J. Math. Biol. (1997) 36: 95–118

Journal of Mathematical Biology

Modelling the control of ovulation and polycystic ovary syndrome

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Received 19 August 1996; received in revised form 14 February 1997

Abstract. The control of ovulation in mammalian species appears to be a highly robust process. The primary mechanism is believed to be competition amongst a group of developing follicles, mediated by a hormonal feedback loop involving in the first instance the pituitary. Successful follicles reach maturity and ovulate, the remainder atrophy and die. A model of this control process has been derived by Lacker and his group. Based on simple qualitative assumptions about the hormonal feedback loop, this is able to reflect many of the basic physiological features of ovulation in mammals. However, a fundamental hypothesis of Lacker's work is that all follicles are identical and respond to hormonal signals in precisely the same way. Not only is this improbable, but it also leads to several aspects of the model which are qualitatively unrealistic, most notable of these is its inability to accurately model the condition known as Polycystic Ovary Syndrome. This common malfunction of the ovulatory control mechanism accounts for up to three-quarters of cases of anovulatory infertility in humans and its understanding is therefore of considerable medical significance. In this paper we extend the analysis of Lacker's model to the case of non-identical follicles; this allows us to obtain behaviour much closer to that observed in *PCOS* patients and to draw some tentative conclusions about the mechanisms underlying this condition.

Key words: Ovulation – Lacker models – Polycystic ovary syndrome – PCOS

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1 Introduction

The production and fertilization of eggs is a remarkably wasteful process in many parts of the animal kingdom. In some species (e.g. fish) vast numbers of eggs are produced and released into the environment. Only a small fraction of these are fertilized, and only a small fraction of the resulting zygotes survive and develop to adulthood. By contrast, in mammalian species selection and competition takes place prior to ovulation with the release of a small number of mature eggs, most of which are then fertilized. In particular, in most mammals the ovaries contain a large (e.g. $\sim 10^6$ in the human) number of immature dormant follicles, each one of which contains an egg. In an adult female numbers of such follicles continuously leave the dormant state and begin to develop. The vast number of these atrophy and die before they reach maturity (through a controlled process known as atresia), and only a small number ovulate, (i.e. release the egg out of the ovary) in each reproductive cycle. This number shows surprisingly little variation within each species, thus for instance in the human it is almost always one. This is despite the fact that the number of follicles which begin to develop at any particular time, or which are ready to proceed to the final stages of maturation at the start of a given cycle, appears to show considerable random variation.

The selection of those follicles which are destined to ovulate appears to take place by a competitive process amongst a group of follicles during each reproductive cycle. Since in many species (including humans) the number of ovulating follicles is unaffected by removal of one ovary, the control mechanisms must at least partly operate outside of the ovary. It is now well known that the maturation process is regulated by the endocrine system involving the hypothalamus, pituitary glands and the ovary itself.

It is useful to model this in a theoretical way in order to understand the factors which control ovulation. In this paper we are particularly interested in developing models that may also explain how this mechanism can go wrong. A particularly important example of this is the medical condition known as *Polycystic Ovary Syndrome* (*PCOS*). In various degrees of severity this affects up to 20% of human females of reproductive age (Polson et al., 1988). In its more serious forms it leads to anovulation, accounting for some three-quarters of cases of anovulatory infertility.

One of the main characteristics of *PCOS* is that the ovary contains a substantial number of large follicles which reach 5–10 mm in diameter but fail to ovulate. A reasonable interpretation is that this is caused by a failure of the selection mechanism; instead of one follicle coming to dominate and the remainder degenerating through atresia, a large group become arrested at some intermediate stage. An understanding of this failure is important medically; whilst many women suffering from anovulatory *PCOS* can be successfully made to ovulate by treatment with appropriate hormones, this can easily result in multiple ovulation, leading to multiple pregnancies with all their attendant adverse side effects. Whilst modern treatment protocols have to

some extent overcome this problem a better understanding of mechanisms leading to *PCOS* is still highly desirable.

A number of models of the control of ovulation have been derived by various authors (e.g. Lacker, 1981; Lacker et al., 1984, 1987, 1988, 1991; Thalabard et al., 1989 and Mariana et al., 1984). Those developed by Lacker and his group are by far the most studied and best understood, and will be the starting point of our analysis. Based on simple qualitative assumptions about the primary hormonal feedback loop involving the pituitary, Lacker's model is able to reflect most of the basic physiological features of the ovulation cycle in mammals, including the regulation of the ovulation number, the fact that almost all of the follicles that start a given cycle atrophy and die, and that it is possible for follicles to arrest at an intermediate stage, neither ovulating nor degenerating through atresia.

However Lacker's model in its present form is incapable of successfully modelling the qualitative features of *polycystic ovaries* (*PCO*) in humans. In particular, if its parameters are set to values appropriate for humans (i.e. one follicle ovulating per cycle) it is impossible to obtain a situation where more than a single follicle can arrest. One can of course achieve the arrest of a larger number of follicles by drastic changes in the parameters. However, this pushes the model into regimes characterized by a large number of follicles ovulating in each cycle, and is hence unrealistic in the human case. Since *PCO* covers a whole spectrum of conditions, ranging from almost normal ovulation to the most severe cases of anovulation, we do not expect to have to make large changes to the model to move from normal to *PCO* behaviour and vice versa. Indeed, since it is possible to find individuals who switch between approximately normal ovulatory cycles and anovulation apparently at random, it should be feasible to observe both types of behaviour for a single set of parameters, just by changing the initial conditions at the start of a cycle (i.e. the number and precise maturity of the follicles entering that cycle).

Lacker's model has also been criticized (Thalabard et al., 1989; Mariana et al., 1984) because it maintains a strict hierarchy amongst the follicles developing in a given cycle; thus follicles which start out largest remain the largest, and hence are the ones that ovulate. Both Thalabard et al. and Mariana et al. have proposed models which overcome this restriction, but neither of these appears to be amendable to the same level of rigorous analysis as is possible with Lacker's model

In fact the root cause of both of the above problems is the perfect symmetry inherent in Lacker's system: thus every follicle is presumed to have identical characteristics and to respond to hormonal signals in exactly the same way. This is unrealistic; it is almost impossible to find two biological systems which behave in absolutely identical fashions. Our aim in this paper is therefore to remove this assumption of symmetry from Lacker's model. It transpires that we can do this in a way which still permits Lacker's mathematical analysis to hold essentially unchanged. The behaviour of the resulting model is, however, much more general, and in particular it is possible to obtain a more realistic model of the behaviour of follicles in *PCO* in this way.

Due to the simplified and rather abstract nature of the models discussed here, it is difficult, and perhaps even dangerous, to extrapolate from behaviour observed in such models to conclusions about the real biological systems they represent. Nevertheless, the analysis and numerical simulations carried out below appear to offer some tentative insight into the mechanisms underlying *PCO*. Thus, within the context of these models the primary cause of *PCO* lies in the response of follicles to hormonal stimulation, rather than in the functioning of the pituitary or the ovary as a whole. This is consistent with clinical thinking about the nature of *PCO* (e.g. Yen, 1980, pp. 192; Franks et al., 1996).

In particular, for an ovary to become polycystic in our model, it must contain a sub-population of follicles which have a significantly different response to gonadotrophins from those follicles involved in normal ovulation. Given the simplicity of the model, it is difficult to be too specific about the types of abnormal gonadotrophin response required to induce "*PCO* type" behaviour. One may tentatively conclude that such abnormal follicles should either achieve their maximal response to gonadotrophins at earlier stages of their maturity (which is measured by their size in this model), or at a given size achieve their maximal response at lower levels of circulating gonadotrophins. The model is too simplistic to distinguish between these two cases, and doubtlessly other response patterns can lead to "*PCO type*" behaviour as well. Furthermore the model currently does not distinguish between different gonadotrophins and we are developing more sophisticated models which incorporate such distinctions. These are likely to be important, since the roles played by the two main gonadotrophins, follicle stimulating hormone (*FSH*) and luteinizing hormone (*LH*) is quite different (Watson et al., 1993; Mason et al., 1994; Franks *et al*., 1996).

However, it should be pointed out that some kind of heightened sensitivity to gonadotrophins which both of the above interpretations imply is in line with recent experimental observations that follicles of *PCOS* patients are much more sensitive to *FSH* than those of normal women (Mason et al., 1994). The model here may therefore help to explain the somewhat paradoxical nature of these observations.

A further interesting aspect of our model is that in certain circumstances the presence of follicles with abnormal gonadotrophin response can suppress the ovulation of a normally functioning follicle. This appears to happen because such abnormal follicles, being more sensitive to gonadotrophins, can produce a sufficiently high level of oestradiol to reduce the production of gonadotrophins by the pituitary to a level so low that normal follicles cannot grow. In the presence of a mixed population of normal and abnormal follicles, therefore, the factor determining whether ovulation will, or will not occur, is the relative proportions of the two types of follicles, and their relative maturities at the start of the cycle. One can thus envisage that in marginal cases of *PCO* the determining factor of whether ovulation occurs in a given cycle or not is the number of maturity of abnormal follicles present at the start of the cycle.

Of course, since our model ignores many important aspects of the real system, such as the mechanisms controlling atresia, or the modulation of the behaviour of the pituitary by the hypothalamus, the above conclusions must be regarded as highly speculative. It would however be interesting to see whether any can be tested experimentally, or even duplicated in more complex and biologically realistic models.

2 Biological background of the models

During ovulation each egg is released from a follicle which has been maturing in the ovary over a period of nine to twelve months (in the human). The period of development of a follicle therefore spans a number of ovulation cycles. However, the mechanism which serves to select those follicles destined to ovulate appears to operate solely in the last of these cycles, and we shall therefore restrict our attention to this cycle. We shall give a brief description of this, focusing on those aspects required to construct a model: the real system is of course more complex and the interested reader should for instance consult (Austin and Short, 1984) for a fuller description.

At the start of each such cycle, the ovary will contain a number of follicles which are ready to enter the final stages of maturation. The ovulating follicles are chosen from amongst this number by a feed-back mechanism involving the pituitary, the ovary and the hypothalamus (e.g. Austin and Short, 1984). The primary feedback loop consists of the maturing follicles and the pituitary. Each maturing follicle produces oestradiol which is released into the blood circulation. The larger and more mature the follicle is the more oestradiol it produces. The oestradiol levels in the blood stream have a negative effect on the rate of release of gonadotrophins (*FSH* and *LH*) by the pituitary, and these gonadotrophins in turn stimulate the growth of the follicles and their production of oestradiol (*FSH* and *LH* do play somewhat different roles, but this is ignored in Lacker's model). Overall, therefore the feedback loop is a negative one: the larger and more mature the follicles are, the less *FSH* and *LH* is released by the pituitary, which serves to limit the further growth of the follicles. However, because more mature follicles are more sensitive to *FSH* and *LH* their growth is restricted less. This serves to amplify differences between follicles with the larger and more mature ones being selected to ovulate, and the others first arresting their growth, and then becoming atretic.

The action of this primary feedback loop is modulated by the hypothalamus which releases Gonadotrophin Releasing Hormone (*GnRH*) which stimulates the release of *FSH* and *LH* by the pituitary. For the purposes of the models described here the effect of *GnRH* is assumed to be constant in time, and hence can be ignored in the selection process. Note also that just prior to ovulation the sign of the feedback in the pituitary changes, leading to the so called *LH* surge. This again is not incorporated in Lacker's model, since by the time of the surge the ovulating follicles have already been selected.

3 Lacker's model of the ovulation cycle

In this section we briefly describe the model developed and analaysed by Lacker and his collaborators (e.g. Lacker, 1981; Lacker et al., 1984, 1987, 1988, 1991). Whilst possibly too simple to be biologically realistic, it is remarkably successful in displaying many of the key features of the selection process. The model seeks to describe the maturation of a group of N follicles, and their interaction via oestradiol and the gonadotrophins with the pituitary. It is based on the following simplifying assumptions:

a) Follicle size, maturity and oestradiol secretion are all proportional.
b) The rate of release of FSH and LH is a function of the blood concentration of oestradiol.
c) The growth rate of a follicle is determined by the blood concentration of FSH and LH, and the follicle's own maturity.
d) All follicles respond identically to FSH and LH and obey the same growth law.
e) No distinction is made between the effects of FSH and LH, which are represented implicitly through their assumed control by a single hormone.
f) The effect of $GnRH$ is ignored.
g) Hormonal clearance rates as well as pituitary response to circulating oestradiol are relatively fast compared to the selection process, and hence hormone levels and pituitary response are always assumed to be in equilibrium.

Each follicle is therefore modelled by a single variable x_i which reflects its size and hence its maturity and oestradiol production. Follicles interact amongst themselves *via* their contribution to the total blood concentration of oestradiol. In a way, they compete between each other in order to be the ones able to ovulate. The growth rate of the ith follicle is thus some function $g(x_i, X)$ of the follicle's size x_i and the total circulating oestradiol concentration X, where

$$X = \sum_{j=1}^{N} x_i \, .$$

The function g incorporates both the response of the pituitary to oestradiol and the follicle's response to the resulting levels of FSH and LH. Since follicles are assumed identical, we have the same function g for each follicle. The dynamicss of the ith follicle is therefore given by

$$\frac{dx_i}{dt} = x_i g(x_i X) \, . \tag{1}$$

See e.g. Lacker, 1981 for more details of the derivation of the model. The initial conditions of the x_i are chosen essentially arbitrarily.

Given that the selection process may be viewed as a competitive one it is not surprising that the above model has much in common with models of competition used in ecology or evolution (e.g. Hofbauer and Sigmund, 1988).

Thus, referring back to the first section of the introduction, we see that it does not matter too much whether selection occurs before or after fertilization, the resulting models will have many similar features.

Since the above model is far too general to be analyzed, Akin and Lacker make the assumption that the growth function g can be separated in the following way (Akin and Lacker, 1984):

$$g(x_i X) = \delta(X)[\rho(X) + \xi(p_i)] \tag{2}$$

where

$$p_i = \frac{x_i}{X}$$

is the relative maturity of the ith follicle, i.e. the oestradiol production of the ith follicle relative to the total oestradiol concentration. Note that without loss of generality we may assume $\xi(0) = 0$, as otherwise we may replace ξ by $\xi - \xi(0)$ and ρ by $\rho + \xi(0)$ without changing the dynamics. The function ρ is assumed to be monotone decreasing for $X > 0$ and $\rho(X) \to -D$ for some constant $D > 0$ as $X \to \infty$, and $\rho(X) \to \infty$ as $X \to 0$.

When g is of the form (2), the dynamics of p_i can be written as:

$$\frac{dp_i}{d\tau} = p_i[\xi(p_i) - \bar{\xi}(p)] \tag{3}$$

where $p = (p_1, \ldots, p_N)$ and

$$\bar{\xi}(p) = \sum_{i=1}^{N} p_i \xi(p_i)$$

$$\sum_{i=1}^{N} p_i = 1 \ .$$

This new system is referred as the *interaction dynamics* where τ is the new rescaled time defined in terms of the *rescaled time function* $\delta(X)$ as:

$$\frac{d\tau}{dt} = \delta(X).$$

The derivation of these equations can be found in for instance (Akin and Lacker, 1984), and is also given in the more general case of non-identical follicles in Sect. 3 below.

System (3) can be transformed into a gradient system on the unit $N - 1$ sphere S, which implies that all initial conditions ultimately tend to some equilibrium point of the system. This means that there is neither oscillatory nor any other kind of complex behaviour within the dynamics. The conditions for this equilibrium point in terms of the *interaction dynamics* are either:

$$p_i = 0$$

or

$$\xi(p_i) = \bar{\xi}(p) \ .$$

Thus at an equilibrium point all non-zero p_i must have the value of ξ. The stability for the resulting equilibrium point is determined by the common value $\bar{\xi}(p)$ also denoted as λ, and by the *interaction function* $\xi(p_i)$. More precisely, if the equilibrium point is non-degenerate then it is stable if and only if $\lambda > 0$ and $\xi'(p_i) < 0$ for all nonzero p_i or $\xi'(p_i) \geqq 0$ for exactly one nonzero p_i and

$$\sum_{i=1}^{M} \frac{1}{\xi'(p_i)} > 0 \, .$$

(Akin and Lacker, 1984).

An equilibrium point of the interaction dynamics can correspond to ovulatory and anovulatory cases depending on the value of λ, and the behaviour of the *intensity dynamics*

$$\frac{dX}{d\tau} = X[\rho(X) + \bar{\xi}(p)]$$

which governs the total concentration of circulating oestradiol. The ovulatory case is characterized by $\rho(X) + \bar{\xi}(p) > 0$, so that X grows without bound (in the biological system it of course cannot grow infinitely, and one assumes that when it reaches a sufficiently large value an *LH* surge is triggered, followed by ovulation). The anovulatory case occurs when the intensity dynamics has a fixed point, i.e. a value of $X > 0$ such that $\rho(X) + \bar{\xi}(p) = 0$; follicles can then grow to a given size but no further. Akin and Lacker also analyse the dynamics of the *time rescaling function* $\delta(X)$ for both situations, finding that under reasonable conditions on δ, in the ovulatory case there is a finite value of T in which X grows to infinity: this is interpreted as the time taken to ovulate (Akin and Lacker, 1984).

The fact that the growth function ξ is the same for all follicles, results in a symmetric situation for which the symmetric point that satisfies both equilibrium conditions of the *interaction dynamics* is:

$$p_i = \begin{cases} \dfrac{1}{M} & 1 \leqq i \leqq M \\ 0 & M < i \leqq N \end{cases}$$

for some $0 < M \leqq N$. The above stability analysis shows that this is stable if $\xi(1/M) > 0$ and $\xi'(1/M) < 0$.

The particular growth function proposed by Lacker is:

$$g(x_i, X) = K - D(X - M_1 x_i)(X - M_2 x_i) \tag{4}$$

where D, K, M_1 and M_2 are parameters. Without loss of generality $M_1 < M_2$ and

$$\frac{1}{M_1} + \frac{1}{M_2} < 1 \tag{5}$$

(by rescaling we may assume $K = D = 1$). In this case

$$\xi(p_i) = Dp_i(M_1 + M_2 - M_1 M_2 p_i)$$

$$\rho(X) = \frac{K}{X^2} - D$$

$$\delta(X) = X^2 \, .$$

The symmetric equilibrium is then stable for all M such that:

$$\frac{1}{M_H} < \frac{1}{M} < \frac{2}{M_H}$$

where M_H is the harmonic mean of M_1 and M_2:

$$\frac{1}{M_H} = \frac{1}{2}\left(\frac{1}{M_1} + \frac{1}{M_2}\right).$$

Thanks to assumption (5) it can be shown geometrically that non-symmetric equilibria are never stable (Akin and Lacker, 1984) and (Lacker and Percus, 1991). Given the parameter values M_1 and M_2 there can be as many different *M-fold* stable equilibrium points as there are different integer values of M within the interval $(M_H/2, M_H)$. From the *intensity dynamics* we see that these M follicles will eventually ovulate if $\xi(1/M) > D$ or they will get stuck if M is such that $\xi(1/M) < D$. If $D = 1$ and $M_1 < M_2$ it can easily be verified that $M_H/2 < M < M_1$ corresponds to anovulation, and $M_1 < M < M_H$ corresponds to ovulation.

We therefore see that if the interval $(M_H/2, M_1)$ contains an integer, the model will exhibit anovulatory states, and if both $(M_H/2, M_1)$ and (M_1, M_H) contain integers then we can get both ovulatory and anovulatory behaviour in the same model starting with different initial conditions (i.e. different initial maturities for the N follicles). This might appear to be the behaviour precisely corresponding to *PCOS*. However, the above analysis immediately shows that in such a situation the number that can arrest must always be less than the number that can ovulate. Thus if we set the parameters to values appropriate to the human, anovulation cannot occur in the initial value problem, and very drastic changes to the parameters are required to achieve large numbers of follicles getting stuck. Thus to see normal human ovulation, we want $0 < M_1 < 1 < M_2 < 2$ (so that 1 is the only integer between M_1 and M_2, whilst to get say 10 follicles to get stuck we require both $M_1 > 10$ and $M_2 > 10$). As we argued in the introduction this does not give a very realistic picture of *PCOS*.

Figures 1 and 2 show a numerical simulation of this model for the two cases of anovulation and ovulation. Both of these were carried out at the same parameter values $D = K = 1$ and $M_1 = 2.9$ and $M_2 = 3.9$, but with different initial conditions. The values of M_1 and M_2 are such that M lies within the interval $(M_H/2, M_H)$ for $M = 2$ and $M = 3$. For $M = 2$ we have that $\xi(1/M) > D$, therefore there are two follicles that get stuck (see Fig. 1). For

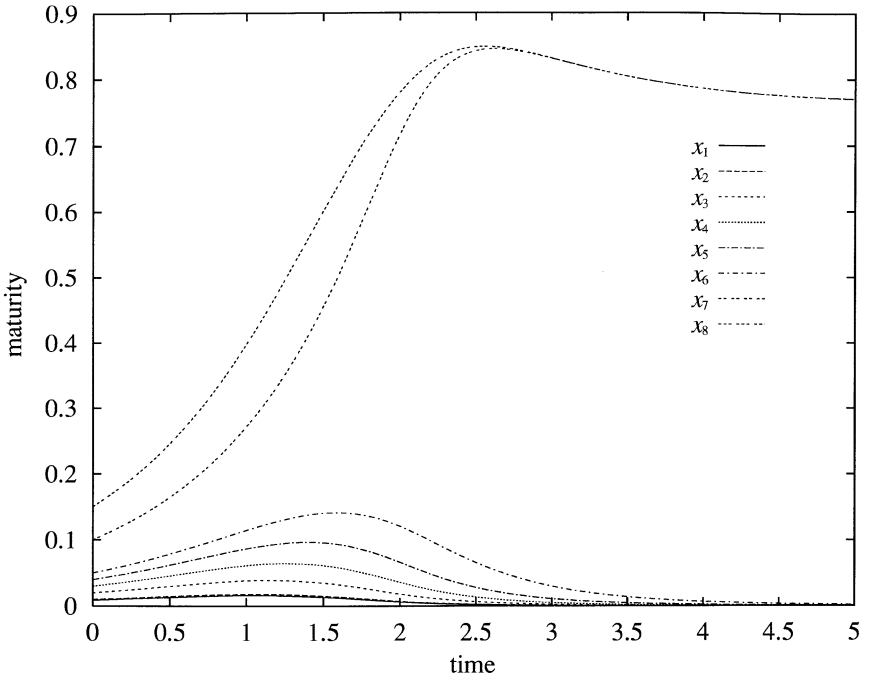

Fig. 1. A numerical simulation of eight follicles interacting according to Lacker's original model given by equations (1) and (4), with parameter values $D = K = 1$, $M_1 = 2.9$, $M_2 = 3.9$. Two follicles x_7 and x_8 have relatively large initial sizes and the remainder $x_1, \ldots, x_6$ have much smaller initial sizes. The two largest follicles tend to a constant maturity value as $t \to \infty$ and the rest atrophy by atresia

$M = 3$ we have that $\xi(1/M) > D$ which means that three follicles may ovulate (see Fig. 2). Therefore for these very particular examples we can see that by changing the initial conditions of the system we can either get three follicles to ovulate or two to arrest. However, no possible set of initial conditions at these parameter values will lead to more than two follicles arresting.

Of course, this argument is only valid for the precise maturation function (4), and one might hope that other choices of ξ would lead to more realistic anovulatory behaviour. It turns out however that functions which can give the right spectrum of ovulatory and anovulatory cases are rather complex and appear rather contrived. Certainly none of the broad class of functions considered by Akin and Lacker (1984) can lead to the desired behaviour. In particular we see that if ξ is to allow a one follicle ovulatory state (and no other ovulatory states) and an anovulatory state involving more than one follicle then it must have at least two maxima in the unit interval, with the left maximum being lower than the right. We are not aware of any kind of biological argument which might even begin to justify such a form for the follicle response, and hence such a model of *PCOS* type behaviour would be tenuous at best.

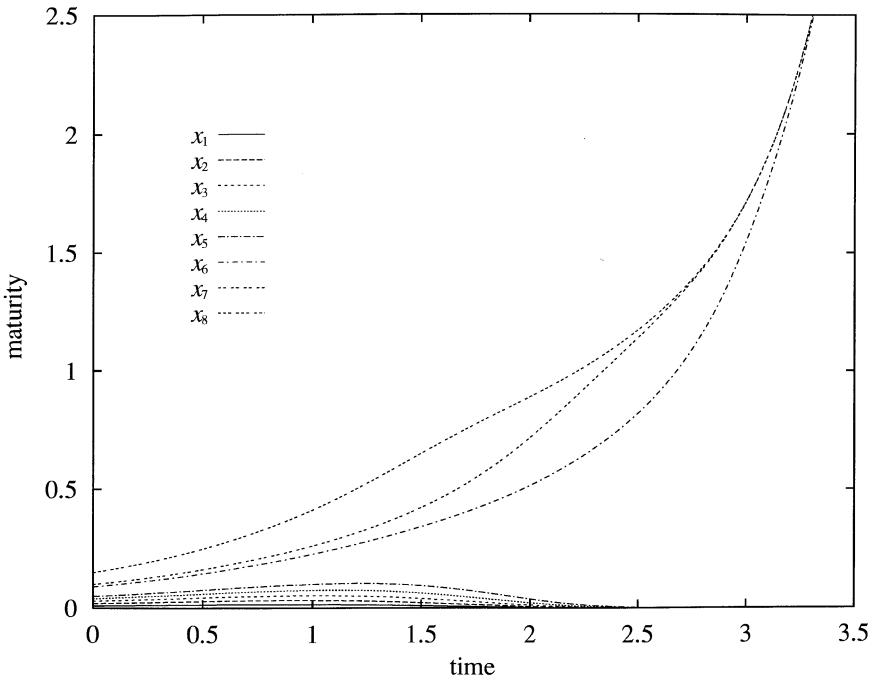

Fig. 2. A simulation with the same parameter values as Fig. 1, but different initial conditions. Three follicles x_6, x_7 and x_8 have similar and relatively large initial sizes with the remaining five follicles $x_1, \ldots, x_5$ having small initial sizes. Follicles x_6, x_7 and x_8 ovulate in a finite time and the remainder die by atresia

We can also notice that due to the fact that all the follicles respond in the same way to oestradiol concentrations, a strict hierarchy is preserved amongst the follicles. Thus if the ith follicle is initially larger than the jth, then it will remain so throughout the ovulation cycle. Hence in the context of this model the largest follicles will always either ovulate or get stuck and the smallest ones will atrophy. As has already been pointed out by other authors (Thalabard et al., 1989; Mariana et al., 1984) such perfect ordering amonst the follicles is unlikely in real life.

4 A non-symmetric generalization

We shall now analyse a generalization of Lacker's model to cases where all the follicles are no longer assumed to have same response to gonadotrophins. It turns out that the mathematical theory of Akin and Lacker holds mostly unchanged thanks to the fact that we can still obtain a gradient system on the unit sphere. As we shall see this generalization allows us to overcome the problems wth Lacker's model described at the end of the previous section.

Basically, the symmetry assumption is broken by making each follicle grow in a different way. In particular we shall assume that the *interaction function* ξ is different for each follicle, but the *intensity* and *time functions* ρ and δ remain the same for all follicle. This allows the follicles to be sufficiently different to give us the behaviour we desire, but maintains sufficient common structure to separate the dynamics in the same way as in the symmetric model (if we were to allow each follicle its own ρ and δ then we can see no hope of analysing the resulting model). The effect is to replace (2) by the following system:

$$g_i(x_i, X) = \delta(X)[\rho(X) + \xi_i(p_i)] \tag{6}$$

Then if as before

$$p_i = \frac{x_i}{X}$$

we have

$$\begin{aligned}
\frac{dp_i}{d\tau} &= \frac{d}{dt}\left(\frac{x_i}{X}\right) \\
&= \frac{1}{X}\frac{dx_i}{dt} - \frac{x_i}{X^2}\sum_{j=1}^{N}\frac{dx_j}{dt} \\
&= \frac{1}{X}(x_i\delta(X)[\rho(X) + \xi_i(p_i)]) - \frac{x_i}{X^2}\sum_{j=1}^{N} x_j\delta(X)[\rho(X) + \xi_j(p_j)] \\
&= \delta(X)\frac{x_i}{X}\xi_i(p_i) - \delta(X)\frac{x_i}{X}\sum_{j=1}^{N}\frac{x_j}{X}\xi_j(p_j) \\
&= \delta(X)p_i[\xi_i(p_i) - \bar{\xi}(p)]
\end{aligned}$$

where now $\bar{\xi}$ is defined by

$$\bar{\xi}(p) = \sum_{j=1}^{N} p_j\xi_j(p_j)\ .$$

Rescaling time by

$$\frac{d\tau}{dt} = \delta(X)$$

as before, we obtan the *interaction dynamics*

$$\frac{\mathrm{d}p_i}{d\tau} = p_i[\xi_i(p_i) - \bar{\xi}(p)]\ . \tag{7}$$

This is identical to the symmetric case (3), apart from the fact that ξ_i replaces ξ. Similarly the *intensity dynamics* is given by

$$\begin{aligned}
\frac{dX}{dt} &= \sum_{j=1}^{N}\frac{dx_j}{dt} \\
&= \sum_{j=1}^{N} x_j\delta(X)[\rho(X) + \xi_j(p_j)] \\
&= \delta(X)X[\rho(X) + \bar{\xi}(p)]
\end{aligned}$$

and hence

$$\frac{dX}{d\tau} = X[\rho(X) + \bar{\xi}(p)]$$

as before.

The equilibrium condition for this *interaction dynamics* is similar as in the symmetric case, i.e.

$$p_i = 0$$

or

$$\xi_i(p_i) = \bar{\xi}(p) .$$

Thus just as before, all the non-zero coordinates have to take a common value. By permuting the follicles if necessary we can always assume that the non-zero coordinates are the first M, and hence will denote an *M-fold* equilibrium as $p_e = (p_1, \ldots, p_M, 0, \ldots, 0)$. Following Lacker's analysis, we obtain a gradient system on the unit sphere by making a variable transformation:

$$y_i = \sqrt{p_i}$$

which implies that

$$\sum_{i=1}^{N} y_i^2 = 1$$

and hence $y = (y_1, \ldots, y_N)$ lies on the unit $N-1$ dimensional sphere S. Now consider the following potential function:

$$V(y) = -\frac{1}{2}\sum_{i=1}^{N} \int_0^{y_i} s\xi_i(s^2)\, ds .$$

Then the dynamics of (7) is given by the gradient dynamics on S

$$\frac{dy}{dt} = -\nabla_s V$$

where $\nabla_s V$ is the gradient restricted to S, i.e.

$$\nabla_s V = \nabla V - \langle \nabla V, y \rangle y .$$

Here ∇V is the usual gradient of V

$$\nabla V = \left(\frac{\partial V}{\partial y_1}, \cdots, \frac{\partial V}{\partial y_N} \right)$$

and $\langle , \rangle$ is the usual inner product

$$\langle u, v \rangle = \sum_{i=1}^{N} u_i v_i .$$

Hence the ith component of the ∇V is such that:

$$[\nabla V]_i = -\tfrac{1}{2} y_i \xi_i(v_i^2) .$$

Therefore

$$\langle \nabla V, y \rangle = -\frac{1}{2} \sum_{i=1}^{N} y_i^2 \xi_i(v^2)$$

thus,

$$[\nabla V - \langle \nabla V, y \rangle y]_i = -\frac{1}{2} y_i \left[\xi_i(y_i^2) - \sum_{j=1}^{N} y_j^2 \xi_j(y_j^2) \right]$$

i.e. the ith component of the projection of ∇V onto the tangent plane of S at y.

An equilibrium point of (7) will be a critical point of the potential function V, i.e. a point such that $\nabla_S V = 0$. Let $y_e = (a_1, \ldots, a_M, 0, \ldots, 0)$ be such critical point, then extending Akin and Lacker's stability theorem we get the following result:

An M-fold nondegenerate equilibrium y_e of the gradient system

$$\frac{dy}{dt} = -\nabla_S V$$

for $y \in S$ is stable if and only if the common value $\lambda > \xi_i(0)$ for all $i = M+1, \ldots, N$ and either $\xi_i'(a_i^2) < 0$ for all nonzero co-ordinates $a_1, \ldots, a_M$ or $\xi_i'(a_i^2) > 0$ for exactly one nonzero co-ordinate and

$$\sum_{i=1}^{M} \frac{1}{\xi_i'(a_i^2)} > 0 .$$

We prove this in a similar way to Lacker and Akin's original demonstration of the analogus result for the symmetric case (Lacker and Akin, 1988). Note that in Lacker's symmetric version the condition on λ is simply $\lambda > 0$ which is difficult to interpret biologically. On the other hand, our formulation $\lambda > \xi_i(0)$ makes this condition much clearer: recall that $\lambda = \bar{\xi}(p)$, and hence at the equilibrium the relative growth rate, $dp_i/d\tau$, of the ith follicle is just $[\xi_i(p_i) - \bar{\xi}(p)] = [\xi_i(p_i) - \lambda]$. For follicle $i = M+1, \ldots, N$, we have $p_i = 0$, and hence the growth rate is exactly $\xi_i(0) - \lambda$. Thus the condition $\lambda > \xi_i(0)$ for $i = M+1, \ldots, N$ is simply saying that at a stable equilibrium those follicles for which $p_i = 0$ have a negative growth rate, in other words such p_i cannot grow. Such a condition is of course intuitively obvious.

We begin the proof of the above result by defining the function $\sigma: \mathbf{R}^N \to \mathbf{R}$ by

$$\sigma(y) = \sum_{i=1}^{N} y_i^2 - 1 .$$

Thus $S = \sigma^{-1}(0)$. Then if y is a critical point of V restricted to S then there exists a *Lagrange multiplier* β such that

$$\nabla L(y) = 0$$

where

$$L(y) = V(v) + \beta \sigma(v) .$$

Now, by above $[\nabla V(v)]_i = -y_i \xi_i(v_i^2)/2$ and $[\nabla \sigma(v)]_i = 2y_i$, and hence the condition for a critical point of L is that $y_i[\xi_i(v_i^2) - 4\beta] = 0$ for all i. Thus $\xi_i(v_i^2) = 4\beta$ for all i such that $y_i \neq 0$, hence we see that

$$\beta = \frac{1}{4}\bar{\xi}(p) .$$

Furthermore recall that

$$\frac{dp_i}{d\tau} = p_i[\xi_i(p_i) - \bar{\xi}(p)]$$

and $y_i^2 = p_i$. Thus $dp_i/d\tau = 0$ if and only if $y_i^2[\xi_i(v_i^2) - 4\beta] = 0$, in other words if and only if $[\nabla L(v)]_i = 0$. Thus y is a critical point of V restricted to S if and only if it is an equilibrium point of the follicle interaction dynamics.

Furthermore, if such an equilibrium point is non-degenerate, then it is stable if and only if it is a local minimum of V on S. Now, a nondegenerate critical point y of a constrained function V on S is a local minimum if and only if $Q(v) = D^2L(v, v) > 0$ for all non-zero $v \in T_yS$, where T_yS, is the tangent space of S at y (e.g. [Fletcher, 1981]). So to prove the above stability theorem it remains to show that $Q(v) > 0$ if and only if $\lambda > \xi_i(0)$ for all $i = M + 1, \ldots, N$ and either $\xi_i'(a_i^2) < 0$ for all $i = 1, \ldots, M$ or $\xi_i'(a_i^2) > 0$ for exactly one $i = 1, \ldots, M$ and

$$\sum_{i=1}^{M} \frac{1}{\xi_i'(a_i^2)} > 0 .$$

In component form we have

$$\begin{aligned} Q(v) &= \sum_{i=1}^{N} \sum_{j=1}^{N} \frac{\partial^2 L}{\partial y_i \partial y_j} v_i v_j \\ &= -\sum_{i=1}^{M} v_i^2 a_i^2 \xi_i'(a_i^2) + \frac{1}{2} \sum_{i=M+1}^{N} v_i^2 [\lambda - \xi_i(0)] \end{aligned}$$

(recall that $a_i = 0$ for $i = M + 1, \ldots, N$ and $\xi_i(a_i^2) = \lambda$ for $i = 1, \ldots, M$). Note that

$$\sum_{i=1}^{N} v_i^2 \neq 0$$

and since v lies in the tangent space of S at y, it must be orthogonal to y, and hence

$$\langle y, v \rangle = \sum_{i=1}^{N} a_i v_i = \sum_{i=1}^{M} a_i v_i = 0 .$$

First consider $v \in T_yS$ such that $v_i = 0$ for all $i = 1, \ldots, M$ and $v_i = 1$ for all $i = M + 1, \ldots, N$. Then

$$Q(v) = \frac{1}{2} \sum_{i=M+1}^{N} [\lambda - \xi_i(0)] .$$

Hence if then $Q(v) > 0$ for all $v \in T_y S$ we must have $\lambda > \xi_i(0)$ for all $i = M+1, \ldots, N$.

Conversely, suppose that $\lambda > \xi_i(0)$ for all $i = M+1, \ldots, N$. We then immediately see that if $\xi_i'(a_i^2) < 0$ for $i = 1, \ldots, M$ then $Q(v) > 0$ for all $v \in T_y S$. On the other hand suppose that $\xi_i'(a_i^2) \geqq 0$ for more than one nonzero co-ordinate. Without loss of generality we may assume $\xi_1'(a_1^2) \geqq 0$ and $\xi_2'(a_2^2) \geqq 0$. Then consider $v = (a_2, -a_1, 0, \ldots, 0)$; this is nonzero and satisfies $\langle y, v \rangle = 0$. Then

$$Q(v) = -(a_1 a_2)^2 (\xi_1'(a_1^2) + \xi_2'(a_2^2)) .$$

Hence if $\xi_1'(a_1^2) = \xi_2'(a_2^2) = 0$, then $Q(v) = 0$ and so y is a degenerate critical point, and if one or both of $\xi_1'(a_1^2)$, $\xi_2'(a_2^2)$ are positive, then $Q(v) < 0$ and y is not a minimum. Hence if y is a non-degenerate minimum at most one of $\xi_1'(a_i^2)$ for $i = 1, \ldots, M$ can be nonnegative or all of them have to be negative.

It remains to consider the case of exactly one $\xi_i'(a_i^2) > 0$ (still assuming that $\lambda > \xi_i(0)$ for all $i = M+1, \ldots, N$). Without loss of generality, we may assume $\xi_1'(a_1^2) > 0$. Let

$$U = \{v \in T_y S \colon v_1 = 0\}$$

$$W = \left\{ v \in T_y S \colon v_1 = -\frac{1}{a_1} \right\} .$$

Then $T_y S = U \cup \{cw \colon w \in W, c \in \mathbf{R}\}$. Since $Q(cw) = c^2 Q(w)$ the stability of y is determined by the sign of Q on U and W. First observe that if $v \in U$ then

$$Q(v) = -\sum_{i=2}^{M} v_i^2 a_i^2 \xi_i'(a_i^2) + \frac{1}{2} \sum_{i=M+1}^{N} v_i^2 [\lambda - \xi_i(0)] .$$

Thus, since $\xi_i'(a_i^2) < 0$ for all $i = 2, \ldots, M$ then $Q(v) > 0$ for all $v \in U$ such that $v \neq 0$. On the other hand if $v \in W$, then

$$Q(v) = -\xi_1'(a_1^2) - \sum_{i=2}^{M} v_i^2 a_i^2 \xi_i'(a_i^2) + \frac{1}{2} \sum_{i=M+1}^{N} v_i^2 [\lambda - \xi_i(0)]$$

Let

$$\bar{Q}(v) = -\xi_1'(a_1^2) - \sum_{i=2}^{M} v_i^2 a_i^2 \xi_i'(a_i^2) .$$

We want to show that $\bar{Q}(v) > 0$ for all $v \in W$. On W, we can regard $\bar{Q}$ as a function of $v_2, \ldots, v_M$, and hence we want to determine the minimum of $\bar{Q}(v)$ subject to the constraint $\langle y, v \rangle = 0$, or in other words $G(v) = 0$ where

$$G(v) = \sum_{i=1}^{M} a_i v_i - 1 .$$

As in Lacker and Akin (1988) we do this using a standard Lagrange multiplier approach, though the precise argument we use somewhat different to that used there. Let $H(v, \gamma) = \bar{Q}(v) + \gamma G(v)$. Then completing the square we have

$$H(v, \gamma) = -\xi_1'(a_1^2) - \sum_{i=2}^{M} a_i^2 \xi_i'(a_i^2)\left(v_i - \frac{\gamma}{2a_i\xi_i'(a_i^2)}\right)^2 + \sum_{i=2}^{M} \frac{\gamma^2}{4\xi_i'(a_i^2)} - \gamma\,.$$

Since $\xi_i'(a_i^2) < 0$ for $i = 2, \ldots, M$, we see that for a fixed γ, the function H takes its minimum when

$$v_i = \frac{\gamma}{2a_i\xi_i'(a_i^2)}\,. \tag{8}$$

In order to satisfy $G(v) = 0$, we must have

$$\frac{\gamma}{2}\sum_{i=2}^{M} \frac{1}{\xi_i'(a_i^2)} = 1\,. \tag{9}$$

Together (8) and (9) determine the global minimum of $\bar{Q}(v)$ subject to the constraint $G(v) = 0$, in particular if v' also satisfies $G(v') = 0$ we have $\bar{Q}(v) = \bar{Q}(v) + \gamma G(v) = H(v, \gamma) \leqq H(v', \gamma) = \bar{Q}(v') + \gamma G(v') = \bar{Q}(v')$. The value that $\bar{Q}$ takes at this minimum is

$$\begin{aligned}\bar{Q}(v) &= -\xi_1'(a_1^2) - \sum_{i=2}^{M}\left(\frac{\gamma}{2a_i\xi_i'(a_i^2)}\right)^2 a_i^2\xi_i'(a_i^2)\\ &= -\xi_1'(a_1^2) - \frac{1}{\sum_{i=2}^{M}\frac{1}{\xi_i'(a_i^2)}}\,.\end{aligned}$$

Thus, since

$$\sum_{i=1}^{M} \frac{1}{\xi_i'(a_i^2)} > 0 \tag{10}$$

we have that

$$\frac{1}{\xi_1'(a_1^2)} > -\sum_{i=2}^{M}\frac{1}{\xi_i'(a_i^2)}$$

which implies that

$$\frac{1}{\sum_{i=2}^{M}\frac{1}{\xi_i'(a_i^2)}} < -\xi_1'(a_1^2)$$

and hence $\bar{Q}(v) > 0$ for all $v \in W$ as required. Finally to complete the proof of the theorem we have to show that if (10) does not hold, then y is not stable. By above if (10) is not satisfied, we have $\bar{Q}(v) \leqq 0$ for some $v \in W$, with $v_i \neq 0$ for at least one $i = 2, \ldots, M$ and $v_i = 0$ for all $i = M + 1, \ldots, N$. But if $v_i = 0$ for all $i = M + 1, \ldots, N$ we have $Q(v) = \bar{Q}(v)$ and hence for this v we have $Q(v) \leqq 0$, and since y is assumed non-degenerate this implies that it cannot be stable, which contradicts the hypothesis, therefore (10) holds as required.

We have analysed the stability conditions for the *interaction dynamics* so far. Now, suppose that we have a stable fixed point y on the unit sphere satisfying the conditions of the above theorem, what can we say about its stability for the full dynamics (1). To answer this, we have to study the stability of the *intensity dynamics*, recall that this is given by:

$$\frac{dX}{d\tau} = X[\rho(X) + \bar{\xi}(p)] .$$

Recall that ρ is monotone decreasing for $X > 0$ and $\rho(X) \to -D$ as $X \to \infty$, and $\rho(X) \to \infty$ as $X \to 0$. This in particular implies that $\rho(X) > -D$ for all $X > 0$. If p is an equilibrium point then $\bar{\xi}(p) = \lambda$, and if p is tending to such an equilibrium point then $\bar{\xi}(p) \to \lambda$ as $\tau \to \infty$.

Then if $\lambda > D$ we have

$$\frac{dX}{d\tau} > (\lambda - D)X$$

with $(\lambda - D) > 0$ and hence $X \to \infty$ as $\tau \to \infty$. The total oestradiol concentration thus tends to infinity, and as already mentioned this corresponds to ovulation: one assumes that when X reaches a sufficiently large values this triggers an *LH* surge. Looking at the dynamics of the individual follicles, we have

$$\frac{dx_i}{d\tau} = x_i[\rho(X) + \xi_i(p_i)]$$

with $\xi_i(p_i) \to \lambda$ as $\tau \to \infty$ for $i = 1, \ldots, M$, and $\xi_i(p_i) \to 0$ as $\tau \to \infty$ for $i = M + 1, \ldots, N$. Hence $x_i \to \infty$ for $i = 1, \ldots, M$, i.e. for those follicles which have non-zero relative maturity at the equilibrium point, and $x_i \to 0$ for $= M + 1, \ldots, N$, i.e. for those follicles which have zero relative maturity. This case therefore corresponds to the first M follicles growing (and by implication ovulating) and the remainder ultimately dying by atresia.

On the other hand if $\lambda < D$ then there exists an X_e such that $\rho(X_e) = -\lambda$. Such an X_e is then a stable equilibrium point of the intensity dynamics (the stability follows from the fact that $\rho(X) > \rho(X_e)$ for $X < X_e$ and $\rho(X) < \rho(X_e)$ for $X > X_e$). This situation thus corresponds to the total oestradiol concentration, and hence the total size of the N follicles limiting to some finite value, and hence may be interpreted as an anovulatory case. As before, if a follicle's relative maturity tends to zero then it will eventually die (i.e. follices $M + 1$ to N), but now if the follicle has a non-zero relative maturity a_i (follicles 1 to M) then its size tends to a finite size $X_e a_i$, corresponding to that follicle getting stuck and neither ovulating nor becoming atretic.

Finally it is left to analyse the dynamics of the *time rescaling function* $\delta(X)$, i.e. what happens to $\tau(t)$ when $t \to \infty$ where τ satisfies the dynamics

$$\frac{d\tau}{dt} = \delta(X) .$$

Since $\delta(X)$ is assumed strictly positive, $\tau(t)$ is invertible. Then if $\lambda > D$ we have

$$\frac{d\tau}{dX} < \frac{1}{\lambda - D}\frac{1}{X}$$

and hence

$$\begin{aligned}\lim_{\tau\to\infty} t(\tau) &= \int_0^{\infty} \frac{d\tau}{\delta(X(\tau))} \\ &= \int_{X(0)}^{X(\infty)} \frac{1}{\delta(X)}\frac{d\tau}{dX}\,dX \\ &< \frac{1}{\lambda - D}\int_{X(0)}^{X(\infty)} \frac{1}{\delta(X)X}\,dX\,.\end{aligned}$$

Thus if $\delta(X)$ grows faster than X^{ε} for some $\varepsilon > 0$, the above integral is finite and $t(\tau)$ tends to a finite value T as $\tau \to \infty$, hence τ goes to ∞ in finite time, corresponding to ovulation in finite time.

On the other hand, if $\lambda < D$, we have $\delta(X) \to \delta(X_e) > 0$, and hence

$$\frac{dt}{d\tau} \sim \frac{1}{\delta(X_e)}\ .$$

Thus $t(\tau) \to \infty$ as $\tau \to \infty$, corresponding to the anovulatory case, i.e. the follicle's size converges to a finite limiting value and stays there for all time.

To summarize, the dynamics of the model as $\tau \to \infty$ can be classified into two different cases:

i) $\lambda > D$: ovulation
   a) $x_i \to 0$ if $p_i \to 0$
   b) $x_i \to \infty$ if $p_i \to a_i^2 \neq 0$
   c) $t \to T$
ii) $\lambda < D$: anovulation
   a) $x_i \to 0$ if $p_i \to 0$
   b) $x_i \to X_e a_i^2$ if $p_i \to a_i^2 \neq 0$
   c) $t \to \infty$

We give an illustration of the dynamics of the non-symmetric model in Figs. 3, 4 and 5. In all these figures the function g_i is Lacker's original function (4), but with different values of M_1 and M_2 for each i. The actual values used are given in Table 1. The parameters D and K were set to 1, as Figs. 1 and 2.

Follicle x_1 thus has parameter values appropriate for normal human ovulation, whilst the other follicles $x_2, \ldots, x_8$ have parameters corresponding to the anovulatory case. We see that in the non-symmetric case we can obtain a much greater variety of behaviours for the same parameter values just by changing the initial conditions of the system. Thus in Fig. 3 we consider a situation where the normal follicle x_1 has a relatively large initial size

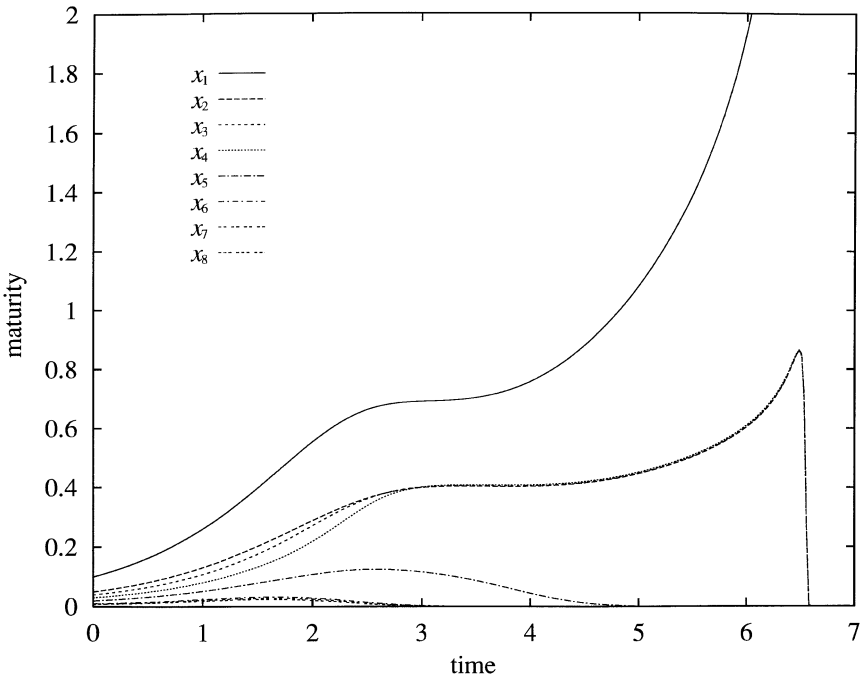

Fig. 3. A numerical simulation for the non-symmetric model (5). The function g_i is given by (4) with $D = K = 1$ and different values of M_1 and M_2 for each i, according to Table 1. Follicle x_1 has parameter values appropriate for normal human ovulation, and a relatively large initial size. The other follicles $x_2, \ldots, x_8$ have parameters corresponding to the anovulatory case, and much smaller initial sizes. In this example their development is suppressed by x_1, and they die by atresia

Table 1. Parameter values M_1 and M_2 for each of the follicles for the non-symmetric model

Follicle	M_1	M_2
x_1	0.9	1.9
x_2	7.1	7.9
x_3	7.1	7.8
x_4	7.1	7.7
x_5	7.1	7.6
x_6	7.1	7.5
x_7	7.2	7.9
x_8	7.3	7.9

compared to the abnormal ones. In this case, $x_2, \ldots, x_8$ are too small to affect the development of x_1 which goes on to ovulate normally. Although on their own $x_2, \ldots, x_8$ would arrest at a finite size, the presence of x_1 suppresses their development and they die by atresia.

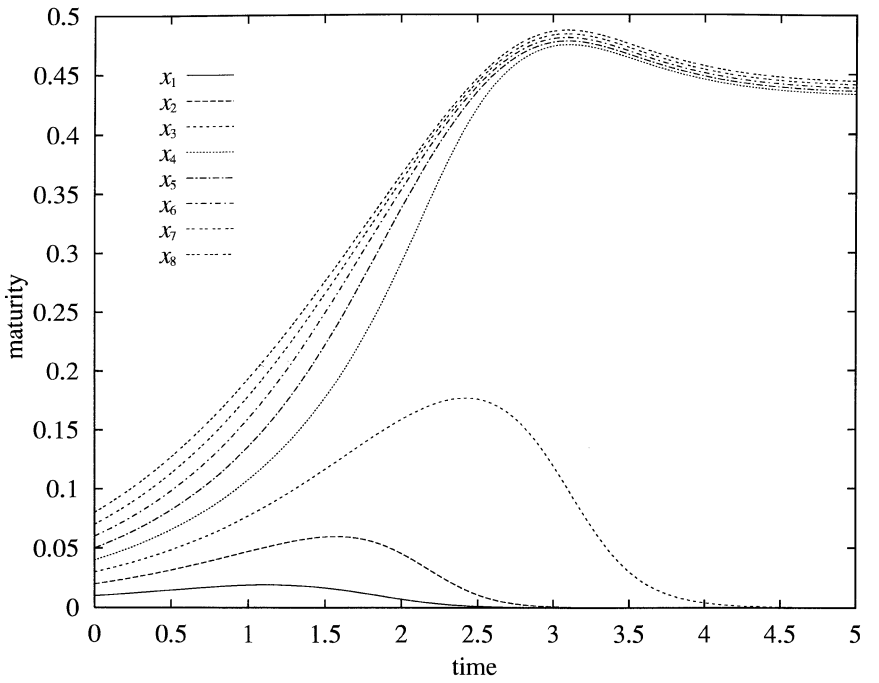

Fig. 4. A simulation of the non-symmetric model with identical parameter to Fig. 3, but different initial conditions. The normal follicle x_1 now has the smallest initial size, with an increasing range of initial sizes for the remaining seven follicles. In this example five of the subgroup of seven abnormal follicles $x_4, \ldots, x_8$ arrest at a fixed size as $t \to \infty$, and the remainder die together with x_1

By contrast, in Fig. 4, we take x_1 to have the smallest initial size, with an increasing range of initial sizes for the remaining seven follicles. The abnormal follicles $x_2, \ldots, x_8$ now dominate and prevent the ovulation of x_1. Instead the largest five abnormal follicles arrest at a finite size leading to anovulatory behaviour with the ovary containing a number of large follicles. This situation is thus consistent with the type of anovulation seen in *PCOS*. The comparison with Fig. 3 shows that we can move from a normal ovulatory case to an anovulatory one with a large number of arrested follicles just by changing the initial sizes of the follicles at the start of the cycle. This is something which cannot be achieved in Lacker's symmetrical model.

Finally in Fig. 5, we reverse the order of sizes compared to Fig. 4, so that x_1 has an initial size identical to x_8 in Fig. 4, and x_8 an identical initial size to x_1 in Fig. 4. We see that even though just as in Fig. 3, x_1 is initially the largest follicle, the overall behaviour is similar to that in Fig. 4, and x_1 dies by atresia, with the largest five abnormal follicles arresting as before. We thus have a situation where the presence of a group of abnormal follicles suppresses the ovulation of a normal follicle, despite the fact that the latter is initially the dominant follicle. This illustrates the fact that, unlike the Lacker's

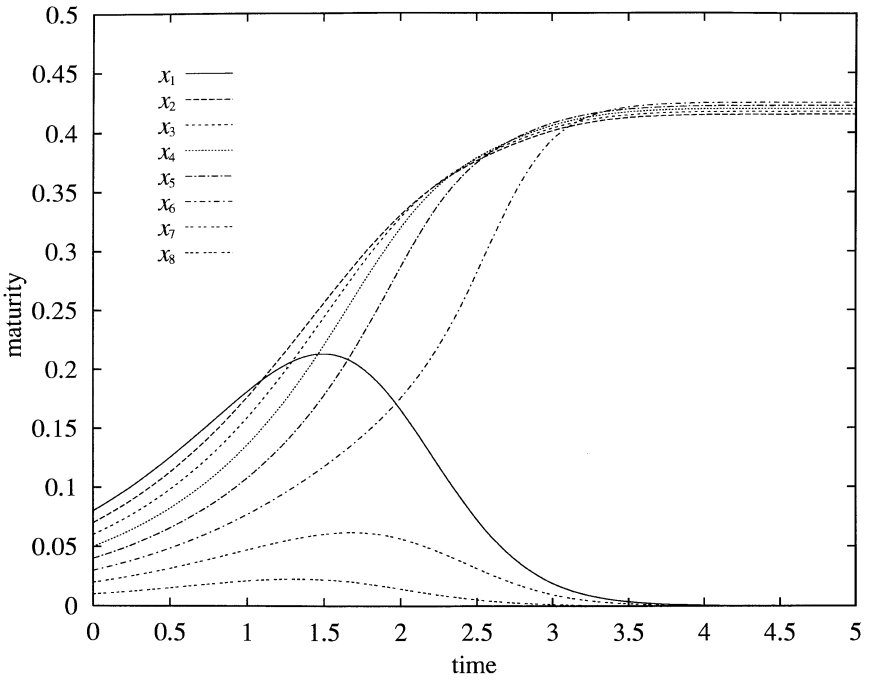

Fig. 5. A simulation of the non-symmetric model with identical parameter to Figs. 3 and 4. he initial conditions are similar to Fig. 4 but with the order of sizes reversed: x_1 thus now has the largest initial size, identical to x_8 in Fig. 4, and x_8 the smallest. In this example, despite the fact that the normal follicle x_1 is initially the largest, the presence of the other abnormal follicles $x_2, \ldots, x_8$ prevents it from ovulating, and it dies by atresia together with the smallest abnormal follicles x_7 and x_8. The remaining abnormal follicles $x_2, \ldots, x_6$ arrest at a fixed size

symmetrical model, the strict dominance of follicle sizes is broken, and the overall behaviour of the system does not just depend on the follicles with the largest initial size.

5 Conclusion

Lacker's model of the control of ovulation is based on simple assumptions about the properties of the primary feedback loop involving the ovary and the pituitary. Because of its simplicity, it is amenable to a complete mathematical analysis, and yet, despite this, it is able to exhibit many of the qualitative features of the mammalian ovulatory cycle and follicle selection process. However, in its current form it makes the unrealistic assumption that all follicles behave identically, and in particular respond to gonadotrophins in precisely the same way. One consequence of this is that Lacker's model cannot correctly reproduce the spectrum of behaviour associated with human *PCOS*.

In this paper we have therefore generalized Lacker's model to the case of non-identical follicle growth functions. The resulting generalized model is able

to successfully display *PCOS* type behaviour where a number of follicles arrest at a pre-ovulatory size, but fail to ovulate. Such behaviour can be seen at identical parameter values where for different initial conditions normal ovulation of a single follicle occurs.

Although highly simplified, our model does suggest a number of tentative conclusions about the nature of *PCOS*:

1. The primary cause of *PCOS* does not lie in a failure of the pituitary, or the ovary as a whole, but rather in the response of individual follicles to gonadotrophins. This is in broad agreement with observations in clinical practice (e.g. Yen, 1980, pp 192; Franks et al., 1996).
2. Those follicles which arrest in pre-ovulatory stages but fail to either ovulate or atrophy have significantly different properties compared to normally ovulating follicles. The potential for the type of anovulation seen in *PCOS* thus appears to be already determined at the pre-antral stage of the follicle.
3. Although a number of different classes of abnormal response by a follicle can probably lead to the type of anovulation observed in *PCOS*, the most likely possibility within the context of our model appears to be a heightened sensitivity to gonadotrophins. This is consistent with experimental evidence that follicles of *PCOS* patients are much more sensitive to *FSH* than those of normal women (Mason et al., 1994).
4. The presence of follicles with abnormal gonadotrophin response can (but need not) suppress the ovulation of normal follicles. The mechanism behind this is that the abnormal follicles, being more sensitive to gonadotrophins produce a sufficiently high level of oestradiol to suppress the production of gonadotrophins by the pituitary to a level so low that normal follicles cannot grow. In the presence of a mixed population of normal and abnormal follicles, therefore, the factor determining whether ovulation will, or will not occur, is the relative proportions of the two types of follicles, and their relative maturities at the start of the cycle.

The current model ignores a number of important aspects of the real system, such as the modulation of the behaviour of the pituitary by the hypothalamus, the pulsatile nature of the release of the relevant hormones, the mechanisms controlling atresia, and the different roles played by *FSH* and *LH*. Work is in progress to incorporate the last two of these and to investigate to what extent these factors might change the above conclusions.

Acknowledgements. A. Chávez-Ross, would like to specially thank R. Carretero-González for all his valuable contributions to this paper and moreover for encouraging her so much to carry on with her scientific career. She would also like to thank Dr. Pedro Miramontes for his assistance and DGAPA-UNAM together with the British Council for their financial support during her Ph.D. studies.

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