Hill functions of activation and inhibition

$$H^{+}(S_i, T_i^j, n_i^j) = \frac{(S_i/T_i^j)^{n_i^j}}{1 + (S_i/T_i^j)^{n_i^j}} \tag{1}$$

$$H^{-}(S_i, T_i^j, n_i^j) = \frac{1}{1 + (S_i/T_i^j)^{n_i^j}} \ , \tag{2}$$

where S_i – concentration of the regulating substrate, T_i^j – threshold (where the response is half-maximal), and n_i^j influences the speed of regulatory process: high n_i^j means rapid response, whereas low n_i^j – gradual Michaelis-Menten-like response.
When S_i approaches T_i^j, it regulates S_j.

Kisspeptin dynamics

Kisspeptin is released in a pulse pattern with a frequency $f(t)$ and amplitude $a(t)$:

$$f(t) = f_0 \times H^{-}(A(t), T_A^f, n_A^f) \times H^{-}(E(t), T_E^f, n_E^f) \times H^{+}(L, T_L^f, n_L^f) \tag{3}$$

$$a(t) = a_0 \times \left(H^{+}(E(t), T_E^a, n_E^a) + H^{-}(E(t), T_E^a, n_E^a)\right) \times H^{+}(L, T_L^a, n_L^a) \ , \tag{4}$$

where f_0 is a basal frequency, and a_0 is a basal amplitude.
Estrogens E and adrogens A regulate kisspeptin frequency and amplitude of pulsates.
During the luteal phase E and A inhibit the kisspeptin frequency; during the follicular phase before the LH surge E suppresses kisspeptin amplitude.

LH dynamics

LH dynamics in the pituitary can be described as follows:

$$\frac{d}{dt} LH_p(t) = s_{LH}(t) - r_{LH}(t) \ , \tag{5}$$

where synthesis of LH is

$$s_{LH}(t) = b_s^{LH} \times H^{+}(E(t), T_E^{LH}, n_E^{LH}) \times H^{-}(A(t), T_A^{LH}, n_A^{LH}) \times b_h \exp(-(f(t) - b_0)^2/b_k) \ , \tag{6}$$

where the kisspeptin influence on LH synthesis is modelled by the bell-shaped function with parameters b_h,b_0, and b_k to reflect its inhibitory effect of both low and high frequencies of GnRH pulses on LH. We treat henceforth $b_s^{LH} \times b_h$ as one parameter by setting $b_h = 1$. Release of LH is

$$r_{LH}(t) = k_r^{LH} \times LH_p(t) \tag{7}$$

LH dynamics in blood can be described as follows:

$$\frac{d}{dt} LH_b(t) = \frac{1}{V_b} r_{LH}(t) - k_{cl}^{LH} \times LH_b(t) \tag{8}$$

The basal LH-synthesis rate b_s^{LH} is stimulated by E and inhibited by A.
LH is released into the blood stream from the pituitary with a release rate k_r^{LH} and is cleared from the blood stream with a clearance rate k_{cl}^{LH}.

FSH

FSH dynamics in the pituitary can be described as follows:

$$\frac{d}{dt} FSH_p(t) = s_{FSH}(t) - r_{FSH}(t) \ , \tag{9}$$

where synthesis of FSH is

$$s_{FSH}(t) = b_s^{FSH} \times H^-(A(t), T_A^{FSH}, n_A^{FSH}) \times H^-(f(t), T_f^{FSH}, n_f^{FSH}) \ , \tag{10}$$

and release of FSH is

$$r_{FSH}(t) = k_r^{FSH} \times FSH_p(t) \tag{11}$$

FSH dynamics in blood can be described as follows:

$$\frac{d}{dt} FSH_b(t) = \frac{1}{V_b} r_{FSH}(t) - k_{cl}^{FSH} \times FSH_b(t) \tag{12}$$

The basal FSH-synthesis rate b_s^{FSH} is inhibited by A and high kisspeptin frequencies f.
FSH is released into the blood stream from the pituitary with a release rate k_r^{FSH} and is cleared from the blood stream with a clearance rate k_{cl}^{FSH}.

Estrogens

Estrogens dynamics in the ovaries can be described as follows:

$$\frac{d}{dt}E_{ov}(t) = s_E(t) - r_E(t) \ , \tag{13}$$

where synthesis of E is

$$s_E(t) = E_0 + E_{max} \times H^+(FSH_p(t), T^E_{FSH}, n^E_{FSH}) \times H^+(A(t), T^E_A, n^E_A) \ , \tag{14}$$

and release of E is

$$r_E(t) = k^E_r \times E_{ov}(t) \tag{15}$$

Note that s_E is also a function of androgens' levels to account for the fact that granulosa cells convert androgens (produced by theca cells) into estrogens. Estrogens dynamics in blood can be described as follows:

$$\frac{d}{dt}E_b(t) = \frac{1}{V_b}k^E_r \times E_{ov}(t) - k^E_{cl} \times E_b(t) \tag{16}$$

Estrogens are released into the blood stream from the ovaries with a release rate k^E_r and are cleared from the blood stream with a clearance rate k^E_{cl}.

Adrogens

Adrogens dynamics in the ovaries can be described as follows:

$$\frac{d}{dt}A_{ov}(t) = s_A(t) - r_A(t) \ , \tag{17}$$

where synthesis of A is

$$s_A(t) = A_0 + A_{max} \times H^+(LH_p(t), T^A_{LH}, n^A_{LH}) \ , \tag{18}$$

and release of A is

$$r_A(t) = k^A_r A_{ov}(t) \tag{19}$$

Adrogens dynamics in blood can be described as follows:

$$\frac{d}{dt}A_b(t) = \frac{1}{V_b}k^A_r \times A_{ov}(t) - k^A_{cl} \times A_b(t) \tag{20}$$

Adrogens are released into the blood stream from the ovaries with a release rate k_r^A and are cleared from the blood stream with a clearance rate k_{cl}^A.

Note: we set A_0 and E_0 to 0, but keep them in the model for future.

Leptin