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RESEARCH ARTICLE

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Metabolic level recognition of progesterone in dairy Holstein cows using probabilistic models

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Abstract

Administration of exogenous progesterone is widely used in hormonal protocols for estrous (re)synchronization of dairy cattle without regarding pharmacological issues for dose calculation. This happens because it is difficult to estimate the metabolic level of progesterone for each individual cow before administration. In the present contribution, progesterone pharmacokinetics has been determined in lactating Holstein cows with different milk production yields. A Bayesian approach has been implemented to build two probabilistic progesterone pharmacokinetic models for high and low yield dairy cows. Such models are based on a one-compartment Hill structure. Posterior probabilistic models have been structurally set up and parametric probability density functions have been empirically estimated. Moreover, a global sensitivity analysis has been done to know sensitivity profile of each model. Finally, posterior probabilistic models have adequately recognized cow's progesterone metabolic level in a validation set when Kullback-Leibler based indices were used. These results suggest that milk yield may be a good index for estimating pharmacokinetic level of progesterone.

Additional key words: progesterone pharmacokinetic; Hill equation; metabolism, milk yield; Bayesian modeling.

Introduction

Getting a good rate of calves per cow and per year makes profitable a dairy farm. Taking into account that a postpartum cow is the best milk producer in a dairy herd, how to get pregnant these cows is an important studied topic for both veterinarians and dairy producers. Unfortunately, factors related with high milk yield, low body condition, high feed intake, low sexual hormone concentrations in the bloodstream, and health problems are associated with low fertility during postpartum (Butler, 2000, 2003; Sangsritavong *et al.*, 2002; Vasconcelos *et al.*, 2003; Ghavi Hossein-Zadeh, 2013). These factors are well interrelated each other making very difficult to predict them. Despite this, administration of exogenous progesterone is widely used in hormonal protocols for estrous (re)synchronization of dairy cattle without regarding pharmacological issues for dose calculation. This happens because it is difficult to estimate the progesterone metabolic level for each individual cow before administration. Recent kinetic analysis revealed a sigmoid saturation pattern of the progesterone depuration curve in lactating Holstein cows. In fact, by non-linear regression analysis, the Hill model has proved to be better than Michaelis-Menten kinetic model for describing such behavior (Turino *et al.*, 2010). An enzyme-catalyzed metabolism of progesterone involving

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Abbreviations used: AIC (Akaike information criterion); AICm (modified version of Akaike information criterion); *Cx* (plasmatic progesterone concentration); DMI (dry matter intake); GSA (global sensitivity analysis); *h* (Hill coefficient); *K* (enzyme-substrate interaction constant); NEBAL (negative energy balance); PDF (probability density function); *Si* (principal sensitivity index); SSQ (residual sum of squares); *STi* (total sensitivity index); *Vm* (volume in which progesterone is distributed).

cooperative substrate-binding sites is suggested by the implementation of Hill equation. Moreover, this kinetic model was successfully used for modeling the linkage of plasma progesterone concentrations with the hormone released from bovine intravaginal inserts (Mariano *et al.*, 2010).

Bayesian modeling is the incorporation of Bayes theorem into modeling framework (Andradóttir & Bier, 2000; Kamath & Pakkala, 2002; Peña *et al.*, 2009). A probabilistic model is the output of the Bayesian approach in modeling (Martínez *et al.*, 2011). Firstly, Bayesian analysis begins with a mathematical model which attempts to describe the dynamic of observed experimental data. However, unlike classical significance testing, the uncertainty about the parameters in the model is described using probability distributions. In a Bayesian analysis, a prior distribution must be supplied for each model parameter which has to reflect the probability that one parameter might assume certain values. These prior distributions can be based on results from historical experimental data, they can be defined by physical or economical constraints, or they might reflect an expert experience and/or intuition. This prior distribution is then updated by the newly acquired data to form a posterior distribution which is used to make inferences about the parameters. In Fig. 1, the difference between a prior and posterior estimated probability density functions is shown. Typically, the posterior distribution is narrower compared to the prior one, which reflects the information gained by considering the data gathered in the evaluation run. In fact, the concept of probabilistic model would help to reduce intra-individual variability which appears as a consequence of adopting a deterministic point of view in modeling. As a probabilistic model has an estimation domain, it could explain more suitable natural variability occurring in live systems. The Bayesian approach is symbolized by the following equation:

$$p(\theta|y)=\frac{f(y|\theta)\Theta(\theta)}{\int f(y|\theta)\Theta(\theta)d\theta} \quad [1]$$

where $f(y|\theta)$ is the probability density function (PDF) of observed data y given the parameters θ; $\Theta(\theta)$ is the prior PDF; and $p(\theta|y)$ is the posterior PDF which shows the PDF changes associated with information introduced by using new data (Carlin & Louis, 2009). These and other Bayesian based tools have been applied in different scientific disciplines as genetic evaluation of dairy sheep breed (Legarra *et al.*, 2005), civil engineering (Yuen, 2010), compositional analyses of transgenic crops (Harrison *et al.*, 2011), and exposure to *Bovine viral diarrhoea virus* in beef cow-calf herds (Lewis *et al.*, 2011).

In the present contribution, we propose to use a simple measure of daily milk yield of postpartum cow to evaluate its progesterone metabolism. First, progesterone pharmacokinetic behaviors of two milk producing groups are analyzed. Information provided by cow progesterone pharmacokinetic assays are used to empirically estimate prior PDFs of parameters in Hill model. Moreover, the effect of incorporating experimental information for two levels of milk-producing cows is evaluated. The resulting posterior probabilistic models have been validated using independent plasmatic progesterone profiles from cows belonging to both high and low milk production groups. Finally, a progesterone metabolic level recognition method based on daily milk yield of cows is proposed. We hypothe-

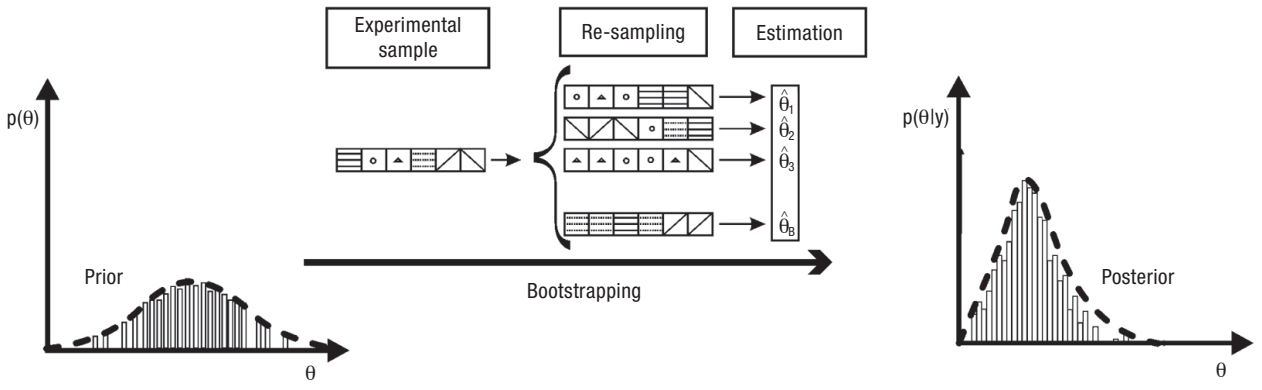

Figure 1. Schematic differences between prior and posterior estimated probability density functions (PDFs) when bootstrapping is done after adding new information to original data.

sized that studied tools could provide a useful starting point for predicting progesterone metabolic rate by linking milk yield of cows with their plasmatic progesterone concentrations after hormone exogenous administration.

Material and methods

Animals and general procedures

In order to avoid endogenous progesterone production, ovarian function of lactating Holstein cows from Experimental Station INTA Rafaela (Santa Fe, Argentina) was monitored and synchronized as previously described (Turino *et al.*, 2010). Cows having basal progesterone concentration greater than 1 ng mL^{-1} in a pretreatment blood sample were specifically excluded from the study. The resulting 19 cows [with a median of two calving (interquartile range = 3)] were used for progesterone pharmacokinetic data acquisition. Cows were milked twice a day, fed ad libitum, weighed (601 ± 85 kg), their body condition evaluated [median = 2.75 (2.25-3.25), 1 = lean, 5 = fat] and their milk production recorded for 7 days before commencement of the pharmacokinetic assay.

Pharmacokinetic assays

The equivalent to 100 mg progesterone (99.2%, USP grade) of a sterile solution based on benzyl alcohol (4% v v^{-1}), 2-pyrrolidone (56% v v^{-1}) and physiological saline solution (40% v v^{-1}) was injected into the jugular vein of each cow. Serial blood samples for pharmacokinetic modeling were collected from coccygeal vessels into tubes containing 0.07 mL of EDTA solution (0.342 mol L^{-1}, pH 7.2, Wiener, Argentina) at 1, 3, 6, 10, 15, 30, 60 and 90 min and at 2, 3 and 6 hours after injection. The time needed to blood collection was monitored and never exceeded 10 s. After centrifugation of blood at 2,000 rpm for 10 min, plasmatic samples were stored at –20°C until progesterone analysis by RIA using a commercial, solid phase, I^{125} kit (Coat-A-Count®, Siemens Medical Solutions Diagnostics, USA). Duplicate analysis was performed on each sample. The intra-assay and inter-assay coefficients of variation were both < 7% for concentrations between 0.1 and 40.0 ng mL^{-1}, and the sensitivity of the method was 0.01 ng mL^{-1}.

Probabilistic model statement

Probabilistic model structure

In a previous work it has been shown the successful use of a simple one-compartment model to describe the dynamic of pharmacokinetic data within a large plasmatic progesterone concentration (Cx) range. Experimental observations and kinetic modeling support the occurrence of a saturated metabolism of progesterone following a sigmoidal behavior, which is well described by Hill model (Turino *et al.*, 2010):

$$\frac{dCx}{dt} = -\frac{1}{Vx}\frac{Vm\,W\,Cx^{h}}{(KW)^{h}+Cx^{h}};\ 0 \le t \le t_{f} \qquad [2]$$

where Vx is the volume in which progesterone is distributed; Vm is the maximum rate of hormone elimination; W is the weight of the individual considered; K is a constant for characterizing enzyme-substrate interaction and h is the Hill coefficient, whose value define positive ($h > 1$) or negative ($h < 1$) cooperation in kinetic profiles.

Parameterization of probabilistic models

Initially, two groups of cows have been built according to milk production. Each group contained 5 animals. Experimental data sets had 52 points for high producing cows (35.4-48.2 L day^{-1}) whereas only 48 for low producing cows (14.6-23.8 L day^{-1}).

Models for plasmatic progesterone concentration (Cx) have been mathematically defined following Hill pharmacokinetic model (Eq. [2]) and taking into account Eqs. [3] and [4]:

$$Cx(0) = C_0 \qquad [3]$$

$$Vx = \frac{D}{C_0} \qquad [4]$$

where D and C_0 have been experimentally found since D is the administered dose (see section *Pharmacokinetic assays*) and C_0 is determined as the coordinate-intercept from linear regression on the concentration data in the initial linear range of the $Cx(t)$ curve.

Using such mathematical structure and above data sets two prior probabilistic models were built. Consequently, PDFs of three parameters of Hill model (Vm, K and h) were empirically bootstrapped (Efron & Tibshirani, 1993; Joshi *et al.*, 2006; De Martini & Rapallo, 2008) using pharmacokinetic data from each group of cows. As initial values for parameter estimations a random parameterization was generated using the Marsaglia's Sub-

tract-with-Borrow algorithm (Marsaglia & Zaman, 1991) associated to a wide initial parameter domain. Once empirical distributions were obtained, frequency histograms were used to compute the expected values of parameters of Hill model among Eq. [5]:

$$E[\theta] = \sum_{i=1}^{k} \theta_i p_i \quad [5]$$

where θ_i is the mid-value of each bin in the empirical histogram and p_i is its probability.

Afterwards, posterior probabilistic models were obtained using the same Bayesian tools that prior probabilistic models but adding sets of two extra cows for each milk producing group (33.2-40.9 and 14.8-20.7 L day^{-1} for high and low groups, respectively) which had 18 experimental *Cx* measures along time. The final number of cows was 7.

Computational model implementation and Bootstrap method

Pharmacokinetic models were fitted by non-linear regression analysis against the experimental data using the residual sum of squares (*SSQ*) for each individual parameter set estimation in bootstrapping. The bootstrap method is a simulation method for statistical inference using re-sampling with replacements (Efron & Tibshirani, 1993). A main application of the method is approximating non-parametric distributions for statistical variables in model fitting. To build a histogram for some parameter set of a model, bootstrapping simulates the effect of artificially excluding some data points in the data set when parameters are estimated. We randomly sampled *n* data points with replacement from the current data set, where the probability of each data point being selected is n^{-1}. These *n* data points are regarded as a re-sampled training data. Accordingly, even though the number of samples in each replicated data set is the same, most of the re-sampled data sets will provide a different estimation of model parameters (see Fig. 1). Histograms for each model parameter are obtained using these alternative estimators acquired using a given fitting criterion, *e.g. SSQ*.

Analysis of probabilistic models

Once posterior probabilistic models have been parameterized, a Global Sensitivity Analysis (GSA) was done taking into account empirically estimated PDF of each set of parameters (Saltelli *et al.*, 2000; Kamath & Pakkala, 2002; Xu & Gertner, 2007; Cristaldi *et al.*, 2011; Martínez *et al.*, 2011). Both principal (*Si*) and total (*STi*) effect indices were computed into the attempt to identify sensitivity profiles of probabilistic model and parameters interactions. For the i^{th} parameter, *Si* gives an idea of the proportion of variability which might be explained if the true parameter value was known. On the other hand, the difference between *STi* and *Si* reflects the degree of interaction of the i^{th} parameter in the whole model structure.

Recognition of physiological state using probabilistic models

Pharmacokinetic assays from five cows (63 ± 12 postpartum days) with levels of milk production ranging from 23.4 to 29.6 L on assay day were carried out and their plasmatic progesterone profiles were used to evaluate discrimination capability of posterior probabilistic models for recognizing between milk production-physiological states.

Two Kullback-Leibler distance based indices were computed taken into account PDF from both probabilistic models: the Akaike Information Criterion (*AIC*) and its modified version for low experimental point (*n*)/model parameters number (*P*) ratios (*AICm*) (Akaike, 1973, 1978; Burman & Nolan, 1995; Burnham & Anderson, 2002):

$$AIC = n \log(\hat{\sigma}^2) + 2P \quad [6]$$

$$AICm = AIC + \frac{2P(P+1)}{n-P-1} \quad [7]$$

$$\hat{\sigma}^2 = \frac{SSQ}{n} \quad [8]$$

Both indices are relative measures and smaller values reflect better model fit. *AIC* has been previously used as model selection criterion to analyse first lactation daily milk yield data in Holstein-Friesian cattle (López-Romero & Carabaño, 2003), to model the final scores in US Holsteins to assess genetic changes over the years (Tsuruta *et al.*, 2004) and, to estimate test-day milk yield genetic parameters of Holstein cows (Bignardi *et al.*, 2009).

Results

In Figs. 2 and 3 empirical prior (a-b) and posterior (c-d) PDFs for *Vm* and *K* in high (a, c) and low (b, d)

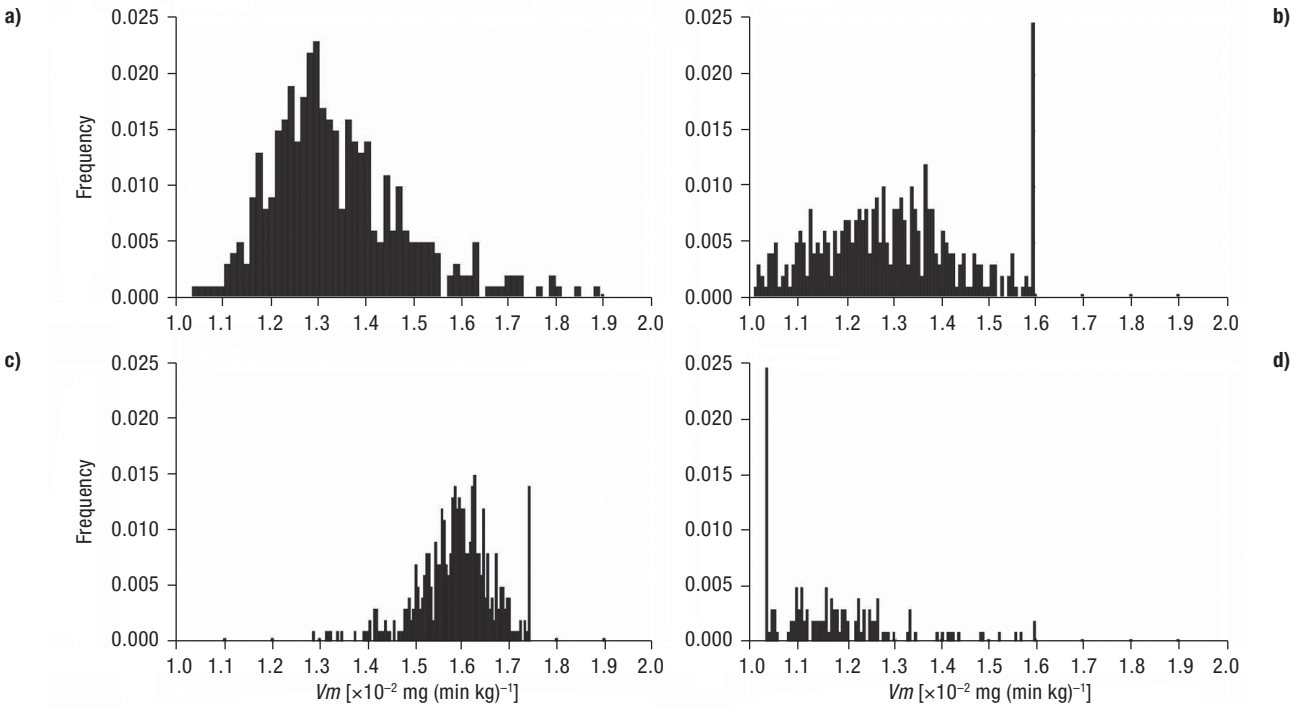

Figure 2. Probability density functions (PDFs) of the maximum rate of hormone elimination (*Vm*) for (a,c) high and (b,d) low milk producing cows. (a,b) Prior and (c,d) posterior probabilistic models.

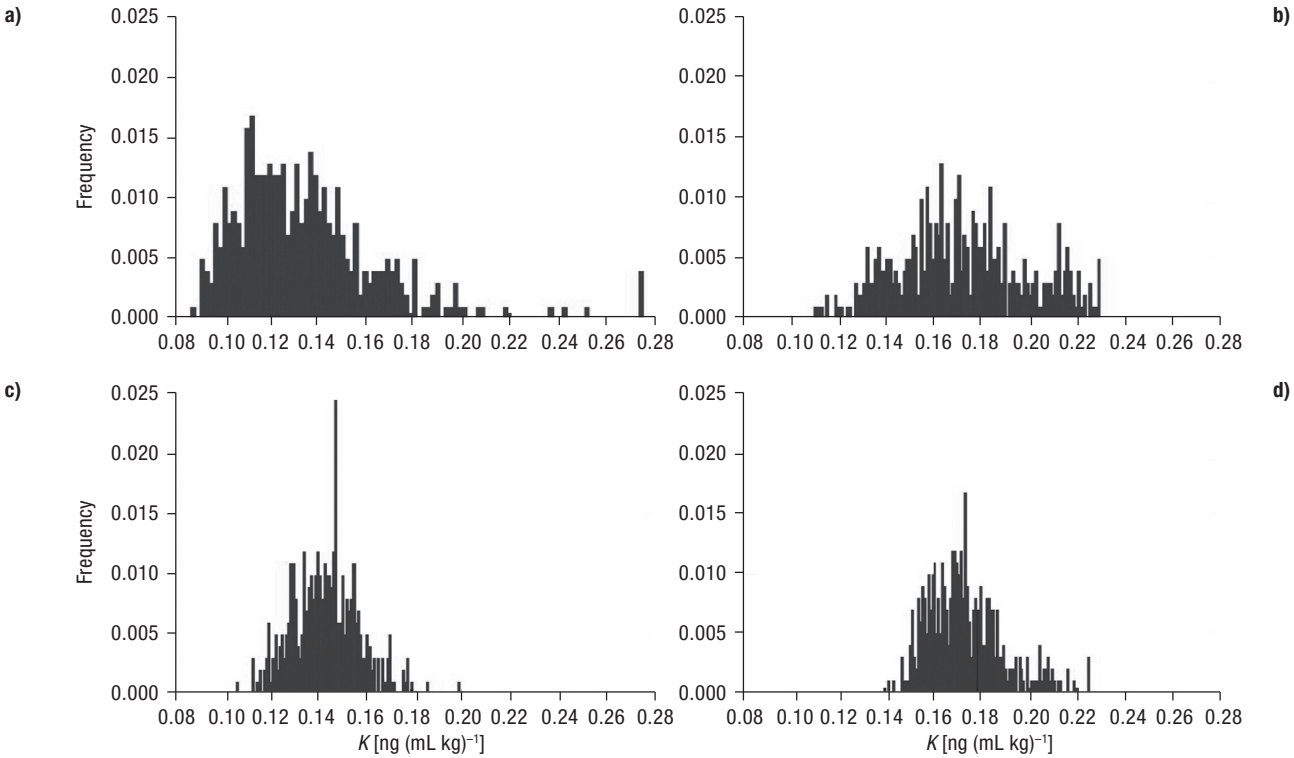

Figure 3. Probability density functions (PDFs) of the constant for characterizing enzyme-substrate interaction (*K*) for (a,c) high and (b,d) low milk producing cows. (a,b) Prior and (c,d) posterior probabilistic models.

Table 1. Statistics from empirical probability density functions for low and high milk producing groups

Parameter[1]	Unit		Prior models		Posterior models	
			High	Low	High	Low
Vm	mg (min kg) $^{-1}$	Minimum	0.0112	0.0102	0.0113	0.0102
		Maximum	0.0174	0.0160	0.0174	0.0141
		Median	0.0131	0.0130	0.0151	0.0102
		E[Vm]	0.0135	0.0131	0.0152	0.0107
K	ng (mL kg) $^{-1}$	Minimum	0.0936	0.1242	0.0936	0.1322
		Maximum	0.2040	0.2246	0.1723	0.2005
		Median	0.1287	0.1701	0.1307	0.1476
		E[K]	0.1339	0.1719	0.1316	0.1520
h	Dimensionless	Minimum	1.7455	1.6450	2.0683	1.6450
		Maximum	2.6605	2.2214	2.6605	1.8687
		Median	2.1937	1.8756	2.5325	1.6834
		E[h]	2.2082	1.8773	2.4811	1.7047

[1] *Vm* is the maximum rate of hormone elimination; *K* is a constant for characterizing enzyme-substrate interaction; *h* is the Hill coefficient. E = expected value.

milk producing groups, respectively, are presented. In Table 1, 95 percentile ranges, median and expected values (Eq. [5]) for parameters in prior and posterior models are shown. Estimation domains of kinetic parameters are highly overlapped if prior PDFs are analyzed. However, a better probabilistic models discrimination is achieved when posterior parameter PDFs are computed. As it can be seen, all confidence intervals of parameters have been narrowed as a consequence of introducing experimental data for posterior PDF estimations, especially whether PDFs for *K* are considered. Furthermore, shapes of parameter PDFs have dramatically changed: whereas in prior models all distribution of parameters could be approximated to normal, in posterior probabilistic models only *K* PDFs could hardly support such hypothesis.

Fig. 4 presents estimation domains of posterior models for both high and low milk producing cows. Based on such figure, two posterior probabilistic models for differentiating between milk production levels in cows have been achieved suggesting two distinctive progesterone metabolic rates associated with different milk yields. Moreover, it is worth to note that experimental data of the two animals added to posterior model were found in areas of high probability for both low and high milk producing models.

In Table 2, sensitivity profiles of posterior probabilistic models are shown. According to GSA, *h* is the less relevant parameter in both probabilistic models. This fact can be explained because both posterior PDFs presented narrow intervals where parameter values could be found with high probability (see Table 1). On the other hand, posterior models highly differ in their

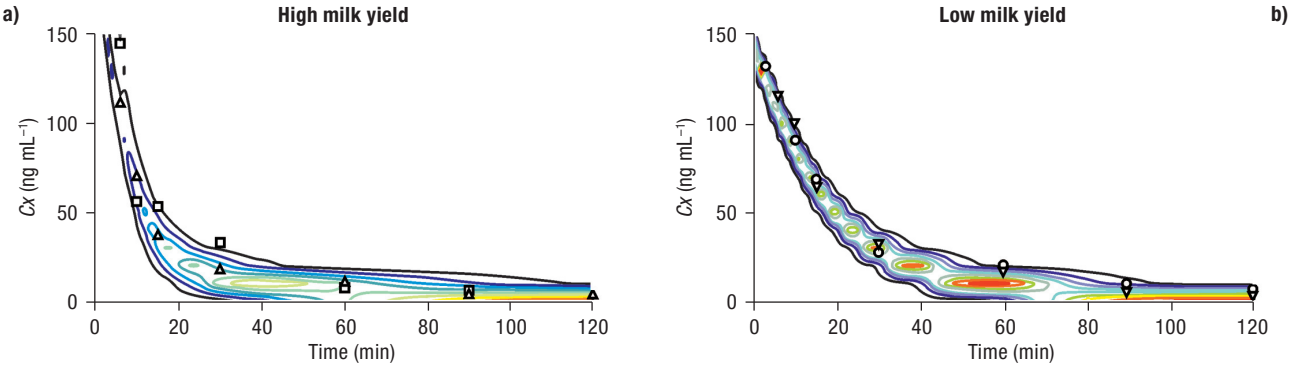

Figure 4. Plasmatic progesterone concentration (*Cx*) data points of two extra animals and estimation domains (red color indicates areas of high probability) of posterior probabilistic models for both (a) high and (b) low milk producing cows.

Table 2. Principal (*Si*) and total (*STi*) sensitivity indices for posterior probabilistic models

Parameter[1]	Milk producing group			
	High		Low	
	Si	*STi*	*Si*	*STi*
Vm	0.53	0.87	0.36	0.60
K	0.12	0.48	0.38	0.64
h	0.02	0.02	0.02	0.02

[1] *Vm* is the maximum rate of hormone elimination; *K* is a constant for characterizing enzyme-substrate interaction; *h* is the Hill coefficient.

sensitivity when the other two parameters are considered. As an example, *K* could be analyzed: if its exact value was known, a large reduction in the variances of estimations would be expected in low production posterior probabilistic model (*Si* = 0.38); however, having the same level of knowledge only a marginal improvement on estimation domain for high production posterior probabilistic model could be gained (*Si* = 0.12).

It is worth to note that in both models a high degree of interaction between *Vm* and *K* has been identified since there are enormous differences between their *Sis* and *STis*. This could be explained taking into account model structure (see Eq. [2]) since at low plasmatic progesterone levels the ratio $Vm\,(KW)^{-h}$ define progesterone elimination rate and both parameters are involved in such ratio.

In Table 3, *AIC* and *AICm* indices for prior and posterior probabilistic models are shown to test milk production levels in a validation set of cows. In general, except for cow N° 4429, the distance between proper model and experimental data is reduced when comparing prior and posterior indices. The opposite is observed when indices evolution against incorrect physiological model is considered. In this way, both Akaike's indices could associate milk production below 23.4 L day^{-1} with a low milk yield level and remaining cows with values above 26.5 L day^{-1} with a high milk yield level when the posterior probabilistic models were used. Consequently, both *AIC* and *AICm* indices for posterior probabilistic models might be used to select a milk production limit to distinguish between low and high milk producing cows.

Discussion

The empirically estimated parameter PDFs in posterior probabilistic models are in well agreement with previous results where a deterministic modeling perspective was implemented (Turino *et al.*, 2010). In this way, 95 percentile ranges for both high and low milk yields include or overlap confidence intervals already reported (except for *Vm* of low producer group), revealing their capability for discriminate different metabolic rates of progesterone between high and low milk producing cows.

An analysis of one the most important metabolic enzyme involved in progesterone metabolism (cP450 enzyme) could explain the differences observed between parameters of probabilistic models for both groups of cows. In the present study, *h* values were positive, *i.e.* the affinity and reaction rate of a vacant site for a progesterone molecule increase when a prior progesterone molecule has bound to enzyme. From this recognition, we cannot reject that the relative increased *h* value in cows with high levels of milk production may further result from a higher cooperativity and interaction between enzyme binding sites and progesterone molecules (see Eq. [2]). Otherwise, *K* was higher for low producing animals when Table 1 and Fig. 3

Table 3. Akaike Information Criterion (*AIC*) and its modified version (*AICm*) for milk production-physiological states classification for both probabilistic models

Milk yield (L day^{-1})	Cow N°	Prior probabilistic model				Posterior probabilistic model			
		High production		Low production		High production		Low production	
		AIC	*AICm*	*AIC*	*AICm*	*AIC*	*AICm*	*AIC*	*AICm*
29.6	4,443	**33.21**	**37.22**	34.47	38.47	**32.86**	**36.86**	34.66	38.66
28.3	4,429	**24.99**	**29.79**	27.47	30.27	**27.26**	**32.06**	28.66	33.46
27.9	3,793	35.54	38.54	35.23	39.23	**33.99**	**37.99**	36.44	40.44
26.5	4,401	**27.66**	**33.66**	28.90	34.90	**26.38**	**32.37**	29.74	35.73
23.4	4,576	37.27	40.70	**34.53**	**38.00**	39.15	42.59	**32.49**	**35.92**

(c,d) are analyzed. This parameter is more a mean interaction constant for all drug-cP450 intermediates than a unique binding constant by itself (Denisov *et al.*, 2009). We cannot reject the possibility that other variables besides milk yield, *e.g.* dry matter intake (DMI) and nutritional condition, could affect the performance of this parameter and the pharmacokinetic of progesterone as discussed below.

The maximum rate of metabolism (*Vm*) for high producing dairy cows was greater than for the low producing cows. Turino *et al.* (2010) have previously discussed this fact and suggested that it is caused not only by an increase in blood flow as a consequence of a greater DMI as it is usually reported (Sangsritavong *et al.*, 2002), but also by a greater negative energy balance (NEBAL) associated with a major abundance of cP450 subunits. Additionally, it was proved that serum insulin concentration is reduced whereas NEBAL increased (Butler, 2000; 2003), which concomitantly rises the relative abundance of hepatic Cyp2C and Cyp3A subunits (Lemley *et al.*, 2008; 2010). From these outcomes, a larger production of Cyp2C and Cyp3A could be expected in high producing dairy cows, as we ascertain from the *Vm* values obtained in the present kinetic study.

Progesterone metabolism discrepancies among high and low milk producing cows are also reflected in estimation domains of posterior probabilistic models (see Fig. 4). Main differences are identified during the first 100 min after progesterone injection: for high producing cows, a sharper plasmatic progesterone decrease is expected during the first 25 min and it is predicted basal levels would be achieved around 50 min. However, for low producing cows, it would take more than 75 min to eliminate injected progesterone. Moreover, low producing cows take around 50 min to reach plasmatic progesterone levels of about 20 ng mL^{-1}, while high producing cows take only 25 min. In addition, good agreement between experimental data points and areas of high probability in Figure 4 might corroborate the improvement of posterior probabilistic models by the addition of experimental information.

Both Akaike's indices (see Table 3) have demonstrated that posterior probabilistic models could identify milk-production physiological state of cows when a validation data set was used. This result can be appreciated when *AIC* and *AICm* for cow N° 3793 are considered: results are unclear when cow's physiological stage classification is attempted using prior probabilistic models. However, milk level is well differentiated when posterior models are used. Additionally, the relationship between milk production yield and progesterone metabolic rate in dairy cows might be used as a tool to estimate progesterone metabolic level with a very simple measure of daily milk production. In this way, both Akaike's indices (see Table 3) could associate milk production values below 23.4 L day^{-1} with a low progesterone metabolic level and values above 26.5 L day^{-1} with a high progesterone metabolic level when posterior probabilistic models were used. We suggest that dairy yield could be a direct measure for progesterone pharmacokinetic profile recognition with a production limit ranging from 24 to 26 L day^{-1} for dairy Holstein cows. This information could be taken into account when a drug intervention program for synchronizing the estrous cycle of dairy cattle is used. This will allow the selection of progesterone dose according to milk daily yield, increasing hormone bioavailability. We recognize, however, that the validity of this assertion has to be corroborated with progesterone metabolism information of cows with milk yields included in the postulated limit level.

In summary, the above mentioned features would distinguish a more important positive cooperative effect during progesterone metabolism for high than for low milk producing cows. Posterior probabilistic models demonstrated to improve prior models by the addition of experimental information and being competent tools for distinguishing progesterone metabolism between high and low milk producing cows. Additionally, both Akaike's indices could associate milk production values below 23.4 L day^{-1} with a low progesterone metabolic level and values above 26.5 L day^{-1} with a high progesterone metabolic level when the posterior probabilistic models were used. Based on the above results we suggest that dairy yield could be a direct measure for progesterone metabolic level recognition in dairy Holstein cows and could be taken into account before progesterone administration during hormonal protocols.

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