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MATHEMATICAL MODELS OF ENDOCRINE SYSTEMS

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There is proposed a generalized mathematical model of endocrine systems, consisting of a set of differential equations which describe a chain of chemical reactions. The product of each reaction stimulates or inhibits some other reaction in the chain except possibly the last, which may or may not influence the system. At least one reaction must be independent and able to proceed without stimulation or inhibition by the products of other reactions.

If only two reactions of the type assumed constitute a closed chain, sustained periodic variations in the concentrations of the reaction products cannot occur. If the chain consists of three or more reactions forming a closed loop, sustained oscillations, such as are observed in the menstrual cycle or in the mental disorder called periodic catatonia, can occur under suitable conditions. In this case, the concentrations of the system components exhibit relaxation oscillations characterized by periodic degeneration of the system when an independent reaction becomes completely inhibited by other reaction products. A set of conditions sufficient to produce periodicities in component concentrations is presented.

Application of the model to the normally periodic system of the menstrual cycle and to the abnormal endocrine system which causes periodic catatonia is discussed.

The endocrine system is often considered to be a mechanism which maintains the concentrations of certain materials within narrow limits. Under certain conditions, the limits are so narrow that the concentrations are practically constant; under other conditions, which may be normal, periodic variations of the concentrations are known to occur.

The maintenance of the concentrations within limits is achieved by action of system components (hormones and activated enzymes) each of which stimulates or inhibits the production of other components. If these reactions constitute a feed-back mechanism, they are arranged in a closed chain, in which each component stimulates or inhibits the production of the next component, and possibly others in the chain. While at least one component must be produced independently of stimulation by another component, inhibition of production of this independent component by another is required if the loop is to be closed.

In such systems, a qualitative description is inadequate to predict performance, and quantitative representation of internal relations must be used in an analysis of the kinetics of the system. Quantitative descriptions of endocrine systems in the form of mathematical models have been proposed previously. The menstrual mechanism, a normally periodic system, has been investigated mathematically by Rapoport (1952); the thyroid-pituitary system, which may exhibit periodicities when not functioning properly, has been treated mathematically by Danziger and Elmergreen (1954, 1956). In the present paper, there is proposed a generalized mathematical model and there is formulated a set of conditions sufficient to yield periodicities in the component concentrations.

Consider a system of n components whose concentrations in the body are functions of time and are denoted by $x_1, x_2, \ldots, x_n$. The kinetics of the system may be described approximately by the set of first-order differential equations

$$dx_i/dt + \lambda_i x_i = Q_i, \qquad (i = 1, 2, 3, \ldots, n) \tag{1}$$

wherein λ_i is the loss rate per unit concentration of the component x_i, and Q_i is the production (activation) rate of the hormone (enzyme) x_i. The production (activation) rate is, in the first approximation, a linear function of the system components and may be represented by

$$Q_i = A_{i0} + \sum_{j=1}^{n} A_{ij} x_j, \tag{2}$$

wherein A_{i0} is zero or a positive constant denoting independent production (activation) of x_i; the A_{ij} are sensitivity constants and may be zero for no effect, positive for production stimulation (activation), or negative for production inhibition (deactivation). The constant A_{ii} is considered to be zero in all cases as auto-stimulation or inhibition is not likely.

The function Q_i as given by (2) may take on negative values for some positive sets of values of the x_j. If x_i is a hormone, a negative production rate is not possible and the restriction $Q_i \geq 0$ must be imposed; from (1) this also limits x_i to non-negative values. If x_i is an enzyme, a negative Q_i represents deactivation and is permissible; in this case the restriction is simply $x_i \geq 0$ as negative concentrations of activated enzymes are not physically possible.

With these restrictions, the mathematical model may be formulated completely as

$$dx_i/dt + \lambda_i x_i = A_{i0} + \sum_{j=1}^{n} A_{ij} x_j = Q_i$$

$$x_i \geq 0, \quad Q_i \geq 0 \text{ if } x_i \text{ is a hormone} \tag{3}$$

$$i = 1, 2, 3, \ldots, n.$$

Rapoport (*loc. cit.*) includes, in his model, the possibility of negative production rates of system hormones by assuming that one hormone can enhance the dissipation or breakdown of another hormone in the blood stream. This assumption leads to linear equations but, as Rapoport points out, is not in accord with observation. The model (3) represents inhibition action wherein components act inhibitively on the cells which produce hormones; this assumption precludes hormone production at negative rates. Accordingly, the model presented here will be characterized by the degeneration of one or more hormone equations when the associated Q_i are driven to zero. Degeneration of one equation, in effect, isolates the mechanism which produces the hormone from the influence of the rest of the system. In the interval during which (2) yields a negative value, the degenerate equation is a first-order, homogeneous, linear differential equation whose solution is an exponential decay of x_i with a decrement λ_i.

The degeneration of the mathematical model produces a system which is not linear in the unrestricted sense. Instead it is piecewise linear comprising a set of linear equations which may possibly be unstable in the normal state and a different and stable set of linear equations in the degenerate state.

The concept of a "push-pull" endocrine system has been applied to the mechanism of the pituitary and thyroid glands in the regulation of the metabolic rate and to the pituitary and ovary in the control of the menstrual cycle. The term "push-pull" indicates stimulation or push by the first gland in the closed loop of production by the second, and inhibition or pull by the second gland of production by the first. Clearly, the "push-pull" system exhibits the phenomenon of feedback. The simplest "push-pull" system can be represented in the form (3) by the following second-order set in which the a_{ij} are positive constants:

$$\begin{aligned} dx_1/dt + \lambda_1 x_1 &= a_{10} - a_{12}x_2 = Q_1, \qquad Q_1 \geq 0 \\ dx_2/dt + \lambda_2 x_2 &= a_{21}x_1 . \end{aligned} \tag{4}$$

The set (4) reflects the following assumptions:

(1) only x_1 is produced independently.
(2) x_1 is a hormone and cannot be produced at a negative rate. The system is degenerate for $x_2 > a_{10}/a_{12}$.
(3) x_1 stimulates the production of the hormone x_2.
(4) x_2 inhibits the production of x_1.
(5) the components dissipate in proportion to their respective concentrations.

As the system (4) exhibits a degeneration point at $x_2 = a_{10}/a_{12}$, different solutions exist for the normal system with $x_2 < a_{10}/a_{12}$ and for the degenerate system with $x_2 > a_{10}/a_{12}$. These two solutions can be obtained by standard methods and pieced together at the degeneration point, $x_2 = a_{10}/a_{12}$. Each solution has the form

$$x_i = b_i + \sum_{j=1}^{2} c_{ij} \exp(r_j t), \qquad (i = 1, 2) \tag{5}$$

where the b_i are the steady states, the c_{ij} are integration constants, and the r_j are the roots of the characteristic equation [multiple roots being excepted if the form (5) applies].

The possibility of sustained oscillations of the component concentrations in a "push-pull" system can be investigated by examining solutions of typical systems. The second-order system (4) for the normal condition, $x_2 < a_{10}/a_{12}$, has steady states which are

$$\begin{aligned} b_1 &= a_{10}\lambda_2/(\lambda_1\lambda_2 + a_{12}a_{21}), \\ b_2 &= a_{10}a_{21}/(\lambda_1\lambda_2 + a_{12}a_{21}), \end{aligned} \tag{6}$$

while the r_j are the roots of the characteristic equation

$$\begin{vmatrix} (D + \lambda_1) & a_{12} \\ -a_{21} & (D + \lambda_2) \end{vmatrix} = 0 \tag{7}$$

For the degenerate condition, $x_2 > a_{10}/a_{12}$, the system differs only in that $Q_1 = 0$. Equivalently, set $a_{10} = a_{12} = 0$ in (6) and (7) yielding, respectively, $b_1 = b_2 = 0$ and $r_1 = -\lambda_1$, $r_2 = -\lambda_2$. In the normal state, the roots of (7) have negative real parts for all positive values of the coefficients, and solutions for $x_2 < a_{10}/a_{12}$ must either be aperiodic or be a damped periodic variation about the steady states of (6). The steady-state concentration, b_2, from (6) is less than the value of x_2 at which degeneration occurs; the steady states for the normal condition are, therefore, stable equilibrium points. The degenerate state, $x_2 > a_{10}/a_{12}$, would obtain only during an initial transient and then only if an initial condition $x_2(t = 0) > a_{10}/a_{12}$ exists. The degenerate state, characterized by zero steady states and negative, real r_j, would exist only until x_2 fell below the degeneration point after which the normal state would exist for all time. Clearly, the second-order system (4) could not exhibit sustained oscillations of the component concentrations.

If, in the system (4), the normal state had been unstable so that the component concentrations would tend to increase without limit, the system would degenerate regardless of initial conditions. Relaxation oscillations would then exist as the system would alternate between the unstable normal state and the stable degenerate state. Although this is not possible in the system (4), a physically realizable set of conditions which would produce sustained oscillations in a similar manner is proposed for "push-pull" systems of order greater than two. These conditions are:

I. at least one of the r_j for the normal system has a positive real part;

II. all the r_j for the degenerate system have negative real parts;

III. the steady-state concentrations for the degenerate system are less than the concentrations at which degeneration occurs.

If these conditions obtain in a "push-pull" system, relaxation oscillations will occur with the following sequence:

(A) with the system in the normal state, the roots, r_j, which have positive real parts would cause the system to be unstable, and all concentrations would ultimately rise. This unstable state would persist until the system degenerates.

(B) when degeneration occurs, the system enters a stable mode of variation for which all the r_j have negative real parts and would tend toward steady states which are lower than the concentrations at which degeneration occurs. The concentrations in this stable mode would ultimately fall until the unstable normal state would again apply.

The processes A and B would repeat cyclically, and the system would be governed alternately by the unstable and stable solutions of the normal and degenerate state equations. The resulting oscillations would be established for any set of initial conditions.

As was shown, the second-order system (4) cannot meet condition I; further no second-order system of the form (3) can meet the requirement of an unstable normal state as the r_j must have negative real parts if the loss constants, λ_i, are positive.

We will examine next the simplest third-order "push-pull" system which has the form

$$\begin{aligned} dx_1/dt + \lambda_1 x_1 &= a_{10} - a_{13}x_3 = Q_1, \qquad Q_1 \geq 0 \\ dx_2/dt + \lambda_2 x_2 &= a_{21}x_1, \\ dx_3/dt + \lambda_3 x_3 &= a_{32}x_2. \end{aligned} \tag{8}$$

If the a_{ij} are positive constants, the set (8) reflects the following assumptions:

(1) only x_1 is produced independently.
(2) x_1 is a hormone and cannot be produced at a negative rate. The system is degenerate for $x_3 > a_{10}/a_{13}$.
(3) x_1 stimulates the production of x_2.
(4) x_2 stimulates the production of x_3.
(5) x_3 inhibits the production of x_1.
(6) the components dissipate in proportion to their respective concentrations.

For the set (8), the normal system, with $x_3 < a_{10}/a_{13}$, has the characteristic equation:

$$\begin{vmatrix} (D+\lambda_1) & 0 & a_{13} \\ -a_{21} & (D+\lambda_2) & 0 \\ 0 & -a_{32} & (D+\lambda_3) \end{vmatrix} = 0. \tag{9}$$

The first of the proposed conditions for sustained oscillations requires that (9) have at least one root with a positive real part. If (9) is expanded as

$$A_0 D^3 + A_1 D^2 + A_2 D + A_3 = 0, \tag{10}$$

the stability criterion of Routh, see Evans (1954), applies and shows that condition I is satisfied if the physically realizable inequality

$$A_0 A_3 > A_1 A_2 \tag{11}$$

obtains. The second and third conditions apply to the degenerate state which differs from the normal state only in that $Q_1 = 0$. Equivalently, set $a_{10} = a_{13} = 0$ in (8) and (9) yielding $r_1 = -\lambda_1$, $r_2 = -\lambda_2$, $r_3 = -\lambda_3$. As the r_j for the degenerate state are all negative and real, condition II is satisfied for all positive values of the loss constants. Condition III is also satisfied for all positive values of the coefficients as with $Q_1 = 0$, x_1 decays exponentially toward a zero steady state, and x_2 and x_3 follow. If the inequality (11) is satisfied, the system (8) will meet all three of the proposed conditions and relaxation oscillations will occur.

Illustratively, consider the hypothetical but possible third-order system:

$$\begin{aligned} dx_1/dt + x_1 &= 1 - 9x_3 = Q_1, \qquad Q_1 \geq 0 \\ dx_2/dt + 0.5x_2 &= x_1, \\ dx_3/dt + 1.5x_3 &= 7x_2. \end{aligned} \tag{12}$$

If the determinant (9) is expanded with the coefficients of (12), the characteristic equation

$$D^3 + 3D^2 + 2.75D + 63.75 = 0 \tag{13}$$

is obtained. Applying the inequality (11) to the coefficients of (13) yields $63.75 > 8.25$, and condition I is satisfied by the system (12). The existence of a root with a positive real part may be verified by factoring (13) as

$$(D + 5)[(D - 1)^2 + 11.75] = 0. \tag{14}$$

The r_j from (14) are -5 and $(1 \pm i3.43)$, and the x_3 solution for the normal state may be written in the form of (5) as

$$x_3 = 0.1098 + c_{31}\epsilon^{-5t} + \epsilon^t\left[c_{32}\epsilon^{i3.43t} + c_{33}\epsilon^{-i3.43t}\right], \tag{15}$$

where $x_3 < 1/9$.

For the degenerate state we have

$$x_3 = c'_{31}\epsilon^{-t} + c'_{32}\epsilon^{-0.5t} + c'_{33}\epsilon^{-1.5t}, \qquad x_3 > 1/9. \tag{16}$$

The solutions (15) and (16) would apply alternately. With $x_3 < 1/9$, the pair of complex roots of (14) yield a periodic term with exponentially increasing amplitude and x_3, from (15), would ultimately reach the concentration of 1/9 unit. At this point, dx_3/dt is positive and x_3 would continue to rise to a maximum value which is greater than 1/9. During the time that $x_3 > 1/9$, (16) applies and x_3 would ultimately fall toward the zero steady state until the transition point, $x_3 = 1/9$, is reached. At this point, dx_3/dt is negative and x_3 would continue to fall to a minimum value which is less than 1/9. During the time that $x_3 < 1/9$, (15) again applies and the cycle repeats. A particular solution for the sustained oscillation would require that the integration constants in (15) and (16) be evaluated at the transition point, $x_3 = 1/9$.

The third-order system (8) has been employed by Danziger and Elmergreen (*loc. cit.*) to describe the thyroid-pituitary system wherein x_1 is the concentration of pituitary hormone, thyrotropin; x_2 is the concentration of an activated enzyme within the thyroid gland; and x_3 is the concentration of thyroid hormone. The periodic variation of metabolic rate observed in periodic catatonia, a mental disorder, was explained by the relaxation oscillation theory presented here. Verification of the form of the solution was obtained using analog computer methods wherein adjustment of system parameters to obtain periodicities was possible; the requirement imposed by condition I and the inequality (II) was confirmed.

Rapoport (*loc. cit.*) gives two models for the pituitary-ovary system which controls the menstrual cycle. If negative hormone production rates are not permitted, the following fourth-order set will include both of these models:

$$
\begin{aligned}
dx_1/dt + \lambda_1 x_1 &= a_{10} - a_{12}x_2 - a_{14}x_4 = Q_1 , \qquad Q_1 \geq 0 \\
dx_2/dt + \lambda_2 x_2 &= a_{21}x_1 , \\
dx_3/dt + \lambda_3 x_3 &= a_{32}x_2 , \\
dx_4/dt + \lambda_4 x_4 &= a_{43}x_3 .
\end{aligned}
\qquad (17)
$$

If the a_{ij} are positive constants, the set (17) reflects the following assumptions:

(1) only x_1 (the pituitary hormone, prolan A) is produced independently.

(2) x_1 cannot be produced at a negative rate. The system is degenerate for $a_{12}x_2 + a_{14}x_4 > a_{10}$.

(3) x_1 stimulates the production of x_2 (the estrogenic hormone of the ovary).

(4) x_2 stimulates the production of x_3 (the pituitary hormone, prolan B).

(5) x_3 stimulates the production of x_4 (the luteal hormone of the ovary).

(6) both x_2 and x_4 inhibit the production of x_1.

(7) the components dissipate in proportion to their respective concentrations.

For the set (17), the normal system, with $a_{12}x_2 + a_{14}x_4 < a_{10}$, has the characteristic equation

$$\begin{vmatrix} (D+\lambda_1) & a_{12} & 0 & a_{14} \\ -a_{21} & (D+\lambda_2) & 0 & 0 \\ 0 & -a_{32} & (D+\lambda_3) & 0 \\ 0 & 0 & -a_{43} & (D+\lambda_4) \end{vmatrix} = 0. \qquad (18)$$

If (18) is expanded as

$$A_0 D^4 + A_1 D^3 + A_2 D^2 + A_3 D + A_4 = 0\,, \qquad (19)$$

Routh's criterion (*loc. cit.*) yields the physically realizable inequality

$$A_1^2 A_4 + A_0 A_3^2 > A_1 A_2 A_3\,. \qquad (20)$$

Condition I is satisfied in this fourth-order system if (20) obtains; conditions II and III are satisfied for any set of positive coefficient values by the same arguments that applied to the set (8). In addition to being of higher order, the set (17) differs from (8) in that degeneration occurs along the line $a_{12}x_2 + a_{14}x_4 = a_{10}$ instead of at a point. This occurs because (17) represents a feed-back system with two loops instead of one as in (8). Application of Routh's criterion to (17) yields two conditions for instability for the normal system: however, only the condition of (20) is physically realizable with positive a_{ij}.

We believe the system (17) is a good mathematical approximation for the control system of the menstrual cycle. Verification would require the determination, by experiment, of the system coefficients. A solution of (17) with numerical coefficients would then yield the time variation of component concentrations and the period of oscillation.

General Remarks

The mathematical model (3) is an improvement on the model of Rapoport (*loc. cit.*) in that it describes the steady-state behavior of endocrine systems exhibiting periodicities in component concentrations. The essential difference between this and earlier models is the exclusion of negative hormone production rates and negative component concentrations. Degenerate equations result producing a limiting action which ensures conditional stability so that component concentrations are bounded even if the system is unstable in the normal state. Although the model becomes nonlinear if the system degenerates, the equations yield to simple analysis from which an existence criterion for periodicities is established. If time solutions are required for periodic systems for which numerical values of coefficients are known, analytical methods will yield only approximations. The use of differential analyzers, analog computers, or other machine methods of solution would be desirable.

Work in progress suggests that the model (3) will also describe, to a first approximation, the mechanism which regulates the blood sugar concentration and the mechanism of the pituitary-adrenal system.

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