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Exploration of different wave patterns in a model of the bovine estrous cycle by Fourier analysis[3]

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Exploration of different wave patterns in a model of the bovine estrous cycle by Fourier analysis

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Abstract

Cows typically have different numbers of follicular waves during their hormonal cycle. Understanding the underlying regulations leads to insights into the reasons for declined fertility, a phenomenon that has been observed during the last decades. We present a systematic approach based on Fourier analysis to examine how parameter changes in a model of the bovine estrous cycle lead to different wave patterns. Even without having biological evidence, this allows to detect the responsible model parameters that control the type of periodicity of the solution, thus supporting experimental planning of animal scientists.

Introduction

In the bovine female, ovulation takes place once in every estrous cycle at the end of the follicular growth and maturation process. Each cycle includes several wave-like patterns of follicle development[1] in which follicles from the pool of primordial follicles start to grow and compete to become the dominant follicle. Only the dominant follicle of the last wave continues to grow and ovulates. The number of anovulatory waves occuring before the ovulatory wave differs between cows. In total, cows have between one to four, but mostly two or three follicular waves per cycle. The motivation to study the number of waves per cow is its relation to fertility that is discussed in literature. Further details will be given in Section 1.

The factors that regulate the number of waves in the bovine are not fully explored, though experimental effort has been made to search for the responsible endocrine mechanisms. In this work, we aim to study the differences in hormonal patterns between two- and three-wave cows based on a mathematical model. We want to identify and study systematically those parameters and mechanisms which are responsible for changing the wave patterns.

An ordinary differential equation model, called BovCycle, has been built for the bovine estrous cycle, which describes the underlying biological mechanisms and their regulation[3],[4]. Model simulations reproduce periodic estrous cycles lasting 21 days including the development of the follicles and the corpus luteum and the key reproductive hormones involved. The BovCycle model consists

Table 1: List of abbreviations for the substances modelled in BovCycle.

Abbreviation	Explanation
$GnRH_{Hyp}$	Gonadotropin Releasing Hormone in the Hypothalamus
$GnRH_{Pit}$	Gonadotropin Releasing Hormone in the Pituitary
FSH_{Pit}	Follicle Stimulating Hormone in the Pituitary
FSH_{Bld}	Follicle Stimulating Hormone in the Blood
LH_{Pit}	Luteinizing Hormone in the Pituitary
LH_{Bld}	Luteinizing Hormone in the Blood
Foll	Follicular Capacity to produce steroids
CL	Corpus Luteum
P4	Progesterone
E2	Estradiol
Inh	Inhibin
Enz	Enzymes
OT	Oxytocin
$PGF_{2\alpha}$	Prostaglandin F2α
IOF	Intra-Ovarian Factors

of 15 ODEs and 60 parameters and is available in SBML at the BioModels database[5].

A systematic approach to analyze how parameter changes lead to different wave patterns can be taken with the help of Fourier analysis. This allows to detect the responsible model parameters that control the type of periodicity of the solution. During the analysis, we calculate the fraction of the first Fourier coefficients while varying parameter values. The order of the coefficients indicates the order of the most dominant oscillations and thus the number of waves per cycle. A change in the order leads also to an abrupt change in the period length. In a one-dimensional approach, all parameters are changed individually. In a two-dimensional approach, two parameters are changed at a time. Fourier analysis based on FFT (Fast Fourier Transformation) is performed for varying parameter values. This requires knowledge of the exact period length and initial values which are obtained by solving a boundary value problem in every step.

The paper is organized as follows. In Section 1, we start with a short review of the biological mechanisms behind different wave numbers, followed by a brief presentation of the model BovCycle in Section 2. In Section 3, the application of the Fourier analysis to BovCyle is explained, and the results are described in Section 4. A list of abbreviations that are used in this work is given in Table 1.

1 Biological Background

The number of follicular waves per cycle differs between cows. Most cows have two or three waves[2],[6], *i.e.* one or two anovulatory waves plus the ovulatory wave in each cycle. Some cows may have only one or even four follicular waves per cycle, and often the number of waves differs from cycle to cycle.

Different productive and reproductive characteristics of cows with different follicular wave patterns have been reported in literature. For example, Bleach *et* *al.*[2] found that cows with two follicular waves during the cycle produce more milk than those with three waves. Another motivation to study this difference is to investigate the relation between the number of waves and fertility.

Two-wave cows, *i.e.* cows with usually two follicular waves per cycle, have a shorter cycle than three-wave cows. Since in a long time span, a two-wave cow ovulates more often, one can derive that, at a randomly chosen time point, a herd of two-wave cows probably includes more cows that are at the stage around ovulation. Therefore, one could assume that two-wave cows have higher fertility rates compared to three-wave cows. However, reality is more complex. While some studies show no difference regarding fertility rates[2],[7], other studies report better fertility in three-wave cycles compared to two-wave cycles[8], and it has been suggested that the older and larger ovulatory follicles in cycles with two waves contain oocytes of less quality than cycles with three waves[9].

The reason for this could be the following. The follicle that is dominant at the moment of CL regression ovulates. Therefore, the number of follicular waves in a cycle is largely affected by the interplay of follicle growth rate and the time point of CL regression. Thus, it is influenced by the timing of two major rhythm drivers of the cycle: follicle growth under control of FSH, and CL regression under control of $PGF_{2\alpha}$. When the CL is regressed at the moment that a prolonged dominant follicle is present, the oocyte could be of inferior quality[9].

The factors that regulate the number of waves in bovine are not fully explored, though experimental effort has been made to search for endocrine mechanisms that could be responsible for controlling these factors. According to Adams *et al.*[12], breed or age do not affect the number of waves per cycle. Also, Wolfenson *et al.*[6] did not find any difference in number of waves between cows and heifers. However, some findings on differences between two- and three-wave cows have been reported. Jaiswal *et al.*[10] observed that CL regression occurs 2.5 days earlier in two-wave compared to three-wave cows. The onset of luteolysis thus might play an important role. Bleach *et al.*[2] found that ovulatory follicles in two-wave cycles have a lower growth rate compared to the ovulatory follicles in three-wave cycles. Parker *et al.*[11] observed that cows with three-wave cycles have lower FSH and Inhibin blood concentrations during non-ovulatory waves compared to two-wave cows. Medan *et al.*[14] found that immunization against Inhibin A increased the number of waves per cycle. Summarizing, three biological mechanisms have been reported to influence the number of waves: the time of CL regression, the growth rate of the follicles, and low Inhibin and FSH concentrations.

2 The model BovCycle

The estrous cycle, *i.e.* the periodic development of multiple substances, is the result of a large feedback loop of regulations. The ODE model BovCycle, presented in Boer *et al.*[3] and extended in Stötzel *et al.*[4], describes the key feedback mechanisms behind the cycle, and is able to generate periodic solutions of length 21 days. The mechanisms are depicted in Figure 1, abbreviations are explained in Table 1. Parameter values and initial values can be found in Stötzel *et al.*[4].

In the hypothalamus, the hormone GnRH is synthetized and released into

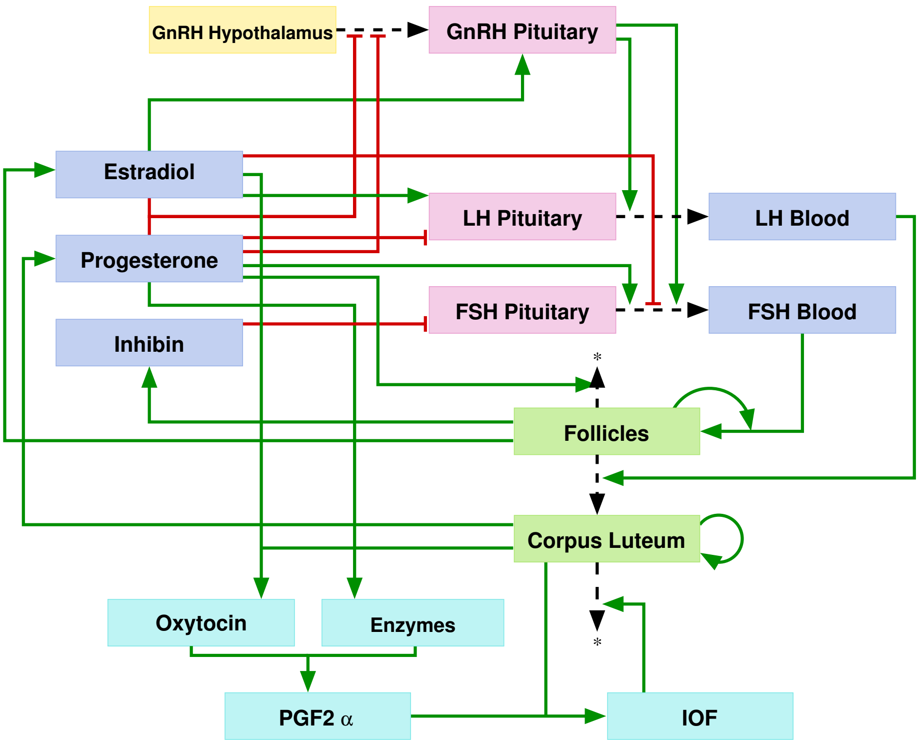
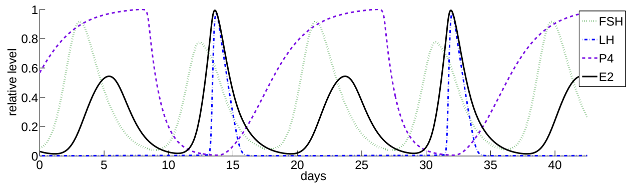
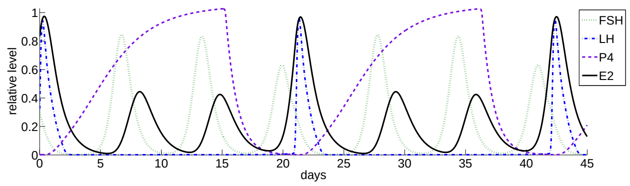


Figure 1: Flowchart for the model BovCycle. A green pointed arrow marks a stimulatory effect, a red stump arrow an inhibitory influence. A black dashed arrow means a transition, and $*$ marks a degraded substance.

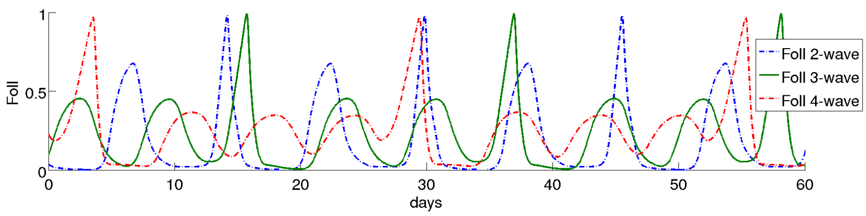
the pituitary. There, it stimulates the release of the hormones FSH and LH into the bloodstream, where they distribute and influence several functions in the body. They regulate processes in the ovaries, where follicles and corpus luteum develop. The ovarian structures produce the steroids E2, P4 and Inh that are released into the blood. From therein, they influence GnRH, FSH and LH in the hypothalamus and pituitary, and stimulate oxytocin and different enzymes that control the action of PGF2α. Together with several intra-ovarian factors, this initiates the decay of the CL. These mechanisms are modelled in BovCycle as a closed system which allows to analyze how the physiological components in different parts of the whole body function together. No external stimuli are needed for the periodic behavior which results only from the developed dynamics and the parameterization of the model.



(a) Two-wave cycle



(b) Three-wave cycle



(c) Cycles with different wave numbers

Figure 2: Different parameterizations of the model BovCycle lead to a simulation output with two, three, or four follicular waves per cycle.

In Boer *et al.*[13], 10 parameters of BovCycle, that can directly be associated with the biological mechanisms described in Section 1, were tested for inducing a change in wave number. Their values were varied, sometimes in combination with each other, and for certain parameters, a change in wave number was obtained. In the following, we present a more systematic approach to test the parameter variations.

3 Exploration of Wave Patterns by Fourier Analysis

From the simulations it is clear that mainly two types of components exist in BovCycle. First, there are variables that peak once every cycle. They are the ones associated with luteal development, *i.e.* the corpus luteum itself, progesterone, or the substances involved in luteolysis. Second, other variables have several peaks per cycle. These are the ones associated with follicular development, *i.e.* the follicles and the hormones produced by them. For substances like GnRH, LH, or OT it is not clear which clock is more dominant, but they represent a bridge between the CL and the follicles and play a role in the change of the model behavior regarding the number of waves in the simulation. However, the number of waves per cycle can be counted by comparing the one-peak variables with the several-wave variables.

For the following analysis, we take the variable describing the follicles, y_{Foll}, as representative for the several-wave-variables, and y_{CL} as representative for the one-peak variables. In the following, the *rhythm* of a variable denotes the time interval between two maxima. The rhythm of the one-peak variables is the cycle length, while the rhythm of the several-wave-variables can be calculated through spectral analysis. To compare the two rhythms via the calculation of their Fourier coefficients, first the precise cycle length is needed.

To obtain the precise cycle length T, we have to solve a boundary value problem of the form

$$y' = f(y, p), \quad y(T) - y(0) = 0,$$

whereby p are fixed parameter values and $y(0)$ and T are the unknowns. For this purpose, the code PERIOD[15] is used. This program is an implementation of a multiple shooting method for the computation of periodic solutions of ODEs together with a global underdetermined Gauss-Newton method with adaptive trust region strategies (algorithm NLSCON)[16].

As the algorithm used in PERIOD is sensitive to starting values, a good first approximation of the cycle length is needed. A rough approximation by hand is not good enough. Thus, the Fourier transformation of the simulation of the variable y_{CL} is used for improvement. The maximum coefficient of the Fourier transformation is then taken as initial guess for the length of the period. With this starting value, PERIOD uses NLSCON to iteratively optimize the initial values of the ODE system to obtain a precise periodic solution.

Knowing the true period length T and initial values of the system, a Fourier analysis is now performed on the several-wave-variable y_{Foll},

$$y_{\text{Foll}}(t) = \sum_{k=1}^{10} c_k \exp(i \frac{k\pi}{T} t).$$

This delivers the contribution of the different frequencies to the total time course of y_{Foll}. Ranking of the c_k according to their amplitude allows for the identification of the most prominent frequencies. For y_{Foll}, generally c_2, c_3, or c_4 are the largest factors because this variable peaks 2, 3, or 4 times per cycle. However, the order of c_2, c_3, or c_4 changes depending on parameter values.

This approach is performed with different parameter values. Possibly, the component that has the most dominant oscillation changes. For example, it

Table 2: Parameters and their regions in which the simulation results in a certain order of Fourier coefficients indicating the number of waves per cycle. One parameter is varied at a time.

par	dominance c_1	dominance c_2	dominance c_3	dominance c_4
$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	.	.	0.14-0.4	0.4-0.62
cl_{FSH}	.	.	1.5 - 5.0	5.0 - 10.7
b_{FSH}	.	.	0.55 - 1.7	1.7 - 24.0
$m_{\mathrm{E2}}^{\mathrm{LH}}$	.	5.5 - 30.0	0 - 5.5	.
$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	.	0.92 - 1.8	0.45 - 0.92	0.36 - 0.45
$T_{\mathrm{Foll}}^{\mathrm{FSH}}$	.	.	0-0.077, 0.62-20	0.077-0.57
$m_{\mathrm{P4}}^{\mathrm{FSH}}$	.	2.17-3.22, 4.26-4.72	0.34-1.45, 1.65-2.0, 3.22-3.32	3.32-3.43
$T_{\mathrm{Enz}}^{\mathrm{PGF}}$	.	.	0.91 - 1.8	1.8 - 2.8
$T_{\mathrm{OT}}^{\mathrm{PGF}}$	.	.	0 - 2.4	2.4 - 7.7
cl_{PGF}	.	.	0 - 4.5	4.5 - 24.0
SF	0.58 - 5.0	0.3 - 0.51	0.15 - 0.3	0.045 - 0.15
$m_{\mathrm{CL}}^{\mathrm{P4}}$	.	5.0 - 15.7	1.62 - 5.0	0.72 - 1.62
cl_{Enz}	.	.	1.8 - 3.9	3.9 - 5.7
$m_{\mathrm{E2}}^{\mathrm{OT}}$	.	.	1.0 - 20.0	0.22 - 1.0
cl_{OT}	.	.	0 - 1.4	1.4 - 5.5

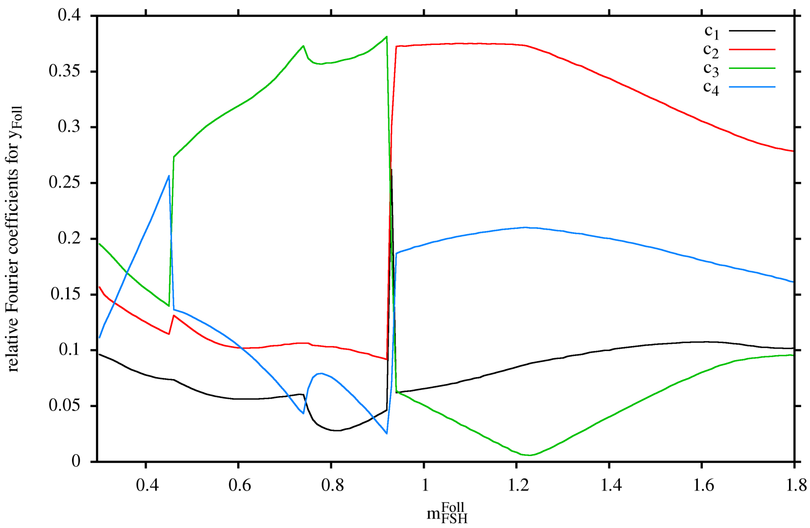
changes from the two-wave component having the highest contribution to the three-wave component being the most dominant oscillation of y_{Foll}, indicating a change from a two-wave to a three-wave cycle pattern of the whole system. Two examples of such changes are depicted in Figure 3. Varying one or two parameters at a time and performing the Fourier analysis simultaneously leads also to a varying period length.

4 Results

The described spectral analysis is performed for all 60 parameters, and the plots have been evaluated visually. For the original parameter value p_{orig}, we here investigate the range of values $[0.1 \cdot p_{orig}, 10 \cdot p_{orig}]$. Within this range, there is a change in the order of the dominant Fourier coefficients for 15 parameters, keeping the other parameter values fixed. This indicates a change in the number of waves per cycle. These 15 parameters, together with the corresponding ranges in which a certain pattern is obtained, are listed in Table 2. For the remaining parameters, there is no change in the order of the oscillatory components in the tested range of values.

One has to keep in mind that a certain order of dominance of the oscillatory components does not guarantee a particular wave pattern. However, the analysis gives a good suggestion about which parameters are able to control the wave pattern of the simulation.

In biology, one expects the number of waves to depend not only on a single parameter, but eventually on a combination of multiple parameters. Extension of the above described analysis technique into higher dimensions, thus vary-



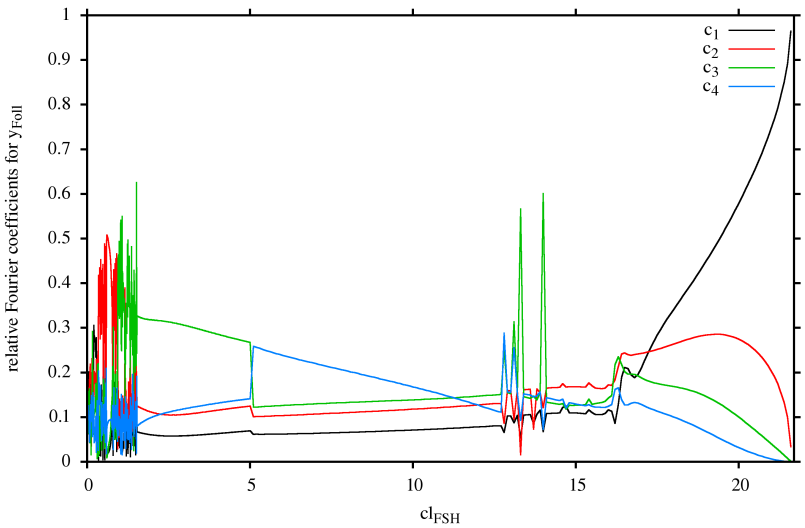


Figure 3: The contribution of the Fourier coefficients $c2$, $c3$, and $c4$ (the most dominant oscillations) to y_{Foll} as function of a single parameter. A change in the order of the lines indicates a change in wave numbers in the simulation at this parameter value.

ing several parameters at a time and investigating the order of the oscillatory components of the simulation, is not difficult. Visual evaluation of the results, however, needs more careful consideration because evaluation of all graphs even for only two dimensions would be too time-consuming. Thus, a systematic approach has been chosen that takes into account sensitivities with respect to the cycle length.

In the one-dimensional case, it has been observed that a change in the order of the oscillatory components comes along with an abrupt change in the cycle length at a specific value of the parameter, which corresponds to a step-like shape of the period-length-curve, see *e.g.* Figure 4. This is reasonable, since this change of order results from the interplay between the wave variables (e.g. follicles) and the peak-variable (e.g. $PGF_{2\alpha}$).

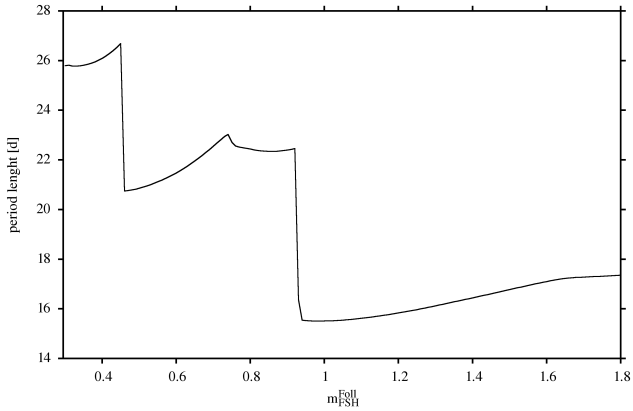


Figure 4: Cycle length during the variation of the parameter $m_{\mathrm{FSH}}^{\mathrm{Foll}}$. At two parameter values, the period length undergoes an immediate large change, which corresponds to a change in the order of the Fourier coefficients, as can be observed in Figure 3.

Thus, a sensitivity analysis of the cycle length L with respect to the parameters, dL/dp, obtained through numerical differentiation, can give a hint to which parameters might lead to a change in the order of the components. Since the period length is quite sensitive to these parameters locally, their changes may lead to a rapid and large change in the cycle length at some point. The most sensitive parameters with respect to the period length are given in Table 3. Note that the sensitivity of the cycle-length to the parameters is not a global information, but a hint to which parameters should be examined further. In the one-dimensional case, the sensitivity analysis yields that out of the 15 parameters which can by themselves control the number of waves, 6 are among the 8 most sensitive.

In the two-dimensional case it is therefore convenient, instead of visually checking all $60 \cdot 59/2 = 1741$ possible combinations, to restrict the examination to the most sensitive parameters, in order to find at least some combinations that lead to a change in the number of waves. It is assumed that a parameter that is itself very sensitive is also sensitive in any combination. It can be observed that in the 58 most sensitive combinations, $m_{\mathrm{P4}}^{\mathrm{Foll}}$ is always one of the two parameters

Table 3: The 10 most sensitive parameters with respect to the period length, together with their investigated ranges and the therein obtained change in the period length.

par	upper bound	lower bound	change in period length
$m_{\mathrm{CL}}^{\mathrm{CL}}$	0.03530	0.00035	-52.73
$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	0.11800	0.00118	-24.26
$m_{\mathrm{Foll}}^{\mathrm{Foll}}$	0.22000	0.00220	-10.97
$m_{\mathrm{P4}}^{\mathrm{Foll}}$	1.10000	0.01100	-6.79
$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	0.56200	0.00562	6.66
$m_{\mathrm{LH}}^{\mathrm{Ovul}}$	0.20000	0.00200	-5.87
$T_{\mathrm{P4}}^{\mathrm{LH}}$	0.02690	0.00027	-4.21
b_{FSH}	0.94800	0.00948	-2.64
$m_{\mathrm{E2}}^{\mathrm{FSH}}$	0.39600	0.00396	-2.45
$T_{\mathrm{E2}}^{\mathrm{GnRH,2}}$	0.64800	0.00648	2.41

Table 4: Parameter combinations and their sensitivities with respect to the period length.

sens. rank	par1	par2	change in period length
1	$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	0.01121
2	$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	0.01033
3	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	$c_{\mathrm{Foll}}^{\mathrm{Inh}}$	0.01033
4	b_{FSH}	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	0.00997
5	$m_{\mathrm{Foll}}^{\mathrm{Foll}}$	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	0.00988
6	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	$m_{\mathrm{CL}}^{\mathrm{CL}}$	0.00933
7	cl_{FSH}	$m_{\mathrm{P4}}^{\mathrm{Foll}}$	0.00926
59	$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	0.00660749
60	$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	$c_{\mathrm{Foll}}^{\mathrm{Inh}}$	0.00660736
61	b_{FSH}	$m_{\mathrm{FSH}}^{\mathrm{Foll}}$	0.00625
63	$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	$c_{\mathrm{Foll}}^{\mathrm{Inh}}$	0.00572
66	$T_{\mathrm{Inh}}^{\mathrm{FSH}}$	b_{FSH}	0.00536

in the combination. To also check different parameter combinations, besides the seven most sensitive combinations, also the five most sensitive combinations without $m_{\mathrm{P4}}^{\mathrm{Foll}}$ have been checked. The corresponding sensitivities with respect to the period length are given in Table 4. Two examples of the development of the Fourier fractions are illustrated in Figure 5. Among all 12 of the checked combinations, there is a change in the order of the most dominant fraction, thus a change of waves depending on the values of the parameters.

Summarizing, for the 15 parameters depicted in Table 2, a change in the number of waves per cycle can be obtained by changing the value of a single parameter. These 15 parameters have been identified by evaluating the developments of the contributions of the first four Fourier coefficients. The ranges for the parameter values that lead to a particular wave pattern have been determined. Regarding the simultaneous change of two parameter values, the sensitivity analysis with respect to the cycle length gives good suggestions which parameter combinations can provoke a change in wave patterns.

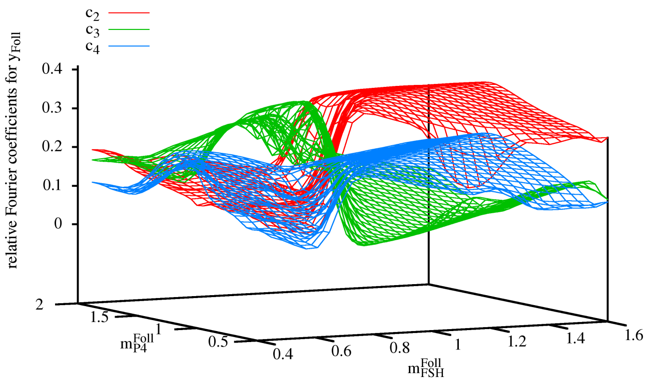
In addition to Boer *et al.*[13], which used biological knowledge to find parameters that regulate the wave patterns, the here presented method represents a more systematic approach that finds such parameters based on mathematical properties of the simulation output. This extends the previous findings, and it gives a more reliable set of candidates on which experimental effort can be focused on. In addition to the previous work, we calculated ranges of parameter values which lead to a certain wave pattern, see Table 2. The parameters $m_{\mathrm{FSH}}^{\mathrm{Foll}}$ and $T_{\mathrm{OT}}^{\mathrm{PGF}}$ have been found to be decisive in Boer *et al.*[13] and in this work. The other parameters found in Boer *et al.*[13], have not been detected by our new approach, which is probably due to the fact that some model mechanisms have changed.

For the parameter $m_{\mathrm{FSH}}^{\mathrm{Foll}}$, which represents the maximum growth rate of the follicles, one can observe in Table 2 that decreasing its value leads to an increase of waves per cycle. This is likely due to a resulting lower oxytocin growth rate, which results in a later $\mathrm{PGF}_{2\alpha}$ appearance and action. Thus, the CL decays later and the inhibitory effect of P4 on the follicles, LH and GnRH is longer. Therefore, the next ovulation takes place later.

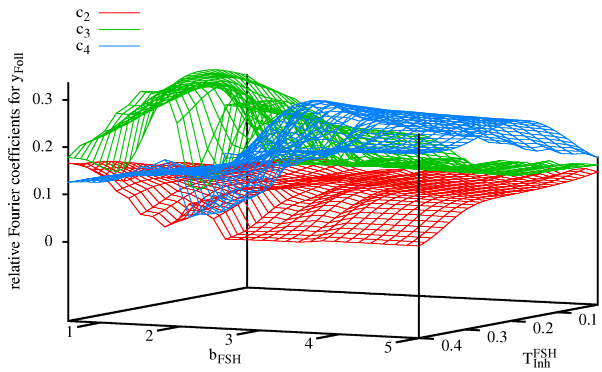
5 Conclusion

The described Fourier analysis has been performed for all model parameters of BovCycle. For 15 parameters there is a change in wave numbers, represented by a change of order of the oscillatory Fourier components in the considered range of values. The ranges for the parameter values that lead to a particular wave pattern have been determined. Furthermore, it has been observed that a change in the order of the oscillatory components comes along with an abrupt change in the cycle length at the specific value of the parameter, which corresponds to a step-like shape of the period-length-curve.

Regarding the simultaneous change of two parameter values, a sensitivity analysis with respect to the cycle length has been performed to obtain an idea which parameter combinations can provoke a change in wave patterns. In the 58 most sensitive combinations it can be observed, that the parameter which stimulates the follicular decay in dependency of the progesterone level, $m_{\mathrm{P4}}^{\mathrm{Foll}}$, is always one of the two parameters in the combination. For all 12 combinations



(a) $m_{\mathrm{FSH}}^{\mathrm{Foll}}$ and $m_{\mathrm{P4}}^{\mathrm{Foll}}$



(b) $T_{\mathrm{Inh}}^{\mathrm{FSH}}$ and b_{FSH}

Figure 5: Two examples of the fraction of the first four Fourier coefficients (the most dominant oscillations) to y_{Foll} as function of two parameters. A change in the order of the lines indicates a change in wave numbers in the simulation in this parameter region.

suspected due to sensitivity analysis, there is a change in the order for the most dominant coefficients, thus changing wave patterns depending on the values of the parameters.

Overall, with the Fourier analysis in combination with PERIOD we were able to identify 15 single parameters and at least 12 parameter combinations that are sensitive for changing wave patterns in the bovine estrous cycle model. Prospectively, these findings provide candidate mechanisms for regulating wave patterns in the cow and might be explored experimentally.

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