*Journal of Dairy Research* (2009) **76** 249–256. © *Proprietors of Journal of Dairy Research 2009* 249
doi:10.1017/S0022029909003987 *Printed in the United Kingdom*

# A compartmental model describing changes in progesterone concentrations during the oestrous cycle

Susanne Meier[1]*, John R Roche[1], Eric S Kolver[1,2] and Ray C Boston[3]

[1] DairyNZ Ltd, Hamilton, New Zealand
[2] Synlait, PO Box 9466, Hamilton, New Zealand
[3] Biostatistics Section, New Bolton Centre, Kennett Square, University of Pennsylvania, USA

Received 10 November 2008; accepted for publication 10 December 2008; first published online 13 March 2009

The objective of this study was to develop a mathematical model that accurately describes the rise and decline in plasma progesterone concentrations, and is able to define parameters describing progesterone appearance and disappearance during the bovine oestrous cycle. Daily plasma progesterone data from 27 cows were used to develop a compartmental model consisting of an appearance function and an appearance modulating function. Model outputs included an apparent appearance or secretion duration, appearance rate and an average disappearance rate (expressed as arbitrary units per day; units/d). Shape-based clustering identified three common shape-based groups (or clusters) of progesterone profiles defined as either 'peaked' profile, with the profile reaching a distinguishable peak, 'structured', with the profile exhibiting a wave-like pattern, or 'flat top', with the profile reaching a plateau. Differences in the model parameters for the three different shapes of progesterone profiles were examined: peaked ($n$=13), flat top ($n$=7) and structured ($n$=7). The mean duration of apparent appearance was 11·49 (SD 0·17 d) for all 27 profiles. The model estimates for total appearance of progesterone (area under the curve; ng/ml per cycle), mean appearance rate and maximum appearance rate were 69·04 ng/ml per cycle (SD 15·2 ng/ml per cycle), 3·19 ng/ml per cycle (SD 0·7 ng/ml per d) and 6·70 ng/ml (SD 1·31 ng/ml), respectively. The average disappearance rate was 1·0 units/d (SD 0·04 units/d). The apparent appearance duration was greatest ($P<0·01$) in the flat top profiles (12·54, SD 0·41 d) followed by the structured (11·77, SD 0·66 d) and the peaked (10·80, SD 0·30 d) profiles. Total and mean progesterone appearance, maximum progesterone appearance rate, and the progesterone disappearance rates were not different between the profiles. The model successfully simulated all components of the progesterone profile and was able to define specific parameters of different shaped progesterone profiles. A simple model able to estimate parameters describing progesterone appearance and disappearance can be used to explore the relationships between profile shapes and reproductive outcomes.

**Keywords:** Model, progesterone, profile, oestrous cycle, bovine.

Subtle changes in progesterone profiles during early pregnancy can affect reproductive outcomes. Elevated plasma progesterone concentrations between days 5 and 7 of the oestrous cycle result in larger embryos (Mann & Lamming, 2001) and improved conception rates (Strong et al. 2005; McNeill et al. 2006) indicating that an early rise in progesterone is positively related to fertility. In comparison, reproductive function is negatively affected by an increase in progesterone metabolism (Wiltbank et al. 2006). In addition, different shaped progesterone profiles exist that are characterized by differences in the timing and speed at which luteolysis occurs (Meier et al. 2009); whether these differences are due to changes in progesterone metabolism and clearance has not yet been investigated.

Oestrous cycle length has also been associated with fertility. Cows with shorter 2-wave oestrous cycles have reduced fertility compared with cows exhibiting 3-wave cycles (Cooperative Regional Research Project NE-161, 1996; Townson et al. 2002) and Cushman et al. (2007) reported that fertility was reduced by 2·2% with each day that oestrous cycle length increased. This effect is probably

*For correspondence; e-mail: Susanne.Meier@DairyNZ.co.nz

associated with follicle dynamics, and indicates that more subtle changes in progesterone secretion and metabolism are important determinants for cow fertility.

Models describing the complex hormonal interactions during the mammalian reproductive cycle are not new. However, few models of the bovine oestrous cycle are available. Yenikoye et al. (1981) presented a static model, with which progesterone profiles were fitted using two distinct temporal phases. Phase 1 was described by a three-parameter logistic function from the onset of progesterone appearance to its peak, with phase 2 using a three-parameter exponential function to describe the disappearance of progesterone. However, this simple model was unable to provide an accurate description of the latter stages of the progesterone profile and, therefore, failed to capture a number of important aspects of the profile. A number of complex models of the human menstrual cycle are also available: these models describe the complex hormonal dynamics and internal interactions controlling ovulation, with progesterone being one component of these complex models (Bogumil et al. 1972; Harris Clark et al. 2003; Reinecke & Deuflhard, 2007). The relevance of these models to dairy cows has not been considered. As progesterone secretion and metabolism rates control the profile characteristics, especially during the early and later stages of the oestrous cycle, the development of a simple and specific model that accurately describes all profile features may provide a tool to examine associations between detailed features and cow fertility.

The objective of the current work was to develop a simple compartmental model that is specific to the bovine oestrous cycle and is capable of accurately describing the dynamic features present in plasma progesterone concentrations. This model also needs to be consistent with the physiological processes controlling the appearance of plasma progesterone concentrations. Accordingly, differences in progesterone appearance and disappearance rates of different shaped progesterone profiles were examined using the newly developed model.

## Materials and Methods

### *Model development*

The compartmental model is described using the differential equation (1):

$$P4^{\bullet}(t) = h(t) \cdot f(t) - L(0,1) \cdot P4(t) \qquad \text{Equation 1}$$

Where $P4^{\bullet}(t)$ is the apparent input of progesterone averaged over a day (progesterone appearance; ng/ml per d)

$P4(t)$ is the measured plasma progesterone concentrations (ng/ml)

$h(t)$ is the appearance modulation function (Equation 2)

$f(t)$ is a polynomial progesterone appearance function (ng/ml per d)

$L(0,1)$ is the rate of progesterone disappearance (arbitrary units/d)

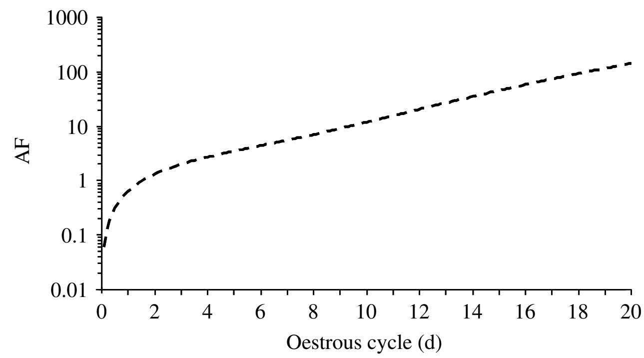


**Fig. 1.** Appearance function (AF) is a function in time, which when multiplied by the appearance modulating function gives the progesterone appearance rate (ng/ml per d).

The appearance function (AF) is a function in time (Fig. 1) which when multiplied by the appearance modulating function (AMF) provides the progesterone appearance rate (ng/ml per d). AMF is a weighted function in time applied to the appearance function, allowing automatic detection of a decline in appearance rate, and permitting the smooth, automated cessation of progesterone appearance in the model. AMF consists of three phases: Phase 1, where appearance is not affected by the modulating function; Phase 2, the onset of decline in progesterone appearance (automatically detected at the time of peak plasma progesterone), and Phase 3, where progesterone appearance stops.

$$h(t) = 1 \quad \text{if } t \leqslant \tau - \tau/\rho$$
$$= (3 - \rho \cdot t/\tau)/2 \quad \text{if } \tau - \tau/\rho < t < \tau + \tau/\rho \qquad \text{Equation 2}$$

where $\tau$ may be viewed as the apparent secretion duration (d) and $\rho$ is the speed with which termination of appearance occurs (Equation 2), and is defined as the half-time taken for the secretion of progesterone to stop (Fig. 2).

The fit of the AF was tested by increasing the order of the polynomial equation (linear to quartic). Both cubic and quartic models produced excellent fits to the plasma progesterone profiles (Fig. 3). Based on the consistency of the fits the quartic model was chosen as it was able to describe the general shape of all the progesterone profiles examined, and it accurately describes the initial upward slope during the early luteal phase of the oestrous cycle (Fig. 4).

The assumptions inherent in the model were that:

(1) The disposition of progesterone is linear ($L(0,1)$; Reinecke & Deuflhard, 2007).
(2) Secretion of progesterone ceases when the progesterone profile is declining (apparent secretion duration).

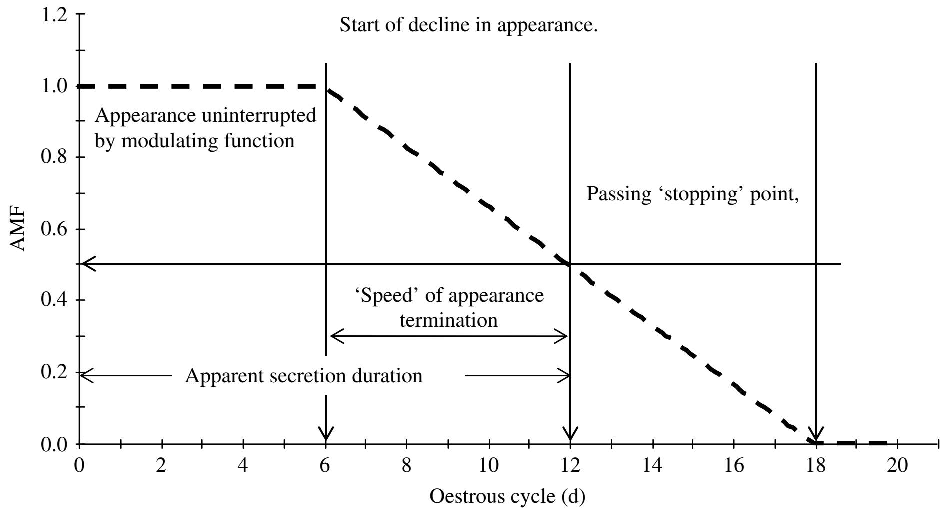


**Fig. 2.** The appearance modulating function (AMF) is a weighted function in time applied to the appearance function, allowing automatic detection of a decline in appearance rate, and permitting the smooth, automated cessation of progesterone appearance in the model. The AMF consists of three phases: Phase 1, where appearance is not affected by the modulating function; Phase 2, the onset of decline in progesterone appearance (automatically detected at the time of peak plasma progesterone), and Phase 3, where progesterone appearance stops.

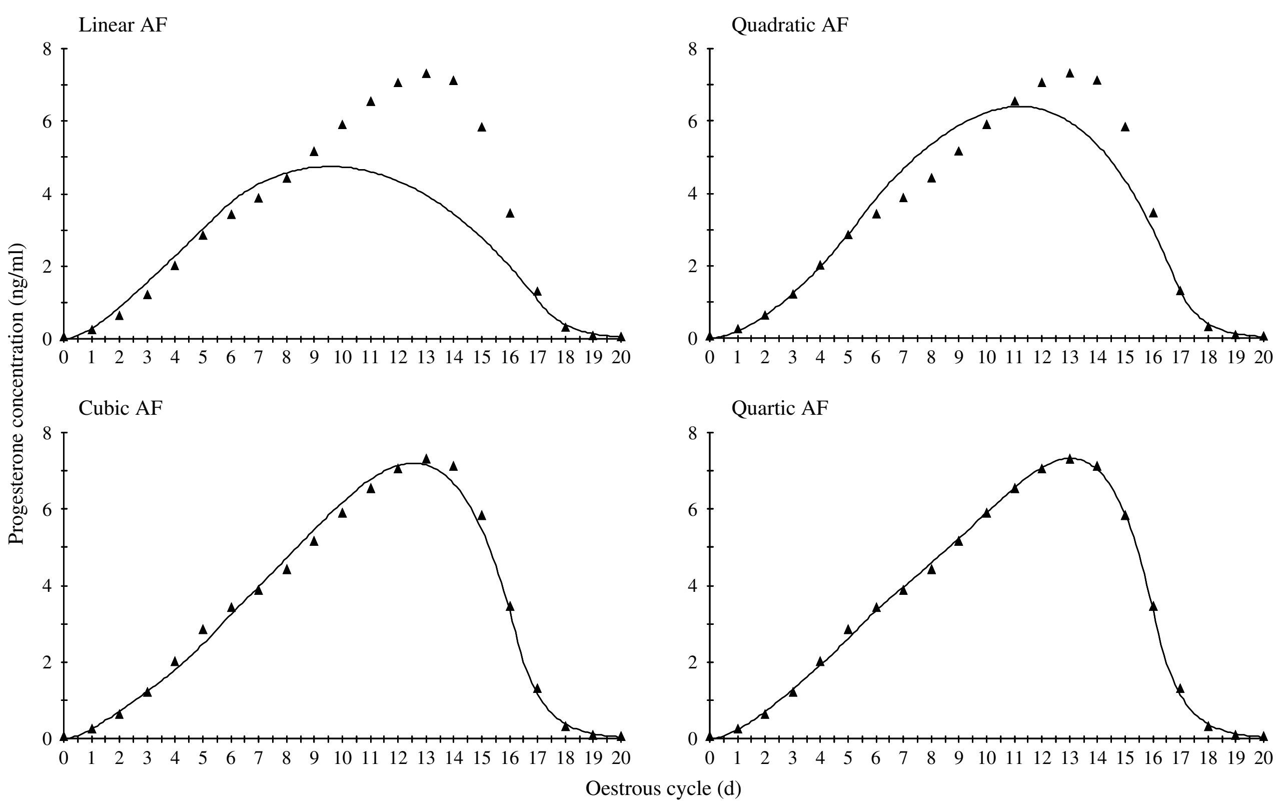


**Fig. 3.** Observed (▲) and predicted (solid line) plasma progesterone concentrations to progressively higher order appearance function (AF) models for a typical cow's progesterone profile.

This constitutes an empirical parametric attempt to quantify the secretion without venturing into the complex details of the actual secretory process.

(3) The space within which the progesterone mixes does not change appreciably in size for the duration of the progesterone cycle. This latter assumption is

https://doi.org/10.1017/S0022029909003987 Published online by Cambridge University Press

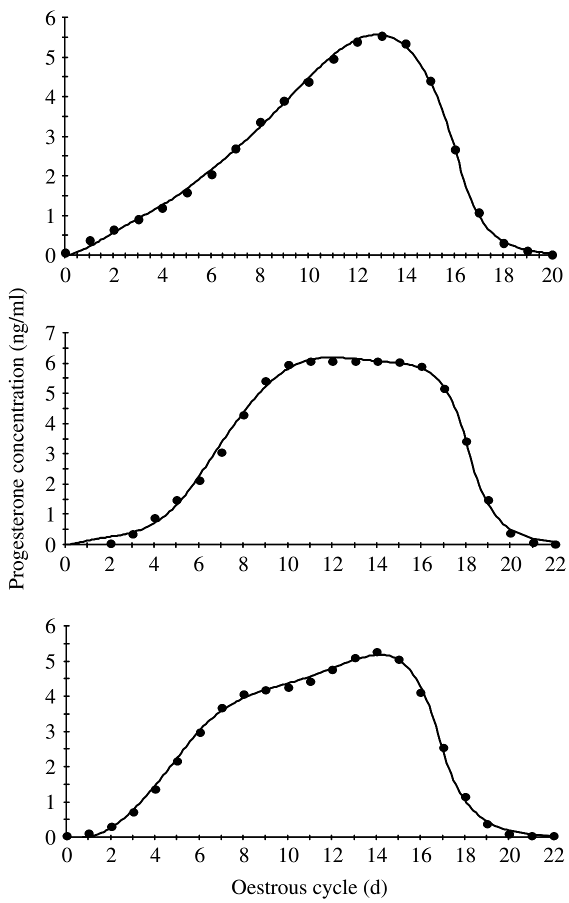


**Fig. 4.** Model outputs (solid line) fitted to observed (●) progesterone profiles for three dairy cows with distinctly different progesterone profiles. The shapes are referred to as; 'peaked' (upper panel), 'flat top' (middle panel), and 'structured' (lower panel).

ubiquitous in kinetic investigations of concentration data, where the size of the distribution space is unknown (Bergman et al. 1979; Wagner et al. 1989).

(4) Errors in a simple linear secretory profile can be explained in terms of expanded powers of secretion duration (Bogumil et al. 1972).

Although the actual progesterone secretion process is complex, mathematical analyses of 'nonlinear' systems have shown that an acceptable alternative representation of advanced complexity can be managed by 'Taylor' (power) series expansions away from a linear portrayal (Stata 10; Stata Corp LP, 2007).

### *Experimental data*

The experimental data used to develop and evaluate profile shapes were obtained from an experimental study. Briefly, 27 Holstein-Friesian dairy cows (3·8 years old, SED 1·1 years) from two diverse genetic strains (North American and New Zealand) and fed either pasture or a total mixed ration successfully responded to an oestrous synchronization treatment. Average 4% fat-corrected milk yield for these animals was 6703 kg/cow SED 1719 kg/cow for the lactation. Average lactation length was 276 d (SED 23·0 d).

A synchronization protocol was initiated at 25–30 d post calving, using a controlled intra-vaginal drug-release device containing 1·38 g progesterone (CIDR-B™ Pfizer Animal Health, Auckland, New Zealand) for 8 d and an i.m. injection of 10 µg of a GnRH analogue (Buserelin; Receptal, Intervet Limited, Auckland, New Zealand) on the day of device insertion. All animals received prostaglandin $F_{2\alpha}$ (25 mg dinoprost; Lutalyse, Pfizer Animal Health, Auckland, New Zealand) on the day before CIDR withdrawal and 1 mg oestradiol benzoate (CIDIROL, Bomac Laboratories Limited, Auckland, New Zealand) 24 h after CIDR withdrawal. All animals responded to the synchrony programme and followed to the next spontaneous ovulation at 63 d (SED 7 d) of lactation, with the subsequent oestrous cycle used in this study. All of the experimental oestrous cycles were considered to be normal oestrous cycles with a mean inter-ovulatory interval was 21·9 d (SED 1·7 d), with two waves of follicular growth.

Ovarian structures were monitored using trans-rectal ultrasonography using a 7·5 mHz linear array transducer (Aloka DX210, Medtel, Auckland, New Zealand) for the complete experimental oestrous cycle. Following spontaneous oestrus (day 0 of the oestrous cycle) daily blood samples were collected from the coccygeal vein into evacuated blood tubes (Vaccutainer, Becton & Dickinson, New York, USA) containing sodium heparin, immediately placed in ice water, and centrifuged within 2 h (1500 ***g*** for 12 min). Aspirated plasma fractions were stored at −20 °C. Plasma progesterone concentrations were determined using a commercial radioimmunoassay (Coat-A-Count™, DPC, California, USA). The intra-assay CV at concentrations of 4·3, 3·1 and 0·4 ng/ml were 4·8, 5·9 and 13·4%, respectively. The sensitivity of the assay was <0·1 ng/ml.

### *Identifying profiles: smoothing and cluster analysis*

Resistant non-linear smoothing methods were used to minimize random variation (Gould, 1993) and separate true plasma progesterone profiles from aberrant spikes and troughs in the raw observations. A high correlation between the smoothed and raw progesterone concentrations was achieved ($R^2$=0·93, ranging from 0·87 to 0·98).

Progesterone profiles were separated into common shape-based groups (or clusters) closely following the methodology of Everitt et al. (2001). Data were firstly scaled and then submitted to hierarchical agglomerative clustering using the average linkage procedure. Three unique profile clusters were identified: 'peaked' profiles ($n$=13), with the profile reaching a distinguishable peak, 'structured' profiles ($n$=7), with the profile exhibiting a

**Table 1.** Parameter estimates for the model of progesterone secretion during the oestrous cycle of lactating cows

| Parameters | Mean (SD) | Median | Minimum | Maximum |
|---|---|---|---|---|
| Total progesterone, AUC, ng/ml per cycle† | 69·04 (15·22) | 67·71 | 25·90 | 102·0 |
| Mean appearance rate, ng/ml per d | 3·19 (0·68) | 3·11 | 1·08 | 4·3 |
| Maximum appearance rate, ng/ml | 6·70 (1·31) | 6·66 | 2·71 | 9·3 |
| Apparent appearance duration, d | 11·49 (0·17) | 11·30 | 10·47 | 13·3 |
| Average progesterone disappearance rate, units/d‡ | 1·04 (0·04) | 1·04 | 0·39 | 1·46 |
| AF Linear secretion co-efficient term, *CT1*§ | 0·46 (0·09) | 0·44 | −0·34 | 1·83 |
| AF Quadratic secretion co-efficient term, *CT2*§ | 0·044 (0·041) | 0·047 | −0·381 | 0·442 |
| AF Cubic secretion co-efficient term, *CT3*§ | −0·004 (0·008) | −0·003 | −0·079 | 0·115 |
| AF Quartic secretion co-efficient term, *CT4*§ | 0·0003 (0·0006) | 0·0006 | −0·1060 | 0·0068 |

† Total progesterone calculated as the area-under-the curve (AUC) during the oestrous cycle
‡ Average progesterone disappearance rate is expressed as arbitrary units (units/d)
§ AF = Appearance function

wave-like pattern and 'flat top' profiles ($n=7$), with the profile reaching a plateau.

### *Function fitting and model parameters*

The model was fitted to both the smoothed and raw plasma progesterone data using generalized least squares functions (Stefanovski et al. 2003). Two features of this approach required examination in greater detail: (1) the impact of data smoothing; and (2) the effect of the abruptness parameter setting on the estimates derived from the model fitting process. Smoothing had little effect on model parameters. Therefore, further analyses were carried out using smoothed data.

Parameters defined by the model include total appearance of progesterone (area under the curve, AUC, ng/ml per cycle), mean and peak appearance rate (ng/ml per d), apparent appearance duration (d) and average progesterone disappearance rate (arbitrary unit/d). In addition, four AF coefficients were examined [linear (*CT1*), quadratic (*CT2*), cubic (*CT3*) and quartic (*CT4*)]. The modelling approach deployed describes actual progesterone secretion processes. The terms appearance and disappearance were used to describe the physiological processes that encompass progesterone secretion and metabolism.

### *Statistical analyses*

Model development and data fitting were performed using WinSAAM (Wastney et al. 1999). Comparisons were made statistically using both parametric and non-parametric methods to ensure that the assumptions implicit in parametric tests did not invalidate the results. Bonferonni's adjustments were applied for comparisons where multiple hypotheses were under examination, and corrections for unequal variances were applied when questions arose regarding the homoscedasticity of the variables under examination across treatments. All statistical analyses were performed using Stata 10 (StataCorp LP, 2007).

## Results

Mean apparent appearance duration and AUC for all 27 profiles were 11·49 (SD 0·17) d and 69·04 (SD 15·22) ng/ml per cycle, respectively. Mean daily appearance was 3·19 (SD 0·68) ng/ml per d, the maximum appearance rate was 6·70 (SD 1·31) ng/ml per d and the average disappearance rate was 1·04 (SD 0·04) units/d. The ranges of all these parameters and *CT1*, *CT2*, *CT3*, and *CT4* are summarized in Table 1.

Comparison of the model parameters for the three types of progesterone profiles is presented in Table 2. Apparent appearance duration was greater ($P<0·01$) in the 'flat top' profiles compared to the 'peaked' and 'structured' profiles, with 'structured' profiles greater ($P<0·001$) than the 'peaked' profiles. Appearance rate, total appearance during the oestrous cycle, mean appearance and the maximum appearance rate were not different between the profile types. Progesterone disappearance was similar across all the three profiles, ranging from 1·10 (SD 0·15) units/d in the 'peaked' profiles to 0·90 (SD 0·28) units/d for the 'structured' and 1·04 (SD 0·15) units/d for the 'flat top' profiles.

The AF linear secretion coefficient (*CT1*) term was greater ($P<0·05$) and the *CT*2 term smaller ($P<0·05$) for the 'peaked' compared with the 'structured' profiles. The *CT*2 and *CT4* terms were greater ($P<0·01$) for the 'structured' compared with 'flat top' profiles, with the *CT3* term greater ($P<0·01$) for the 'flat top' compared with 'structured' profiles. The AF coefficients for each profile are summarized in Table 2.

## Discussion

The present model successfully described all components of the bovine progesterone profile, accurately fitting the dynamic features during all stages of the oestrous cycle. The model used two functions: an appearance function and a weighted appearance modulating function. These functions allow the reduction in progesterone appearance

**Table 2.** Parameter estimates for a progesterone secretion model and the appearance function (AF) co-efficient terms for different shapes of progesterone profiles (peaked, structures and flat top). Values presented are means (SD)

| Parameter | Profile | | | *P* values ‡ | | |
|---|---|---|---|---|---|---|
| | Peaked | Structured | Flat top | CS1 | CS2 | CS3 |
| Profiles, *n* | 13 | 7 | 7 | | | |
| Total progesterone, AUC, ng/ml per cycle† | 67·66 (11·48) | 62·09 (20·32) | 78·54 (12·72) | 0·81 | 0·32 | 0·13 |
| Mean appearance rate, ng/ml per d | 3·30 (0·51) | 2·83 (1·03) | 3·33 (0·48) | 0·39 | 0·96 | 0·45 |
| Maximum appearance rate, ng/ml | 7·18 (1·04) | 5·91 (1·85) | 6·62 (0·77) | 0·11 | 0·73 | 0·64 |
| Apparent appearance duration, d | 10·80 (0·30) | 11·77 (0·66) | 12·54 (0·41) | <0·001 | <0·001 | <0·01 |
| Average progesterone disappearance rate, units/d‡ | 1·10 (0·15) | 0·90 (0·28) | 1·04 (0·12) | 0·13 | 0·90 | 0·59 |
| AF Linear secretion coefficient term, *CT1* | 0·60 (0·501) | 0·02 (0·372) | 0·58 (0·291) | <0·05 | 0·99 | 0·09 |
| AF Quadratic secretion coefficient term, *CT2* | 0·012 (0·176) | 0·247 (0·196) | 0·070 (0·172) | <0·05 | 0·99 | <0·01 |
| AF Cubic secretion coefficient term, *CT3* | −0·003 (0·0241) | −0·376 (0·0327) | 0·024 (0·0463) | 0·14 | 0·29 | <0·01 |
| AF Quartic secretion coefficient term, *CT4* | 0·0007 (0·0011) | 0·0024 (0·0024) | 0·0028 (0·0042) | 0·60 | 0·06 | <0·01 |

† Average progesterone disappearance rate is expressed as arbitrary units (units/d)
‡ Comparisons between different profile groups are: CS1 = peak *v.* structured, CS2 = peak *v.* flat top, CS3 = structured *v.* flat top

to be detected automatically, thereby permitting the smooth disappearance of progesterone. This feature ensures that the model is highly accurate in predicting progesterone during luteal regression, a significant improvement to the model described by Yenikoye et al. (1981), which was unable to estimate the changes in progesterone during the latter stages of the oestrous cycle. The model used a known approach for estimating the input function, where rate of progesterone appearance (input function) equalled the appearance function multiplied by the appearance modulating function (Dalla Man et al. 2002; Macdonald & Tuncer, 2007). The current model has been developed specifically for the bovine oestrous cycle, and although less complex than those models developed to describe the human menstrual cycle (Bogumil et al. 1972; Harris Clark et al. 2003; Reinecke & Deuflhard, 2007), the current model is able to model different progesterone shapes. In addition, the current model provides parameters that describe both progesterone secretion (the appearance rate) and metabolism (the disappearance rate).

As previously reported, three different shaped profiles, each unique with regard to the timing of luteolysis and the clearance of progesterone during the latter stages of the oestrous cycle, have been identified from a population of normal profiles (Meier et al. 2009). The model described here was able to accurately predict the different profile shapes and quantify differences in appearance duration between profiles. These differences in appearance duration corresponded with the previously reported differences in luteal phase length (Meier et al. 2009). Interestingly, the reported differences in luteal function associated with the profile shapes were not associated with differences in the number of follicle waves, as all oestrous cycles consisted of only 2-waves of follicular development (Meier et al. 2009). Differences in the length of the luteal phase and the duration of progesterone appearance are important findings, providing evidence of diverse profile types within an otherwise normal population.

Length of the luteal phase, the duration of progesterone appearance and disappearance are involved in determining oestrous cycle length. Conception rate has been reported to decrease when cycle length increases (Cushman et al. 2007) implying that cows with shorter oestrous cycle have improved fertility compared with their counterparts with extended oestrous cycles. However, taking into account the number of waves of follicular growth, the longer 3-wave oestrous cycles have greater conception rates compared with the shorter 2-wave oestrous cycles (Townson et al. 2002). The effect of oestrous cycle length on conception rate may therefore be confounded by the number of follicle waves, possibly through the negative association between age of the follicle and fertility (Roche et al. 1999; Inskeep, 2004). Within the current study, the number of follicular waves was uniform; the physiological mechanisms determining the progesterone appearance duration and the clearance of progesterone (as represented by the different appearance functions) remain unknown.

The model estimates of average rate of progesterone disappearance ranged from 0·39 to 1·46 units/d across the 27 profiles, and although the duration of progesterone appearance and the appearance function were different for the different profile shapes, the average disappearance rate was not different. However, the observed variations in disappearance rates indicate that the model has the potential to describe progesterone metabolism. With further validation, this model may help researchers examine how progesterone metabolism alters the progesterone profiles and subsequent reproduction of lactating cows. Progesterone metabolism and clearance is an area of increasing interest, as high steroid metabolism results in sub-optimal progesterone concentration, and probably contributes to the lower fertility of high-yielding cows

(Wiltbank et al. 2006). Increased dry matter intake associated with greater milk yield leads to increased liver blood flow, and consequently results in increased progesterone metabolism (Rabiee et al. 2001; Sangsritavong et al. 2002). Owing to the technical difficulties associated with accurately measuring progesterone metabolism and clearance, a model able to provide an estimate of progesterone metabolism and clearance may help in advancing our understanding of progesterone metabolism, progesterone profiles, and fertility. In future, the ability to describe and predict profile shapes may be a useful tool to investigate the effect of diet, lactation and management on progesterone metabolism.

When combined with in-line technologies that allow for real-time progesterone measurements (Claycomb & Delwiche, 1998; Delwiche et al. 2001), a model able to predict progesterone profiles and which allows for the evaluation of reproductive status will enhance models currently available (Friggins & Changunda, 2005). To achieve these outcomes, further validation of both plasma and milk progesterone profiles and their associations with reproductive parameters (conception or pregnancy rates) is needed. Development of these tools may result in increased reproductive efficiencies, as reproductive irregularities can be identified and timely reproductive management decisions made.

## Conclusion

The mathematical model presented was able to define the complete progesterone profile during the bovine oestrous cycle, and predict progesterone appearance and disappearance rates for three different shaped progesterone profiles. This model may be a practical tool in the future to investigate differences in progesterone appearance and metabolism, and their association with fertility.

The authors acknowledge the help of both farm and technical staff involved in the collection of samples and laboratory analyses. This research was supported by funding from DairyNZ Inc. (New Zealand) and the Foundation for Research, Science and Technology (New Zealand, DRCX0202).

## References

**Bergman RN, Ider YZ, Bowden CR & Cobelli C** 1979 Quantitiative estimation of insulin sensitivity. *American Journal of Physiology* **236** E667–E677

**Bogumil RJ, Ferin M, Rootenberg J, Speroff L & WandeWiele RL** 1972 Mathematical studies on the human menstrual cycle. I Formulation of a Mathematical Model. *Jouranl of Clinical Endocrinology and Metabolism* **35** 126–143

**Claycomb RW & Delwiche MJ** 1998 Biosensor for on-line measurement of bovine progesterone during milking. *Biosensors and Bioelectronics* **13** 1173–1180

**Cooperative Regional Research Project NE-161** 1996 Relationship of fertility to patterns of ovarian follicular development and associated hormonal profiles in dairy cows and heifers. *Journal of Animal Science* **74** 1943–1952

**Cushman RA, Allan MF, Thallman RM & Cundiff LV** 2007 Characterisation of biological types of cattle (Cycle VII): Influence of postpartum interval and oestrous cycle length on fertility. *Journal of Animal Science* **85** 2156–2162

**Cutler DJ** 1978 Numerical deconvolution by least squares: use of prescribed input functions. *Journal of Pharmacokinetics and Biopharmacology* **6** 227–241

**Dalla Man C, Caumo A & Cobelli C** 2002 The oral glucose minimal model: estimation of insulin sensitivity from a meal test. *IEEE Transactions on Biomedical Engineering* **49** 419–429

**Delwiche MJ, Tang X, BonDurant RH & Munro CJ** 2001 Improved biosensor for measurement of progesterone in bovine milk. *Transactions of the American Society of Agricultural Engineers* **44** 1997–2002

**Everitt BS, Landau S & Leese M** 2001 *Cluster Analysis, 4th Edition* Oxford University Press, USA: A Hodder Arnold Publication

**Friggens NC & Chagunda MG** 2005 Prediction of the reproductive status of cattle on the basis of milk progesterone measures: model description. *Theriogenology* **64** 155–190

**Gould W** 1993 Resistant nonlinear smoothing using Stata. *Stata Technical Bulletin Reprints* **ST7–ST12** 104–107

**Harris Clark LA, Schlosser EC & Selgrade JF** 2003 Multiple stable periodic solutions in e model for hormonal control of the menstrual cycle. *Bulletin of Mathematical Biology* **65** 157–173

**Inskeep EK** 2004 Preovulatory, postovulatory, and postmaternal recognition effects of concentrations of progesterone on embryo survival in the cow. *Journal of Animal Science* **82** (**E.Suppl.**) E24–E39

**Macdonald JR & Tuncer E** 2007 Deconvolution of immitance data: some old and new methods. *Journal of Electroanalytical Chemistry* **602** 255–262

**Mann GE & Lamming GE** 2001 Relationship between maternal endocrine environment, early embryo development and inhibition of the luteolytic mechanism in cows. *Reproduction* **121** 175–180

**McNeill RE, Diskin MG, Sreenan JM & Morris DG** 2006 Association between milk progesterone concentrations on different days and with embryo survival during the early luteal phase in dairy cows. *Theriogenology* **65** 1435–1441

**Meier S, Roche JR, Kolver ES, Verkerk GA & Boston RC** 2009 Comparing sub-populations of plasma progesterone using cluster analysis. *Journal of Dairy Science* In press

**Rabiee AR, Macmillan KL & Schwarzenberger F** 2001 The effect of level of feed intake on progesterone clearance rate by measuring faecal progesterone metabolites in grazing dairy cows. *Animal Reproduction Science* **67** 205–214

**Reinecke I & Deuflhard P** 2007 A Complex mathematical model of the human menstrual cycle. *Journal of Theoretical Biology* **247** 303–330

**Roche JF, Austin EJ, Ryan M, O'Rourke M, Mihm M & Diskin MG** 1999 Regulation of follicle waves to maximise fertility in cattle. *Journal of Reproduction and Fertility* **54** (**Suppl.**) 61–71

**Sangsritavong S, Combs DK, Sartori R, Armentano LE & Wiltbank MC** 2002 High feed intake increases liver blood flow and metabolism of progesterone and oestradiol-17beta in dairy cattle. *Journal of Dairy Science* **85** 2831–2842

**Stata 10** 2007 StataCorp LP, College Station, Texas 77845, USA

**Stefanovski D, Moate PJ & Boston RC** 2003 WinSAAM: a windows-based compartmental modeling system. *Metabolism* **52** 1153–1166

**Strong AJ, Sreenan JM, Diskin MG, Mee JF, Kenny DA & Morris DG** 2005 Post-insemination milk progesterone concentrations and embryo survival in dairy cows. *Theriogenology* **64** 1212–1224

**Townson DH, Tsang PCW, Butler WR, Frajblat M, Griel Jr LC, Johnson CJ, Milvae RA, Niksic GM & Pate JL** 2002 Relationship of fertility to ovarian follicular waves before breeding in dairy cows. *Journal of Animal Science* **80** 1053–1058

**Wagner JG, Wilkinson PK & Ganes DA** 1989 Parameters Vm and Km for elimination of alcohol in young males subjects following low doses of alcohol. *Alcohol and Alcoholism* **24** 555–564

**Wastney ME, Patterson BH, Linares OH, Greif PC & Boston RC** 1999 *Investigating Biological Systems Using Modeling: Strategies and Software*. New York, USA: Academic Press

**Wiltbank M, Lopez H, Sartori R, Sangsritavong S & Gumen A** 2006 Changes in reproductive physiology of lactating dairy cows due to elevated steroid metabolism. *Theriogenology* **65** 17–29

**Yenikoye A, Mariana JC, Ley JP, Jolivet E, Terqui M & Lemon-Resplandy M** 1981 Mathematical model on the development of progesterone in the cow: application and proof of differences between breeds. *Reproduction, Nutrition and Development* **21** 561–575