

Article

Resonance in the menstrual cycle: a new model of the LH surge



Dr Mary Lou Zeeman

Mary Lou Zeeman received her honours undergraduate degree from the University of Oxford, UK, in 1984, and her PhD in Mathematics from U.C. Berkeley in 1989. She held post-doctoral positions at the Institute for Mathematics and its Applications at the University of Minnesota and at MIT, and is now Associate Professor at UT San Antonio. She currently collaborates with experimentalists and physicians to focus on applications of mathematics to the reproductive system, including statistical analysis of IVF data, development of mathematical models of hypothalamus pituitary interactions over the menstrual cycle, interaction between the endocrine axes, and follicular maturation.

ML Zeeman^{1,3}, W Weckesser², D Gokhman¹

¹Department of Applied Mathematics, University of Texas at San Antonio, San Antonio, TX 78249, USA; ²Department of Mathematics, Colgate University, Hamilton, NY 13346, USA

³Correspondence: Tel: 210-458-5533; Fax: 210-458-4439; e-mail zeeman@math.utsa.edu

Abstract

In vertebrates, ovulation is triggered by a surge of LH from the pituitary. The precise mechanism by which rising oestradiol concentrations initiate the LH surge in the human menstrual cycle remains a fundamental open question of reproductive biology. It is well known that sampling of serum LH on a time scale of minutes reveals pulsatile release from the pituitary in response to pulses of gonadotrophin releasing hormone from the hypothalamus. The LH pulse frequency and amplitude vary considerably over the cycle, with the highest frequency and amplitude at the midcycle surge. Here a new mathematical model is presented of the pituitary as a damped oscillator (pulse generator) driven by the hypothalamus. The model LH surge is consistent with LH data on the time scales of both minutes and days. The model is used to explain the surprising pulse frequency characteristics required to treat human infertility disorders such as Kallmann's syndrome, and new experimental predictions are made.

Keywords: frequency interaction, GnRH pulses, LH surge, mathematical model, oestradiol, resonance

Introduction

The elusive LH surge

The precise mechanism by which rising oestradiol concentrations initiate the LH surge in the human menstrual cycle has 'defied compelling explanation' (Ordog *et al.*, 1998), despite being the subject of intensive research over the last two decades. The apparent variation in the LH surge mechanism among species has contributed to the difficulty in modelling. For example, the surge is initiated by the act of mating in rabbits (Haighton, 1797), it is entrained to the circadian rhythm in rats (Everett *et al.*, 1949; McElhinny *et al.*, 1999), and is accompanied by a hypothalamic surge of GnRH in sheep (Moenter *et al.*, 1992). While at least some of these mechanisms play a role in a normal human LH surge (Edwards, 1985), none of them appear to be necessary. In particular, LH surges, ovulation and pregnancy can occur in humans and other primates without an accompanying GnRH surge, as demonstrated by GnRH replacement therapies of constant frequency and amplitude (Knobil *et al.*, 1980; Leyendecker *et al.*, 1980; Pohl *et al.*, 1983).

Model assumptions

The pituitary is viewed here as a damped oscillator (pulse generator) driven by the hypothalamic oscillator, so that pituitary responsiveness to pulses of GnRH depends, in part, on frequency interactions between the two oscillators. It is like playing with a child on a swing. If you push at the intrinsic frequency of the swing, the amplitude builds up. If you push at the wrong frequency, working against the swing, the swing may be forced to follow your driving frequency, but the amplitude remains small. A similar underlying structure of frequency interaction as the hypothalamus drives the pituitary is proposed. It is assumed that the intrinsic frequency of each oscillator is modulated by the circulating ovarian hormones, and it is shown how the LH surge can thereby arise as transient resonance (amplitude enhancement) when these frequencies temporarily agree. The proposed model is based on the following experimental results: (i) there is a GnRH pulse generator at the hypothalamus (Rasmussen *et al.*, 1989); (ii) there is an intrinsic LH pulse generator at the pituitary (Gambacciani *et al.*, 1987a; Rossmann *et al.*, 1990); (iii) the hypothalamic oscillator

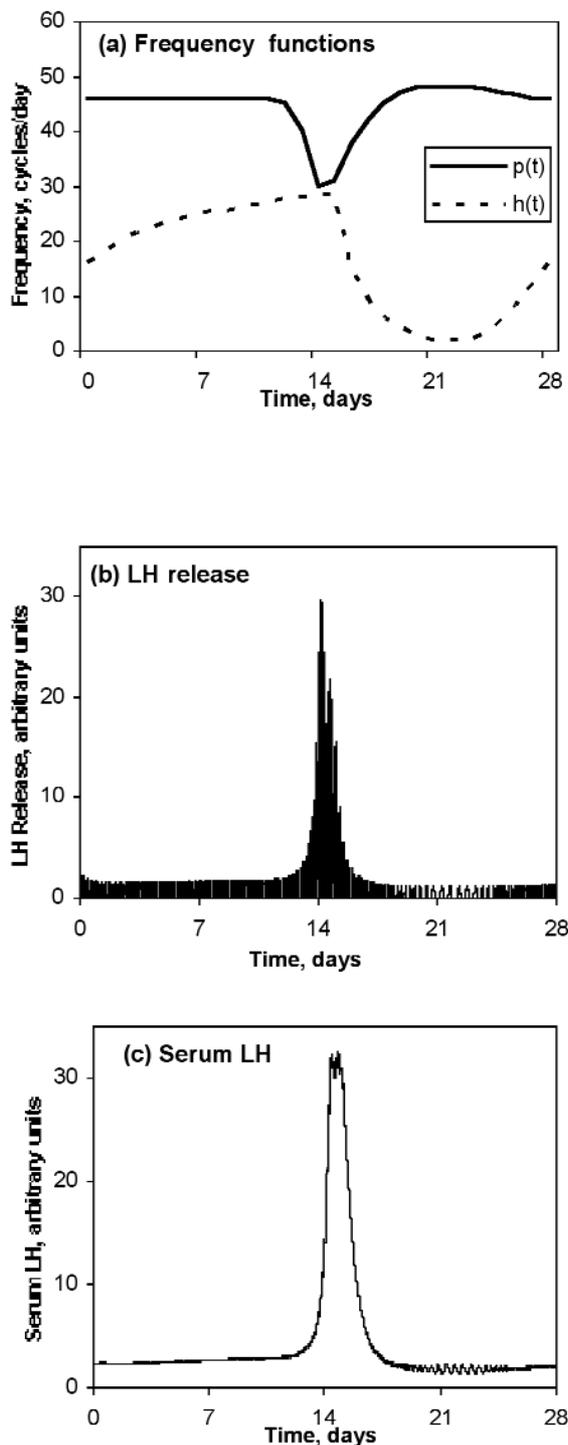


Figure 1. Model LH surge. (a) Intrinsic hypothalamic and pituitary frequency functions, $h(t)$ and $p(t)$ respectively, representing normally cycling women. (b) Model simulation of pituitary LH release. (c) Model simulation of serum LH surge.

drives the pituitary oscillator (Moenter *et al.*, 1992; O'Byrne *et al.*, 1993) and (iv) the ovarian hormones modulate the intrinsic frequency of the hypothalamic oscillator (Soules *et al.*, 1984; Hotchkiss and Knobil, 1994).

In addition, it is proposed that (v) the ovarian hormones modulate the intrinsic frequency of the pituitary oscillator.

The key to the new approach presented is in the potential role of an intrinsic pituitary pulse generator of variable frequency. A description follows of how intrinsic pituitary pulsatility could generate pituitary responses of varying amplitude to hypothalamic stimuli of varying frequency (as in a normal menstrual cycle), and how variable intrinsic pituitary frequency could lead to responses of varying amplitude to GnRH stimuli of constant frequency (as in the treatment of Kallmann's syndrome).

Mechanisms for pituitary pulsatility

Pulsatile hormone secretion has been observed from human and monkey pituitaries *in vitro* (Stewart *et al.*, 1985; Gambacciani *et al.*, 1987a,b; Rossmannith *et al.*, 1990). It is also known that the rat pituitary contains a connected network of excitable folliculo-stellate cells, permitting global communication, and hence synchrony, within the anterior pituitary (Fauquier *et al.*, 2001). Moreover, in female rats, the folliculo-stellate network gap junction connection strength depends on the circulating concentrations of ovarian hormones (Kurono, 1996; Soji *et al.*, 1997), thereby offering a mechanism by which ovarian hormones could modulate intrinsic pituitary frequency (Tabak *et al.*, 2000). Another mechanism for transient resonance in frequency interactions between the hypothalamus and pituitary may be ovarian hormone modulation of the frequency encoding by receptor desensitization and resensitization rates proposed by Li and Goldbeter (Li and Goldbeter, 1989; Goldbeter, 1996).

Methods

The simplest differential equation modelling one oscillator driving (or forcing) another, with variable intrinsic frequencies, is given by:

$$x'' + 4\pi^2 p(t)^2 x + \nu x' = \cos(2\pi h(t)) \quad (1)$$

See Blanchard *et al.* (2002) for an excellent introduction to forced oscillators. Here, positive values of x represent LH release from the pituitary, and the prime denotes rate of change (differentiation with respect to time). It is assumed that there is no LH release when x is negative. The left-hand side of equation (1) models the pituitary as a damped harmonic oscillator (i.e. the child's swing). If the amount of damping, ν , is small, the intrinsic pituitary frequency at time t is approximately $p(t)$. The right-hand side models sinusoidal periodic driving by the hypothalamus (i.e. pushing the swing) with frequency $h(t) = H'(t)$. The frequencies $p(t)$ and $h(t)$ are modelled as functions of the ovarian hormones, and hence of time.

The important feature of this model is that it captures, as simply as possible, the resonance phenomenon of amplitude enhancement or attenuation as the driving and driven frequencies interact. This phenomenon is extremely robust, and will hold for a wide variety of more physiologically based models. Work on such models is currently under way. Here the simple qualitative model is used to describe an underlying biological structure of coupled oscillators with frequency modulation through which the LH surge could arise as transient resonance.

Results and discussion

Site of action of oestradiol

In a normally cycling woman, the first half of the menstrual cycle is dominated by rising concentrations of oestradiol, triggering the LH surge and ovulation, which in turn lead to waning concentrations of oestradiol while progesterone and inhibin concentrations rise (McLachlan *et al.*, 1990; Hotchkiss and Knobil, 1994; Selgrade, 2001). In his excellent survey lecture, Knobil (1999) argues that the site of action of oestradiol is at the pituitary and not at the hypothalamus. The model presented here proposes that in a normal human cycle there is a robust mechanistic redundancy, in the sense that both the hypothalamic and pituitary intrinsic frequency functions, $p(t)$ and $h(t)$, are modulated by circulating concentrations of ovarian hormones. This type of mechanistic redundancy is typical for systems evolving under natural selection. It is shown below that the redundancy assumption can explain why the variations seen in GnRH pulse frequency over a normal human cycle (Filicori and Crowley, 1983; Filicori *et al.*, 1986) are not necessary for ovulation, but certain GnRH pulse frequency characteristics are nevertheless required (Knobil *et al.*, 1980; Leyendecker *et al.*, 1980; Wildt *et al.*, 1981; Pohl *et al.*, 1983).

Intrinsic hypothalamic and pituitary frequencies

The frequency functions presented graphically in **Figure 1(a)** are chosen to represent those of a normally cycling woman. *In vivo*, serum LH pulses reflect the intrinsic hypothalamic frequency driving the pituitary. Thus $h(t)$ in **Figure 1(a)** is interpolated from LH pulse frequency data (Filicori and Crowley, 1983; Filicori *et al.*, 1986) and from hypothalamic multiunit electrical activity data (O'Byrne *et al.*, 1991). During the first half of the cycle $h(t)$ gradually rises with rising oestradiol. Then $h(t)$ plummets after the LH surge, and stays low while progesterone concentrations are high. As far as is known, there are no direct data available for the intrinsic pulse frequency of the pituitary *in vivo*. To capture the indirect data given by the LH pulse amplitude (Filicori and Crowley, 1983; Filicori *et al.*, 1986), $p(t)$ was chosen to be higher than $h(t)$ for most of the cycle, dropping at midcycle when oestradiol concentrations are high, and rising again after the LH surge. The model then predicts that early in the cycle, while the pituitary oscillator is being driven at a frequency lower than its

own intrinsic frequency, there will be low-amplitude LH pulses at the frequency of the driver. At midcycle, as the hypothalamic and pituitary frequencies converge under rising oestradiol concentrations, the oscillators will resonate, leading to a burst of LH release. Note that the oestradiol strength–duration characteristics required to initiate an LH surge (Karsch *et al.*, 1973) suggest that it takes 2 or 3 days of high oestradiol concentrations for $h(t)$ and $p(t)$ to converge. Finally, as the frequencies diverge in response to the surge, LH pulse frequency and amplitude will drop again.

The precise shape of the hypothalamic and pituitary intrinsic frequency functions may vary considerably among individuals. The essential features are simply that $h(t)$ and $p(t)$ gradually converge under high oestradiol concentrations, thereby causing the LH surge, and consequently diverge again. In particular, $h(t)$ and $p(t)$ may approach without touching, as shown; they may touch, or they may cross over and back again. Thus no degeneracy is assumed. Individual differences in the rates at which $h(t)$ and $p(t)$ converge may contribute to the wide range of cycle lengths typical among women (Harlow *et al.*, 2000). Modulation of the rates of convergence could provide a mechanism for the phenomenon of ovulatory synchrony observed among closely interacting women (McClintock, 1971).

Model LH surge

In **Figure 1(b)** the positive part of a solution $x(t)$ to equation (1) with frequency functions as in **Figure 1(a)** is shown. The transient resonance is clearly visible at midcycle. The serum LH profile corresponding to this pattern of pituitary LH release is computed by convolving with exponential decay, representing LH accumulation combined with clearance. The result is a well defined surge in serum LH concentrations, as shown in **Figure 1(c)**. In **Figures 2** and **3**, model serum LH concentrations are sampled on the daily and 10 min time scales respectively, for comparison with data (Filicori and Crowley, 1983; McLachlan *et al.*, 1990; Selgrade, 2001). At both time scales, the model captures qualitative features of the data. In particular, LH pulses have low amplitude and high frequency early in the cycle, extra high amplitude and frequency during the surge, and medium high amplitude and low frequency late in the cycle.

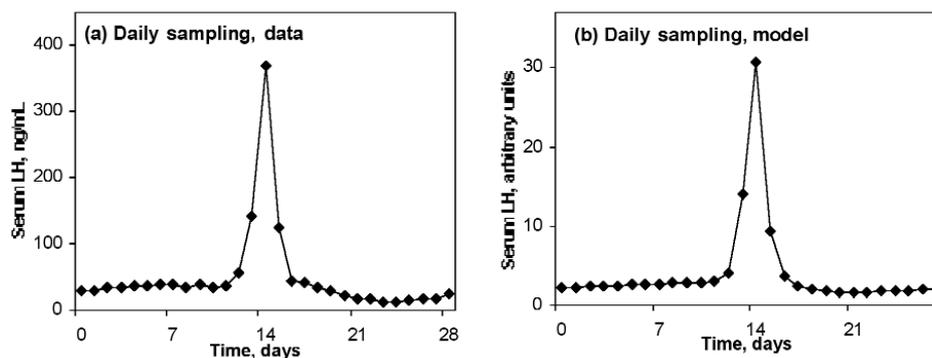


Figure 2. Serum LH, sampled daily. (a) Data (McLachlan *et al.*, 1990; Selgrade, 2001). (b) Model simulation.

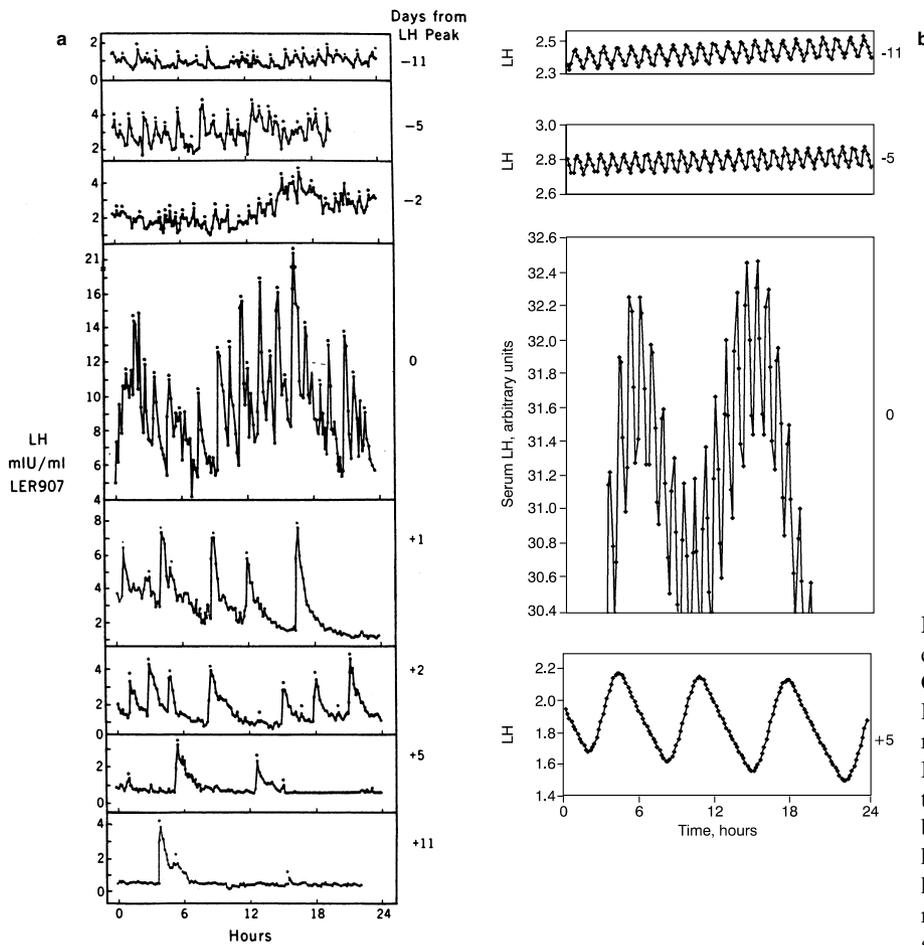


Figure 3. Serum LH, sampled every 10 min. (a) Data (Filicori and Crowley, 1983, as redrawn by Hotchkiss and Knobil, 1994), reproduced with permission. (b) Model simulations. Top: early in the cycle; middle: day of LH surge; bottom: late in the cycle. The horizontal axis measures time in hours. Time in days is given at the right of each panel, with the LH surge on day 0.

GnRH replacement therapy: frequency requirements

Now consider the case when the pituitary frequency p varies in time, but the hypothalamic frequency h is held constant. This corresponds to women with no endogenous GnRH (as in Kallmann's syndrome) undergoing pulsatile GnRH replacement therapy (Leyendecker *et al.*, 1980). If the constant frequency h is chosen within the physiological range of values that can be achieved by p , as shown by $h1(t)$ in **Figure 4**, then the frequency functions can still converge, producing transient resonance and a LH surge. If the hypothalamic frequency h is chosen above the range of p ($h2(t)$ in **Figure 4**), then the frequency functions cannot converge, and the model has no LH surge. Instead, low-amplitude LH pulses are released at the consistently high frequency of the driver, as observed in patients with polycystic ovarian syndrome (Yen, 1999). Similarly, if h is held below the range of p ($h3(t)$ in **Figure 4**), the model has no surge and LH pulses are released at consistently low frequency, as observed in some patients with secondary amenorrhoea (Perkins *et al.*, 1999).

The model can therefore explain why GnRH replacement therapy must be pulsatile (Belchetz *et al.*, 1978) with frequency approximately one pulse every 60–90 min (Knobil *et al.*, 1980; Leyendecker *et al.*, 1980). Note that replacement GnRH pulse frequencies above one pulse per 30 min or below one pulse per 90 min do not produce a LH surge in other

primates (Wildt *et al.*, 1981; Pohl *et al.*, 1983), indicating a normal physiological range of p between these values. The model also suggests that some infertility conditions may result from the hypothalamic frequency h remaining outside of the

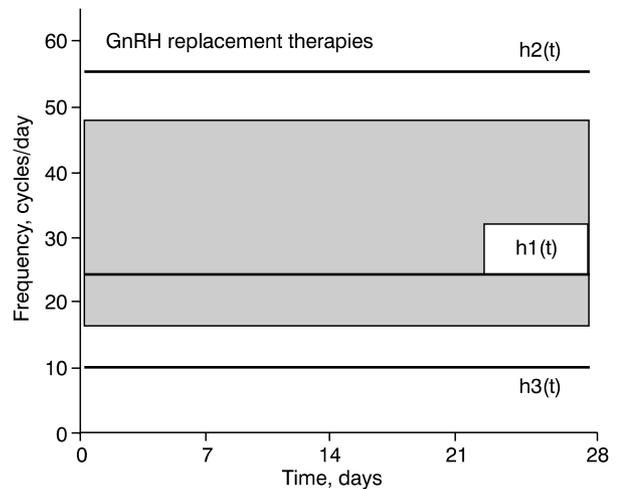


Figure 4. Holding $h(t)$ constant to simulate the treatment of Kallmann's syndrome. The physiological range of intrinsic frequencies the pituitary can achieve is indicated by the shaded region. Constant frequency GnRH replacement therapy $h1(t)$ is within the physiological pituitary range, but $h2(t)$ is too high and $h3(t)$ is too low.

range of p , either through dysfunction of the pituitary or the hypothalamus, or as a result of the hormone environment created by the ovaries. Measurement of the effect of hormone treatment on LH pulse frequency may aid diagnosis in these cases.

Predictions

As an experimental test, the model predicts that if a subject with Kallmann's syndrome is given a single bolus of GnRH, then 10 min sampling for several hours may reveal damped oscillations of serum LH. Moreover, if the experiment is repeated after a pretreatment with oestradiol or progesterone at physiological concentrations, then the frequency and amplitude of the observed oscillations in serum LH will depend on the pretreatment. By contrast, if the pituitary frequency p is held constant, the model further predicts that varying the frequency h of exogenous GnRH treatment so that h crosses p will produce a LH surge.

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