**Validation of a mathematical model of the bovine estrous cycle for cows with different estrous cycle characteristics**

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**Supplementary** **Table S4**

Description and explanation of the 60 parameters of the mathematical model1. The differential equations and Hill functions (*H+, H−*) referred to are given in Supplementary Tables S1 and S2.

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| No. | Parameter | Description and explanation | In eq. |
| 1 |  | *Rate constant for the synthesis of GnRH in the hypothalamus.* The GnRH synthesis rate is determined by this constant and by the concentration of GnRH in the hypothalamus. | Eq.1a |
| 2 |  | *Maximum concentration of GnRH in the hypothalamus.* The model assumes a maximum concentration of GnRH in the hypothalamus. GnRH synthesis is assumed to depend on how low the GnRH concentration is compared with that maximum. | Eq. 1a |
| 3 |  | *Maximum rate constant for (P4&E2)-dependent GnRH release*.  The release of GnRH from the hypothalamus is considered to consist of two parts. The first part can be inhibited by the combined presence of E2 and P4. Parameter 3 is the maximum rate constant for that part. | Eq.1b  (in ) |
| 4 |  | *Threshold for E2 to suppress GnRH release*. The release of GnRH from the hypothalamus is considered to consist of two parts. The first part can be inhibited by the combined presence of E2 and P4. Parameter 4 is the E2 threshold for that inhibition. | Eq.1b  (in ) |
| 5 |  | *Threshold for P4 to enable E2 to suppress GnRH release*. The release of GnRH from the hypothalamus is considered to consist of two parts. The first part can be inhibited by the combined presence of E2 and P4. Parameter 5 is the P4 threshold for that inhibition. | Eq.1b  (in ) |
| 6 |  | *Maximum rate constant for P4-dependent GnRH release*. The release of GnRH from the hypothalamus is considered to consist of two parts. The second part can be inhibited by P4 directly. Parameter 6 is the maximum rate constant for that part. | Eq.1b  (in ) |
| 7 |  | *Threshold for P4 to inhibit GnRH release directly*. The release of GnRH from the hypothalamus is considered to consist of two parts. The second part can be inhibited by P4 directly. Parameter 7 is the P4 threshold for that inhibition. | Eq.1b  (in ) |
| 8 |  | Ma*ximum ability of the pituitary to sense GnRH*. GnRH is transported from the hypothalamus to the pituitary. The ability of the pituitary to bind and ‘sense’ the GnRH is stimulated by E2. Parameter 8 is the maximum for that ability. | Eq.2  (in ) |
| 9 |  | *Threshold for E2 to increase the ability of the pituitary to sense GnRH*. GnRH is transported from the hypothalamus to the pituitary. The ability of the pituitary to bind and ‘sense’ the GnRH is stimulated by E2. Parameter 9 is the E2 threshold for this stimulation. | Eq.2  (in ) |
| 10 |  | *Rate constant for the clearance of GnRH from the pituitary*. The GnRH clearance rate is determined by the concentration of GnRH in the pituitary times this rate constant. | Eq. 2 |
| 11 |  | *Maximum FSH synthesis rate in the pituitary*. FSH synthesis in the pituitary can be inhibited by Inhibin. Parameter 11 is the maximum FSH synthesis rate (i.e. in the absence of inhibin). | Eq.3a  (in ) |
| 12 |  | *Threshold for Inhibin to inhibit FSH synthesis*. Inhibin (Inh) can inhibit the FSH synthesis in the pituitary. Parameter 12 is the Inh threshold for this inhibition. | Eq.3a  (in ) |
| 13 |  | *Maximum rate constant for P4-stimulated FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The first part is stimulated by P4. Parameter 13 is the maximum rate constant for that part. | Eq.3b  (in ) |
| 14 |  | *Threshold for P4 to stimulate FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The first part is stimulated by P4. Parameter 14 is the P4 threshold for that stimulation. | Eq.3b  (in ) |
| 15 |  | *Maximum rate constant for E2-inhibited FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The second part is inhibited by E2. Parameter 15 is the maximum rate constant for that part. | Eq.3b  (in ) |
| 16 |  | *Threshold for E2 to inhibit FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The second part is inhibited by E2. Parameter 16 is the E2 threshold for that inhibition. | Eq.3b  (in ) |
| 17 |  | *Maximum rate constant for GnRH-stimulated FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The third part is stimulated by GnRH. Parameter 17 is the maximum rate constant for that part. | Eq.3b  (in ) |
| 18 |  | *Threshold for GnRH to stimulate FSH release*. Release of FSH from the pituitary into the peripheral blood is considered to consist of four parts. The third part is is stimulated by GnRH. Parameter 18 is the GnRH threshold for that stimulation. | Eq.3b  (in ) |
| 19 |  | *Rate constant for the clearance of FSH from peripheral blood*. The FSH clearance rate is determined by the concentration of FSH in the blood times this rate constant. | Eq. 4 |
| 20 |  | *Rate constant for basal FSH release from the pituitary*. The model assumes that in addition to the P4-, E2-, and GnRH-dependent FSH release, there is also a basal part of FSH release, for which parameter 20 is the rate constant. | Eq. 3b |
| 21 |  | *Maximum rate of E2-stimulated LH synthesis*. LH synthesis in the pituitary is considered to consist of two parts. The first part is stimulated by E2. Parameter 21 is the maximum rate for that part. | Eq.5a  (in ) |
| 22 |  | *Threshold for E2 to stimulate LH synthesis*. LH synthesis in the pituitary is considered to consist of two parts. The first part is stimulated by E2. Parameter 22 is the E2 threshold for that stimulation. | Eq.5a  (in ) |
| 23 |  | *Maximum rate of P4-inhibited LH synthesis*. LH synthesis in the pituitary is considered to consist of two parts. The second part is inhibited by P4. Parameter 23 is the maximum rate for that part. | Eq.5a  (in ) |
| 24 |  | *Threshold for P4 to inhibit LH synthesis*. LH synthesis in the pituitary is considered to consist of two parts. The second part is inhibited by P4. Parameter 24 is the P4 threshold for that inhibition. | Eq.5a  (in ) |
| 25 |  | *Maximum rate constant for GnRH-stimulated LH release*. Release of LH from the pituitary into the peripheral blood is considered to consist of two parts. The first part is stimulated by GnRH. Parameter 25 is the maximum rate constant for that part. | Eq.5b  (in ) |
| 26 |  | *Threshold for GnRH to stimulate LH release*. Release of LH from the pituitary is considered to consist of two parts. The first part is stimulated by GnRH. Parameter 26 is the GnRH threshold for that stimulation. | Eq.5b  (in ) |
| 27 |  | *Rate constant for basal LH release from the pituitary*. The model assumes that in addition to the GnRH-dependent LH release, there is also a basal part of LH release, for which parameter 27 is the rate constant. | Eq. 5b |
| 28 |  | *Rate constant for the clearance of LH from peripheral blood*. The rate of LH clearance in peripheral blood is determined by the concentration of LH times this rate constant. | Eq. 6 |
| 29 |  | *Maximum rate of the FSH-dependent increase of Follicle size*. The rate of change of Follicle size is described as the sum of three parts. The first part is FSH-stimulated growth, Parameter 29 is the maximum rate of this part. | Eq.7  (in ) |
| 30 |  | *Maximum threshold for FSH to stimulate increase of Follicle size*. The rate of change of Follicle size is described as the sum of three parts. The first part is FSH-stimulated growth, The FSH threshold for this stimulation () is itself a function of Follicle size (‘larger follicles require less FSH to be stimulated’). Parameter 30 is the maximum value of this function (i.e. the highest value for the FSH threshold). | Eq.7  (in ) |
| 31 |  | *Threshold for Follicle size to reduce the FSH threshold*. The rate of change of Follicle size is described as the sum of three parts. The first part is FSH-stimulated growth, The FSH threshold for this stimulation () is itself a function of Follicle size (‘larger follicles require less FSH to be stimulated’). Parameter 31 is the threshold for Follicle size for this effect on the FSH threshold. | Eq.7  (in ) |
| 32 |  | *Maximum rate constant for the P4-dependent decrease of Follicle size*. The rate of change of Follicle size is described as the sum of three parts. The second part is P4-induced regression. Parameter 32 is the maximum rate constant for this part. | Eq.7  (in ) |
| 33 |  | *Threshold for P4 to stimulate decrease of follicle size*. The rate of change of Follicle size is described as the sum of three parts. The second part is P4-induced regression. Parameter 33 is the P4 threshold for this negative effect on Follicle size. | Eq.7  (in ) |
| 34 |  | *Maximum rate constant for the LH-dependent change of Follicle size*. The rate of change of Follicle size is described as the sum of three parts. The third part is LH-induced regression, representing that LH at very high concentrations (LH surge) can trigger ovulation. Parameter 34 is the maximum rate constant for this part. | Eq.7  (in ) |
| 35 |  | *Threshold for LH to stimulate decrease of follicle size*. The rate of change of Follicle size is described as the sum of three parts. The third part is LH-induced regression, representing that LH at very high concentrations (LH surge) can trigger ovulation. Parameter 35 is the LH threshold for this negative effect on Follicle size. | Eq.7  (in ) |
| 36 |  | *Maximum rate of PGF2α secretion*. The secretion of PGF2α in the endometrium is stimulated by oxytocin (OT), which, of course is dependent on the presence of the oxytocin receptor (OTR). Parameter 36 is the maximum PGF2α secretion rate (i.e. with maximal stimulation by OT through the OTR). | Eq.15  (in ) |
| 37 |  | *Threshold for OTR to allow OT to stimulate PGF2α secretion*. The secretion of PGF2α in the endometrium is stimulated by oxytocin (OT), which, in turn, depends on the presence of the oxytocin receptor (OTR). Parameter 37 is the threshold concentration for OTR to allow OT to stimulate PGF2α secretion. | Eq.15  (in ) |
| 38 |  | *Threshold for OT to stimulate PGF2α secretion*. Oxytocin (OT) can stimulate secretion of PGF2α in the endometrium. Parameter 38 is the OT threshold for that stimulation. | Eq.15  (in ) |
| 39 |  | *PGF2α clearance rate constant*. The change of PGF2α depends on PGF2α secretion minus clearance. Parameter 39 is the rate constant for the PGF2α clearance. | Eq.15 |
| 40 |  | *Scaling factor for LH-induced rise of CL*. The rate of change of corpus luteum volume (CL) is considered to consist of three parts. The first part is the LH-induced luteinization of the ovulated follicle, representing the contribution of the ovulated follicle in forming the rising CL. Parameter 40 (SF, scaling factor) is introduced to scale this first part (between 0 and 1) and adjust dimensions. | Eq. 8 |
| 41 |  | *Maximum rate of increase of CL stimulated by itself*. The rate of change of corpus luteum volume (CL) is considered to consist of three parts. The second part is self-stimulation of the CL. Parameter 41 is the maximum rate of this part. | Eq.8  (in ) |
| 42 |  | *Threshold volume of CL to stimulate self-growth*. The rate of change of corpus luteum volume (CL) is considered to consist of three parts. The second part is self-stimulation of the CL. Parameter 42 is the CL threshold for self-stimulation. | Eq.8  (in ) |
| 43 |  | *Maximum rate of decrease of CL stimulated by IOF*. The rate of change of CL is considered to consist of three parts. The third part is regression of CL, induced by ‘intra ovarian factors’ (IOF). Parameter 43 is the maximum rate of that part. | Eq.8  (in ) |
| 44 |  | *Threshold for IOF to stimulate CL regression*. The change of CL is considered to consist of three parts. The third part is regression of CL, induced by ‘intra ovarian factors’ (IOF). Parameter 44 is the IOF threshold for its negative effect on CL volume. | Eq.8  (in ) |
| 45 |  | *Proportionality constant for P4 secretion by the CL*. The rate of change of P4 equals the rate of P4 secretion by the CL minus the rate of P4 clearance in the blood. P4 secretion rate is considered to be equal to the square of CL volume times the proportionality constant for P4 secretion. | Eq.9 |
| 46 |  | *Rate constant for P4 clearance in peripheral blood*.  The rate of change of P4 equals the rate of P4 secretion by the CL minus the rate of P4 clearance in peripheral blood. P4 clearance rate is equal to the concentration of P4 times the rate constant for P4 clearance. | Eq.9 |
| 47 |  | *Proportionality constant for E2 secretion by the follicles*. The rate of change of E2 equals the rate of E2 secretion by the follicles minus the rate of E2 clearance in peripheral blood. The E2 secretion rate is considered to be equal to the square of follicle diameter times the proportionality constant for E2 secretion. | Eq.10 |
| 48 |  | *Rate constant for E2 clearance in peripheral blood*. The rate of change of E2 equals the rate of E2 secretion by the follicles minus the rate of E2 clearance in peripheral blood. E2 clearance rate is equal to the concentration of E2 times the rate constant for E2 clearance. | Eq.10 |
| 49 |  | *Proportionality constant for Inh secretion by the follicles*. The rate of change of Inhibin (Inh) equals the rate of Inh secretion by the follicles minus the rate of Inh clearance in peripheral blood. The Inh secretion rate is considered to be equal to the square of follicle diameter times the proportionality constant for Inh secretion. | Eq.11 |
| 50 |  | *Rate constant for Inh clearance in peripheral blood*. The rate of change of Inhibin (Inh) equals the rate of Inh secretion by the follicles minus the rate of Inh clearance in peripheral blood. Inh clearance rate is equal to the Inh concentration times the rate constant for Inh clearance. | Eq.11 |
| 51 |  | *Maximum rate of P4-dependent OTR synthesis in the endometrium*. The rate of change of OTR in the endometrium equals the rate of synthesis minus the rate of clearance in the endometrium. The OTR synthesis rate is stimulated by the P4 concentration. Parameter 51 is the maximum OTR synthesis rate | Eq.12  (in ) |
| 52 |  | *Threshold for P4 to stimulate OTR synthesis in the endometrium*. The rate of change of OTR in the endometrium equals the rate of synthesis minus the rate of clearance. The OTR synthesis rate is stimulated by the P4 concentration. Parameter 52 is the P4 threshold for this stimulation. | Eq.12  (in ) |
| 53 |  | *Rate constant for OTR clearance in the endometrium*. The rate of change of OTR in the endometrium equals the rate of synthesis minus the rate of clearance in the endometrium. The OTR clearance rate equals the concentration of OTR in the endometrium times the rate constant for OTR clearance. | Eq. 12 |
| 54 |  | *Maximum proportionality factor for OT secretion by the CL*. The rate of change of oxytocin (OT) equals the rate of OT secretion by the CL minus the rate of clearance. The OT secretion rate is considered to be equal to the square of CL volume times an E2-dependent proportionality factor. Parameter 54 is the maximum for that proportionality factor. | Eq.13  (in ) |
| 55 |  | *Threshold for E2 to stimulate OT secretion by the CL*. The rate of change of oxytocin (OT) equals the rate of OT secretion by the CL minus the rate of clearance. OT synthesis is stimulated by E2. Parameter 55 is the E2 threshold for that stimulation. | Eq.13  (in ) |
| 56 |  | *Rate constant for OT clearance*. The rate of change of oxytocin (OT) equals the rate of OT secretion by the CL minus the rate of clearance. The OT clearance rate is equal to the OT concentration times the rate constant for OT clearance. | Eq.13 |
| 57 |  | *Maximum rate of synthesis of ‘intra-ovarian factor’ (IOF)*. The rate of change of IOF in the ovaries equals the rate of IOF synthesis minus the rate of IOF clearance. The rate of synthesis of IOF is considered to be stimulated by PGF2α and by CL volume. Parameter 57 is the maximum rate constant for IOF synthesis. | Eq.14  (in ) |
| 58 |  | *Threshold for PGF2α to stimulate synthesis of ‘intra-ovarian factor’*. The rate of change of intra-ovarian factor (IOF) in the ovaries equals the rate of IOF synthesis minus the rate of IOF clearance. The rate of synthesis of IOF is stimulated by PGF2α and by CL volume. Parameter 58 is the PGF2α threshold for that stimulation. | Eq.14  (in ) |
| 59 |  | *Threshold CL volume to stimulate synthesis of ‘intra-ovarian factor’*. The rate of change of intra-ovarian factor (IOF) in the ovaries equals the rate of IOF synthesis minus the rate of IOF clearance. The rate of synthesis of IOF is stimulated by PGF2α and by CL volume. Parameter 59 is the CL threshold for that stimulation. | Eq.14  (in ) |
| 60 |  | *Rate constant for clearance of ‘intra-ovarian factor’ (IOF)*. The rate of change of IOF in the ovaries equals the rate of IOF synthesis minus the rate of IOF clearance. The IOF clearance rate is equal to the IOF concentration times the rate constant for IOF clearance. | Eq. 14 |

1 E2 = estradiol, P4 = progesterone, GnRH = gonadotropin releasing hormone, Inh = inhibin, OT = oxytocin, OTR = oxytocin receptor, FSH = follicle stimulating hormone, LH = luteinizing hormone, IOF = intra-ovarian factors, PGF2α = prostaglandin2α, CL = corpus luteum size. Foll = follicle size, Ovul. Foll. = ovulated follicle,  *Pit* =pituitary, *Hypo* = hypothalamus, *c* = rate constant, *t* = time, *T* = threshold for change of behaviorof the Hill functions, *m* = maximum value of the switched parameter.