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CONTROL OF OVULATION NUMBER IN A MODEL OF OVARIAN FOLLICULAR MATURATION [1]

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ABSTRACT. We assume that interactions between developing follicles occur through circulating hormones that control cell growth. This leads to a system of ordinary differential equations of the form

$$d\xi_i/dt = f(\xi_i, \xi) \quad \text{where} \quad \xi = \sum \xi_i$$

and where ξ_i measures the maturity of the i-th follicle. We give a particular choice of f for which the stable trajectories of this system correspond to a limited range of ovulation numbers. Along these stable trajectories, the population of follicles is divided into two parts: a few follicles mature to ovulation and the rest atrophy and disappear. For some parameter values there are also stable trajectories that lead to pathological, anovulatory states. The model takes on a probabilistic aspect when we add the assumption that entry into the class of interacting follicles occurs by a stochastic process from a reserve pool of immature, noninteracting follicles. We simulate this situation numerically, and we compute the distribution of ovulation times and ovulation numbers.

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1. Introduction

> As the female, in most classes of animals, has two ovaria, I imagined that by removing one it might be possible to determine how far their actions were reciprocally influenced by each other ... . There are two views in which this subject may be considered. The first, that the ovaria, when properly employed, may be bodies determined and unalterable respecting the number of young to be produced... . The second view of the subject is, by supposing, that there is not originally any fixed number which the ovarium must produce, but that the number is increased or diminished according to circumstances; that is it is rather the constitution at large that determines the number; and that if one ovarium is removed, the other will be called upon by the constitution to perform the operations of both, by which means the animal should produce with one ovarium the same number of young as would have been produced if both had remained [1].
>
> John Hunter, 1787

In mammals the number of offspring produced in a litter is usually characteristic of the species or breed. This is a reflection of the relatively constant number of eggs that are periodically shed from the ovaries at the time of ovulation.

Each egg is released from a developmental unit called a follicle which matures in the ovary over a period of weeks. Follicles initiate growth continually from a large reserve pool which is formed at birth. Only a few of those follicles which start to grow in each cycle actually mature and release ova; the rest atrophy and die. The observed variation in ovulation number for a given mammal is sufficiently small to rule out the hypothesis of independent follicle growth. In fact, follicle interaction occurs through circulating hormones. It is our hypothesis that this interaction determines the number of follicles that eventually mature to ovulation.

The assumption of interaction through the circulation is important. It will impose a particular symmetry on the class of dynamical systems that can be used to describe

follicle growth. We shall use the word global to describe this kind of interaction.

2. Support for Global Interaction

The first evidence suggesting the possibility that global interaction regulates ovulation number appeared in 1787. The famous Scottish surgeon John Hunter removed an ovary from a sow in order to determine what effect this might have on the size of its litters (see the quote that introduces this paper). He found that although the reproductive life span was significantly reduced by this manipulation, the size of each litter did not change. Further examination showed that the number of eggs released by the remaining ovary doubles at each ovulation. If the operation is performed at the right time in the cycle, compensation by the remaining ovary will occur at the next scheduled ovulatory period [2,3]. This compensation has been observed in many mammals and is called the law of follicular constancy [4].

If ovulation number is controlled only by local interactions between follicles, then the number of eggs released at ovulation by one ovary should be independent of the number released by the other. One would expect the removal of one ovary to reduce the ovulation number by one-half. However, if ovulation number is controlled by follicle interactions that occur through the circulation then any two given follicles will interact in the same way whether they are nearest neighbors or in different ovaries. Removing one ovary should not change the number of eggs released at ovulation provided that the size of the developing population of follicles is still large compared to the number which eventually ovulate in a cycle.

Since global interaction is spatially independent, it cannot be sensitive to the way a given set of follicles is distributed between the two ovaries. This is unlikely to be true if local, spatially dependent, interaction is important. If follicles interact primarily through the circulation then the distribution of eggs shed between the two ovaries when conditioned on a given total ovulation

number should satisfy binomial statistics. If local interaction plays an important role then some deviation from the binomial law might be expected. In fact, no significant deviation from binomial statistics is observed in those species which have been examined [5-10]. In mice, where this distribution has been most extensively tested, p is very close to 1/2.

It should be noted that binomial statistics and the law of follicular constancy would also be satisfied if follicles did not interact at all. However, as previously mentioned, the assumption of independent follicle growth cannot explain the small variation in ovulation number that mammals can achieve. For example, the number of follicles activated per cycle in a young woman is on the order of 10^3. Since the mean ovulation number is one, the assumption of independent follicle growth leads to a prediction of 2 eggs being released in 18% of her cycles. One would think that this would lead to a higher rate of fraternal twins than the observed rate of about 1% [11].

3. The Physiological Mechanism which Mediates Global Interaction

Developing follicles might communicate directly through their own secretions or they might interact indirectly by controlling the release of growth mediating hormones from a distant site. The latter possibility would appear to be more compatible with a global mechanism and is, in fact, supported by a large body of evidence. The distant site is the pituitary, whose secretions also help regulate other endocrine glands.

Pituitary removal arrests follicle maturation in its early stages. A chemical fraction from the gland, called gonadotropin, can make follicles mature to ovulation in both sexually immature animals and in animals whose pituitaries have been removed. Gonadotropin consists of 2 protein hormones called follicle-stimulating hormones (FSH) and luteinizing hormone (LH). Specific receptors with extremely high affinity for each of these hormones are found on follicle cells. The number of receptors a follicle contains

appears to depend on its maturity [12]. Both FSH and LH are secreted in different amounts throughout the cycle. During most of the cycle the ratio of FSH/LH is greater than 1, however, in the few hours which precede ovulation there is an abrupt increase in gonadotropin and the ratio reverses.

Indirect communication between follicles is established by the fact that steroid secretions from developing follicles regulate the release of gonadotropin. In several species, the principal steroid hormone which regulates gonadotropin release during follicle growth is estradiol. As a follicle develops morphologically its estradiol secretory rate increases [13,14]. The different cell types within a follicle cooperate in producing estradiol from cholesterol. In addition to its ability to regulate gonadotropin release, estradiol is a potent stimulator of cell division within a follicle. Many of the effects of FSH and LH on follicle development may be mediated through estradiol and its precursors [15]. These local effects may explain the influence of a follicle's maturity on its own growth rate.

On the time-scale of follicle maturation (days), estradiol is rapidly removed from the circulation. The rate of removal is proportional to the concentration with a time-constant measured in minutes [16,17]. Thus equilibrium is rapidly achieved. The resulting serum concentrations of estradiol are at least an order of magnitude lower than those concentrations measured in follicular fluid [18].

4. Follicle Maturation

Mammals are born with a large reserve pool of immature follicles that decays exponentially with age [19]. Once a follicle leaves this pool it will either ovulate or atrophy. Each follicle in the immature pool consists of an egg cell which is surrounded by a small number of granulosa cells (order 10^1). A basement membrane separates the granulosa cells from the remaining ovarian tissue.

No new follicles enter the reserve pool after birth and follicles only leave by starting to grow. A growing follicle can be recognized microscopically by an increase in the

number of its granulosa cells. The mechanism which triggers granulosa cell division in a reserve follicle is not understood. Activation from the reserve pool continues in the absence of gonadotropin although follicle maturation does not proceed beyond its early stages. Exponential decay of the reserve pool suggests that follicle activation may be described by a poisson process.

Each follicle is surrounded by a vascular net which forms outside the basement membrane. In this area the surrounding ovarian tissue differentiates to form an indistinct shell called the theca. At the biochemical level follicle maturation is a very complex process. Many interconnected reactions between granulosa and theca appear to unfold in a coordinated way that is just beginning to be understood.

At any given time there is a distribution of follicle maturities in the ovary. In humans follicles range in size from 10^{-2} cm in diameter to 2.5 cm. The largest follicles contain 10^{7} granulosa cells. Before puberty all growing follicles atrophy at different times and stages of growth. Periodically, after puberty, a small and remarkably constant number, depending on the species, complete maturation and release their eggs nearly simultaneously on the time scale of follicle growth. In mice, where the most careful measurements have been made, the estimated time from growth initiation to ovulation is 3 weeks [20].

5. Formulation of the Model

In this section, a model is proposed to describe the interaction of developing follicles by means of circulating hormones. For the sake of clarity, very simple and specific physiological assumptions are made. In fact, however, the model is not critically dependent on all of these assumptions. A more general derivation has been given in (21).

Consider a population of N developing follicles. Each follicle will be characterized by the number of granulosa cells $X_i(t)$, $i = 1,2,\ldots,N$. We will assume that follicle

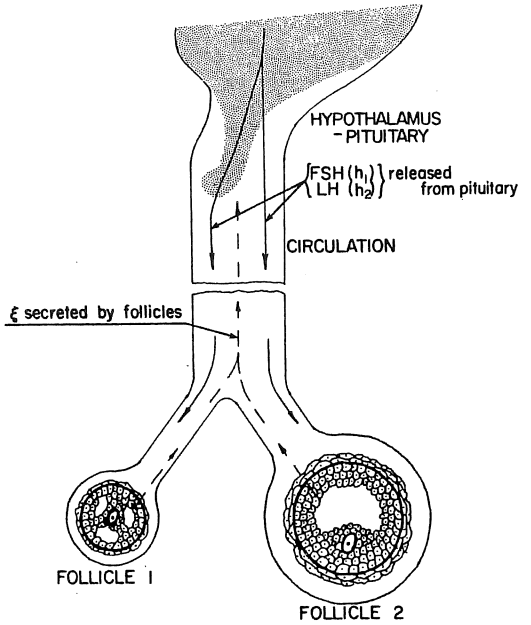

Figure 1. Schematic representation of the interaction between 2 developing follicles. Follicle estradiol secretory rate is used as a measure of follicle maturity. The circulating concentration of estradiol, ξ, is assumed to control the release of the pituitary gonadotropins FSH and LH. These pituitary hormones regulate the rate of follicle maturation. However, the response of a follicle to the circulating concentrations of FSH(h_1) and LH(h_2) at any particular time is also assumed to depend on follicle maturity. (Reprinted from [21].)

extradiol secretory rate is proportional to X_i although any increasing monotonic relationship between these two quantities could be used without altering the form of the model that is eventually proposed. Let σ be the constant of proportionality.

Assume that estradiol is distributed in the serum volume V at concentration $\xi(t)$ and that it is removed from the serum at a rate $\gamma\xi$. Since the rate of change of serum estradiol must be equal to the difference between its production rate and removal rate, it follows that

$$V \frac{d\xi}{dt} = \sum_{i=1}^{N} \sigma X_i(t) - \gamma \xi \ . \tag{1}$$

If estradiol is removed from the circulation at rates which are fast on the time scale of follicle growth [22-24] then $\xi(t)$ is always near its equilibrium value. More precisely, if $X_i(t)$ are slowly varying on the time scale given by $\tau = V/\gamma$, then

$$\xi(t) = \frac{\sigma}{\gamma} \sum_{i=1}^{N} X_i(t) \ . \tag{2a}$$

It is convenient to write (2a) in the form

$$\xi(t) = \sum_{i=1}^{N} \xi_i(t) \tag{2}$$

where $\xi_i(t) = \sigma X_i(t)/\gamma$ is the contribution that the i^{th} follicle makes to the estradiol concentration at time t. Since $\xi_i(t)$ is proportional to $X_i(t)$ it is also a measure of follicle maturity.

We assume that serum estradiol regulates the pituitary production of LH and FSH. As above, we assume that the equilibration rates for the circulating concentrations of these hormones are fast compared to the time scale of follicle maturation [25-27]. Then we can define the functions

$$\begin{aligned} h_1 &: \xi \mapsto h_1(\xi) \\ h_2 &: \xi \mapsto h_2(\xi) \end{aligned} \tag{3}$$

where h_1 and h_2 are the circulating concentrations of FSH and LH.

Finally, we assume that the specific growth rate of granulosa cells in a follicle depends on the concentrations of circulating gonadotropins and the maturity of the follicle. That is

$$dX_i/dt = X_i \bar{\Phi}(X_i, h_1, h_2) \ . \tag{3a}$$

X_i appears explicitly on the right-hand side to emphasize the underlying exponential character of cell growth. The function $\bar{\Phi}$ can be given a simple physiologic interpretation as follows: If for any given follicle we define the net growth rate as the net difference between the rate of cell division and the rate of cell death, then $\bar{\Phi}$ is the net growth rate per cell, or the specific growth rate.

Equation (3a) can be rewritten in terms of ξ_i as follows

$$d\xi_i/dt = \xi_i \phi(\xi_i, \xi) \tag{4}$$

where we have introduced the function ϕ defined by

$$\phi(\xi_i, \xi) = \bar{\Phi}\left(\frac{\gamma}{\sigma} \xi_i, h_1(\xi), h_2(\xi)\right) \ . \tag{5}$$

Our model consists of equations (2) and (4) which we write together as a system for future reference:

$$\left.\begin{aligned} d\xi_i/dt &= \xi_i \phi(\xi_i, \xi) \quad i = 1, \ldots, N \\ \xi &= \sum_{j=1}^{N} \xi_j \end{aligned}\right\} \tag{6}$$

It is important to recognize that the effects of FSH and LH on follicle growth are still present in equation (6). They are represented implicitly through equations (3) and (5). The system (6) really represents a class of models which becomes a particular model when ϕ is specified, as we shall do.

There are two important symmetries in (6). First, the form of ϕ is the same for all i. This means that all follicles satisfy the same law of growth. The actual growth rate may differ in different follicles at the same time because the value of the growth rate depends on maturity ξ_i. The second symmetry in (6) is that interaction between follicles occurs only through ξ which is a symmetrical function of the ξ_i. This is an expression of the assumption that follicle growth is regulated by global interactions that are exerted through circulating hormones. All follicles

with identical maturity ξ_i are assumed to respond in the same way when exposed to a given circulating hormonal environment. At any time the environment is controlled by ξ.

6. The Growth Law Function ϕ

Since ϕ is arbitrary, it might seem that the class of models represented by the system (6) is too broad to be useful. In fact, as we have just shown, the symmetries in (6) are very restrictive. Is it possible for a model to exhibit the correct qualitative features of follicle maturation given the restrictions that all follicles have the same program for development and interact only through the circulation? Such a model should possess the following properties:

(1) It should allow a few follicles to emerge from the the developing population with ovulatory maturity while the remainder atrophy and die at different times and stages of growth;

(2) The number of ovulatory follicles should be relatively constant and emerge at regular intervals even though follicles start growing at random times;

(3) It should be able to account for the fact that mammalian species and breeds have different characteristic ovulation numbers.

A priori, it is not clear whether a growth law ϕ exists which will generate this qualitative behavior. We shall answer this question by giving an example. Whether or not this example actually corresponds to the developmental program of follicles in the ovary remains to be seen.

The specific example which we will analyze is:

$$d\xi_i/dt = \xi_i \, \phi(\xi_i,\xi) \quad , \quad i = 1,\ldots,N$$
$$\xi = \sum_{j=1}^{N} \xi_j \tag{7}$$
$$\phi(\xi_i,\xi) = 1 - (\xi - M_1\xi_i)(\xi - M_2\xi_i)$$

where M_1 and M_2 are constants that remain unchanged for each i.

At this point the reader who is familiar with the biochemical complexities involved in the hormonal regulation of cell growth may protest that the model is clearly too simple to be realistic. The answer to this objection is that the growth law ϕ is not intended as a detailed description of all the processes involved in the regulation of follicle maturation. Instead, ϕ is supposed to summarize the relevant consequences of the biochemistry. In fact, we have not arrived at ϕ by studying the biochemistry but by a process of unnatural selection in which various growth laws were tried out and their predictions compared with the behavior of the ovary. A major task for the future is to relate the growth law to the underlying biochemistry.

The particular model represented by the system (7) is motivated by the stability of its equilibria and the properties of its symmetric solutions. These will now be discussed.

Consider the behavior of (7) when M follicles have exactly the same maturity and all others are dormant. Since ξ is the sum of the contribution made by M identical follicles, it follows that

$$\xi_i(t) = \begin{cases} \xi(t)/M \, , & i = 1,\ldots,M \\ 0 \, , & i = M+1,\ldots,N. \end{cases} \tag{8}$$

When (8) is substituted into (7) the dynamics simplify to

$$d\xi/dt = \xi + \mu\xi^3 \tag{9}$$

where $\mu = -(1 - M_1/M)(1 - M_2/M)$. Without loss of generality we will assume $M_2 > M_1$.

When the M follicles are sufficiently small the linear term in (9) dominates and the follicles grow independently and exponentially. As the follicles grow the cubic term begins to play a role. The role that it plays depends on the number of interacting follicles M (Fig. 2).

If M is outside the interval (M_1,M_2), then $\mu < 0$ and the follicles will approach an equilibrium maturity

$$\xi_M = 1/\sqrt{(M-M_1)(M-M_2)} \tag{10}$$

independent of the initial maturity. This equilibrium is

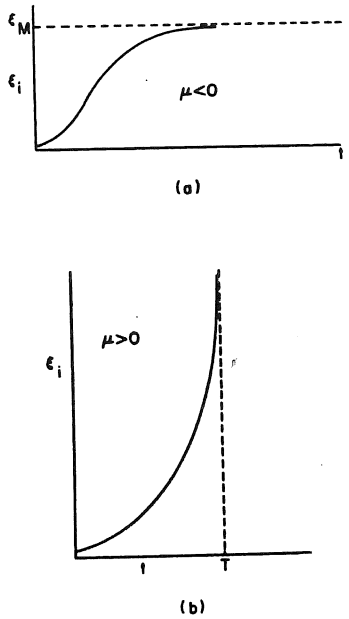

Figure 2. Qualitative behavior of the symmetric solutions of equation (6). These correspond to the special case where M developing follicles are imagined to interact with exactly the same maturity and all other follicles are assumed dormant. If the number of follicles, M, is between M_1 and M_2 ($\mu>0$), then an ovulatory solution develops (2b). However, if M lies outside the interval (M_1,M_2) then the M follicles approach an equilibrium $\xi_M = 1/\sqrt{(M-M_1)(M-M_2)}$ maturity (2a). Note that the idealized ovulation time, T, (2b) depends on M and initial maturity (see equation (11)). (Reprinted from [21].)

stable within the framework of the symmetric solutions given by (8), but it usually becomes unstable when unsymmetric perturbations are considered (see below).

If on the other hand the number of identical follicles M is within the interval (M_1,M_2) then the interaction will be stimulatory ($\mu > 0$) and the M follicles will "ovulate" in a finite time given by

$$T = \frac{1}{2} \ell n \left((1+\mu\xi_0^2)/\mu\xi_0^2\right), \qquad (11)$$

where ξ_0 is the initial value of ξ. Solutions which "blow up" in finite time are appropriate to represent ovulatory solutions for the following reason. In women and primates $\xi_i(t)$ for an ovulatory follicle has actually been measured during the later part of the follicular growth phase of the cycle. This is possible because the serum estradiol concentration at this time is almost entirely due to a single ovulatory follicle. The concentration does not approach an equilibrium but continues to increase in slope [28] even on a logarithmic scale. High, fast rising serum estradiol levels appear to be important in triggering the gonadotropin surge. On the time scale of follicle growth, this surge is essentially an instantaneous event that causes follicle rupture and egg release.

Thus, when M identical follicles interact, ovulation numbers are restricted to lie within the range (M_1,M_2). In reality follicles interact with different maturities because they start to grow at different times. However, at any instant, there is only one concentration of each circulating gonadotropin. This suggests that it might be instructive to consider the behavior of the function ϕ when ξ is fixed and ξ_i varies.

As a function of the maturity ξ_i the growth rate ϕ has a parabolic form with a maximum at a particular maturity

$$\xi_{i_{max}} = \frac{1}{2}(M_1M_2/(M_1+M_2))\xi$$

that depends on the instantaneous value of ξ. When ξ_i differs too much in either direction from this optimal maturity the growth rate is negative. Thus the model promotes the growth of follicles whose individual maturities lie in a

certain range. Since the optimal maturity is proportional to ξ a group of follicles will be selected for growth as ξ increases in time. Of course, the estradiol concentration develops in time as the net result of the simultaneous growth and atrophy of all follicles in the interacting population.

If we assign to each of the N follicles a coordinate axis in N-dimensional space, then any set of maturities can be represented by a point P with coordinates $(\xi_1,\xi_2,\ldots,\xi_N)$. The special solutions (8) of M identical follicles will lie along the line of symmetry ℓ_M associated with each M-dimensional coordinate hyperplane (see Fig. 3a). Those lines of symmetry in coordinate hyperplanes with dimension outside the interval (M_1,M_2) will contain an equilibrium point P_M which blocks ovulation. (Each P_M has M coordinates equal to the equilibrium maturity $\xi_M = 1/\sqrt{(M-M_1)(M-M_2)}$, and the remaining N-M coordinates equal to 0.) If M is within the interval (M_1,M_2) then no equilibria will lie on ℓ_M. Any starting point on one of these ℓ_M will escape along this line to ∞ in a finite time given by equation (11). These correspond to ovulatory solutions.

7. Stability of Symmetric Equilibria

Additional insight about the behavior of the growth law is obtained by examining its linearized behavior near each of the equilibria P_M. Because of the symmetry in the problem it is enough to consider the equilibrium whose first M coordinates are ξ_M. Let $\tilde{P} = (\tilde{\xi}_1,\tilde{\xi}_2,\ldots,\tilde{\xi}_N)$ be a perturbation from this equilibrium. Substituing $P_M + \tilde{P}$ into equation (7) and assuming that $\tilde{P}$ is small produces the linear system.

$$\dot{\tilde{P}} = A\tilde{P}$$

$$A = \begin{pmatrix} a_1+b_1 & & b_1 & \vdots & b_1 \\ & \ddots & & \vdots & \\ b_1 & & a_1+b_1 & \vdots & \\ \cdots & \cdots & \cdots & M & \cdots \\ & & & \vdots & a_2 \quad 0 \\ & & & \vdots & \quad\ddots \\ 0 & & & \vdots & 0 \quad a_2 \end{pmatrix} \qquad (12)$$

where $a_1 = \xi_M \left.\frac{\partial\phi}{\partial\xi_i}\right|_{\xi_M,M\xi_M}$, $a_2 = \phi(0,M\xi_M)$, and $b_1 = \xi_M \left.\frac{\partial\phi}{\partial\xi}\right|_{\xi_M,M\xi_M}$ are functions of M and the growth law parameters M_1 and M_2 (see Table 1). It should be noted that the symmetric equilibria P_M do not exhaust the set of stationary states of (7). Equilibria off the lines of symmetry also exist. They are all unstable and will not be analyzed in any great detail.

It is easily demonstrated that the eigenvalues of A are either the eigenvalues of the symmetric block in the upper left or the diagonal block in the lower right. Although there is a complete set of N independent eigenvectors for each P_M, there are only 3 distinct eigenvalues $\lambda_S = a_1+Mb_1$, $\lambda_{in} = a_1$ and $\lambda_{out} = a_2$ (see Table 1).

The eigenvectors of A have a simple geometric interpretation which is most clearly illustrated by considering the following example (see Fig. 3a). Suppose the number of interacting follicles, N, is 3 and the growth law parameters of (7) are $M_1 = 1.9$ and $M_2 = 2.9$. The stability analysis suggests that, with probability 1, two follicles will ovulate and one will atrophy.

Since the interval (M_1,M_2) includes the integer 2, the lines of symmetry, ℓ_2, in each 2-dimensional coordinate plane will be ovulatory. That is, if 2 follicles start with exactly the same maturity and the third is dormant, then both follicles will ovulate. However, since 1 and 3 are both outside (M_1,M_2), the coordinate axis, ℓ_1, and the line of symmetry in 3-space, ℓ_3, will each contain a stationary point. These are labelled P_1 and P_3 in Fig. 3a. P_1 prevents one follicle from ovulating when the other 2 are dormant. P_3 prevents 3 follicles from ovulating when they all have the same maturity. The three eigenvectors of A at P_1 and P_3 will now be considered.

The eigenvector associated with $\lambda_S = a_1 + Mb_1$ lies along ℓ_M. From the behavior of the symmetric solutions (Fig. 2a) we expect $\lambda_S < 0$ for M outside (M_1,M_2). Table 1 shows that this is indeed true. There are N-M independent eigenvectors associated with $\lambda_{out} = a_2$. They correspond to perturbations from P_M which are out of the M-dimensional

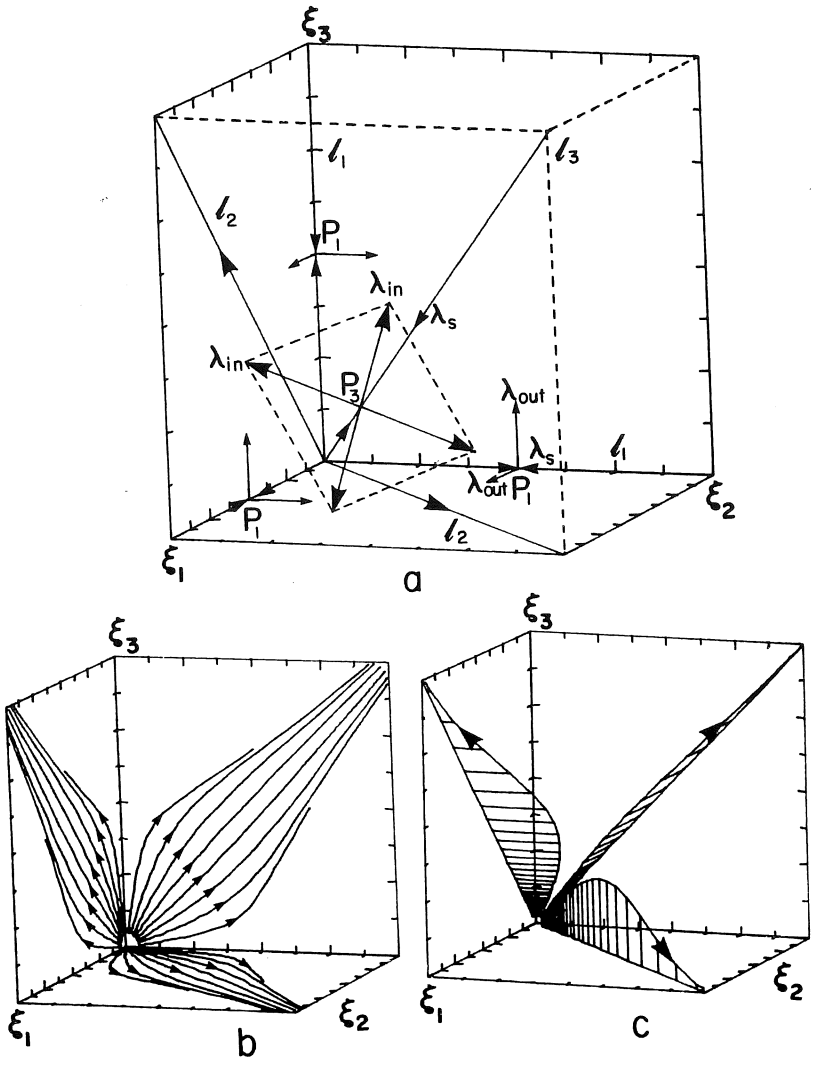

Figure 3. See text for explanation. The dashed lines in (a) are out of the plane of the paper. The origin is in the plane. The curves in (b) are in the coordinate planes and those in (c) are in 3-space.

(Reprinted from [21].)

coordinate hyperplane. For P_1, there are N - M = 2 perturbations out of the 1-dimensional coordinate hyperplane (the coordinate axis). These are illustrated in Fig. 3a. $\lambda_{out} > 0$ for P_1, since $1 = M < M_* = M_1M_2/(M_1+M_2) = 1.15$ (see Fig. 4 where λ_{out} is sketched as a function of M).

Fig. 3b illustrates that P_1 directs nearby solutions in the coordinate planes towards ℓ_2. In fact, all solutions in the plane will asymptotically approach ℓ_2 and "blow-up" in finite time. Thus two small nondormant follicles of unequal maturity will both grow and the smaller one will "catch-up" in finite time and ovulate.

The final eigenvalue $\lambda_{in} = a_1$ has an M-1 dimensional eigenspace that corresponds to perturbations from P_M that lie in the M-dimensional coordinate hyperplane but are orthogonal to ℓ_M. For P_1 no such space exists (the eigenvectors of P_1 are already complete). For P_3, M-1 = 2. The perturbations from P_3 which lie in the 2-dimensional space orthogonal to ℓ_3 are shown in Fig. 3a. $\lambda_{in} > 0$, because $M = 3 > 2.9 = M_2$ (see sketch of λ_{in} as a function of M in Fig. 4. P_3 directs all nearby solutions towards the 2-dimensional coordinate planes which contain ovulatory solutions (Fig. 3c). In fact all phase curves except ℓ_1 and ℓ_3 asymptotically approach ℓ_2 and "blow-up" in finite time. Since any small perturbation from ℓ_1 and ℓ_3 will approach ℓ_2 in finite time, two of the three interacting follicles will ovulate and one will atrophy and die.

If the growth law parameters are kept the same as in the example above but the number of interacting follicle N is made larger than three, then the stability analysis suggests that all but two follicles will atrophy and die. In this case, all the stationary states P_M in higher dimensional coordinate hyperplanes than three are unstable saddle point equilibria which direct nearby solutions toward lower dimensional coordinate subspaces (see Table 1 and Figs. 4 and 5). This suggests that all phase curves will asymptotically approach the 2-dimensional coordinate hyperplanes which are filled with ovulatory trajectories.

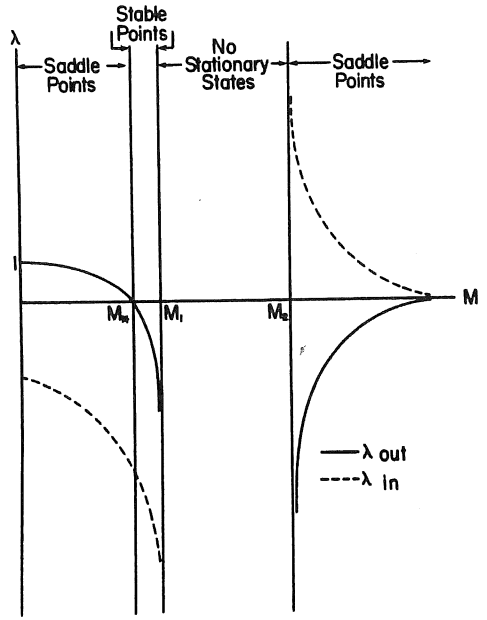

Figure 4. Sketch of the eigenvalues of A (see (12)) as a function of M (see Table 1). λ_{out} is associated with those eigenvectors which are orthogonal to the M-dimensional coordinate hyperplane. λ_{in} is associated with perturbations which are orthogonal to ℓ_M but within the M-dimensional coordinate hyperplane. The eigenvalue λ_s associated with the eigenvector along the line of symmetry ℓ_M is always stable and is not indicated in the diagram. Only integer values of M have physical meaning.
(Reprinted from [21].)

TABLE 1
(Reprinted from [21].)

A Summary of the Stability Analysis for Equilibria P_M.

Eigenvalues of the variational matrix A	Eigenvalue Multiplicity	Perturbation Eigenvectors $\bar{Z}=(\delta\xi_1,\ldots,\delta\xi_N)$	Geometric Interpretation in N-Dimensional Phase Space of $\bar{Z}=(\delta\xi_1,\ldots,\delta\xi_N)$
$\lambda_s = a_1 + Mb_1 = -2$	1	$\bar{Z}_s$ satisfies $\delta\xi_i = \begin{cases} 1, & i=1,\ldots,M \\ 0, & i=M+1,\ldots,N \end{cases}$	A perturbation from the stationary point P_M along ℓ_M.
$\lambda_{in} = a_1 = \frac{(M_1+M_2)M-2M_1M_2}{(M-M_1)(M-M_2)}$	M-1	$\bar{Z}_1,\ldots,\bar{Z}_{M-1}$ independent vectors which satisfy $\sum_{i=1}^{M} \delta\xi_i = 0$, $\delta\xi_i=0$, $i=M+1,\ldots,N$	Any perturbation from the stationary point P_M perpendicular to ℓ_M but within the M-dimensional coordinate hyperplane.
$\lambda_{out} = a_2 = 1 - \frac{M^2}{(M-M_1)(M-M_2)}$	N-M	$\bar{Z}_{M+1},\ldots,\bar{Z}_{N-1}$ satisfy $\delta\xi_i = 0$, $i=1,\ldots,M$ $\sum_{i=M+1}^{N} \xi_i = 0$, $i=1,\ldots M$ and $\bar{Z}_N$ satisfies $\delta\xi_i = \begin{cases} (M-N)b_1, & i=1,..M \\ (a_1-a_2)+Mb_1, & i=M+1,\ldots,N \end{cases}$	Perturbation out of the M-dimensional coordinate hyperplane.

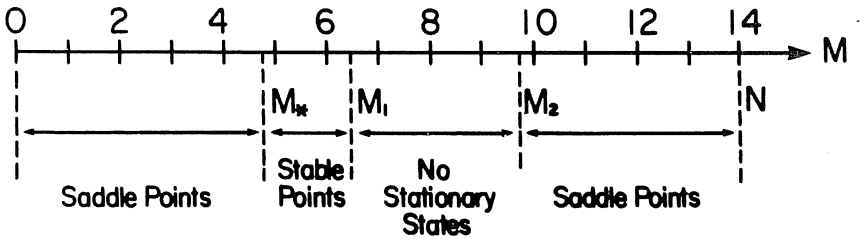

Figure 5. Stability of equilibria P_M located on lines of symmetry ℓ_M. (Reprinted from [21].)

Of course, ovulatory solutions need not be restricted to a single ovulation number. M_1 and M_2 can be chosen so that several coordinate hyperplanes will contain ovulatory solutions (those M-dimensional coordinate hyperplanes in the interval (M_1,M_2)). In addition, for special values of M_1 and M_2 it is possible for some of the equilibria P_M to become asymptotically stable. As shown in Fig. 4 all eigenvalues are negative when M is between $M_* = M_1M_2/(M_1+M_2)$ and M_1. Integers in this interval will correspond to stable P_M.

Each of these stable equilibria has a domain of attraction, and when the initial condition lies within such a domain, ovulation will not occur. Instead M follicles will become stuck at an equilibrium maturity given by equation (10). Since these "stuck" follicles continue to secrete hormones, they can be a source of additional pathology in the uterus and breast where cell growth is regulated by steroids secreted from the developing follicles.

8. Numerical Solutions

In this section we will test and further develop our intuition about the behavior of the growth law by solving the system (7) numerically. The numerical method used to obtain these results will be described after we discuss the change of variables on which it is based (Section 9).

Initial conditions are determined in the following way. Each of N follicles is independently assigned a starting maturity that is chosen at random from a uniform distribution on the interval $(0,\xi^0_{max})$. The observation that the reserve pool decays exponentially with age suggests that follicle activation could be modeled as a poisson process. For now, however, we will consider each cycle to begin with N follicles activated at the same time but with different maturities.

Figure 6 shows the results of 4 cycles in which 10 follicles are activated in each cycle. Although each follicle satisfies the same growth law (M_1 = 3.85, M_2 = 15.15 for each follicle), some follicles continue to mature while others atrophy and die. The results of many cycles, with

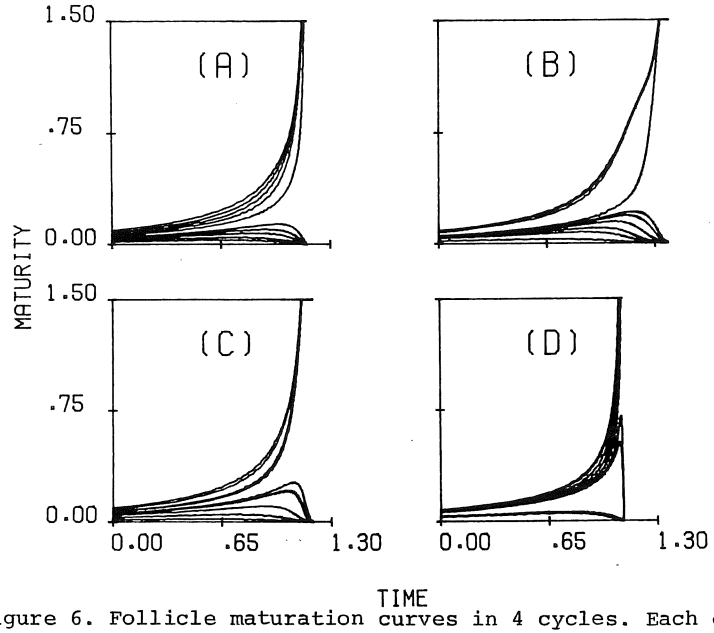

Figure 6. Follicle maturation curves in 4 cycles. Each curve represents the development of a follicle whose initial maturity is chosen at random from a uniform distribution of maturities between 0 and 0.1. Although every follicle obeys the same law of growth, some follicles are selected for continued development while others become atretic. The growth growth law parameters M_1 and M_2 of equation (7) are are the same for each follicle (M_1 = 3.85, M_2=15.15). In cycles (A) and (D) 5 ovulatory follicles emerge. In (B) and (C) the ovulation number is 4. In each cycle 10 follicles interact. Note that it is possible for an ovulatory follicle and an atretic follicle to have almost the same maturation curve for most of the length of the cycle (see cycle D). On the other hand, a significantly smaller follicle can occasionally "catch-up" and ovulate (see cycle B). The ovulation time is slightly different in each cycle.
(Reprinted from [21].)

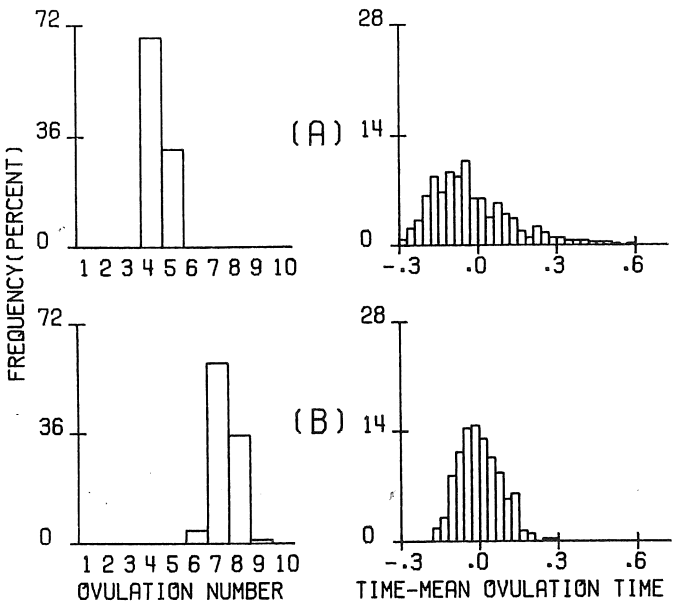

Figure 7. Distribution of ovulation numbers and ovulation times. In (A) the growth law parameters are the same as for Fig. 6 ($M_1 = 3.85$, $M_2 = 15.15$). The statistics are obtained for 500 cycles. In every cycle 30 follicles interact. Each follicle is given an initial maturity that is chosen independently from a uniform distribution in the interval (0, 0.075). In (B) the growth law parameters have been changed to $M_1 = 5.5$, $M_2 = 61.7$. The results summarize 300 cycles. As in (A), 30 follicles interact in each cycle but the initial maturities are uniformly distributed in the interval (0, 0.02). Statistics (mean $\pm$ SD): (A) ovulation number = 4.32 ± 0.47, ovulation time = 1.39 ± 0.23; (B) ovulation number = 7.34 ± 0.58, ovulation time = 1.12 ± 0.08.

the same parameters as above, show that two ovulation numbers are highly favored (Fig. 7). Even though ovulatory solutions have been shown to exist for all integers in the interval (M_1, M_2), the larger ovulation numbers are not observed at all! This surprising result will be explained in Section 9. Figure 6 could be interpreted in terms of a threshold initial maturity which separates ovulatory from atretic follicles. However, the results indicate that this threshold is "automatically adjusted" in each cycle so that number of follicles which ovulate is nearly independent of the initial maturities. Figure 7 also shows the distribution of ovulation times which is unimodal and skewed in favor of shorter intervals. This qualitative shape is observed in many species including humans.

The distribution of ovulation numbers is independent of ξ^0_{max}. The shape of the ovulation time distribution is unaffected by the choice of ξ^0_{max} so long as follicles start at maturities dominated by the independent exponential growth phase.

An interesting and perhaps important physiologic feature of the model occurs when the size of the interacting population changes. Figure 8 shows a shift in the distribution of ovulation numbers towards lower integers in the interval (M_1, M_2) as the size of the interacting population increases. There is also striking improvement in the control of ovulation time as N increases. These results suggest that the large number of follicles which initiate growth but atrophy and die in each cycle are playing an important role in the regulation of ovulation number and time.

The distribution of ovulation number seems to converge with increasing N to some limiting distribution. The probability density of ovulation times appears to have a singular limit with the standard deviation decreasing by a factor of $1/\sqrt{N}$. Although each ovulation number has its own distribution of ovulation times (Fig. 9), nevertheless all of these conditional distributions appear to converge to the same singular limit as $N \to \infty$. This means that the limiting cycle time is independent of the ovulation number.

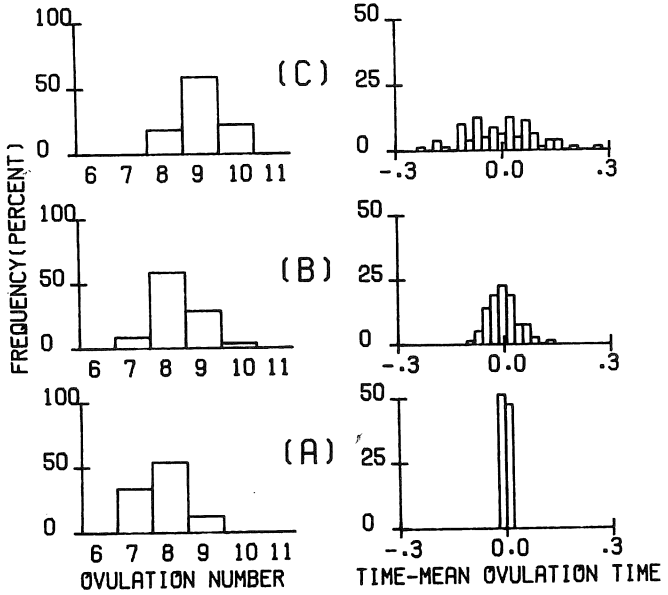

Figure 8. The effect of interacting follicle population size on the distribution of ovulation times and numbers. Larger numbers of interacting follicles improve control of ovulation time and favor smaller ovulation numbers. In (A) 1000 follicles interact in each cycle. In (B) 100 follicles interact per cycle and in (C) 30 follicles interact. Each graph represents the results of 80 cycles. Every follicle obeys equation (7) with $M_1 = 6.1$, $M_2 = 5000.0$. Initial maturities are chosen at random to be a number from a uniform distribution between 0 and 10^{-5}. Statistics (mean $\pm$ S.D.): (A) ovulation number = 7.79 $\pm$ 0.65; ovulation time = 4.37$\pm$0.01; (B) ovulation number = 8.82 $\pm$ 0.67, ovulation time = 5.55 $\pm$ 0.04; (C) ovulation number = 9.04 $\pm$ 0.65, ovulation time = 6.33 $\pm$ 0.10.
(Reprinted from [21].)

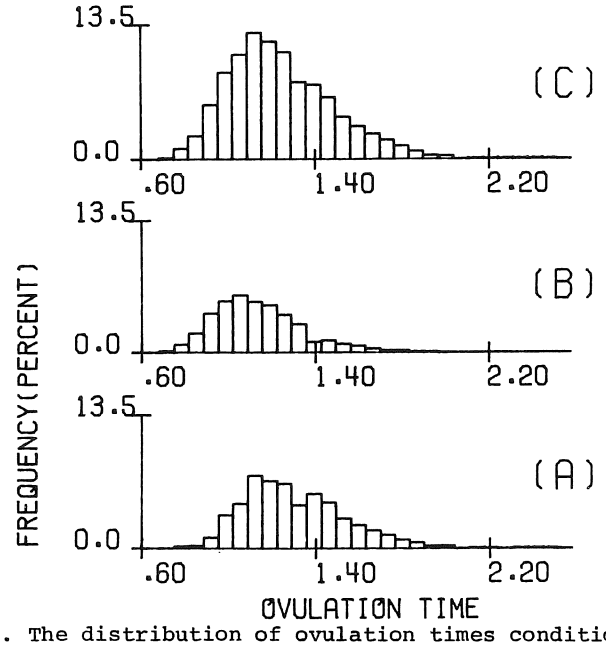

Figure 9. The distribution of ovulation times conditioned on ovulation number. The initial maturity of each follicle is chosen independently from a uniform distribution in the interval (0, 0.05). The growth law parameters ($M_1 = 5.5$, $M_2 = 61.7$) are the same as for Figure 7 (B). In each cycle the number, N, of interacting follicles is 10. (A) represents the ovulation time frequencies for those cycles in which 7 follicles ovulate (mean $\pm$ S.D. = 1.31$\pm$0.25). (B) represents the distribution of ovulation times for those cycles in which 8 follicles ovulate (mean $\pm$ S.D. = 1.13 $\pm$ 0.20). The area under each graph is equal to the probability of achieving that ovulation number. The results are obtained from a total of 1500 cycles. The distribution of ovulation times for all cycles is represented in (C) (mean $\pm$ .S.D = 1.25 $\pm$ 0.25).
(Reprinted from [21].)

Figure 10 illustrates the results of 4 cycles when the growth law parameters are $M_1 = 6.5$ and $M_2 = 15.5$. As predicted from the stability analysis, these parameters admit the possibility of both ovulatory solutions and anovulatory states, since the interval (M_*, M_1) contains the integers 5 and 6. In Fig. 10B, 6 follicles become "stuck" at the predicated equilibrium maturity. Much more infrequently 5 follicles (Fig. 10D) become "stuck" (2 out of 1000 trials).

We now briefly consider the behavior of the growth law when follicles are activated from the reserve pool at random times. In Fig. 11 (preliminary results), follicles initiate growth at random times given by a poisson process. Each activated follicle is given the same initial maturity and obeys the same growth law (equation (7) $M_1 = 3.15$, $M_2 = 15.15$. Note that the number of interacting follicles, N, is now a function of time.

Although there is no source of periodicity, a relatively constant number of follicles periodically emerge as ovulatory. Just before ovulation the serum estradiol concentration is almost entirely due to the ovulatory follicles. At ovulation, these follicles are removed from the interacting population. This results in a precipitous drop of circulating estradiol to levels where stimulatory interactions can again occur and allow a new crop of follicles to mature. The ovulation number and time need not be the same as the previous cycle because of the assumed stochastic nature of growth initiation from the reserve pool.

An intriguing property of this form of the model is that successive cycles are completely uncorrelated. That is, any two random variables (e.g. ovulation times) associated with different cycles are independent. This follows from the fact that, in our model, atretic follicles are driven to $\xi_i = 0$ (zero rate of estradiol production) at the moment of ovulation, so they are completely removed at the same time as the ovulatory follicles. Thus the process has no memory from one cycle to the next. This raises the question whether successive cycles are correlated or not (the answer may be different in different species). Some preliminary evidence

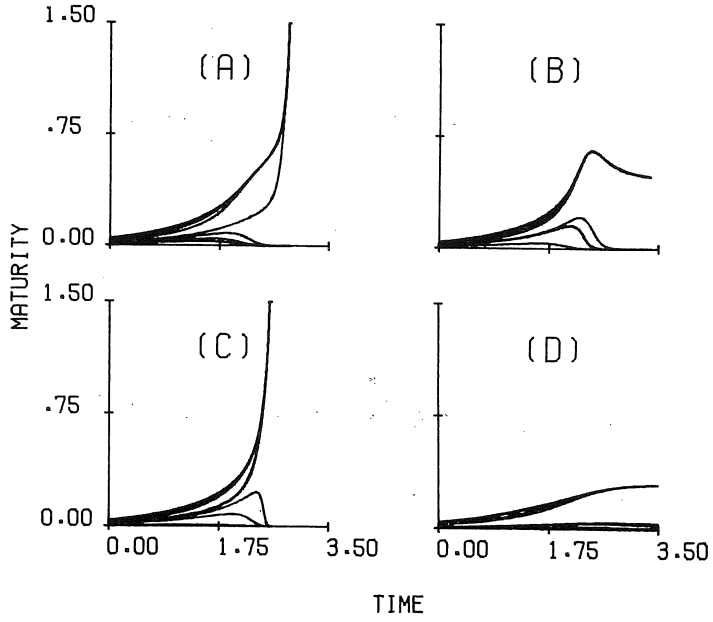

Figure 10. Follicle maturation curves for parameters which admit both ovulatory solutions and anovulatory states. Every follicle satisfies equation (7) with the same parameter values $M_1 = 6.5$, $M_2 = 15.5$. The initial maturity of each follicle is chosen at random from a uniform distribution in the interval (0, 0.05). In (A) and (C) 7 follicles ovulate. In (B) an anovulatory state occurs in which 6 follicles approach an equilibrium maturity of 0.46. In (D) 5 follicles approach a maturity of 0.25. Note that the approach to equilibrium need not be monotonic (B).

(Reprinted from [21].)

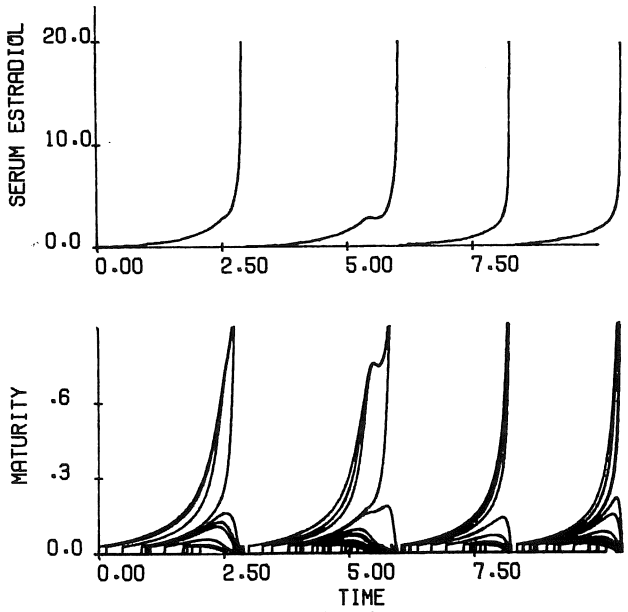

Figure 11. (Preliminary results.) Behavior of the growth law (7) when follicles begin to develop at random times determined by a poisson process. Each small vertical mark on the time axis represents the activation of a follicle. All activated follicles start with the same maturity (0.03) and obey the same law of growth. (M_1 = 3.85, M_2 = 15.15). Although there is no source of periodicity, a relatively constant number of follicles mature at periodic intervals. The results of the 4 illustrated cycles are tabulated below:

Cycle	Ovulation Number	Ovulation Time	Follicles Activated per Cycle
1	4	2.91	18
2	4	3.12	27
3	5	2.20	17
4	5	2.21	20
TOTAL	18	10.44	82.

The mean activation rate is set at 8.

bearing on this question is discussed in [29].

In this idealized model ovulation number and time are determined entirely by interactions between activated follicles. These interactions are exerted indirectly through the effects of serum estradiol on the release of circulating pituitary hormones. In several species other factors besides secretions from developing follicles influence gonadotropin release. Some of these are in the external environment and periodically change with the season or day (light). Other factors include steroid production by sources other than growing follicles including, for example, the corpus luteum. As previously mentioned these factors cannot alone account for the small variance in ovulation number that mammals achieve. They can, of course, modulate the mechanism proposed for the regulation of ovulation number and time and therefore should be considered in more detailed schemes.

9. Stability of N-Space Trajectories

The stability analysis of symmetric equilibria suggested that the phase curves in N-space would approach the lines of symmetry, ℓ_M, in coordinate hyperplanes with dimensions in the interval (M_*, M_2). It was shown that these lines either contained ovulatory solutions (for M between M_1 and M_2) or stable anovulatory equilibria (for M between M_* and M_1). Although the numerical results agree with these theoretical predictions, in the sense that all of the observed values of M fall within the allowed interval, the larger ovulation numbers in this interval are not observed even though ovulatory solutions for these numbers exist. It might be thought that these ovulation numbers simply have a low probability of occurring. In fact, however, the larger allowed ovulation numbers have probability zero. As we now show, this is because ovulatory solutions in the interval $(2M_*, M_2)$ are unstable.

Since ovulatory phase curves blow up in finite time, a change of variables is chosen in which these curves approach finite equilibria whose stability can be analyzed by the methods employed in Section 7. This is accomplished

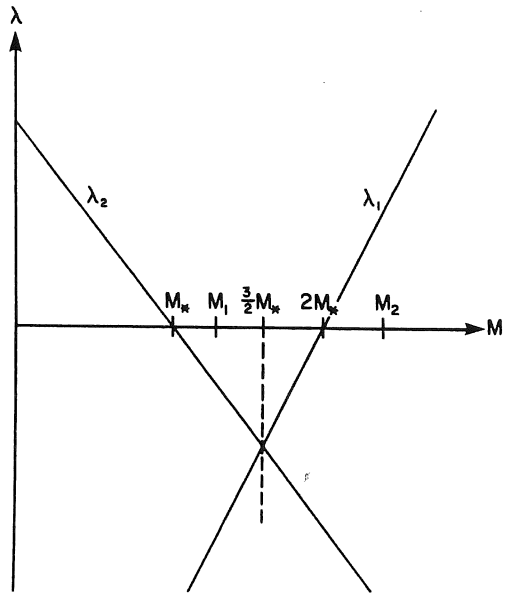

Figure 12. Stability analysis of the equilibria represented by equation (16). Each equilibrium is characterized by M, the number of follicles with relative maturity $\gamma_i = 1$. λ_1 and λ_2 are the distinct eigenvalues associated with each equilibrium. These eigenvalues are linear in M (see equation (17)) and divide the range of ovulation numbers in the interval (M_1, M_2) into a stable range $(M_1, 2M_*)$ and an unstable range $(2M_*, M_2)$. This explains why larger ovulation numbers in the interval (M_1, M_2) are not observed even though solutions for these ovulation numbers have been shown to exist (see Section 6). The figure also shows a stable region between $M_* = M_1M_2/M_1 + M_2$ and M_1. If integers exist in this interval they correspond to the presence of stable anovulatory states.

(Reprinted from [21].)

in the following way which was suggested to us by J. Moser.

Arrange the N follicles in order of their maturities with ξ_1 the most mature. (Since the $\xi_i(t)$ do not cross, the order of maturities is preserved in time.) We now rescale the time by defining

$$\tau(t) = \int_0^t \xi_1^2(t')\, dt' \,. \tag{13}$$

As t approaches the finite time of ovulation, $\tau \to \infty$. This follows from the fact that $d\xi_1/dt \sim \xi_1^3$ as $\xi_1 \to \infty$. Since the inverse of $\tau(t)$ exists we can use it to define the variables.

$$\gamma_i(\tau) = \xi_i(t(\tau))/\xi_1(t(\tau)) \quad \text{and} \quad \Gamma(\tau) = \xi(t(\tau))/\xi_1(t(\tau)). \tag{14}$$

We can now rewrite the system (7) in the following form.

$$\left.\begin{aligned} d\gamma_i/d\tau &= \gamma_i\, \psi(\gamma_i, \Gamma), \quad i = 1, N \\ \Gamma &= \sum_{j=1}^{N} \gamma_j \end{aligned}\right\} \tag{15}$$

where

$$\psi(\gamma_i, \Gamma) = (1-\gamma_i)[M_1M_2(\gamma_i+1) - \Gamma(M_1+M_2)].$$

Note that $\gamma_1(\tau) \equiv 1$, and $0 \le \gamma_i(\tau) \le 1$.

Since we expect $\xi_i(t)/\xi_1(t) \to 1$ for ovulatory follicles we look for stationary points of (15) of the form

$$\gamma_i = \begin{cases} 1, & i = 1,\ldots,M \\ 0, & i = M+1,\ldots,N \,. \end{cases} \tag{16}$$

In fact, this form is also applicable to anovulatory states, and the only way to tell the difference is to see whether ξ_1 is infinite or finite. The stability analysis of (15) near these stationary states is summarized in Fig. 12. There are only 2 distinct eigenvalues λ_1 and λ_2. They are linear in M.

$$\begin{aligned} \lambda_1 &= (M_1+M_2)M - 2M_1M_2 \\ \lambda_2 &= -(M_1+M_2)M + M_1M_2 \end{aligned} \tag{17}$$

Since ovulatory solutions correspond to integers between M_1 and M_2, we see that this interval is broken into a stable and unstable region. The stable ovulation numbers lie at the lower end between M_1 and the harmonic mean, $2M_*$, of M_1

and M_2. The larger ovulation numbers are unstable. The region between M_* and M_1 is also stable. As noted earlier in Section 7, if integers exist in this region they correspond to stable anovulatory states.

The above analysis is consistent with the numerical results obtained in Section 8. For example, consider Fig. 7B. Although symmetric solutions for ovulation numbers between 6 and 61 exist, only ovulation numbers 6 through 9 are observed. Since $M_1 = 5.5$, $2M_* = 10.1$, these results match the stability analysis perfectly except that the ovulation number 10 should have been seen. Presumably its low probability is related to the fact that 10 is very close to the stability boundary in this case.

It should be noted that the range of stable ovulation numbers is not affected by the number of interacting follicles since the eigenvalues λ_1 and λ_2 are independent of N. Changing N, however, alters the dimension of the phase space and presumably the geometry of the capturing region associated with a given stable ovulation number. This could change the frequencey with which a given stable ovulation number will be observed.

10. Numerical Methods

The numerical solutions of Section 8 were not obtained by direct integration of (7). Advantage was taken of the fact that the solutions of (15) do not "blow-up" in finite time but rather approach finite stationary points asymptotically as $\tau \to \infty$. The initial maturities $\xi_i(0)$ are converted to relative maturities $\gamma_i(0)=\xi_i(0)/\xi_1(0)$. The system (15) is then directly integrated by utilizing a standard explicit finite difference method (a second order Runge-Kutta scheme was used). The value of $\Gamma(\tau) = \sum_{i=1}^{N} \gamma_i(\tau)$ converges to an integer which is the ovulation number (or number of follicles stuck in an anovulatory state). Since the distribution of relative maturities determines the ovulation number, it is easy to understand why the distribution of ovulation numbers is independent of ξ^0_{max}.

Once $\gamma_i(\tau)$ and $\Gamma(\tau)$ have been obtained, transformation to $\xi_i(t)$ is accomplished by solving the differential equation which is satisfied by $\bar{\xi}_1(\tau) = \xi_1(t(\tau))$,

$$\frac{1}{2}\frac{d}{d\tau}\bar{\xi}_1^2 = 1 - (\Gamma - M_1)(\Gamma - M_2)\,\bar{\xi}_1^{-2}. \tag{18}$$

The actual time t which corresponds to τ is obtained by integration

$$t(\tau) = \int_0^{\tau} \frac{1}{\bar{\xi}_1^2(\tau')}\, d\tau' . \tag{19}$$

Using the inverse $\tau(t)$ we finally obtain,

$$\xi_i(t) = \bar{\xi}_1(\tau(t))\ \gamma_i(\tau(t)) . \tag{20}$$

The solutions obtained were checked against a scheme which solved the untransformed equations (7) directly. Both numerical methods converged to the same solution.

The advantages of using the change of variables are that the dependent variables γ_i are bounded while the ξ_i are not and that high time resolution is automatically achieved near the blow up time because $\tau \to \infty$ as t approaches the time of ovulation.

Conclusion

We have proposed a simple and specific model in which developing follicles regulate their growth through interactions that are exerted by circulating hormones. These interactions occur indirectly through follicle secretions that control the release of pituitary hormones. Although all follicles obey the same developmental program and start growing at random times from an immature reserve pool, a small and relatively constant number of follicles emerge at regular intervals with ovulatory maturity. The remainder atrophy and die at different times and stages of development. A change in the parameters of the growth law can alter the distribution of ovulation numbers and times. Thus, the observation that mammalian species and breeds have different characteristic litter sizes can be accounted for by the same basic developmental scheme.

An interesting and perhaps important physiologic feature of the model occurs when the size of the interacting population changes. As the number of interacting follicles increases, there is striking improvement in the control of ovulation time. There is also a shift in the distribution of ovulation numbers towards smaller integers. Since the number of interacting follicles in a cycle decreases with age, these results partially explain the increased variance in the time of ovulation as women approach menopause [30]. The behavior of the model is also consistent with the observed increase in the occurrence of dizygotic twins as women age [31].

The model therefore suggests two important functions for the large number of follicles that are activated during each cycle, even though an overwhelming fraction (about 99.9% in humans) of these are destined to atrophy and die. The functions of these nonovulatory follicles are to hold down the ovulation number and to reduce the variance in the time required for the ovulatory follicles to mature.

This makes sense in evolutionary terms when we consider that, in primitive species, the reproductive strategy is to produce as many offspring as possible. Mammals have a different reproductive strategy in which a large effort is invested in a small number of offspring. Often in evolution, older mechanisms are not discarded but are adapted to new ends when the demands of the environment change. This is often accomplished by superimposing a new layer of control mechanisms upon an older scheme. In the case of the ovary, the model suggests that the old strategy of producing as many ova as possible has been adapted to the (opposite) purpose of tight control on the reproductive process. Before the present model was proposed, the significance of the nonovulatory follicles was completely mysterious.

Another important feature of the model is that it predicts, under special conditions, the existence of (pathological) anovulatory states. These have been shown to correspond to stable equilibria in which a certain number of follicles become "stuck" and produce nearly steady levels of

circulating estradiol. In some women it has been observed that such states may exist for long periods of time [32]. It is important to understand such states because estradiol and its metabolites are potent stimulators of cell growth in the uterus and breast. Persistent exposure to steady, relatively high levels of estradiol may have serious consequences including a greater risk for the development of carcinoma of the breast and endometrium [33].

The duration of these states and their frequency of occurrence in a given individual varies over a wide spectrum in the female population [34]. Spontaneous escape does occur and may be the result of random perturbations. Such perturbations could occur naturally, for example, by the continual and random entry of follicles into the interacting population from the reserve pool. The factors in the model which influence the duration and frequency of occurrence of these states are presently being investigated. It should be noted that these stable anovulatory equilibria exist only for special values of the parameters. Therefore the model is consistent with the observation that some species and some individuals within a species do not exhibt these states.

Clearly, at the biochemical level, the mechanisms that regulate the growth of follicles are far too complicated to be described by any equation as simple as our growth law ϕ. The question, however, is not whether this growth law contains a detailed description of all of the processes involved but whether it is an adequate summary of the relevant consequences of these complicated biochemical events. One important test of this is whether the growth law generates behavior consistent with observations on the control of ovulation number. Another important test is whether the growth law is actually obeyed by individual follicles. The first test has already been passed, as demonstrated in this paper. Experiments designed to test the second point are proposed in [21].

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