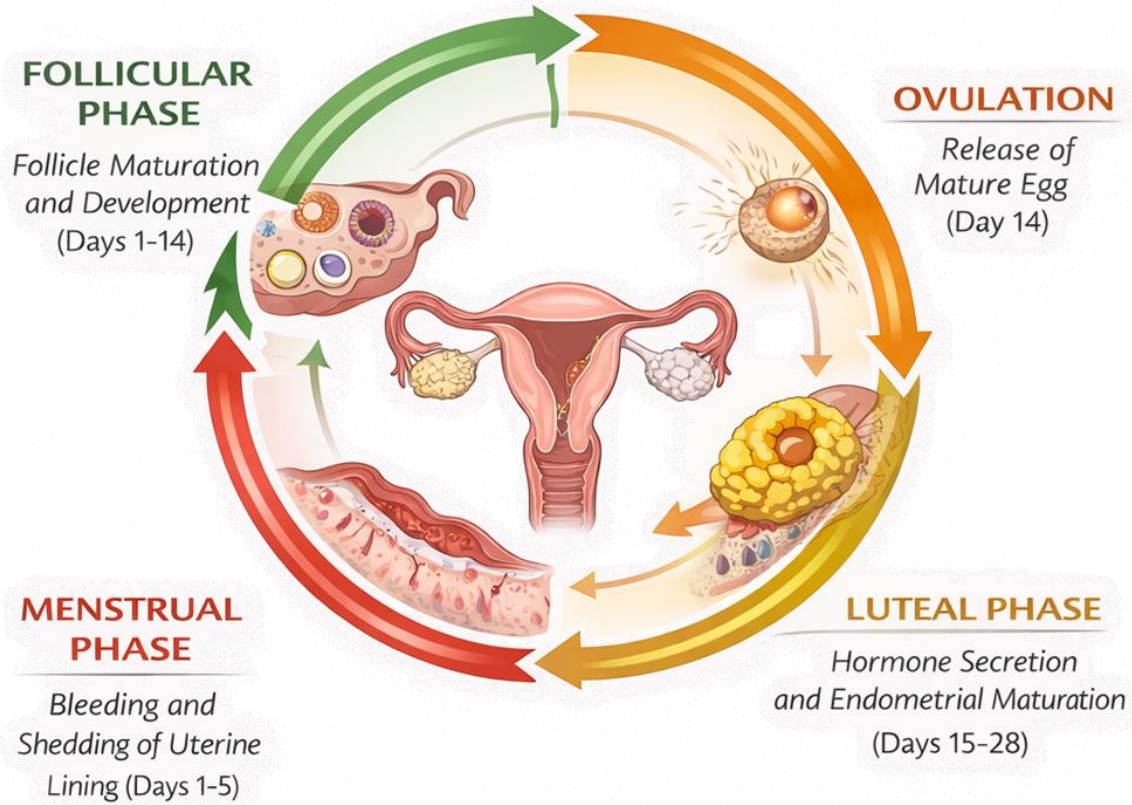


From Empirical Protocols to Feedback-Controlled Therapy: Closed-Loop Possibilities in IVF Stimulation

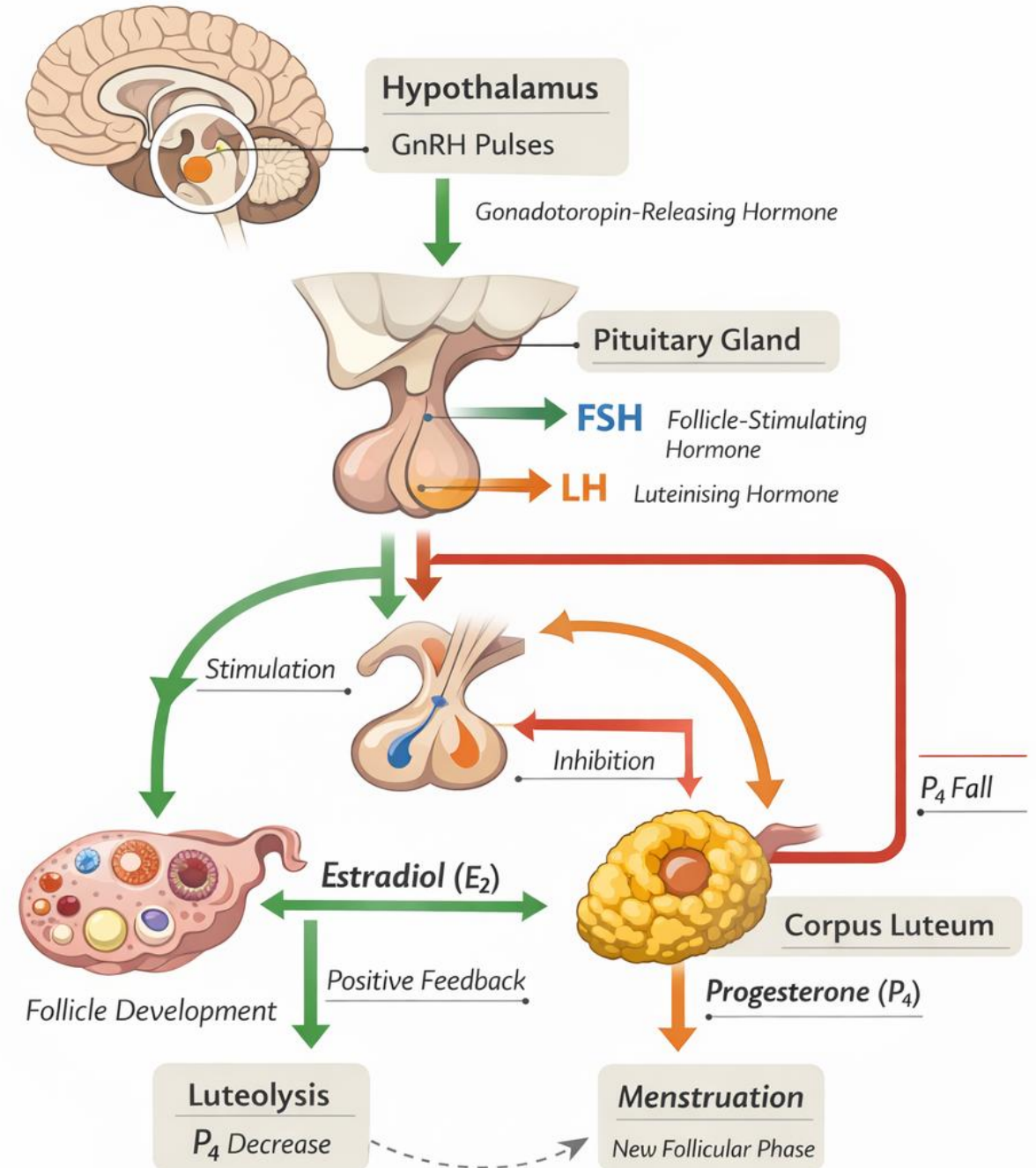
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Menstrual cycle



Hypothalamic-pituitary-gonadal (HPG) axis



Minimal four-state ODE model

Source model	ODEs	Params	Key feature retained
Selgrade & Schlosser (2003)	13	41	Pituitary + 8 ovarian compartments; E2-LH positive feedback structure
Panza et al. (2020)	13 DDEs	51	P4 inhibition of LH; follicle wave concept
Fischer et al. (2021)	30+	82	GnRH receptor dynamics; calibrated LH clearance rate
Zavala et al. (2020)	8	20	HPA-HPG cortisol stress coupling
New minimal four-state ODE model, „ELCP” (2026)	4	17	Minimal self-sustained limit cycle; explicit stress coupling



derived by systematic reduction of four published high-fidelity models

State variables

Variable	Symbol	Units	Biological role
Estradiol	$E(t)$	pg/mL	Lumped follicular E2; drives positive LH feedback above threshold θ_{EL}
LH	$L(t)$	IU/L	Ovulation trigger; activates corpus luteum formation via $H^+(L)$
CL state	$C(t)$	[0, 1]	Fractional corpus luteum activity; $C=0$ absent, $C=1$ fully active
Progesterone	$P(t)$	ng/mL	Luteal hormone; negative feedback on E2 production and LH synthesis

Model equations

- all regulatory interactions are modelled as Hill functions → providing smooth sigmoidal transitions between low and high activation states

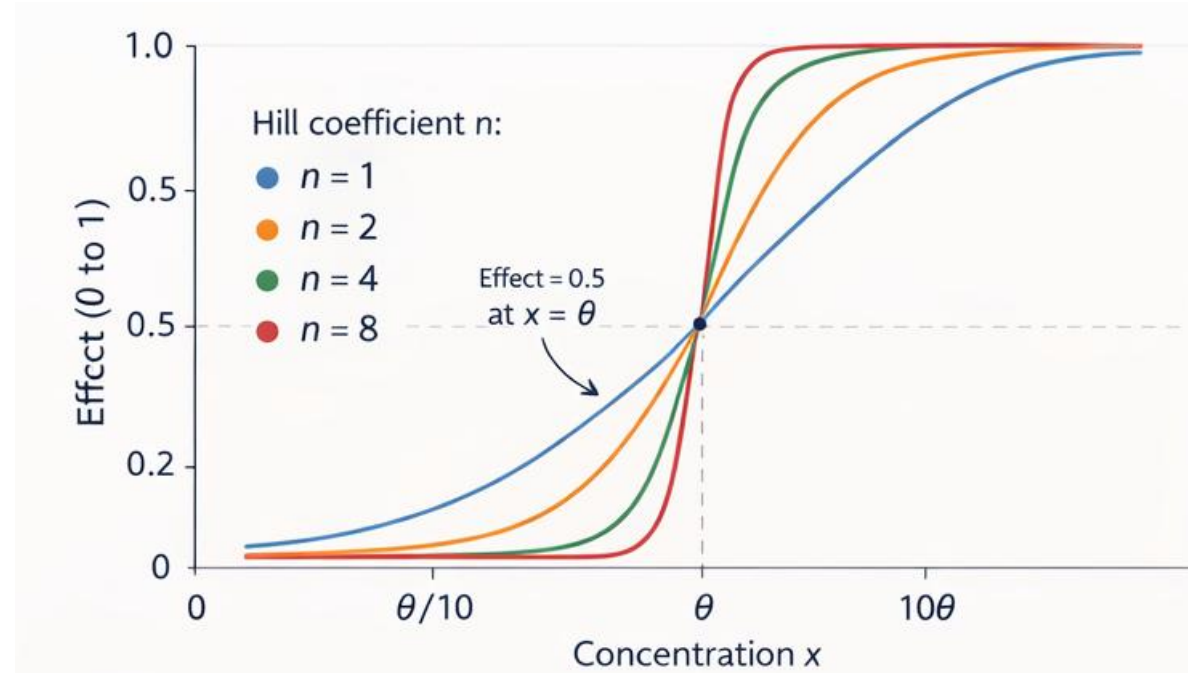
Activation Hill function

$$H^+(x, \theta, n) = \frac{x^n}{\theta^n + x^n}$$

Inhibition Hill function

$$H^-(x, \theta, n) = \frac{\theta^n}{\theta^n + x^n} = 1 - H^+(x, \theta, n)$$

- x : total ligand concentration
- θ : half-saturation concentration (function equals 0.5 at $x = \theta$)
- n : Hill coefficient (control steepness/cooperativity)



What it means:

- Larger $n \rightarrow$ sharper response
- $n = 1 \rightarrow$ simple response
- $n > 1 \rightarrow$ cooperative binding
- $n \gg 1 \rightarrow$ switch-like behavior

$$\frac{dE}{dt} = k_1 \cdot H^-(P, \theta_{PE}, n_1) - a_E \cdot E \quad (1)$$

$$\frac{dL}{dt} = [k_2 + k_3 \cdot H^+(E, \theta_{EL}, h)] \cdot H^-(P, \theta_{PL}, n_2) \cdot H^-(\text{CORT}, \theta_{\text{CORT}}, n_{\text{CORT}}) - a_L \cdot L \quad (2)$$

$$\frac{dC}{dt} = k_4 \cdot H^+(L, \theta_{LC}, \gamma) \cdot (1 - C) - d_C \cdot C \quad (3)$$

$$\frac{dP}{dt} = k_5 \cdot C - a_P \cdot P \quad (4)$$

Estradiol

$$\frac{dE}{dt} = \underbrace{k_1 \cdot H^-(P, \theta_{PE}, n_1)}_1 - \underbrace{a_E \cdot E}_2$$

- 1 P inhibits E production \rightarrow
 - E production is near-maximal when P is low (follicular phase)
 - E production is suppressed when P is high (luteal phase)
- 2 E is cleared with rate a_E

Luteinizing hormone (LH)

$$\frac{dL}{dt} = \underbrace{[k_2 + k_3 \cdot H^+(E, \theta_{EL}, h)]}_{1} \cdot \underbrace{H^-(P, \theta_{PL}, n_2)}_{2} \cdot \underbrace{H^-(CORT, \theta_{CORT}, n_{CORT})}_{3} - \underbrace{a_L \cdot L}_{4}$$

- 1 k_2 : basal component, E activates L production
- 2 P inhibits L production \rightarrow preventing luteal-phase LH surges
- 3 $CORT$ inhibits L production \rightarrow encoding HPA-HPG stress coupling
- 4 L is cleared with rate a_L (rapid, $t_{1/2} \approx 60$ min)

Corpus luteum state

$$\frac{dC}{dt} = k_4 \cdot \underbrace{H^+(L, \theta_{LC}, \gamma)}_1 \cdot \underbrace{(1 - C)}_2 - \underbrace{d_C \cdot C}_3$$

- 1 L activates $C \rightarrow C$ is driven toward 1
- 2 implements saturation $\rightarrow C$ cannot exceed 1
- 3 C decays at rate $d_C \rightarrow$ luteolysis

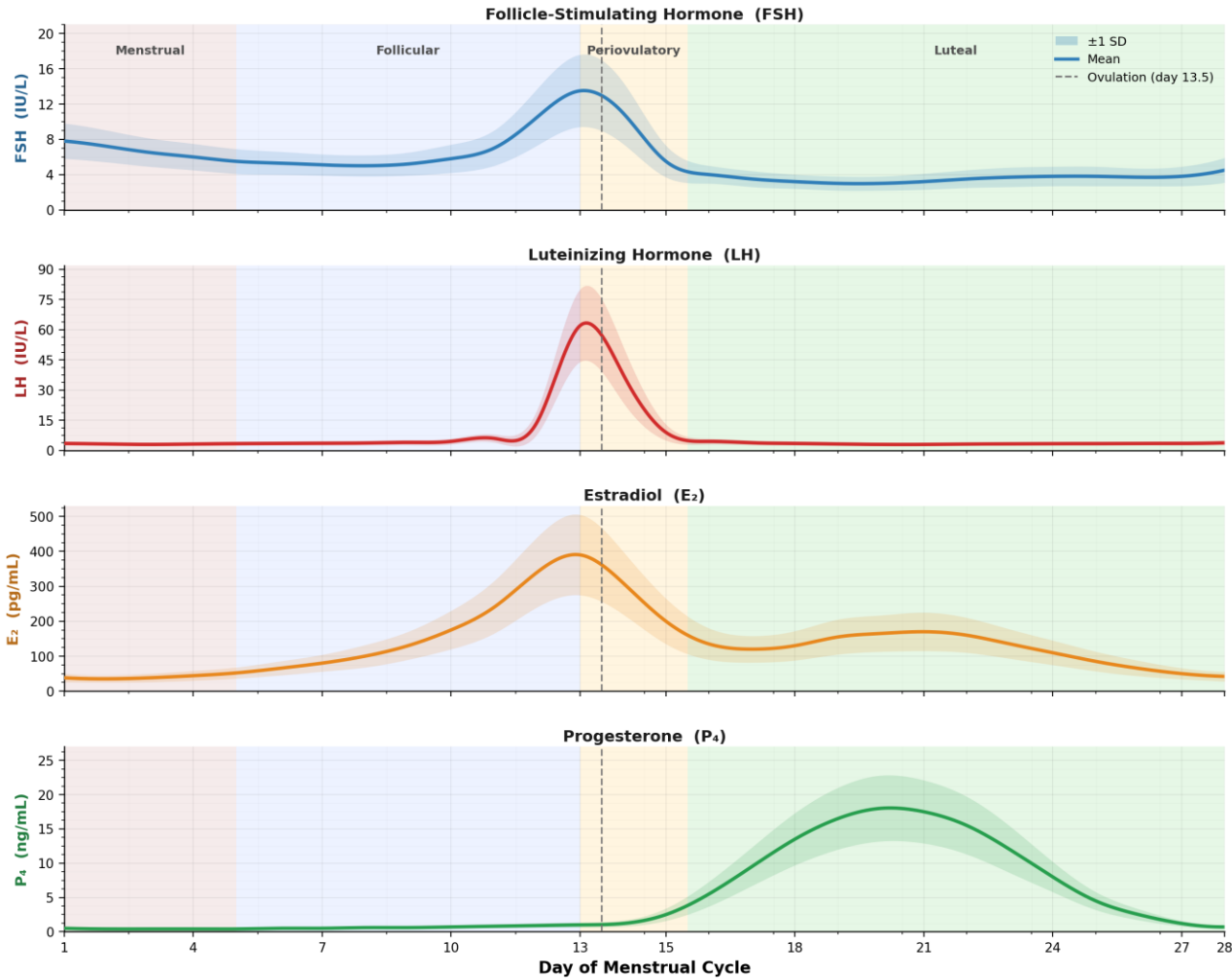
Progesterone

$$\frac{dP}{dt} = \underbrace{k_5 \cdot C}_1 - \underbrace{a_P \cdot P}_2$$

- 1 P is secreted by the corpus luteum
- 2 P is cleared with rate a_P

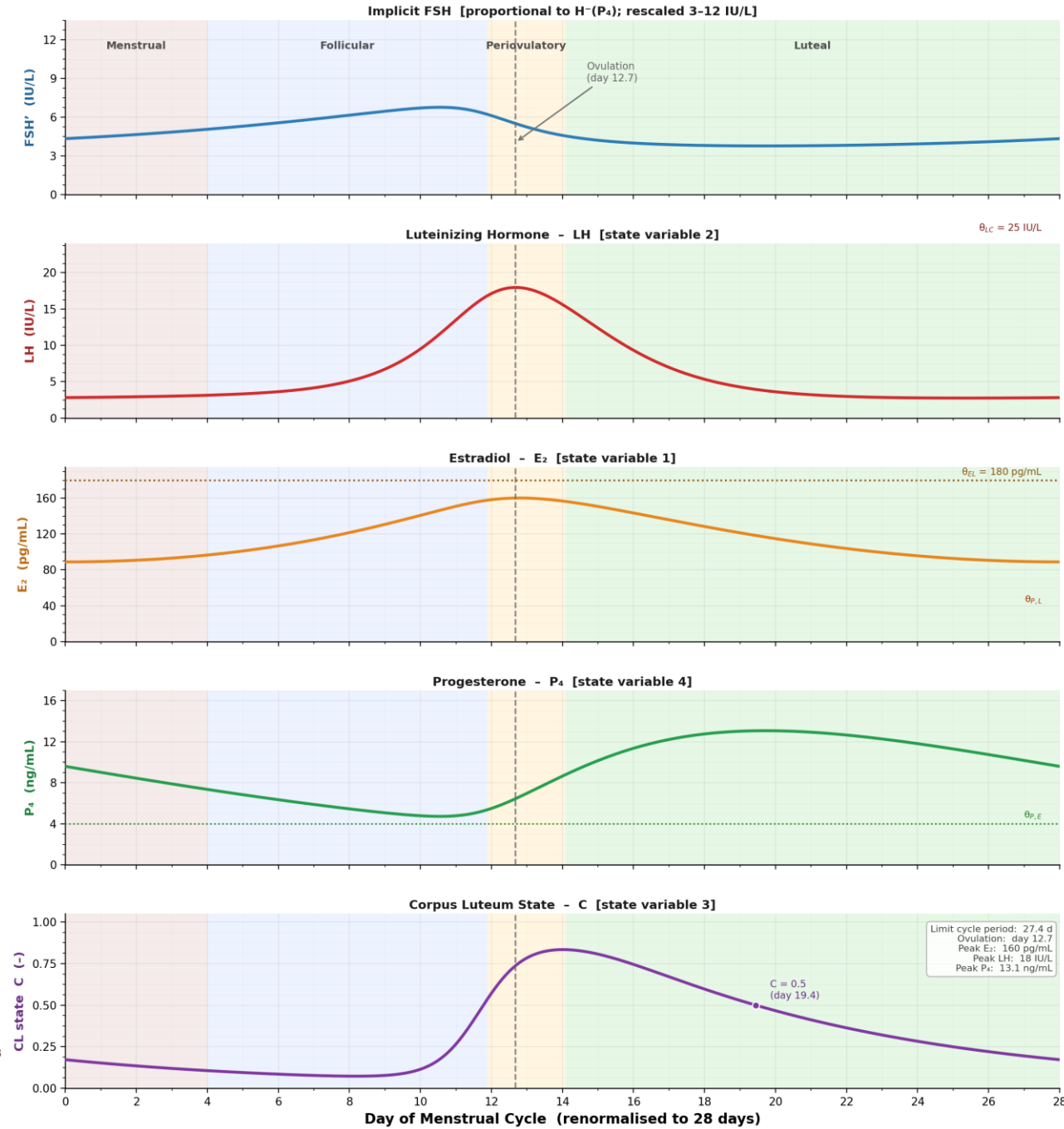
Simulations: high-fidelity models vs ELCP

Figure 1 - Literature Reference: Hormone Concentrations Across the Normal Menstrual Cycle (Mean \pm 1 SD)



Sources: McLachlan et al. 1990 (Hum Reprod) · Welt et al. 1999 (Endocrinology) · Hale et al. 2007 (Fertil Steril) · Stricker et al. 2006 (Clin Chem Lab Med)

Figure 2 - Reduced-Order Model Simulation: Hormone State Variables E₂, LH, P₄, C and Implicit FSH (Settled Limit Cycle)



$dE/dt = k_1 \cdot H \cdot (P) - a_E \cdot E$ | $dL/dt = [k_2 + k_3 \cdot H \cdot (E, h=8)] \cdot H \cdot (P) - a_L \cdot L$ | $dC/dt = k_4 \cdot H \cdot (L) \cdot (1-C) - d_{CC} \cdot C$ | $dP/dt = k_5 \cdot C - a_P \cdot P$ | 17 free parameters

Settled limit cycle – properties

- Starting from any physiologically reasonable initial condition, the system converges to a stable limit cycle after approximately 300 days (≈ 10 cycles)

Property	Model	Literature range	Match
Limit-cycle period	27.4 days	24–32 days	✓ Match
Ovulation day	12.4	10–16	✓ Match
Peak E2 (preovulatory)	160 pg/mL	250–450 pg/mL	≈ Low
Peak LH (surge)	18 IU/L	30–80 IU/L	≈ Low
Peak P4 (luteal)	13.1 ng/mL	10–20 ng/mL	✓ Match
Basal LH (follicular)	2.8–3.5 IU/L	2–5 IU/L	✓ Match
FSH proxy range	4–12 IU/L	3–14 IU/L	✓ Match
Follicular phase	≈ 12 d	10–16 d	✓ Match
Luteal phase	≈ 16 d	12–16 d	✓ Match

Current limitations

- Peak LH (18 IU/L) and preovulatory E2 (160 pg/mL) are below clinical ranges due to the absence of an explicit pituitary LH pool and FSH-dependent folliculogenesis.
- No spatial structure; all concentrations are assumed to be well-mixed blood values.
- Inhibin A/B and follistatin, which refine FSH regulation during the follicular phase, are subsumed into the implicit FSH approximation.
- GnRH pulses are not represented; pulsatile LH dynamics require a higher-dimensional model.

Suggested extensions

- Add an explicit FSH state variable and pituitary LH pool to recover correct E2 and LH surge amplitudes.
- Introduce inhibin A as a fourth explicit feedback signal (following the Panza model approach).
- Replace the scalar CORT coupling with a 2-state HPA oscillator (Zavala framework) for circadian-menstrual interaction modelling.
- Incorporate time delays ($\tau \approx 1-2$ d on P4 feedback) via DDE formulation to improve luteal-phase accuracy.
- Extend to patient-specific models by treating parameters as random variables with log-normal distributions, calibrated by Approximate Bayesian Computation against serum hormone time series.

Thank you for
your attention!

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