has a unique, globally attractive equilibrium if and only if the equation $S(S(x)) = x$ has a unique solution.*

*Proof.* If the system has a unique, globally attractive equilibrium $\bar{u}$, then this point is a solution of the equation $S^2(x) = S(S(x)) = x$. Any other point $u$ cannot be a solution of this equation, as $S^n(u)$ must converge to $\bar{u}$. This proves the 'only if' part of the lemma.

Conversely, suppose that the equation $S^2(x) = x$ has a unique solution. Let $u \in \mathbb{R}_+$ be arbitrary, and consider the sequence $u_n = S^n(u)$. If $u \leq u_2$, then since $S^2$ is a nondecreasing function, we have $u_2 \leq u_4$, and so

$$u \leq u_2 \leq u_4 \leq u_6 \leq \ldots\,.$$

But the sequence $u_2, u_4 \ldots$ is bounded (by $S(0)$), and so $u_{2n}$ must converge to some point $v_0$. The same argument applies if $u_2 < u$, and also for the sequence $u_1, u_3, u_5, \ldots$, which must converge to some point $v_1$. But the continuity of $S$ implies that both $v_0$ and $v_1$ are solutions of $S^2(x) = x$, so $v_0 = v_1$ are both equal to our unique solution, and $u^n$ thus converges to this point, independently of the choice of $u$. □

Consider for instance $S(x) = p/(q+x)$, where $p, q$ are positive real numbers. If $x$ satisfies $S^2(x) = x$, then it holds that

$$x = \frac{p}{q + S(x)}$$

which can be rearranged as $x^2 + qx - p = 0$. Using the quadratic formula, it becomes clear that there is always exactly one *positive* solution.

This example will be useful in what follows.

**Theorem 3.** *All solutions of the system (8), with $f = A/(K+x)$, converge towards the unique equilibrium, for any choice of the parameters $b_1, b_2, b_3, g_1, g_2, \tau, A, K$.*

*Proof.* Consider any initial condition $\phi \in X$, and the corresponding solution $x(t) = (R(t), L(t), T(t))$ of (8). Defining the input $u(t) = f(T(t))$, and using it to solve the system (9) with initial condition $\phi$, we arrive of course at exactly the same solution $x(t)$.

Let $v$ bound $u(t)$ from below for all $t$ – for instance, $v = 0$ will do. Then by Theorem 2, $k(v)$ is a lower hyperbound of $x(t)$. In particular,

$$Qv = \frac{g_1 g_2}{b_1 b_2 b_3} v$$

is a lower hyperbound of $T(t)$. But, since $f$ is a nonincreasing function, this implies that $f(Qv)$ is an upper hyperbound of $f(T(t)) = u(t)$. Defining $v_1 = f(Qv)$, we apply the same theorem once again to show that $k(v_1)$ is an upper hyperbound of $x(t)$, $v_2 = f(Qv_1)$ is a lower hyperbound of $u(t)$, etc. But

$$f(Qx) = \frac{A}{K + Qx} = \frac{p}{q + x} = S(x)$$

for $p = A/Q,\ q = K/Q$. Thus we see that $v_n = S^n(v)$ is a convergent sequence of numbers that are alternatingly upper and lower hyperbounds of $u(t)$. This easily implies that $u(t)$ itself converges to the unique solution $\bar{u}$ of the equation $S^2(x) = x$. By Theorem 1, $x(t)$ converges towards $k(\bar{u})$, independently of the choice of the initial condition $\phi$.

Finally, this implies that $k(\bar{u})$ is the unique equilibrium of the system, otherwise one could reach a contradiction by taking this equilibrium as constant initial condition. □

## 4. Discussion

Several remarks are in order: first, the actual value of the delay $\tau$ was never used, and indeed can be arbitrarily large or small. In fact, we can introduce different delays, large or small, in all of the first terms at the right hand sides of (1), and the results will apply with almost no variation. If delays are introduced in the second terms, the system will not be *monotone*, that is, won't satisfy the second property of Theorem 1, which is essential for this argument. But then again, introducing a delay in the degradation terms wouldn't be very biologically meaningful. For more on monotone systems, the reader is referred to the excellent textbook by Hal Smith [15] and [10].

The above argument is an illustration of a more general analysis of a class of delayed dynamical systems with monotone subsystems and negative feedback interconnection. The underlying order may be generalized as $x \leq y$ iff $y - x$ lies in a *cone* $K \subseteq \mathbb{R}^3$ (see [1]). This provides for more generality and applicability in biological problems. The key sufficient condition is that the discrete dynamical system $u_{n+1} = S(u_n)$ be globally attractive; in a sense the dynamics of the continuous system is reduced to that of the discrete one, which may eventually involve state spaces with substantially fewer dimensions. See [1,2] for background material and work to appear by the authors [6] for this more general treatment.

As for the conclusions in pp. 244-253 of *Mathematical Biology*, we may venture to suggest that in eq 7.49, p. 247, the author writes the characteristic equation (5) of the linearized system (4) as

$$\lambda^3 + a\lambda^2 + b\lambda + c + de^{-\lambda\tau} = 0 \tag{10}$$

where $a, b, c, d$ are all written in terms of the original parameters of the system: $a = b_1 + b_2 + b_3$, etc. From here on the efforts are concentrated in finding a root $\lambda$ of this equation with Re $\lambda = 0$, for some well-chosen coefficients $a, b, c, d$. But the author seems to disregard in the remaining argument the fact that $a, b, c, d$ cannot be chosen arbitrarily and independently, *but rather that their values are determined from choosing arbitrarily* $b_1, b_2, b_3, g_1, g_2, \tau$. Thus for instance, it is assumed in the last line of p.251 that $d > c$, without justification from the original variables. It turns out that the former assumption cannot be satisfied for the particular choice of $f$, as seen in the proof of Proposition 1.

We point out that a simple modification can make oscillatory behavior possible. In p. 246 of [12], the author discusses varying cooperativity coefficients of $f(x) = A/(K + x^m)$, then settles for $m = 1$ for the delayed model. If indeed $m$ is increased, then it is very possible to have $d > c$ and the remaining argument in the section will be valid. One example of this is when parameters are picked as follows:

$$m = 2,\ A = 10,\ K = 2,\ b_1 = 1,\ b_2 = 1,\ b_3 = 1,\ g_1 = 10,\ g_2 = 10\,.$$

Another interesting contribution to the modeling of testosterone dynamics is the paper [13] by Ruan et al., where sufficient conditions are found for stable and oscillatory behavior in a neighborhood of an equilibrium. We would like to describe the relationship between [13] and our own result, given the similarity of the hypotheses and the potentially conflicting conclusions: global stability in our results vs. Hopf bifurcations in [13]. Moreover, we will simplify the statement of that result. In that paper, several new quantities are introduced in order to state the main result, Theorem 3.1. In terms of the original variables of the system ($b_1, b_2, b_3$, etc.), these are as follows:

$$\begin{aligned} p &= b_1^2 + b_2^2 + b_3^2 \geq 0 \\ q &= b_1^2 b_2^2 + b_2^2 b_3^2 + b_1^2 b_3^2 \geq 0 \\ \Delta &= p^2 - 3q = \frac{1}{2}((b_1^2 - b_2^2)^2 + (b_2^2 - b_3^2)^2 + (b_1^2 - b_3^2)^2) \geq 0 \\ z_1 &= \frac{1}{3}(-p + \sqrt{\Delta})\,. \end{aligned}$$

Theorem 3.1 holds under the assumption that

$$(b_1 + b_2)(b_1 + b_3)(b_3 + b_2) < d \tag{11}$$

and deals essentially with the following three special cases:

1. $b_1 b_2 b_3 \geq d$ and $\Delta < 0$,
2. $b_1 b_2 b_3 \geq d$ and $z_1 > 0$,
3. $b_1 b_2 b_3 < d$ .

In case 1, (local) asymptotic stability is guaranteed for arbitrary delay lengths (part (i) of the Theorem), while in cases 2 and 3, and under some additional conditions (parts (ii) and (iii) of the Theorem), stability holds for small enough delays, but a Hopf bifurcation occurs at some critical value of this delay length. In light of the above computation, case 1 can never be satisfied (for variables $p$, $q$, $r$ generated from the original set of parameters $b_1$, $b_2$, $b_3$, etc.). Similarly, the condition $z_1 > 0$ will never be satisfied, since

$$z_1 > 0 \Leftrightarrow \Delta > p^2 \Leftrightarrow 3q < 0$$

so case 2 cannot hold either. One is only left with case 3, which is actually a consequence of (11). On the other hand, for the particular choice of $f(x)$ made in [12] and the present paper, Proposition 1 shows that we always have $b_1b_2b_3 > d$. Thus Theorem 3.1 does not apply for the present model, as well as for any choice of the function $f$ and any set of parameters such that $b_1b_2b_3 > d$.

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