

COMPUTER SIMULATION OF A MATHEMATICAL MODEL OF THE ESTROGEN-PROGESTERONE CYCLE

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ABSTRACT

Linear and non-linear differential equations are developed to model the blood concentrations of the human female hormones progesterone, luteinizing hormone (LH), follicle stimulating hormone (FSH) and estrogen. The non-linear equation set is integrated numerically using a fourth order Runge-Kutta algorithm.

INTRODUCTION

The control system governing sexual reproduction operates in two widely different but complementary ways. It is partly nervous and partly chemical. Many of the events occurring within the body are coordinated by the nervous system. Some aspects of reproduction are under the control of the nerves and of different regions of the brain. (Dorner, G. 1976) Courtship and sexual behavior, the muscular activity of the female reproductive tract, and at least some occurrences in the birth process are also coordinated by nervous pathways.

Hormones, the biochemical messengers of the body are produced in the endocrine or ductless glands, from which they are secreted into the blood stream. Hormones are capable of exerting powerful and characteristic effects on one particular type of tissue, or organ, which is usually called the target organ for that hormone. Some hormones cause the target organ suddenly to start secreting a particular substance, or to stop secreting a particular substance. Some cause it to grow or stop growing. However, the actual mechanism by which hormones interact with their target organs is not fully understood. Hormones are present in such small quantities that they cannot significantly contribute matter or energy to the processes which they bring about. In fact they seem to have a catalytic action, simply by their physical presence causing the target organ to undergo a sudden and marked change in its normal activity. (Goldman, B.D., 1978)

There are at least a dozen endocrine glands in the human body, and the effects that their hormonal secretions produce are extremely varied. However, the one thing that most hormone producing tissues, endocrine glands have in common is that the secretion of their hormones is controlled by a master gland called the pituitary.

From the perspective of reproduction, the most important pituitary hormones are those that govern the secretion of the sex hormones from

the testes and the ovaries, called gonadotrophic hormones or more simply, the gonadotrophins. (Arimura, A., 1977)

THE HUMAN FEMALE HORMONES

The ovary produces two different types of hormones, estrogen and progesterone. The term estrogen does not describe any single substance. There are at least three different estrogenic hormones which all have similar biological properties, though they differ in their stimulating power. These substances are known as estradiol, estrone, and estriol. For the sake of simplicity, the continued use of the blanket term estrogens will be employed for this point on. Estrogens are produced within the walls of the ovarian follicle. Estrogen controls the development of female characteristics, such as the growth of the uterus and external genitalia as well as the laying down of the subcutaneous fat peculiar to all human females. The changes that occur in the uterine endometrium, particularly during the first half of the menstrual cycle. The other main ovarian hormone is progesterone. Chemically related to the estrogen, it has a very different biological action. Progesterone is produced by the corpus luteum which is formed each month after ovulation. It stimulates the growth and persistence of the endometrial lining of the uterus. In so doing, it often acts in conjunction with estrogen, thus bringing about the uterine changes essential to the implantation of the fertilized egg and the development of the placenta. (Bancroft, N. et al 1983)

In the female the pituitary gland secretes two important gonadotrophic hormones. Two of these hormones control the ovaries: the follicle stimulating hormone, (FSH), and the luteinizing hormone, (LH). Although both can readily be extracted from pituitary tissue, it has proved difficult to separate them from each other and thus to distinguish their properties clearly. However, it seems clear that FSH acts upon the immature ovarian follicle and causes the great increase in size accompanying its maturation before ovulation. Luteinizing hormone on the other hand has little or no effect on the immature follicles but seems to act only upon those that have come under the influence of FSH. It stimulates the final maturation of the egg and the rupture of the follicle wall. Thus for ovulation to occur at all, the ovary must come successively under the influence of both hormones. (Brown-Grant, K., 1977)

MODEL DEVELOPMENT

FSH is also responsible for another extremely important change in the ovary: it causes the production and secretion of estrogen. The estrogen arises in the cells of the follicle wall. These cells also increase in number under the influence of FSH, and their output of estrogen is further increased. When this happens feedback occurs: the circulating estrogen produced by the ovary causes the pituitary, via the hypothalamus, to slow down and stop the secretion of further FSH.

Each month the ovary comes under the influence of the pituitary FSH, which stimulates follicle growth and thereby the secretion of estrogen. In women usually only one follicle reaches maturity during each cycle; others which have come under the influence of FSH degenerate before they are fully formed. LH causes the mature follicle to rupture and it remains to be transformed into a corpus luteum which secretes progesterone as well as small amounts of estrogen. If the egg is not fertilized, the corpus luteum persists for about nine days after which time it too degenerates. FSH is again secreted and the cycle begins again. The presence of estrogen in the blood stimulates growth of the uterine endometrium, while progesterone acting in concert with estrogen, maintains the newly grown endometrium. In the absence of both hormones, however, the endometrium is unable to maintain itself and degenerates in a very short time.

A 28 day cycle is to be perceived as the norm for most females. The day on which the menses begins is day one of the cycle. For about four days after menstruation the endometrium undergoes a series of repairs. Any extraneous blood in the uterine cavity is removed and the innermost layer of the endometrium is re-constituted. In the ovary, the corpus luteum from the last cycle is degenerating and a new follicle is developing. During the next five or six days the endometrium slowly increases in thickness, and in the ovary the follicle is growing and estrogen is secreted. Ovulation occurs and the corpus luteum is formed. For about the next ten days the uterus is under the influence of the ovarian hormones, particularly, progesterone. During this time the endometrium reaches a thickness of perhaps half a centimeter and becomes distinguishable into three layers, the region nearest the myometrium being relatively compact, while the other two layers are much softer and more diffuse.

About twenty four days after the beginning of the cycle, the corpus luteum starts to degenerate and its hormonal secretion ceases. Deprived of this hormonal support the two inner layers of the endometrium start to breakdown, their remains passing out through the cervix and vagina as the menstrual discharge. The remaining endometrial layer is retained to become the foundation of the new endometrium which will be built up during the next follicular phase. (Owens J.A., 1975)

The trophic hormones regulate the activity of the endocrine glands upon which they act. Clearly a regulating mechanism is at work and is frequently referred to as a "negative feedback mechanism."

As the blood levels of a particular hormone, say one of the sex hormones, increases, the hypothalamus acts upon the pituitary and slows down secretion of the gonadotrophin. The

trophic stimulus gets weaker and the gonads slow down the release of their own hormone. Accordingly, the sex hormone concentration in the blood reaches a lower level and gonadotrophin secretion is reestablished. The pituitary and the gonads therefore regulate the release of each other's hormones, each exerting a very fine control over the activity of the other. (Sanders D. & Brancroft J., 1982) The oscillations in the hormone levels can be seen in Fig. 1, as adopted from Speroff, Glass

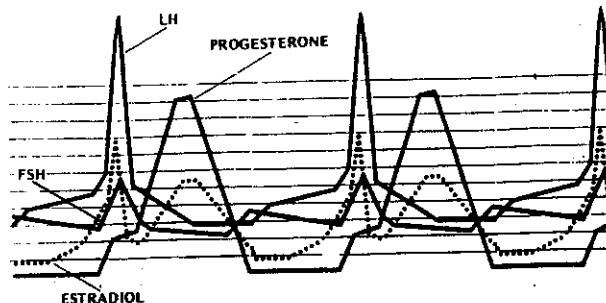


FIGURE 1

and Kase. Ideally we would like to be able to relate the changes in all the hormones, the byproducts and the intermediate products to each other (Brenner R.M. & West N.B., 1975). The relationships can sometimes be derived in differential or integral formulations. If a closed form solution cannot be obtained then alternatives must be sought. Linear differential equation models with constant coefficients will be developed which can be accepted as first order approximations to the actual feedback mechanism which in all likelihood is nonlinear. As can be seen in Fig. 1, LH and progesterone peak at different times but follow a similar path. The production of Progesterone (P) starts after the formation of the corpus luteum, which is caused by LH (via the follicle which secretes the estrogen.) Thus in this model, we can further simplify the problem by taking into consideration the interactions (via Estrogen) of LH and Progesterone. To model this situation, we let

$$(1a) \quad L = L_* + L$$

$$(1b) \quad \text{Progesterone} = P_* + P$$

where the concentrations of the hormones have been written as the sum of a constant value $(\cdot)_*$ and an oscillating value. We will

start with the simplest linear differential equation model for P and L

$$(2a) \quad \dot{L} = -a_1 P$$

$$(2b) \quad \dot{P} = a_2 L$$

The rate of change of Progesterone is taken to be positively proportional to LH since, it is the LH (through estrogen production of the follicle) that causes the Progesterone to be secreted. The rate of change of LH is negatively influenced by Progesterone since its secretion signals the beginning of the end of the cycle. It can be easily verified that the solution of these equations is given by

$$(3a) \quad L = L_0 \cos wt$$

$$(3b) \quad P = P_0 \sin wt$$

$$\text{where } w = \sqrt{a_1 a_2}$$

$$\text{and } L_0 = \sqrt{a_1/a_2} P_0$$

the results are plotted in Fig. 2 for $L_0 < P_0$.

The production of estrogen on the other hand is a function of P and L. (ie. $E = f(L,P)$). For the simplest model, we can expand $f(L,P)$ in a Taylor Series about some point (L_0, P_0) . This expansion, up to and including second order terms, becomes;

$$\{4\} \quad E = f(L,P) = f_0 + b_1 L + b_2 P + b_3 P^2 + b_4 L^2 + b_5 PL$$

where the b's are the proper partial derivatives.

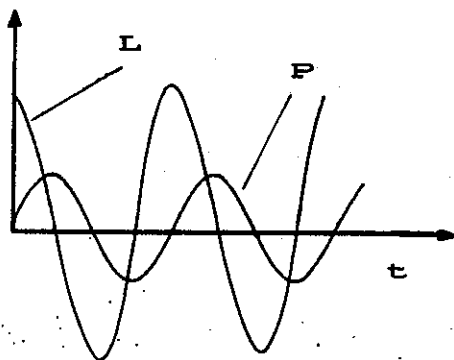


FIGURE 2

The linear terms

$$\{5\} \quad b_1 L + b_2 P = b_1 L_0 \cos wt + b_2 P_0 \sin wt$$

using the identity:

$$\{6\} \quad \sin(a+b) = \sin a \cos b + \cos a \sin b$$

can be reduced to

$$\{7\} \quad A \sin(wt + \beta_1)$$

$$\text{where } \beta_1 = \tan^{-1}(b_1 L_0 / b_2 P_0)$$

$$\text{and } A = b_1^2 L_0^2 + b_2^2 P_0^2$$

Similarly, using the identity:

$$\{8\} \quad \sin 2a = 2 \sin a \cos a$$

the PL term which is

$$\{9\} \quad PL = P_0 L_0 \sin wt \cos wt$$

can be written as $B \sin(2wt)$ where

$$B = b_5 P_0 L_0 / 2$$

The two remaining terms, namely, the P^2 and L^2 terms

$$\{10\} \quad b_3 P^2 + b_4 L^2 = b_3 P_0^2 \sin^2 wt + b_4 L_0^2 \cos^2 wt$$

can be written as

$$\{11\} \quad b_4 L_0^2 \cos(2wt)$$

if we assume

$$\{12\} \quad b_3 P_0^2 = -b_4 L_0^2$$

Hence, the second order terms

$$\{13\} \quad b_3 P^2 + b_4 L^2 + b_5 PL$$

can be combined to give

$$\{14\} \quad G \sin(2wt + \beta_2)$$

The equation for estrogen, then, becomes

$$\{15\} \quad E \sim \sin(wt + \beta_1) + \sin(2wt + \beta_2)$$

Figure 3 shows the relationship between the sinusoidal terms given above.

NON-LINEAR MODEL

We can model the L and P interaction non-linearly with the equations

$$\{16a\} \quad \dot{L} = a_{11} L - a_{12} LP$$

$$\{16b\} \quad \dot{P} = -a_{22} P + a_{21} LP$$

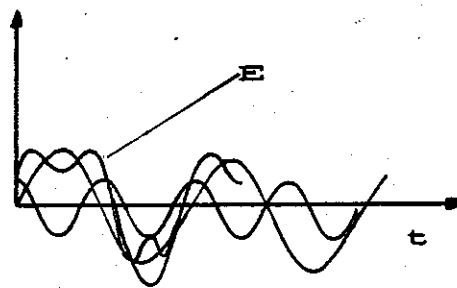


FIGURE 3

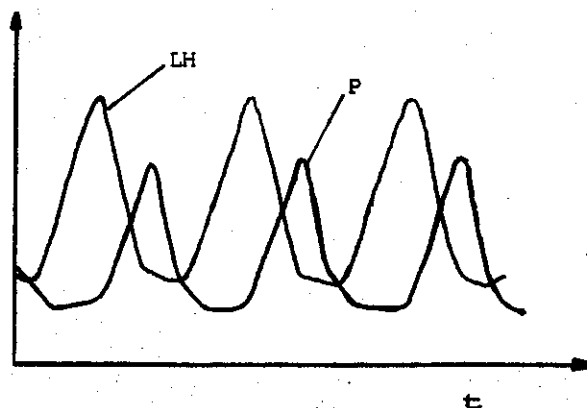


FIGURE 4

Equations 16a and 16b were integrated numerically via a fourth-order Runge-Kutta algorithm. A typical output is shown in Fig. 4. As is clearly seen the non-linear model much more clearly resembles the experimental results shown in Fig. 1.

SUMMARY

It is readily seen that the linear model (Fig. 3) is a good first-order approximation to the experimentally observed values (Fig. 1). The nonlinear model given by Eqs. 16 gives much better results. The coefficients in Eqs. 16 should be estimated using probabilistic methods for an optimal fit of the experimentally observed values.

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