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Herausgegeben vom  
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URL: <http://www.zib.de>

ZIB-Report (Print) ISSN 1438-0064  
ZIB-Report (Internet) ISSN 2192-7782

# A reduced ODE model of the Bovine Estrous Cycle

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## Zusammenfassung

This work deals with the reduction of a previously developed ODE model for the bovine estrous cycle. After applying a method for exploring the parameter space by Apri et al. (2012), we perform structure-based reduction steps and several system specific adaptations. Overall, the original model consisting of 15 ODEs and 60 parameters is reduced to a model of 10 odes and 38 parameters. The reduced model qualitatively reproduces the state trajectories of the original model.

**AMS MSC 2000:** 34A05, 65L07, 92C42

**Keywords:** cow, reproduction, hormone patterns, differential equations, systems biology

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## Introduction

Nowadays, the simulation of large ODE systems usually does not present any difficulties. However, model reduction can lead to interesting insights regarding the underlying dynamics of the modeled phenomenon. Biological models are often based on a variety of assumptions, and it is up to the modeler which mechanisms to include and which not. Validation of a model is performed with the help of experimental measurements, thus by checking the output of the model. Whether the chosen mechanisms are unique, or whether there exist other mechanisms that lead to the same model behavior, can usually not be proven. Model reduction techniques aim at finding simpler models that result in the same validated model output. They can help to decide which components are essential for the predictive power of a model.

In [1], a mathematical model of the bovine estrous cycle has been presented. This model has been modified in [2, 3], where also certain characteristics of the cycle were analyzed. In [4], the model was further enhanced towards the administration of  $\text{PGF2}\alpha$ , and synchronization protocols were simulated. Here, this model serves as a basis for model reduction.

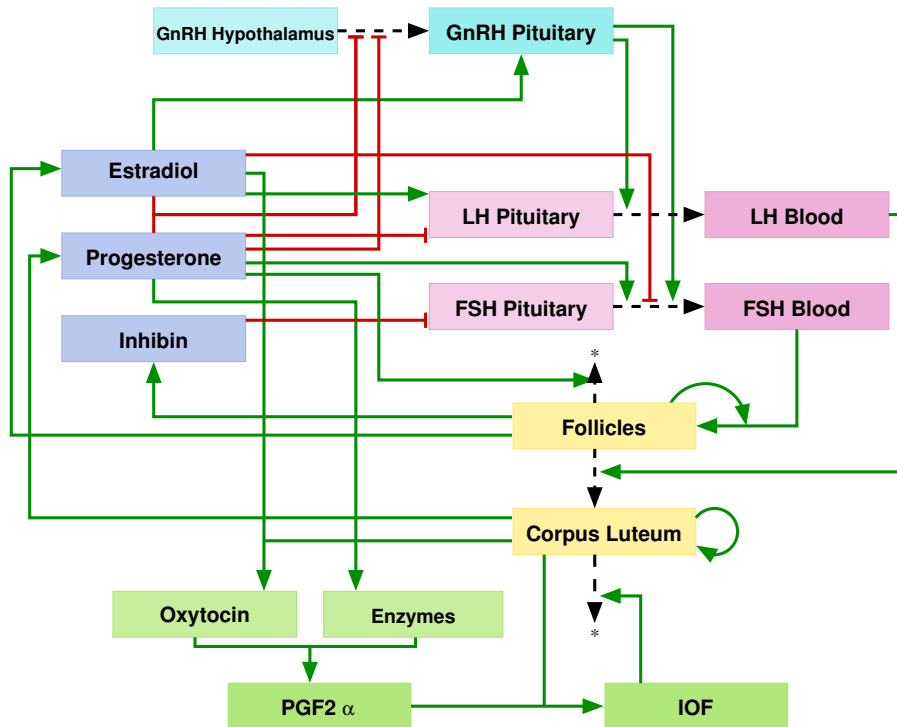


Abbildung 1: Flowchart for the unreduced model of the bovine estrous cycle in [4]. A green pointed arrow marks a stimulatory effect, a red stump arrow an inhibitory influence. A black dashed arrow means a transition, and \* marks a degraded substance.

## 1 Model Reduction

A lot of model reduction techniques are based on quasi steady state assumptions. For models where all variables are periodic, such methods cannot be used. Therefore, we use a method that reduces an ODE system based on its logical structure as proposed in [5]. After applying this method, additional structure-based ideas are used which are presented in this section.

## 1.1 Setting parameters to zero

The method in [5] is based on the exploration of the *admissible parameter region*. A certain model output is specified that needs to be captured by the model. In our case, time series for  $y_{LH}$ ,  $y_{FSH}$ ,  $y_{P4}$ ,  $y_{E2}$ , and  $y_{Inh}$ , that are taken from the simulation of BovCycle, need to be reproduced with a certain tolerance while varying the parameter values. The admissible region is the subspace of the parameter space in which this output changes only within the specified tolerance  $\epsilon$ . If the admissible region includes zero for some parameters, these parameters are set to zero in the reduction procedure.

Let  $p = [p_1, \dots, p_q]$  denote the current vector of parameter values. Then, assuming that there is only one dataset available, the admissible region is the set of all parameter values  $\tilde{p} = [\tilde{p}_1, \dots, \tilde{p}_q]$  for which the distance of the two solutions is small,

$$\frac{1}{n \cdot m} \sum_{j=1}^n \sum_{i=1}^m \left( \frac{y_j(t_i, \tilde{p}) - y_j(t_i, p)}{y_j(t_i)} \right)^2 < \epsilon,$$

$m$  being the number of time points, and  $n$  the dimension of the unreduced ODE system [5].

To determine the admissible region for BovCycle, first single parameters are set to zero. It is tested whether the simulation output can be obtained by adjusting the other parameters. This is performed for all parameters, in the order suggested by the sensitivity analysis. It turned out that for 10 out of 60 parameters, the deviation at 50 time points of the specified substances is about 3 % in average. These parameters are

- $m_{P4\&E2}^{GnRH}$ ,  $T_{E2}^{GnRH}$ ,  $T_{P4}^{GnRH}$  within the function  $H_{P4\&E2,G}^-$ ,
- $m_{P4}^{FSH}$  and  $T_{P4}^{FSH}$  within  $H_{P4,FSH}^+$ ,
- $m_{GnRH}^{FSH}$  and  $T_{GnRH}^{FSH}$  within  $H_{GnRH,FSH}^+$ ,
- $m_{E2}^{LH}$  and  $T_{E2}^{LH}$  within  $H_{E2,LH}^+$ , and
- $T_{P4}^{Enz}$  within  $H_{P4,Enz}^+$ .

Among these parameters are thus some scaling factors for Hill functions. It follows that the Hill functions  $H_{P4\&E2,G}^-$ ,  $H_{P4,FSH}^+$ ,  $H_{GnRH,FSH}^+$ , and  $H_{E2,LH}^+$  can be omitted in the model. With  $T_{P4}^{Enz} := 0$ , the function  $H_{P4,Enz}^+$  can be replaced by its scaling factor  $m_{P4}^{Enz}$ . Thus, all of the 10 parameters can be omitted.

The model now consists of 15 ODEs and 50 parameters. Besides removing the above functions and parameters, further reduction can be performed by exploiting the structure of the model.

## 1.2 Lumping of variables that occur in two compartments

Most of the reduction can be obtained for substances that occur in two compartments simultaneously, namely for GnRH, LH, and FSH. For each of these substances, the two compartments of their occurrence can be lumped, i.e. merged together, and the processes for the particular substance can be described in one ODE instead of two. In particular, the ODEs are modified via the following scheme:

$$\left. \begin{aligned} \frac{d}{dt} y_i(t) &= Syn_i(t) - Rel_i(t) \\ \frac{d}{dt} y_j(t) &= Rel_i(t) - c_j \cdot y_j(t) \end{aligned} \right\} \rightarrow \left\{ \begin{array}{l} \text{set } \frac{d}{dt} \tilde{y}_j(t) := Syn_i(t) \cdot Rel_i(t) - c_j \cdot y_j(t), \\ \text{delete } y_i \text{ and adapt growth rates.} \end{array} \right.$$

For GnRH, the compartments hypothalamus and pituitary can be lumped together. For LH and FSH, the compartments pituitary and blood can be merged, and the ODE describing their development is interpreted as blood levels. As described, the lumping is performed by integrating the first compartment into the second via multiplication and scaling. On the way, a few more terms can be omitted as will be explained in the following.

One can observe that the threshold that restricts GnRH synthesis in the hypothalamus,  $GnRH_{Hypo}^{max}$ , is never reached in the simulation. Therefore, the term restricting GnRH synthesis can be omitted, and  $Syn_{GnRH}$  can be replaced by the constant synthesis rate  $c_{GnRH,1}$ . After lumping GnRH in the hypothalamus and in the pituitary, the three parameters  $c_{GnRH,1}$ ,  $m_{E2}^{GnRH}$ , and  $m_{P4}^{GnRH,2}$  can be replaced by one parameter, namely their product, which is denoted as  $m_{P4,E2}^{GnRH}$ . The Hill function  $H_{P4\&E2,G}^-$  was already omitted above. It follows that  $y_G$  can be modeled with one ODE instead of two, and four parameters instead of ten,

$$\frac{d}{dt}y_G(t) = m_{P4,E2}^{GnRH} \cdot h^-(y_{P4}(t); T_{P4}^{GnRH}, 2) \cdot h^+(y_{E2}(t); T_{E2}^{GnRH}, 5) - c_{GnRH} \cdot y_G(t).$$

After lumping FSH in the pituitary and in the blood, and omitting the Hill functions  $H_{P4,FSH}^+$  and  $H_{GnRH,FSH}^+$  as suggested above, the product of  $H_{E2,FSH}^-$  and  $H_{Inh,FSH}^-$  is left as growth term for  $y_{FSH}$ . The effect of the basal release parameter  $b_{FSH}$  can be included through scaling of the Hill functions. As  $y_{E2}$  and  $y_{Inh}$  have similar profiles, and the threshold for the effect of  $y_{E2}$  is low compared to the threshold for  $y_{Inh}$ ,  $H_{E2,FSH}^-$  can be omitted. In total, one instead of two ODEs, and three instead of nine parameters are sufficient to describe the development of FSH,

$$\frac{d}{dt}y_{FSH}(t) = m_{Inh}^{FSH} \cdot h^-(y_{Inh}(t); T_{Inh}^{FSH}, 5) - c_{FSH} \cdot y_{FSH}(t).$$

Lumping LH in the pituitary and in the blood together saves another ODE. As suggested above, the Hill function  $H_{E2,LH}^+$  is omitted. Also, the parameter for the basal LH release is so low ( $b_{LH} = 0.0141$ ) that its effect does not play a significant role. Due to the multiplication of synthesis and release term during the lumping, the scaling factors of the Hill functions,  $m_{P4}^{LH}$  and  $m_{GnRH}^{LH}$ , can be replaced by their product,  $m_{GnRH,P4}^{LH}$ . Thus four parameters could be deleted from the model, and LH is described by

$$\frac{d}{dt}y_{LH}(t) = m_{GnRH,P4}^{LH} \cdot h^-(y_{P4}(t); T_{P4}^{LH}, 2) \cdot h^+(y_G(t); T_{GnRH}^{LH}, 2) - c_{LH} \cdot y_{LH}(t).$$

Until now, the model for the bovine estrous cycle has been reduced by 3 ODEs and in total 17 parameters. It thus consists of 12 ODEs and 43 parameters. In the following subsection, further reduction steps are described.

### 1.3 System specific reduction steps

The processes controlling the rise of PGF2 $\alpha$  can be simplified, as the three involved variables  $y_{Enz}$ ,  $y_{OT}$ , and  $y_{PGF}$  are only regulated by the two variables  $y_{P4}$  and  $y_{E2}$ . Since the function  $H_{P4,Enz}^+$  was replaced by its scaling factor  $m_{P4}^{Enz}$ , the variable  $y_{Enz}$  is constant. Therefore, its occurrence in the right hand sides of other variables can be replaced by a parameter, and the equation for  $y_{Enz}$  can be deleted from the model.

Also,  $y_{OT}$  is just an upstream of  $y_{PGF}$ , thus it is possible to merge these substances as well.

In total, two ODEs and six parameters can be saved, and the ODE describing the development of PGF2 $\alpha$  becomes

$$\frac{d}{dt}y_{PGF}(t) = h^+(y_{E2}(t); T_{E2}^{PGF}, 2) \cdot h^+(y_{P4}(t); T_{P4}^{PGF}, 5) - c_{PGF} \cdot y_{PGF}(t).$$

Now, the remaining model consists of 10 ODEs and 37 parameters. The rest of it is not essentially changed. The Hill exponent for the influence of  $y_{CL}$  on  $y_{IOF}$  is lowered from ten to five,

$$\frac{d}{dt}y_{IOF}(t) = m_{PGF,CL}^{IOF} \cdot h_{PGF,IOF}^+(y_{PGF}(t); T_{PGF}^{IOF}, 5) \cdot h_{CL,IOF}^+(y_{CL}(t); T_{CL}^{IOF}, 5) - c_{IOF} \cdot y_{IOF}(t),$$

the quadratic dependencies of the steroid hormones on the CL and the follicles is replaced by a linear relationship,

$$\begin{aligned} \frac{d}{dt}y_{P4}(t) &= k_{CL}^{P4} \cdot y_{CL}(t) - c_{P4} \cdot y_{P4}(t), \\ \frac{d}{dt}y_{E2}(t) &= k_{Foll}^{E2} \cdot y_{Foll}(t) - c_{E2} \cdot y_{E2}(t), \\ \frac{d}{dt}y_{Inh}(t) &= k_{Foll}^{Inh} \cdot y_{Foll}(t) - c_{Inh} \cdot y_{Inh}(t), \end{aligned}$$

and the equation for the follicles is simplified to

$$\begin{aligned} \frac{d}{dt}y_{Foll}(t) &= m_{FSH}^{Foll} \cdot h^+(y_{FSH}(t); T_{FSH}^{Foll}, 2) \cdot (1 + h^+(y_{Foll}(t); T_{Foll}^{Foll}, 2)) \\ &\quad - (m_{P4}^{Foll} \cdot h^+(y_{P4}(t); T_{P4}^{Foll}, 5) + m_{LH}^{Ovul} \cdot h^+(y_{LH}(t); T_{LH}^{Ovul}, 2) \cdot y_{Foll}(t)). \end{aligned}$$

The parameter  $T_{Foll}^{Foll}$  is introduced as threshold above which there is a positive effect of the follicles on themselves. This replaces the more complex formulation of a rising FSH sensitivity of the larger follicles.

The only equation that is not changed in the reduced model is the ODE for the corpus luteum, it stays

$$\begin{aligned} \frac{d}{dt}y_{CL}(t) &= SF \cdot m_{LH}^{Ovul} \cdot h^+(y_{LH}(t); T_{LH}^{Ovul}, 2) \cdot y_{Foll}(t) \\ &\quad + m_{CL}^{CL} \cdot h^+(y_{CL}(t); T_{CL}^{CL}, 2) - m_{IOF}^{CL} \cdot h^+(y_{IOF}(t); T_{IOF}^{CL}, 5) \cdot y_{CL}(t). \end{aligned}$$

In total, the reduced system consists of 10 ODEs and only 38 parameters.

The flowchart for the reduced model is shown in Figure 2. In comparison with the original flowchart in Figure 1, several substances and mechanisms have been omitted. In particular, the changes compared to the model in [4] are

- the variables occurring in two compartments have been merged,
- GnRH synthesis is not restricted by a maximum level anymore,
- E2 has only one effect on GnRH,
- P4 also has only one effect on GnRH,
- there is no basal FSH,
- there is no direct influence of E2 on FSH, only via GnRH,
- there is no influence of P4 on FSH,
- there is no direct influence of E2 on LH, only via GnRH,

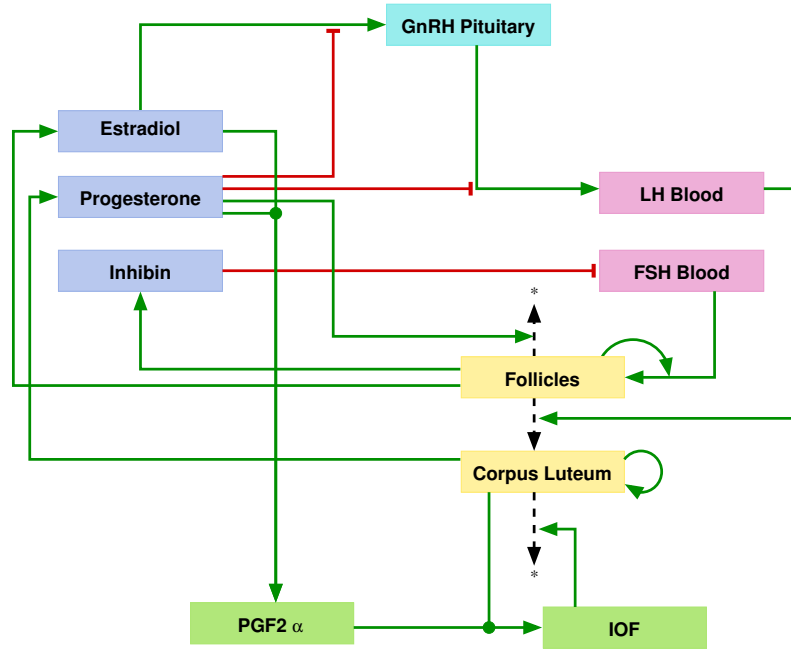


Abbildung 2: Interaction graph of the reduced model. A green pointed arrow marks a stimulatory effect, a red stump arrow an inhibitory influence. A black dashed arrow means a transition, and \* marks a degraded substance. The substances GnRH in the hypothalamus, LH in the pituitary, FSH in the pituitary, Oxytocin, and the Enzymes could be omitted in the model.

- there is no basal LH,
- the quadratic dependencies of Foll and CL on the steroid hormones P4, E2 and Inh have been replaced by linear relationships,
- the variable for the enzymes has been omitted,
- the variable for oxytocin has been omitted.

In the Appendix, the reduced model for the bovine estrous cycle can be found in Table 1, together with a list of parameter values (Table 2) and initial values (Table 3), that have been used for the simulation depicted in Figure 3.

## 2 Simulation results

Simulations for all components with the reduced model for a normal cycle show no qualitative difference to the unreduced model. For the variables  $y_{\text{FSH}}$ ,  $y_{\text{LH}}$ ,  $y_{\text{P4}}$ , and  $y_{\text{E2}}$ , simulations of both the unreduced and the reduced model are depicted in Figure 3. It is remarkable that the system of highly nonlinear ODEs could be reduced by 30% of the equations, and 36.7% of the parameters, while keeping the simulation output for the remaining variables close to the original one.

The evolution of such perturbations of the initial values of a system of ODEs can be described by the Wronskian matrix [6]. It is calculated by solving a variational equation derived from the right hand side of the ODE system. This provides an analytical tool to investigate model stability.



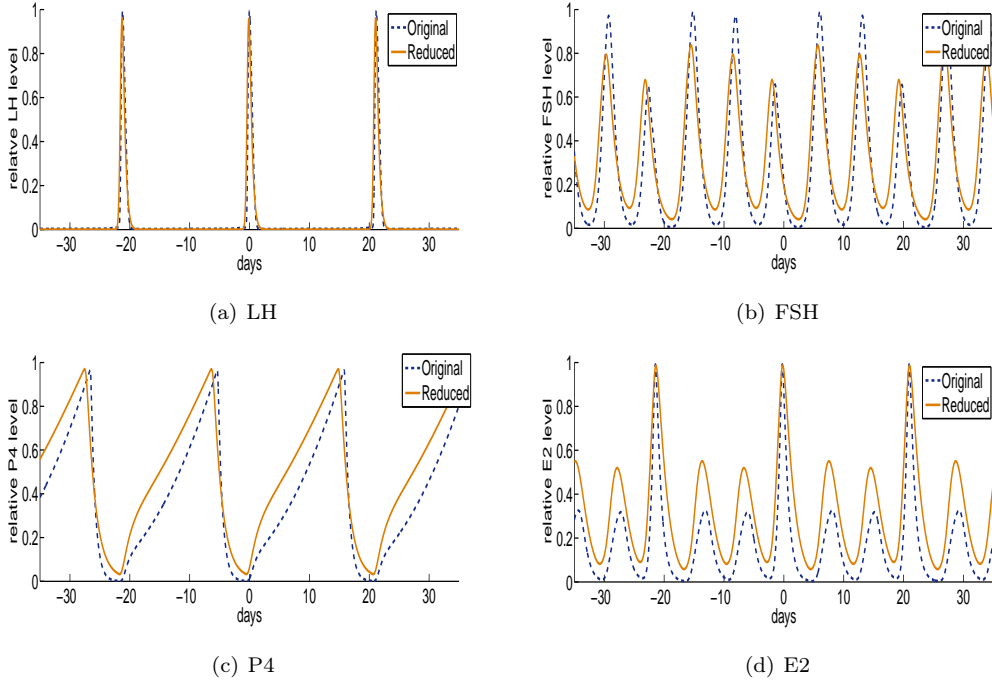


Abbildung 3: Simulation with the original and the reduced bovine model. The blue dashed lines show the course of the hormones as simulated with the original model of 15 ODEs, the orange solid lines show simulations with the reduced model of 10 ODEs.

For the ODE system  $y' = f(y)$ , the Wronskian matrix is obtained as the solution of the variational equation

$$\frac{dW}{dt}(t) = f_y(y(t)) \cdot W(t), \quad W(0) = Id,$$

Let  $T$  be the period length of the solution of the ODE system, and let the solution be disturbed at time  $t = 0$ . The Wronskian  $W$  evaluated at time  $t = T$  tells how this disturbance has impacted the solution after one period,  $\delta y_T = W(T) \cdot \delta y_0$ . If the perturbation has become smaller,  $\delta y_T < \delta y_0$ , i.e. closer to the real limit cycle, the system is stable.

Thus, with the columns of the Wronskian denoted as  $W_i(t)$ ,

$$W(T) = [W_1(T), W_2(T), \dots, W_n(T)],$$

the Wronskian matrix is obtained by numerically solving the system

$$\begin{pmatrix} y' \\ W_1'(T) \\ \vdots \\ W_n'(T) \end{pmatrix} = \begin{pmatrix} f(y) & & & \\ & f_y(y(T)) & & \\ & & \ddots & \\ & & & f_y(y(T)) \end{pmatrix} \cdot \begin{pmatrix} 1 \\ W_1(T) \\ \vdots \\ W_n(T) \end{pmatrix}. \quad (*)$$

The eigenvalues of the Wronskian are called *Floquet multipliers* of the system. If the Floquet multipliers are all in the unit circle, the system is locally stable, see e.g. [6].

The nonzero entries of the Jacobian with respect to the variables,  $f_y(y(T))$ , as well as the Wronskian matrix for the system of the bovine estrous cycle can be found in the Appendix.

The numerically computed eigenvalues of the Wronskian matrix are

$$\begin{pmatrix} -8.1670 \cdot 10^{-1} \\ 1.8524 \cdot 10^{-} \\ -1.1043 \cdot 10^{-3} + 1.2969 \cdot 10^{-3i} \\ -1.1043 \cdot 10^{-3} - 1.2969 \cdot 10^{-3i} \\ -7.2608 \cdot 10^{-6} \\ 4.9507 \cdot 10^{-08} \\ -1.3857 \cdot 10^{-09} \\ -9.4016 \cdot 10^{-10} \\ -7.5256 \cdot 10^{-11} \\ 4.4700 \cdot 10^{-13} \end{pmatrix}$$

All eigenvalues are within the unit circle, thus, the reduced model for the bovine estrous cycle is locally stable.

### 3 Conclusion and Outlook

The herein presented approach for model reduction can partially be generalized to other ODE systems. In particular, the first two steps of setting parameters to zero and merging ODEs that represent substances in different compartments are transferable to other models. The system specific reduction steps can naturally not be directly translated, but similar model structures in other systems might lead to similar reduction considerations.

A risk of model reduction is that some effects that can be captured with the original model can no longer be reproduced. In our case, the reduced model for the bovine estrous cycle is not able to equally well reproduce the results from the synchronization protocols from [4]. Hence, it is important to keep in mind the both versions of the model for further investigations.

The presented reduced model is an ideal starting point for the translation into a discrete model, whose finite state space could be analyzed comprehensively.

### Acknowledgements

S. Röblitz and C. Stötzel have been supported by the DFG Research Center MATHEON “Mathematics for Key Technologies” in Berlin, Germany.

## Appendix

Table 1: Reduced model for the bovine estrous cycle. It consists of 10 ODEs and 38 parameters.

$\frac{d}{dt}y_G(t)$	$= H_{P_4, GnRH}^- (y_{P_4}(t)) \cdot H_{E_2, GnRH}^+ (y_{E_2}(t)) - c_{GnRH} \cdot y_G(t)$	(BR1)
$\frac{d}{dt}y_{FSH}(t)$	$= H_{Inh, FSH}^- (y_{Inh}(t)) - c_{FSH} \cdot y_{FSH}(t)$	(BR2)
$\frac{d}{dt}y_{LH}(t)$	$= H_{P_4, LH}^- (y_{P_4}(t)) \cdot H_{GnRH, LH}^+ (y_G(t)) - c_{LH} \cdot y_{LH}(t)$	(BR3)
$\frac{d}{dt}y_{Foll}(t)$	$= H_{FSH, Foll}^+ (y_{FSH}(t)) \cdot \left(1 + H_{Foll, Foll}^+ (y_{Foll}(t))\right) - \left(H_{P_4, Foll}^+ (y_{P_4}(t)) + H_{LH, Ovul}^+ (y_{LH}(t))\right) \cdot y_{Foll}(t)$	(BR4)
$\frac{d}{dt}y_{CL}(t)$	$= H_{LH, Ovul}^+ (y_{LH}(t)) \cdot y_{Foll}(t) + H_{CL, CL}^+ (y_{CL}(t)) - H_{IOF, CL}^+ (y_{IOF}(t)) \cdot y_{CL}(t)$	(BR5)
$\frac{d}{dt}y_{P_4}(t)$	$= k_{CL}^{P_4} \cdot y_{CL}(t) - c_{P_4} \cdot y_{P_4}(t)$	(BR6)
$\frac{d}{dt}y_{E_2}(t)$	$= k_{Foll}^{E_2} \cdot y_{Foll}(t) - c_{E_2} \cdot y_{E_2}(t)$	(BR7)
$\frac{d}{dt}y_{Inh}(t)$	$= k_{Foll}^{Inh} \cdot y_{Foll}(t) - c_{Inh} \cdot y_{Inh}(t)$	(BR8)
$\frac{d}{dt}y_{PGF}(t)$	$= H_{E_2, PGF}^+ (y_{E_2}(t)) \cdot H_{P_4, PGF}^+ - c_{PGF} \cdot y_{PGF}(t)$	(BR9)
$\frac{d}{dt}y_{IOF}(t)$	$= H_{PGF, IOF}^+ (y_{PGF}(t)) \cdot H_{CL, IOF}^+ (y_{CL}(t)) - c_{IOF} \cdot y_{IOF}(t)$	(BR10)

### The Jacobian for the reduced model of the bovine estrous cycle

$$J = \begin{pmatrix}
 -1.664 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & -0.761 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 \frac{0.123004ygnrh}{(ygnrh^2+0.514089)^2(y p4^2+0.00299209)} & 0 & -12.253 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & \frac{(1.548yfol^2+0.0241073)yfsh}{(yfol^2+0.076729)(yfsh^2+0.447561)^2} & -\frac{1.42492yfolylh}{(ylh^2+0.308025)^2} & -\frac{1.075yp4^5}{yp4^5+0.000031758} + \frac{0.211523yfolyfsh^2}{(yfol^2+0.076729)^2(yfsh^2+0.447561)} & -\frac{2.313ylh^2}{ylh^2+0.308025} & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & \frac{0.360506yfolylh}{(ylh^2+0.308025)^2} & 0 & \frac{0.585189ylh^2}{ylh^2+0.308025} & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 1.402 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0.652 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & -\frac{0.932744ye2^5yp4}{(ye2^5+1.64001)(yp4^2+0.075076)^2} & \frac{3.82426ye2^4}{(ye2^5+1.64001)^2(yp4^2+0.075076)} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & -\frac{0.000539928yih^4}{(yih^5+0.0000894661)^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & -\frac{0.239265ygnrh^2yp4}{(ygnrh^2+0.514089)(yp4^2+0.00299209)^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & -\frac{0.000170699yfolyp4^4}{(yp4^5+0.000031758)^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 -\frac{10.25yiof^5}{yiof^5+1.51757} + \frac{0.1012ycl}{ycl^2+0.063001} - \frac{0.1012ycl^3}{(ycl^2+0.063001)^2} & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -\frac{77.7753ycl yiof^4}{(yiof^5+1.51757)^2} & 0 \\
 0.969 & -0.725 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & -0.98 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\
 0 & 0 & 0 & 0 & 0 & -0.501 & 0 & 0 & 0 & 0 & 0 \\
 0 & \frac{8.29172ye2^2yp4^4}{(ye2^2+0.047089)(yp4^5+0.899318)^2} & \frac{0.173664ye2yp4^5}{(ye2^2+0.047089)^2(yp4^5+0.899318)} & 0 & -0.484 & 0 & 0 & 0 & 0 & 0 & 0 \\
 \frac{3.05339ycl^4ypgf^5}{(ycl^5+0.0348421)^2(ypgf^5+4.418)} & 0 & 0 & 0 & \frac{387.171ycl^5ypgf^4}{(ycl^5+0.0348421)(ypgf^5+4.418)^2} & 0 & 0 & 0 & 0 & -0.292 & 0
 \end{pmatrix}$$

Table 2: Parameter values for the reduced bovine model. Hill exponents have been set fixed as  $n_{E2}^{GnRH} = n_{Inh}^{FSH} = n_{P4}^{Foll} = n_{IOF}^{CL} = n_{P4}^{PGF} = n_{PGF}^{IOF} = n_{CL}^{IOF} = 5$ , the rest of the Hill exponents are set to 2.

No.	Symbol	Value	Unit
1	$m_{E2, P4}^{GnRH}$	6.212	[GnRH]/[t]
2	$T_{P4}^{GnRH}$	0.274	[P4]
3	$T_{E2}^{GnRH}$	1.104	[E2]
4	$cl_{GnRH}$	1.664	1/[t]
5	$m_{Inh}^{FSH}$	1.207	[FSH]/[t]
6	$T_{Inh}^{FSH}$	0.155	[Inh]
7	$cl_{FSH}$	0.761	1/[t]
8	$m_{GnRH, P4}^{LH}$	39.983	[LH]/[t]
9	$T_{P4}^{LH}$	0.0547	[P4]
10	$T_{GnRH}^{LH}$	0.717	[GnRH]
11	$cl_{LH}$	12.253	1/[t]
12	$m_{FSH}^{Foll}$	0.351	[Foll]/[t]
13	$T_{FSH}^{Foll}$	0.669	[FSH]
14	$m_{Foll}$	3.927	-
15	$T_{Foll}$	0.277	[Foll]
16	$m_{P4}^{Foll}$	1.075	1/[t]
17	$T_{P4}^{Foll}$	0.126	[P4]
18	$m_{LH}^{Foll}$	2.313	1/[t]
19	$T_{LH}^{Foll}$	0.555	[LH]
20	$SF_{CL}$	0.253	[CL]
21	$m_{CL}$	0.0506	[CL]/[t]
22	$T_{CL}^{CL}$	0.251	[CL]
23	$m_{IOF}^{CL}$	10.25	1/[t]
24	$T_{IOF}^{CL}$	1.087	[IOF]
25	$k_{CL}^{P4}$	0.969	[P4]/[t]
26	$cl_{P4}$	0.725	1/[t]
27	$k_{Foll}^{E2}$	1.402	[E2]/[t]
28	$cl_{E2}$	0.98	1/[t]
29	$k_{Foll}^{Inh}$	0.652	[Inh]/[t]
30	$cl_{Inh}$	0.501	1/[t]
31	$m_{E2, P4}^{PGF}$	1.844	[PGF]/[t]
32	$T_{E2}^{PGF}$	0.217	[E2]
33	$T_{P4}^{PGF}$	0.979	[P4]
34	$cl_{PGF}$	0.484	1/[t]
35	$m_{PGF, CL}^{IOF}$	17.527	[IOF]/[t]
36	$T_{PGF}^{IOF}$	1.346	[PGF]
37	$T_{CL}^{IOF}$	0.511	[CL]
38	$cl_{IOF}$	0.292	1/[t]

Tabelle 3: Initial values for the reduced bovine model

No.	Symbol	Value
1	$y_G$	0.0027
2	$y_{FSH}$	0.5706
3	$y_{LH}$	0.0000
4	$y_{Foll}$	0.6131
5	$y_{CL}$	0.0098
6	$y_{P4}$	0.0504
7	$y_{E2}$	0.3650
8	$y_{Inh}$	0.2603
9	$y_{PGF}$	0.1418
10	$y_{IOF}$	0.2630

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