Qualitative mathematical models of endocrine systems

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REPRODUCTIVE ENDOCRINE SYSTEM MODELS

In humans and in many other species, the secretion of luteinizing hormone (LH) from the anterior pituitary gland is controlled primarily by LH-releasing hormone (LHRH). LHRH is normally secreted by the hypothalamus and carried to the pituitary in the blood via the hypophyseal portal vessels. LH in turn influences the gonadal secretion of testosterone (T) in males and estradiol (E) in females. These hormones are then thought to have a feedback effect on their precursor hormones, LHRH and T. The male LHRH-LH-T system is considered here. Because of its relative simplicity, study of the male reproductive system constitutes a fruitful avenue of approach, both in its own right and as an aid in ultimately understanding the more complex female system.

Recent reviews of the LHRH-LH-T system include those of Arimura (1) and Brown-Grant (6, 7). Although experimental observations on the system are often difficult to interpret, a recurrent theme is that the observed serum concentrations of both LH and T in intact adult males of many species undergo rapid cyclic fluctuations in time, which vary among individuals and species. This is called the phenomenon of pulsatile or episodic release. Time series of these hormonal concentrations can be roughly interpreted as exhibiting a pattern of either periodic, "noisy" periodic, or "chaotic" behavior.

Another recurrent theme (although by no means universal) is that during the prepubertal period, the observed serum concentrations of LH and T are roughly constant in time. One qualitative observation often associated with puberty is the transition from the prepubertal pattern of constant hormonal concentrations to the adult pattern of episodic release.

Mathematical models of the reproductive endocrine system in the literature include those of Schwartz (18) for the female rat, Bogumil et al. (2, 3) for the female human, Schotkin (16, 17) for the castrated male rat, and Melnyk et al. (12) for the male human. Finally, Smith (19) considered a general dynamical model applicable to a number of different species. The models considered here are essentially extensions of those of Smith.

Among the many possible interactions between the three main hormonal components of the system discussed above, we consider here only one. This is a negative feedback from the gonads to the hypothalamus. Although other interactions are surely present in the actual biological system, we will see that this basic model is a very pregnant one. The particular models are chosen here essentially for illustrative purposes, and no claim is
made that they are biologically precise. The models are capable of giving rise to a multitude of modes of hormonal dynamics, which may be regarded as metaphors for the observed behavior of the system. These modes are independent of the form of input to the hypothalamus, but we also consider, as an elaboration of the basic model, the effects of a periodic stimulus to the hypothalamus.

The basic structural model considered is illustrated in Fig. 1. The hypothalamus secretes LHRH (R) at a rate \( f(T) \) depending on the serum concentration of testosterone (T). The pituitary secretes LH (L) at a rate \( g_1(R) \) depending on the local concentration of R in the hypophyseal portal vessels. The gonads secrete T at a rate \( g_2(L) \) depending on the local gonadal concentration of L. Finally each hormone is removed from the system at a rate \( b_i \) depending on its own concentration.

The mathematical model describing the system depicted in Fig. 1 is the following system of three ordinary differential equations:

\[
\begin{align*}
\dot{R} &= f(T) - b_1(R) \\
\dot{L} &= g_1(R) - b_2(L) \\
\dot{T} &= g_2(L) - b_3(T)
\end{align*}
\]

where the overdot denotes differentiation with respect to time. The basic general properties we assume initially regarding the functions \( f, g_1, g_2, b_1, b_2, \) and \( b_3 \) are that all are nonnegative, sufficiently smooth, and bounded. We also assume that \( f \) is monotone decreasing and all the other functions are monotone increasing; \( f \) thus accounts for some hypothalamic source of LHRH, which is repressed by the presence of \( T \). All the above properties are entirely reasonable from a biological point of view.

Equation 1 is called a feedback repression model, and general models of this type have been considered in other biological settings in the literature (10, 13–15).

We also consider here three of the many possible elaborations of the basic model of Eq. 1. The first elaboration allows \( f \) to be nonmonotonic, with both increasing and decreasing portions. The second allows for the presence of time delays in the system. An example of this, reflecting the fact that LH requires a finite time to travel through the bloodstream to reach its site of action at the gonads, is given by

\[
\begin{align*}
\dot{R} &= f(T) - b_1(R) \\
\dot{L} &= g_1(R) - b_2(L) \\
\dot{T} &= g_2(L) - b_3(T)
\end{align*}
\]

where \( \lambda \) is the time delay.

Finally we consider the effects of a periodic input to the system at the hypothalamic level. Biologically this may represent the effects of the light-dark cycle on the function \( f \) via the retinal connection to the hypothalamus, or it may represent an oscillatory source of LHRH from within, or to, the hypothalamus. A model describing such a system (without time delays) is

\[
\begin{align*}
\dot{R} &= f(T) - b_1(R) + a \sin \omega t \\
\dot{L} &= g_1(R) - b_2(L) \\
\dot{T} &= g_2(L) - b_3(T)
\end{align*}
\]

where \( a \) is some nonzero constant and \( \omega/2\pi \) is the frequency of the driving oscillation. Although Eq. 3 is a nonautonomous system (time appears explicitly on the right-hand side), it may be transformed to an autonomous system of four equations

\[
\begin{align*}
\dot{R} &= f(T) - b_1(R) + a \sin \omega t \\
\dot{L} &= g_1(R) - b_2(L) \\
\dot{T} &= g_2(L) - b_3(T) \\ \omega &= \omega
\end{align*}
\]

**ANALYSIS OF THE MODELS**

The qualitative analysis of the models of the previous section proceeds by determining the so-called \( \alpha \) - and \( \omega \)-limit sets for each system of differential equations. The \( \omega \)-limit sets are, roughly speaking, "target" sets of points
(R, L, T) in concentration space to which solutions of the
equations tend as time increases. (The ω-limit sets have a similar interpretation in negative time.) The ω-
limit sets are the mathematical analogues of the various observed types of possible qualitative hormonal time
behavior.

The ω-limit set may be a single concentration point
(R0, L0, T0) to which all hormonal concentrations tend
in time, regardless of the initial state of the system. (R0,
L0, T0) may then be regarded physiologically as a "ho-
meostatic point." The ω-limit set may be a closed curve
in concentration space, which all hormonal concentra-
tions tend to approach and then traverse in a periodic
manner. This closed curve then may be regarded phys-
ically as a "homeostatic limit cycle." Finally ω-limit
sets may be sets of points whose topological character is
complex (e.g., a Canter set). In this case, the hormonal concentrations may tend to some behavior that
may be described by various terms, which are denoted by
the general term of "chaotic." Hormonal concentration-
vs.-time curves exhibiting this type of behavior are typ-
cically fairly erratic in appearance, even though they arise
from a deterministic model. The detailed mathematical elaboration of the precise meanings and classifications
of the different nuances of this latter type of ω-limit set
are subjects of much current mathematical interest (see,
e.g., Ref. 8).

The basic model of Eq. 1 has been discussed in detail
by Smith (19) in the case of a simple specific realization
of the functions f, g1, g2, b1, b2, and b3. In the general case,
the qualitative mode of behavior of the system is either
either a stable constant solution or a stable periodic solution.
In the former case, the equilibrium point is the ω-limit
set of all concentration points. In the latter case, the periodic solution is the ω-limit set of all concentration
points except the single unstable equilibrium solution.
The mode of behavior exhibited by the system depends on the
quantity
\[ K = -g_1(R_0)g_2(L_0)f'(T_0)/[b_1(R_0)b_2(L_0)b_3(T_0)] - a_1a_2/a_3 + 1 \]  
(5)
where (R0, L0, T0) is the (unique) equilibrium solution of
Eq. 1 obtained by setting to zero the right-hand side.
Thus the equilibrium solution satisfies
\[ f(T_0) - b_1(R_0) = 0 \]
(6)
\[ g_1(R_0) - b_2(L_0) = 0 \]
\[ g_2(L_0) - b_3(T_0) = 0 \]
The a; in Eq. 5 are given by
\[ a_1 = b_1'(R_0) + b_2'(L_0) + b_3'(T_0) \]
\[ a_2 = b_1'(R_0)b_2'(L_0) + b_1'(R_0)b_3'(T_0) + b_2'(L_0)b_3'(T_0) \]
\[ a_3 = b_1'(R_0)b_2'(L_0)b_3'(T_0) \]
(7)
It is important in the analysis to note that the quantities
a1 always satisfy the relation
\[ a_1a_2/a_3 > 9 \]  
(8)
infusion terms are present in the model. The net effect is that if $W_R$, $W_L$, and $W_T$ are collectively large enough to force $(R_0, L_0, T_0)$ into a region of concentration space that makes $K$ negative (when it was formerly positive), then the episodic secretion pattern will change to a constant pattern. If the infusion rates are not large enough to make $K$ negative, then the episodic pattern will persist (its detailed behavior will be altered, however). Such effects have been observed experimentally (4, 5).

Although the basic model is useful, it omits many known features of the system and also exhibits only two modes of behavior. The three elaborations discussed in the previous section lead to other possible modes, and these are now briefly discussed. The detailed analysis of these models is currently under way, in collaboration with R. Abraham of Santa Cruz, J. Murray of Oxford, and L. Sauve of Royal Military College, Kingston. Although this analysis is not yet complete, we present some conjectures concerning the results and their relevance to the biological system (see also Ref. 8).

When $f$ is not monotonic, then the system can have more than one equilibrium point that solves Eq. 6. The equilibria are determined in general by the nonlinear equation

$$f(T) = g_1^{-1} \circ b_2 \circ g_2^{-1} \circ b_3(T) = h(T)$$

where $\circ$ denotes the composition of functions. An example of the possible behavior of solutions of Eq. 9 is illustrated in Fig. 3. The intersections of $f$ and $h$ yield $T_0$, and ultimately $R_0$ and $L_0$ from Eq. 6. When $f$ is nonmonotonic, as illustrated in Fig. 3, there are normally one or three possibilities for $T_0$. In the case of multiple equilibria, Eq. 1 may have more complex types of $\omega$-limit sets than is the case when $f$ is monotonic and only a single value of $T_0$ is possible. Possibilities include different modes of periodic and also chaotic behavior.

In the second elaboration (Eq. 2), the stability of the equilibrium solution depends on the magnitude of $\lambda$. If when $\lambda = 0$ the system parameters are such that $(R_0, L_0, T_0)$ is stable, then as $\lambda$ is increased instability may occur at sufficiently large $\lambda$. This may be expected to be manifested initially in a periodic mode of system behavior. As $\lambda$ is further increased, successive bifurcations to more complicated types of periodic behavior may occur, perhaps culminating in a chaotic mode (see, e.g., Ref. 11). New branches of solutions may also occur as $\lambda$ is increased. If, for $\lambda = 0$, $(R_0, L_0, T_0)$ is unstable, then the possibilities are increased for complicated behavioral modes.

Finally, in the third elaboration (Eqs. 3 or 4), we may expect analogues of the phenomena of resonance and entrainment commonly observed for linear differential systems. In the case when $(R_0, L_0, T_0)$ is unstable with $\lambda = 0$, we also expect chaotic behavior resulting from the interaction of the periodic driving force with the intrinsically oscillating unforced system.

**DISCUSSION**

An important use of the models discussed here is as a guide for devising experiments that can differentiate between them. An important general point to stress here is that experiments of this type should be conducted on single animals wherever possible; pooled results obtained from several animals should not be used, because individual animals may be expected to have slightly different parameter values and hence exhibit quantitatively different hormonal dynamics. For example, two animals may both exhibit episodic secretion patterns, but they may be out of phase. The same experimental intervention administered at the same (absolute) time may produce quite different results in the two cases.

The models and methods of analysis discussed in this paper may assist in suggesting possible mechanisms for the observed hormonal dynamics of the reproductive, as well as of other, endocrine systems. Application of such an approach to the thyroid-pituitary system discussed at this conference might lead to useful insights.

Perhaps the most significant point concerning the models considered here is that complex hormonal dynamics may be a result of the internal system interactions alone (an emergent property of the system) and that no external driving force (a "deus ex machina") need be invoked to explain the observed dynamics. This is not to claim that the reproductive endocrine system is best modeled by one of the simple autonomous models considered here. For example, other feedback loops may also be required in any correct model. In addition, the most important model considered here may be that of Eq. 3 supplemented by a more accurate description of the hypothalamic driving term. However, the main point is that such nonautonomous models are not the only possibilities. A related point is that the analysis of alternative models is best carried out by general qualitative methods similar to those discussed in this paper, whether or not the basic model is autonomous.

A final point to emphasize is that the richness of behavior of the models discussed in this paper results from their intrinsic nonlinearity. Linear models are of very limited use in understanding such systems. For example, linear dynamical systems can exhibit no long-term periodic or chaotic behavior, unless driven by an external force with such behavior (the deus ex machina again). This conference is thus especially timely if it serves to arouse interest in the importance of nonlinear phenomena in biological systems.
REFERENCES


