A SIMPLIFIED MATHEMATICAL MODEL AND SIMULATIONS OF THE HYPOPHYSIS-OVARIAN ENDOCRINE CONTROL SYSTEM

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ABSTRACT The dynamic relationship between the follicle stimulating hormone of the hypophysis and the estrogenic hormone of the ovaries is investigated. A mather matical model for this system is proposed, which unlike previous models, includet the growing follicle as an explicit part of the model. The size of this estrogen-producing follicle is postulated as a determining factor in the periodicity of the system. Simulation of this simplified piece-wise linear model yields solutions which are persistent and periodic. In addition, the results are in good agreement with known physiological data. The results also suggest that the modeling approach is extremely useful in understanding the changes in the system's behavior caused by alterations in its parameters, whether produced by disease or therapeutic measures.

INTRODUCTION

In one of the earliest attempts to describe mathematically the periodic fluctuations of the estrogenic hormone in the female, Lamport (8) in 1940 proposed a system of two first-order differential equations to represent the interaction of the anterior lobe of the hypophysis and the ovary. He thus represented, in mathematical form, the so-called push-pull theory which held that estrogen secreted by the ovary and a circulating "effective" gonadotrophic hormone secreted by the hypophysis were related in a negative feedback fashion. Estrogen production was assumed to be stimulated by the gonadotrophic hormone, but estrogen in turn decreased the secretion of that hormone. The solutions to these differential equations did not describe the persistent periodic variations in estrogen level then known to exist, and thus that investigation did not lead to a satisfactory representation.

In 1952, Rapoport (14) examined the conditions under which a linear system possessed periodic solutions with positive steady states such as exist in hormonal systems. He then showed why Lamport's model had failed. Rapoport also considered

certain three and four variable models proposed in 1948 by R. Kesselman (unpublished). These models were also shown to be inadequate.

Subsequently, Danziger and Elmergreen (3) in 1957 proposed a generalized mathematical model for all endocrine systems. In their paper they discussed the conditions necessary to produce oscillations in various orders of their model. They used a third-order model to describe an abnormality of the thyroid-pituitary system—periodic catatonia. They proposed a fourth-order model for the control system of the menstrual cycle—the hypophysis-ovarian system. However, they did not verify by either analytical or computer solution that the postulated model was, in fact, a good approximation.

As this work was being done, it became evident to the authors that the ultimate model of this system would probably be a mathematical model of the actual biosynthetic steps involved. The oscillating metabolic systems investigated by Chance (1), Chance et al. (2), and MacNichol (10) are some of the biochemical systems which have been modeled at this molecular level. These studies have also involved both analog and digital computer simulations. Such studies will have additional value as the mechanisms of control in the hypophysis-ovarian system are ultimately traced to the molecular level.

Recently, a number of excellent articles have reviewed the individual roles of the hypophysis and of the ovary, and in particular, their interactions in the processes of reproduction (5, 6, 11, 13, 16).

A more complete analysis of the hypophysis-ovarian endocrine control system indicates that the menstrual cycle appears to involve the dynamic interplay of five hormones: the follicle-stimulating hormone (FSH), the luteinizing hormone (LH), the luteotrophic hormone (LTH), estrogen (EH), and progesterone (PROG). The dynamics also involve the changing size of the follicle itself and its transformation into the corpus luteum. The purpose of this paper is to investigate the inter-relationships between these variables through the development of a mathematical model describing these relationships. Such a quantitative representation may lead to a better understanding of this complex endocrine control system.

METHOD OF ANALYSIS

The first objective in this investigation has been to develop a simple model, closely related to that of Lamport, but extensive enough to produce periodic undamped variations in estrogen level. The model is shown in Fig. 1. In this model the follicle-stimulating hormone, FSH, is assumed to be produced by the hypophysis and released into the circulatory system which carries it throughout the body. When FSH reaches the ovary, it increases this gland's production of estrogen (EH). The EH is similarly secreted into the circulatory system and some of it returns to the hypophysis where it reduces the secretion rate of FSH. This system is therefore a negative feedback, closed loop system. The relation of estrogen to the follicle stimulating hormone is similar to Lamport's earlier push-pull relationship between estrogen and the circulating "effective" gonadotrophic hormone. However, in the model of Fig. 1, another important physiological fact has been represented. The size and growth rate of the

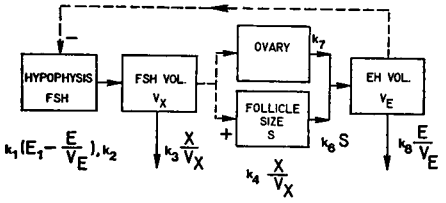

FIGURE 1 Model of the FSH-EH control system which includes the effect of follicle size.

ovarian follicle which produces estrogen varies considerably over the menstrual cycle. In this model, the estrogen secretion rate is not assumed to be simply proportional to the concentration of the gonadotrophic hormone, as in Lamport's representation; rather, as the follicle grows under the influence of FSH, the estrogen secretion rate is assumed to be proportional to the size of this follicle. Then, at some time during its growth phase, the follicle ovulates and the luteal phase begins. The size of the follicle producing the estrogen is, therefore, postulated as a determining factor in the periodicity of this system. The secretion of FSH by the hypophysis is then assumed to be inhibited by the estrogen in the blood.

The differential equations corresponding to this model are obtained following a procedure similar to that of Roston (15). The following assumptions have been made:

1. Assume that V_X, the physiological volume containing the FSH, remains essentially constant and is positive.

2. Assume that V_E, the physiological volume containing the EH, remains essentially constant and is positive.

3. Denote the total amount of FSH by $X(t)$ and the total amount of EH by $E(t)$; assume each is positive at all times and that each hormone is uniformly distributed throughout its volume.

4. Denote the size of the growing follicle by $S(t)$ and assume that it is always positive.

FSH Subsystem

5. Assume that the rate of secretion of FSH by the hypophysis is proportional to the difference between the concentration of EH in volume V_E and some physiological standard concentration E_1 and that an increase in EH concentration reduces the rate of FSH production (i.e., inhibitory effect).
Thus

$$r_1 = k_1(E_1 - E/V_E). \tag{1}$$

6. Assume that there is some stray secretion of FSH at a rate k_2 even when $E/V_E = E_1$.
Thus

$$r_2 = k_2. \tag{2}$$

7. Assume that the FSH in volume V_X is removed at a rate proportional to the concentration of FSH in V_X.
Thus

$$r_3 = k_3X/V_X. \tag{3}$$

S or Follicle Size Subsystem

8. Assume that there is a single growing follicle and that the growth rate of this follicle is proportional to the FSH concentration in volume V_X.
Thus

$$r_4 = k_4 X/V_X . \tag{4}$$

9. Assume that when the follicle reaches a certain size, $S = S_{max}$, that ovulation occurs, the size of the active follicle is reduced to zero, and that growth of a new follicle begins. In formal mathematical terms this means that the growth equation for S contains a term

$$r_5 = S\delta(S - S_{max}) \tag{5}$$

where $\delta(x)$ is the Dirac delta or impulse function. However for the present purposes, setting the follicle size S to zero everytime its size exceeds S_{max} is sufficient. Therefore, let

$$r_5 = k_5 = 0$$

for the present time.

EH Subsystem

10. Assume that the secretion of EH by the growing follicle is proportional to the size of that follicle.
Thus

$$r_6 = k_6 S. \tag{6}$$

11. Assume that the ovary and the other follicles can secrete EH at a rate k_7.
Thus

$$r_7 = k_7 . \tag{7}$$

12. Assume that the EH in volume V_E is removed at a rate proportional to the concentration of EH in volume V_E.
Thus

$$r_8 = k_8 E/V_E . \tag{8}$$

13. As the last assumption, let all the coefficients be positive.

The complete block diagram of this system is given in Fig. 2. This diagram and the previous assumptions, together with the concept of conservation of mass applied to the volumes containing FSH and EH, are the basis for the equations below:

$$dX/dt = k_1(E_1 - E/V_E) + k_2 - k_3 X/V_X \tag{9}$$

$$dS/dt = k_4 X/V_X \qquad S = 0 \quad \text{when} \quad S \geqq S_{max} \tag{10}$$

$$dE/dt = k_6 S + k_7 - k_8 E/V_E . \tag{11}$$

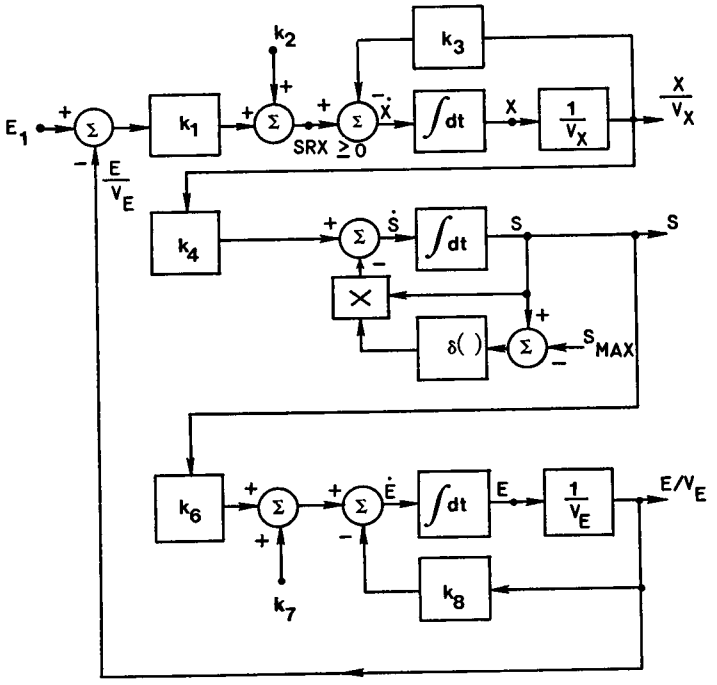

FIGURE 2 Block diagram of the FSH-EH-*S* control system.

These three equations are also subject to the restriction that the FSH secretion rate must be positive.
Therefore

$$(r_1 + r_2) \geqq 0 \tag{12}$$

must be true, or it will be necessary to set

$$r_1 + r_2 = 0. \tag{13}$$

A graphical representation of the nonlinear nature of the secretion rates and of the follicular growth rate is given in Figs. 3, 4, and 5. In these three figures, the linearized rates of the model are given together with a continuous smooth curve which represents the probable rate function. The shapes postulated in Fig. 3 seem plausible for the following reasons.

1. Even though the body's processes are in many instances highly nonlinear, one would not expect these functions to be piece-wise linear. Therefore, one might reasonably assume that the actual secretion rate function is a continuous smooth function.

2. It is highly improbable that the pituitary gland can continue to produce FSH at an increasing rate under the effect of decreasing EH concentration toward zero. Therefore, there must be some maximum production rate of FSH which cannot be exceeded no matter how small the EH concentration is.

3. Also, it is conceivable that not all of the FSH secretion rate is controlled by the EH

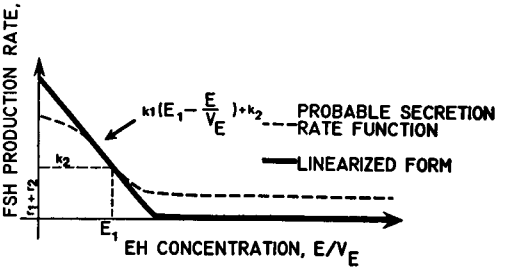

FIGURE 3 Hypophysis production rate of FSH vs. EH concentration in volume V_E.

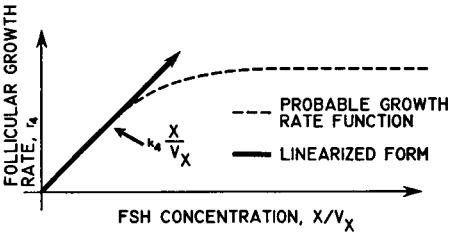

FIGURE 4 Follicular growth rate vs. FSH concentration in volume V_X.

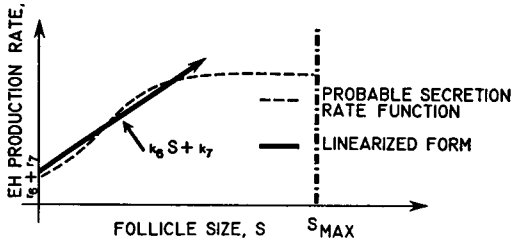

FIGURE 5 Ovarian production rate of EH vs. follicle size S.

concentration in volume V_E. Therefore, it is possible that increasing the EH concentration without limit will only serve to decrease FSH secretion to some minimum value.

These three characteristics—a smooth curve, a maximum production rate, and a minimum production rate—can be applied to any gland whose hormone production rate is controlled by hormonal or neural factors. In this paper, however, the secretion rate is represented by a linearized form. When this is done, it must be remembered that these forms are only approximations and that the actual secretion rates must be used to achieve more accurate results.

Digital Computer Simulation

The differential equations of the model can be solved by a numerical technique. This numerical solution is preferred rather than the more complex mathematical analysis.

Unlike a mathematical analysis which can be carried out for all possible values of the coefficients, a computer solution is good only for the actual numerical values assigned to the

TABLE I

THE VARIABLES, COEFFICIENTS, AND THEIR UNITS

Symbol	Description	Units
E	Blood estrogen level	IU
X	Blood FSH level	IU
V_E	Physiological volume of EH	liters
V_X	Physiological volume of FSH	liters
S	Volume size of follicle	cc
t	Time	days
E_1	A standard concentration of EH	IU/liter
k_1	Coefficient of FSH production	liters/day
k_2	Stray secretion rate of FSH	IU/day
k_3	Coefficient of disappearance of FSH	liters/day
k_4	Coefficient of follicular growth	cc-liter/IU-day
k_6	Coefficient of EH production by follicle	IU/cc-day
k_7	Stray secretion rate of EH	IU/day
k_8	Coefficient of disappearance of EH	liters/day

coefficients. In order to perform the numerical solution with a digital computer, it is therefore necessary that all coefficients and variables of the model be assigned definite dimensional units and numerical values.

The units for the coefficients and the variables, as given in Table I, are obtained by using international units (IU)[1] for the total amounts of FSH and EH in the body, liters for the volumes V_X and V_E, cubic centimeters (cc) for the volume size of the follicle, and days for the unit of time.

Numerical values for the coefficients and variables were assigned in the following manner:

1. Lamport (8) concludes that the average amount of total circulating EH in the human female is 47 IU/liter of blood or 282 IU, assuming 6 liters of blood. Therefore, let

$$E_{avg} = 282 \text{ IU}. \tag{14}$$

2. Initially, let it be assumed that the coefficient of disappearance of EH is[2]

$$k_8 = 0.6 \text{ liters/day}. \tag{15}$$

3. Assume that the physiological volumes V_E and V_X which contain the EH and FSH, respectively, are

$$V_E = V_X = 6.0 \text{ liters}, \tag{16}$$

the approximate blood volume of an adult human.

4. Further, assume that the coefficient of disappearance of FSH, k_3, has the value

$$k_3 = 0.5 \text{ liters/day}. \tag{17}$$

[1] One IU is the amount of a given hormone necessary to elicit a specific response in the experimental animal. The amount is different for each hormone (e.g., 0.1 μg of estrone = 1 IU, 1 mg of progesterone = 1 IU).

[2] Lamport used a coefficient of disappearance of EH of 1.2, which is equivalent to a value of k_8 = (1.2) (6) = 7.2. A k_8 value of 4.0 will be used. See Table II.

It is reasonable to assume that k_3, the coefficient of disappearance of FSH, is similar to that of EH, therefore the value of k_3 was chosen to be approximately the same as k_8.

5. Assume that the FSH level in the body has some average value and assign a value to X_{avg}.

Therefore, let

$$X_{avg} = 400 \text{ IU}. \tag{18}$$

This is of the same magnitude as E_{avg} but is sufficiently different to be easily distinguished from EH.

6. Let the gain coefficient k_1 in equation 9 be equal initially to

$$k_1 = 0.5 \text{ liters/day}. \tag{19}$$

The constants which must now be computed from desired steady-state values are E_1, k_2, k_4, k_6, and k_7.

7. Since it is desired that the physiological standard concentration of EH be

$$E_1 = E_{avg}/V_E \tag{20}$$

it must be true in the steady state that the stray rate of production of FSH is

$$k_2 = k_3 X_{avg}/V_E. \tag{21}$$

8. It is known that the follicle sometimes becomes 2 cm in diameter before ovulation occurs (7). Since this corresponds to a volume of

$$\tfrac{4}{3}\pi r^3 = \tfrac{4}{3}\pi(2/2)^3 = \tfrac{4}{3}\pi \text{ cc} \tag{22}$$

let the maximum size of the follicle be chosen as

$$S_{max} = 3 \text{ cc}. \tag{23}$$

9. With equation 23 and the assumption that the period of the cycle is

$$t_{period} = 28 \text{ days} \tag{24}$$

it is possible to arrive at a value of k_4, the coefficient of follicular growth. From equation 10, which is repeated below as equation 25,

$$dS/dt = k_4 X/V_X \tag{25}$$

it is also possible to assume that the maximum size of the follicle S_{max} is achieved by a linear growth during the interval t_{period}. This gives a value for k_4 in terms of S_{max}, t_{period}, X_{avg}, and V_X:

$$k_4 = S_{max}/t_{period} \cdot V_X/X_{avg}. \tag{26}$$

10. By assuming that the average size of the follicle is

$$S_{avg} = S_{max}/2 = 1.5 \text{ cc} \tag{27}$$

it is then possible to calculate either k_6 or k_7 if a particular value is assigned to one of these two coefficients. From equation 11 it can be determined that in the steady state

$$k_6 S_{avg} + k_7 = k_8 E_{avg}/V_E . \tag{28}$$

Solving for k_6, the coefficient of EH production by the follicle, yields

$$k_6 = (k_8 E_{avg}/V_E - k_7)/S_{avg} . \tag{29}$$

11. Let a small numerical value for k_7, the stray secretion rate of EH, be arbitrarily assumed.

$$k_7 = 5.0 \text{ IU/day.}$$

Therefore

$$k_6 = 15.46 \text{ IU/cc-day.} \tag{30}$$

12. Assume a time increment for the simulation. Let this be

$$\Delta t = 0.5 \text{ days.} \tag{31}$$

13. Let the gain coefficient k_1 be equal to 0.0 in at least one simulation run. This is equivalent to opening the feedback loop which allows EH to affect FSH.

$$k_1 = 0.0 \text{ liters/day.} \tag{32}$$

PHYSIOLOGICAL DATA AND SIMULATION RESULTS

It is generally believed that the blood FSH level is periodic in its fluctuations, rising during the early growth of the follicle and then decreasing during the period around ovulation.[3] It has been postulated by many researchers that the source of this rise and fall of FSH is a feedback mechanism controlled by blood EH. This qualitiative variation in blood FSH is indicated in Fig. 6.

Experimental data regarding the blood EH level is also given in Fig. 6. Two EH curves are presented: the first, data of Frank and Goldberger as used by Lamport

[3] Since this work was done, the serum FSH level has been shown to have two peaks, one near ovulation and the other near the menses (Faiman and Ryan, 4). The model of this paper can account for either one, but not both, of these peaks. With negative feedback, EH produces the FSH peak near the menses. With the admission of positive feedback (e.g. $k_1 = -0.5$) in the effect EH has upon FSH secretion, the peak near ovulation can be produced, but then the model is not consistent with the fact that FSH levels rise after bilateral ovariotomy.

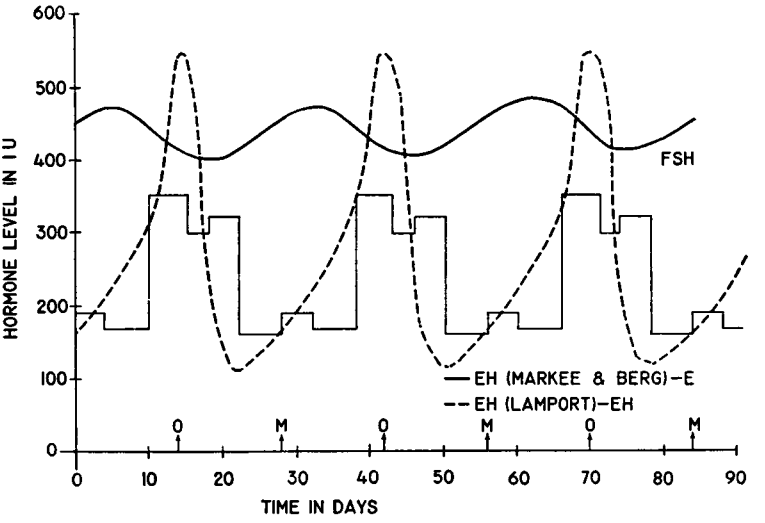

FIGURE 6 FSH and EH blood levels vs. time in days.

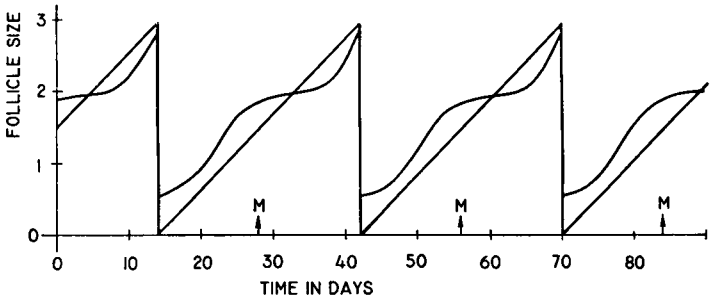

FIGURE 7 Follicle size vs. time in days: probable and linearized forms.

(9), the second, data of Markee and Berg (12).[4] The article by Markee and Berg is significant because it reports work done on normal young women.

A curve of follicle size is given in Fig. 7. Two forms of this curve are shown: the first is data of Myers, Young, and Dempsey (1936) from a book edited by Young (17). The data shown has been transformed to a period of 28 days and a maximum follicle size of 3 units. Although this follicular growth curve is for a guinea pig, it is assumed that humans and other mammals have similar follicular growth curves. The second curve is a linear approximation to the given follicular growth curve.

Using the parameter values given in Table II, the equations representing the model in Fig. 1 were programmed in Fortran A and solved on an IBM 1620 digital computer (International Business Machines Corp., New York).

[4] The data of Frank and Goldberger and of Markee and Berg have been adjusted to the total amount in the blood, assuming 6 liters for the blood volume.

TABLE II

SIMULATION PARAMETER VALUES

Identification								
Fig.	Run No.	k_1	k_2	k_3	k_4	k_6	k_7	k_8
8	7/16-1	0.0	33.333	0.5	0.001607	15.46	5.0	0.6
9	7/22-1	1.0	33.333	0.5	0.001607	15.46	5.0	0.6
10	8/2-1	1.0	200.0	3.0	0.001607	122.0	5.0	4.0

Additional Constants:

$X_{avg} = 400.0$	$E_{avg} = 282.0$	$S_{avg} = 1.5$	$E_1 = 47.0$
$X_0 = 0.0$	$E_0 = 0.0$	$S_0 = 0.0$	$t_{period} = 28.0$
$V_X = 6.0$	$V_E = 6.0$	$S_{max} = 3.0$	$\Delta t = 0.5$

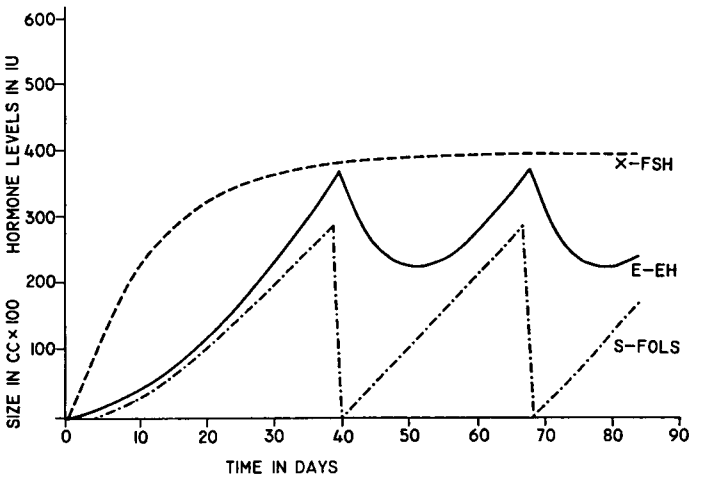

FIGURE 8 Henry E. Thompson—FSH-EH Model 2. Marquette University Computing Center. Run 1, 16 July 1963. $k_1 = 0$, $k_3 = 0.5$, $k_8 = 0.6$.

The numerical technique used in the computer program is presented in the Appendix. The approximate amount of object program run time required by the IBM 1620 Model 1 (with floating point hardware) to simulate the system for a 90 day time course of events was (1) 1–2 min with $\Delta t = 0.5$ days, and (2) 10–15 min with $\Delta t = 0.05$ days. (Exact timings are no longer available for this program on the IBM 1620-I.) The effect of the time increment Δt upon the numerical solution was determined from several simulations using $\Delta t = 0.5$ and $\Delta t = 0.05$ days with the same parameter set. The solutions did not differ significantly enough to justify the 10-fold increase in computer time required for the execution of the program with the smaller Δt. The digital simulation has also been checked by implementing the block diagram of Fig. 2 on an analog computer. Both methods gave solutions which are in good agreement with each other.

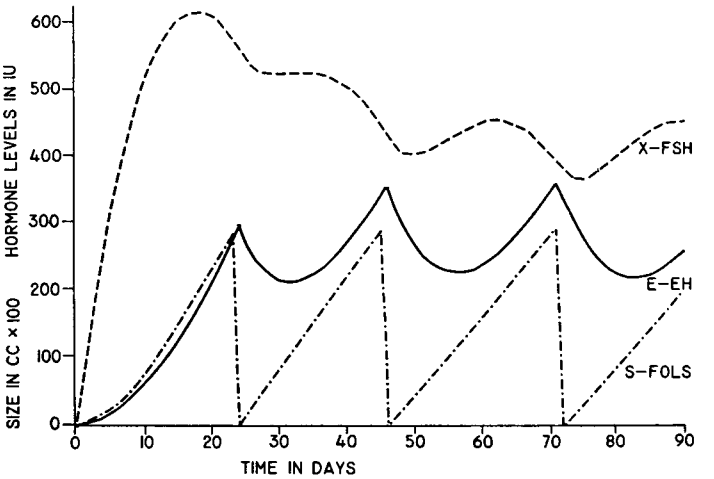

FIGURE 9 Henry E. Thompson—FSH-EH Model 2. Marquette University Computing Center. Run 1, 22 July 1963. $k_1 = 1.0$, $k_3 = 0.5$, $k_8 = 0.6$.

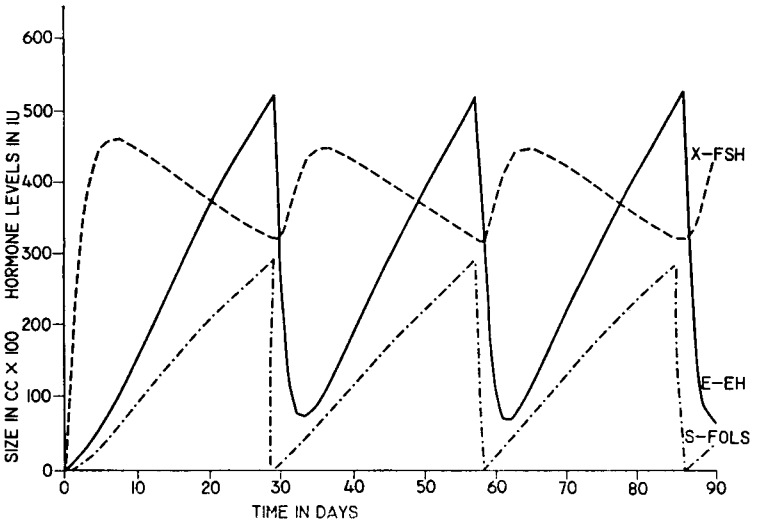

FIGURE 10 Henry E. Thompson—FSH-EH Model 2B. Marquette University Computing Center. Run 1, 2 August 1963. $k_1 = 1.0$, $k_3 = 3.0$, $k_8 = 4.0$.

The estrogen level, the FSH level, and the follicle size are depicted in Figs. 8, 9, and 10 as functions of time.[5] Most important of course, is that, unlike the models proposed by Lamport and Kesselman, persistent periodic behavior is represented in

[5] In Figs. 8, 9, and 10 simulation results displayed are reproductions of actual computer output data. The results were recorded on an IBM 870 autoplotter system operating offline from an IBM 1620 computer system.

this model. In addition, the shapes of the simulated functions and the physiological data are in good agreement.

Figs. 8 and 9 show the effect that the gain coefficient k_1 has on the shape of the FSH curve. Because the average value of the FSH curve is affected by k_1, the growth rate of the follicle changes and consequently the period of the oscillation is also different.

A comparison of Fig. 9 with Fig. 10 shows the effect of a change in the coefficients of disappearance of FSH, k_3, and EH, k_8. In the curve of EH vs. time, the larger value of k_8 causes a very pronounced drop in the EH curve between ovulations.

CONCLUSION

In this paper a model has been proposed for the FSH-EH-*S* endocrine control system. This system is similar in some ways to the FSH-EH system of Lamport. The important difference is that the growing follicle is included in this model of the system. This additional physiological fact changes a damped oscillatory solution into the undamped periodic solution of this model. The FSH, EH, and *S* curves in Figs. 9 and 10 are very similar to the physiological data represented in Figs. 6 and 7.

As is true of previous models, this one is an open system with a single compartment for each hormone. It also uses the concentration of the hormones in the respective compartments as a physiological variable.

It has been shown in this paper that even a simple model of the FSH-EH endocrine control system, if it includes the growing follicle as part of the system, does display the undamped periodic behavior which characterizes this physiological system.

APPENDIX

The digital computer requires the application of vast amounts of simple arithmetic to effect the solution of the system's equations. In this numerical solution a particular computational procedure must be selected and used. The selection of the particular algorithm is somewhat a matter of individual preference, influenced by the system's complexities and the accuracy desired for the solution. Among some of the numerical approaches available are the repeated application of Taylor's series, the Adam-Bashforth, the Milne, and the Runge-Kutta procedures. The simplest of these is the Taylor's series. Euler's method and the various forms of this method are all related to the Taylor's series.

The method which has been selected for use in this program is the most basic of the Euler's methods. This method was elected not only because it is fairly easy to apply to large systems of simultaneous differential equations with nonlinearities, but because it is computationally simple and the accuracy obtained is consistent with the range of accuracy to be expected in physiological data.

The solution of systems of simultaneous differential equations requires the application of the chosen algorithm to all the equations in a relatively simultaneous fashion. The method used here is to evaluate all the derivatives

$$\frac{dx_i}{dt} = f_i(t, x_1, x_2, \cdots, x_m) \qquad i = 1, m \tag{A1}$$

at the point "n" using the current values of "t_n , x_{1n} , x_{2n} , $\cdots$, x_{mn}" and then to update the values of the independent and dependent variables by application of the selected algorithm. If Euler's method is used, the equations become

$$\Delta x_{in} = \left.\frac{dx_i}{dt}\right|_n \Delta t \qquad i = 1, m \tag{A2}$$

$$t_{n+1} = t_n + \Delta t \tag{A3}$$

$$x_{i,n+1} = x_{in} + \Delta x_{in} \qquad i = 1, m \tag{A4}$$

Any algorithm can be used in a similar procedure to obtain the numerical solution of a system of simultaneous differential equations.

This paper is based upon part of a thesis submitted by Henry E. Thompson in partial fulfillment of the requirements for the Degree of Master of Science in Electrical Engineering at Marquette University in December, 1966. This work was previously presented in an abbreviated form at the 18th Annual Conference on Engineering in Medicine and Biology (1965).

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