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Mathematical characterization of the milk progesterone profile as a leg up to individualized monitoring of reproduction status in dairy cows

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ABSTRACT

Reproductive performance is an important factor affecting the profitability of dairy farms. Optimal fertility results are often confined by the time-consuming nature of classical heat detection, the fact that high-producing dairy cows show estrous symptoms shorter and less clearly, and the occurrence of ovarian problems. Today's commercially available solutions for automatic estrus detection include monitoring of activity, temperature and progesterone. The latter has the advantage that, besides estrus, it also allows to detect pregnancy and ovarian problems. Due to the large variation in progesterone profiles, even between cycles within the same cow, the use of general thresholds is suboptimal. To this end, an intelligent and individual interpretation of the progesterone measurements is required. Therefore, an alternative solution is proposed, which takes individual and complete cycle progesterone profiles into account for reproduction monitoring. In this way, profile characteristics can be translated into specific attentions for the farmers, based on individual rather than general guidelines. To enable the use of the profile and cycle characteristics, an appropriate model to describe the milk progesterone profile was developed. The proposed model describes the basal adrenal progesterone production and the growing and regressing cyclic corpus luteum. To identify the most appropriate way to describe the increasing and decreasing part of each cycle, three mathematical candidate functions were evaluated on the increasing and decreasing parts of the progesterone cycle separately: the Hill function, the logistic growth curve and the Gompertz growth curve. These functions differ in the way they describe the sigmoidal shape of each profile. The increasing and decreasing parts of the P4 cycles were described best by the model based on respectively the Hill and Gompertz function. Combining these two functions, a full mathematical model to characterize the progesterone cycle was obtained. It was shown that this approach retains the flexibility to deal with both varying baseline and luteal progesterone values, as well as prolonged or delayed cycles.

1. Introduction

An optimal reproductive performance is key for the profitability of modern dairy farms [1,2]. However, an increased milk production is typically accompanied by a reduced reproductive performance. This is reflected by extended anestrus periods after partus, an increased incidence of luteal or follicular cysts and less pronounced estrous behavior [1,3,4].

While accurate monitoring of the reproduction status is essential, the time-consuming nature of visual heat detection, in combination with increasing herd sizes limits its practical relevance. Therefore, automated heat detection systems have been developed [5]. A clear overview of estrous detection methods and available sensors was given by Rutten et al. [6] and Saint-Dizier and

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Chastant-Maillard [5]. Most tools use activity meters to register the increased cow activity associated with estrus. Although these sensors have already proven their usefulness and effectiveness [7], their sensitivity is limited by the occurrence of silent estruses [8]. Moreover, as these techniques mainly focus on the detection of heat, they are not able to chart a global image of the reproduction cycle [5].

Progesterone (P4) is considered the gold standard for evaluation of the reproduction status for research purposes. In addition, monitoring the milk P4-hormone patterns, rather than the behavioral symptoms of a cow in estrus, would allow farmers to observe estrus, pregnancy, embryonic mortality, prolonged acyclicity after partus and the occurrence of ovarian cysts [9–11]. This requires a clear understanding of the P4 profile of lactating dairy cows. The fertility status of dairy cattle can be divided into three parts: (1) post-partum anestrus; (2) a cyclic part; and (3) pregnancy [12]. During post-partum anestrus the adrenal gland cortex produces a small amount of P4 (<0.1 ng/mL serum [13]). The cyclic part starts with the onset of follicular activity. When the first dominant follicle ovulates (day 0), a *corpus luteum* (CL) starts the production of P4. During its development phase, the P4 production is proportional to the size of the CL. Further into the cycle, P4 production is no longer directly correlated with CL size [14]. Around day 17, the uterus endometrium produces luteolytic factor $PGF_{2\alpha}$, which results in the regression of the CL and a drop in P4. During the period of low P4 following luteolysis, a new dominant follicle develops and ovulates around day 21. Likewise, the second part of the reproductive profile is defined by a cyclic P4 pattern [12]. This cyclic pattern of P4 was described in depth by Meier et al. and Blavy et al. [15,16], who also mentioned a large variation between cycles, partly caused by the differences in number of follicular waves [17]. The third and last part of the fertility status (pregnancy) starts after successful insemination and is accompanied by an increase in P4 produced by the developing pregnancy CL [18]. This pregnancy CL maintains a high P4 production throughout the entire gestation period. A cow's P4 profile can be disturbed by several causes such as a prolonged postpartum anestrus, which delays the start of the second part of the reproductive cycle [19], and the presence of cystic ovary disease (incidence rate of 1–30%), covering both luteal and follicular cysts [20]. A luteal cyst is defined by the presence of a persistent CL on one of the ovaries, resulting in an abnormal long luteal (high P4) phase. A follicular cyst on the other hand, is a persistent follicle in absence of a CL, indicated by a prolonged follicular phase (low P4) [20].

Despite the fact that online measurement of P4 is possible [21], little research has been conducted to translate the acquired P4 data into concrete guidelines for the farmers, e.g. to identify the optimal time point for insemination or to check for embryonic loss and ovarian problems. The monitoring algorithm used in the Herd Navigator® system [22–24] uses fixed thresholds for smoothed P4 levels to detect estrus. Additionally, by taking various other factors into account (e.g. lactation stadium, time of previous inseminations, pregnancy determinations, milk urea, body energy status), the model can predict the risk of prolonged postpartum anestrus, ovarian cysts, the potential insemination success and the likelihood of pregnancy. As the P4 levels of each individual cow are processed according to the same general procedure by comparing them against a fixed threshold, this algorithm does not account for the individual and biological variability. Moreover, it is well known that milk P4 measurements and the resulting profiles differ between cows and even between succeeding cycles within cows [24]. In previous research, using a fixed threshold on the P4 level, the time of ovulation could only be predicted with an accuracy of 48 h, which is 4 times larger than the optimal insemination window of 12 h [25].

Employing an individualized approach instead of using fixed thresholds for P4 measurements will likely improve the interpretation of the P4 data. For this, the basal and luteal P4 levels, as well as the growth and decline of the P4 production rates should be covered for each P4 cycle individually with a suitable model. Moreover, the approach should allow for online detection and update of the model parameters as new P4 measurements become continuously available in a practical setting.

In this study, it is hypothesized that the profile characteristics of each individual cycle can be identified with sufficient accuracy by fitting a model that describes the P4 production by the adrenal gland cortex and the growing and regressing cyclic CL. In this context, the performance of three mathematical growth functions was evaluated and compared.

2. Materials and methods

2.1. Model development

In an earlier study, Boer used sigmoidal Hill functions to successfully describe serum P4 profiles by modelling the growth and regression of the CL [17]. Unlike serum, where the P4 concentration is more directly linked to the size of the CL, the transfer of P4 from the serum to the milk depends on numerous factors: actual P4 secretion by the CL, rate of clearance in blood, fat content of milk and amount of P4 dissolved in the milk fat, etc. [16,26,27]. Still, milk and serum P4 profiles generally follow a high correlation (own unpublished data: $R^2 = 0.67$ [26,28,29]). Therefore, three sigmoidal candidate functions, were compared for the description of the increasing and decreasing parts of each P4 profile. The P4 baseline was established by an intercept representing the adrenal P4 production.

The first model tested was based on the Hill function, also used by Boer [17] (cfr. Hill model, eq. (1)):

$$[P4] = b_0 \pm \frac{A^*t^C}{B^C + t^C} \tag{1}$$

The logistic and Gompertz function are selected as a second and third candidate. These functions are mainly used to model population and cell growth in a limited environment [30]. Both the logistic function (cfr. Logistic model, eq. (2)) and the Hill function are symmetrical functions [31]. The Gompertz function (cfr. Gompertz model, eq. (3)) is asymmetrical with a fast rate of change in the beginning and a slower evolution when the asymptote is approached. As the CL grows and proliferates during the cyclic phase, they might all be well suitable to describe the P4 profiles.

$$[P4] = b_0 \pm \frac{A}{1 + \exp(C^*(B - t))} \tag{2}$$

$$[P4] = b_0 \pm A^*\exp[-\exp(C^*(B - t))] \tag{3}$$

All three equations have four parameters with a similar interpretation. In the increasing functions, the b_0 parameter represents the baseline P4 production when no functional CL is present. A is the upper horizontal asymptote, which represents the P4 production when the size of the CL is maximal. In the decreasing functions, the baseline production is estimated as b_0 minus A. The B parameter is a measure for the shift of the inflection point over time (t-axis). The slope is determined by A, B and C, where the latter is the main growth rate determining parameter. In the Hill function, C must be larger than 1 to preserve the sigmoidal shape. Both the logistic function and the Hill function have the inflection point midway between the upper and lower asymptote. For the Hill function, the