Evaluation of models for somatic cell score lactation patterns in Holsteins

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Abstract

Milk somatic cell score (SCS) typically reaches a minimum early in lactation and then rises. Nonlinear mixed effects models were used to describe this trajectory while accounting for between and within-cow variation. A total of 2387 SCS records from 217 Holsteins were analyzed. Four nonlinear and two linear functions were studied. Approximate maximum likelihood estimates indicated that cows free of intramammary infection had sharper SCS decreases after calving, and lower overall levels. Lactations starting between October and December had the highest fall of SCS levels at the beginning of lactation, and the smallest increases thereafter. In general, there was significant variation between cows’ individual trajectories. For some parameters and models, however, this variation was small. A four-parameter model suggested by Morant and Gnanasakthy was supported better by the data than the other five functional forms. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Longitudinal data; Maximum likelihood; Nonlinear mixed effects models; Mastitis

1. Introduction

Mastitis is an udder health disorder that causes substantial economic losses to the dairy industry (Shook, 1989). This inflammation of the mammary gland, usually in response to invasive agents, can be characterized by an increase in the somatic cell count (SCC) in milk. This trait or a logarithmic transform, called somatic cell score (SCS), is used as an indicator of udder health status for management and selection purposes.

After the beginning of lactation, SCS decreases to a minimum at around 60 days post-calving and increases thereafter (Wiggans and Shook, 1987). Variation in the shape and level of the SCS pattern is related to lactation number (Wiggans and Shook, 1987), to udder infection status (Sheldrake et al., 1983) and to individual cows. Heritability estimates of test-day SCS range between 0.07 and 0.44 (Ali and Shook, 1980; Kennedy et al., 1982; Emanuelson and Philipsson, 1984; Gadini et al., 1996). Monardes and Hayes (1985) reported repeatability estimates of test-day SCS of 0.36–0.42 across parities, and repeatability within lactations ranged from 0.47 to

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0.59 (Emanuelson and Persson, 1984). These results suggest the need to consider both the variation within and between cows for an adequate modeling of SCS trends. Further, an important fraction of the variation seems to be related to genetic factors.

Lactation average SCS measures are used currently in some national genetic evaluation schemes, the objective being to lower the prevalence of mastitis by indirect selection for SCC. This approach does not use all the information and masks short-term variation in SCS (Shook and Schutz, 1994; Emanuelson, 1997). Test-day somatic cell records are taken on the same cow at various times, providing longitudinal information that can be related more meaningfully to episodes of infection. A statistical model for longitudinal data may provide more accurate estimates of the influence of risk factors than lactation average models. This additional information should be beneficial in the study of a trait with seemingly low heritability, such as SCS.

A reasonable model for describing SCS variation during lactation must consider the ‘typical’ lactation pattern and allow for differences associated with explanatory variables (e.g. age of cow) and with the individual cows themselves. Nonlinear mathematical functions are natural candidates for describing SCS lactation patterns, and their parameters can be modeled to account for known sources of variation. Estimates of these parameters can be used for management and breeding purposes to the extent that at least some of the variation detected is heritable.

The main objective of this study was to explore the feasibility of nonlinear mixed effects models to describe the SCS lactation curves. Another objective was to compare the fit of four nonlinear models and two linear models when applied to SCS lactation records in Holstein cows. An approximate maximum likelihood analysis was used for these purposes.

2. Materials and methods

2.1. Data

The Ohio Agricultural Research and Development Center (Wooster) provided the SCC data used. After edits, the data consisted of 2387 test-day observations from 217 first to third lactation Holstein cows recorded between July 1982 and June 1989. The herd was maintained free of Streptococcus agalactiae, and less than 1% of the quarters were infected with Staphylococcus aureus at any one time (Todhunter et al., 1991). The bacteriological status was assessed by 0.01 ml of milk streaked onto the surface of a 0.25 plate of Trypticase soy agar containing 5% whole bovine blood and esculin (Smith et al., 1985). Forty-five percent of the test-day observations were negative for IMI. The two most common pathogens were Staphylococcus spp. (excluding Staphylococcus aureus) and Corynebacterium spp. (31 and 15% of the observations, respectively). Approximately 10% of the observations were associated with clinical mastitis symptoms. A description of the herd management-health practices is in Smith et al. (1985) and Todhunter et al. (1991). Milk samples were taken on each cow at 14 and 30 days in lactation, and every 30 days thereafter until the end of lactation or 300 days in milk, whichever occurred first. Each milk sample was tested for presence of pathogens and SCC was assessed electronically using a Coulter Counter. Here: \( \text{SCS} = 3 + \log_2(\text{SCC}/100) \) where SCC is in cells/\( \mu \)l.

A binary variable describing intramammary infection status (IMI) was created for each cow-lactation. A single positive pathogen isolation (e.g. bacteria, yeast) during lactation was enough to code IMI as ‘one’; otherwise, it was coded as zero. Most cow-lactations that were free of infection early in lactation (91% of all cow-lactations) remained so until the end of lactation. Similarly, most cows that were culture-positive after calving remained positive in subsequent test-days (84%). Roughly the same number of cows was positive for IMI at every test day with values ranging between 107 cows at 14 days and 128 cows at 300 days. The majority of the cows positive for IMI at one test-day were positive in subsequent test-days. Eight percent of all the lactations had one, two or three infection episodes. Obviously, a single measure of IMI status does not capture the dynamics of infection in the course of lactation and does not differentiate between a cow positive for pathogen isolation at 30 days, and one being positive at the last 3 test-days. This way of coding IMI is time independent however, and can be permitted to be included as a covariate for the parameters at the second stage of a model and to be
evaluated as modulator of the SCS trends. Better forms of modelling SCS pattern may include test-day IMI status. Alternative ways of accounting for the dynamics of IMI infection during lactation are considered in Section 4.

The calvings in 1983, 1984 and 1985 were grouped in period 1; calvings in 1986 and 1987 were in period 2, and period 3 included 1988 and 1989 calvings. Months of calving were grouped into four seasons: season 1 included calvings from January 1 through March 31, and so on. Lactations were coded as first, second or third. To be included in the data set, cows in a given lactation needed to have records in the preceding ones. However, there were animals with first lactations without second lactations, etc.

2.2. Statistical procedures

The nonlinear mixed effects models used here can be represented with two equations:

\[ y_i = f_i(\theta_i) + e_i \quad (1) \]

\[ \theta_i = X_i\beta + Z_i b_i. \quad (2) \]

Eq. (1) describes how the longitudinal data are generated given a nonlinear function \( f_i(\theta_i) \). Here, \( y_i \) is an \( n_i \times 1 \) vector of test-day SCS of the \( i \)th cow \( (y = [y_1, y_2, \ldots, y_{n_i}]') \) and \( M \) is the number of cows; \( \theta_i \) is an \( r \times 1 \) vector of parameters peculiar to the \( i \)th cow; \( f_i(\theta_i) \) is an \( n_i \times 1 \) vector of expected values (given \( \theta_i \)) of scores of cow \( i \) and \( e_i \) is an \( n_i \times 1 \) vector of residuals. The second equation expresses how the parameters \( \theta_i \) vary according to explanatory variables \( \beta \) (fixed) and \( b_i \) (random). In (2) \( X_i \) is an \( r \times p \) incidence matrix relating fixed effects (\( p = \) number of uniquely estimable fixed effects) to \( \theta_i \); \( \beta \) is a \( p \times 1 \) vector of fixed effects affecting \( \theta_i \); \( Z_i \) is an incidence matrix of appropriate order relating the random effects \( b_i \) \( (r \times 1) \) to \( \theta_i \). Note that each cow has an effect on each of the \( \theta_i \) parameters so (1) and (2) embed a multivariate structure within a univariate longitudinal model.

Random variables in (1) and (2) are the cow effects \( b_i \sim \text{NIID} (0, \Sigma) \) and \( e_i \sim N(0, \sigma^2 I_{n_i}) \), where NIID denotes normal, independent and identically distributed. An analysis of these models in a Bayesian Markov chain Monte Carlo framework indicated that the normality assumption was adequate (Rodriguez-Zas, 1998). The cow effects represent a combination of genetic and permanent environmental effects, and these were assumed to be independent from the residuals. Although cow effects were assumed to be independent, this assumption can be relaxed; the independence assumption was used in view of the sparse structure of the genetic relationship matrix between cows. The matrix \( \Sigma \) is a positive-definite matrix containing variances and covariances of cow effects on parameters and \( \sigma^2 \) is the residual variance. Hence, conditionally on the cow effects, the observations had a Gaussian distribution with mean \( f_i(\theta_i) \) and unknown, homoscedastic, variance \( \sigma^2 \). The assumption of constant residual variance was made following Shook (1982).

A preliminary time series analysis gave no indication of violation of the assumption of lack of correlation between residuals within cows.

2.3. Approximate maximum likelihood estimation

The unknown parameters \( (\beta, \Sigma, \sigma^2) \) were estimated by maximizing an approximation to the likelihood function. The joint density of all observations, conditionally on the random effects is:

\[ p(y | \beta, b, \sigma^2) = \prod_{i=1}^{M} p(y_i | \beta, b_i, \sigma^2) \]

with

\[ y_i | \beta, b_i, \sigma^2 \sim N(f_i(\beta, b_i), \sigma^2 I_{n_i}). \quad (3) \]

The marginal density of \( y \) results from integrating over \( R_b \), the sampling space of the random effects:

\[ p(y | \beta, \Sigma, \sigma^2) = \int_{R_b} p(y | \beta, b, \Sigma, \sigma^2) p(b | \Sigma) \, db \quad (4) \]

where \( p(b | \Sigma) \) is the density of the sampling distribution of the random effects. These effects were assumed to be independent, thus \( p(b | \Sigma) = \prod_{i=1}^{M} p(b_i | \Sigma) \). The required integration is complex because of the nonlinear relation between the observations and the random effects. The residual or restricted likelihood obtained after integration of \( \beta \) and \( b \), can be represented as:
\[
\ell(\Sigma, \sigma^2|y) = (2\pi)^{-NM/2}|R|^{-1/2}\left|\Sigma + \frac{1}{2}R^{-1}(y - f(\beta, b))\right|^{-1/2}
\]

\[
\cdot \int \exp\left\{ -\frac{1}{2} \left[ y - f(\beta, b) \right] \left[ \Sigma + \frac{1}{2}R^{-1}(y - f(\beta, b)) \right] + b'(I \otimes \Sigma)^{-1}b \right\} db \partial \beta
\]  

(5)

where \( N = \sum_{i=1}^{M} n_i, R = I \sigma^2 \) in the present study and \( f(\beta, b) = \{f(\beta, b_i)\} \) is the conditional expectation (given \( \beta \) and \( b \)) of the observations. The integration in Eq. (5) cannot be done analytically (due to nonlinearity), a Laplacian approximation proposed by Wolfinger (1993) and Wolfinger and Lin (1997) was used. At a given value of \( \Sigma \) and \( \sigma^2 \), the Laplacian approach consists in approximating the integral in (5) with a second-order Taylor series expansion centered at the mode of the maximizers \( \hat{\beta} \) and \( \hat{b} \) of the ‘penalized log likelihood’:

\[
- \frac{1}{2} [y - f(\beta, b)]' R^{-1} [y - f(\beta, b)] + b'(I \otimes \Sigma)^{-1}b.
\]  

(6)

Letting \( \hat{X} = \partial f(\beta, b)/\partial \beta \) and \( \hat{Z} = \partial f(\beta, b)/\partial b \) and using Fisher’s method of scoring to locate the mode leads to the iterative system:

\[
\begin{bmatrix}
\hat{X}'R^{-1}\hat{X} & \hat{X}'R^{-1}\hat{Z} \\
\hat{Z}'R^{-1}\hat{X} & \hat{Z}'R^{-1}\hat{Z} + \Omega^{-1}
\end{bmatrix}^{[t+1]}
\begin{bmatrix}
\beta \\
b
\end{bmatrix}^{[t+1]}

= \begin{bmatrix}
\hat{X}'R^{-1}y^* \\
\hat{Z}'R^{-1}y^*
\end{bmatrix}^{[t]}
\]  

(7)

Here, \( t \) denotes iteration number, \( \Omega^{-1} = I \otimes \Sigma^{-1} \) and \( y^* = y - f(\hat{\beta}, \hat{b}) + \hat{X}\hat{\beta} + \hat{Z}\hat{b} \) is a pseudo-data vector. The matrices \( \hat{X}, \hat{Z} \) and the vector \( y^* \) need to be evaluated at each iteration, starting from an arbitrary \( \beta_0 \) and \( b_0 \).

Given \( \Sigma \) and \( \sigma^2 \), the inverse of the coefficient matrix of (7) evaluated at \( \hat{\beta} \) and \( \hat{b} \) gives, approximately, the variance-covariance matrix of the estimates of fixed effects and of the prediction errors of the random effects \( b \). Maximizing the penalized log likelihood (6) gives the same estimating equations obtained by Gianola and Kachman (1983) and Kachman (1985) in a Bayesian setting with flat priors for \( \beta \) and known variance components. With the new values of \( \beta \) and \( b \) model (1) can be linearized as:

\[
y = f(\beta, \hat{b}) + \hat{X}(\beta - \hat{\beta}) + \hat{Z}(b - \hat{b}) + e,
\]  

(8)

or equivalently

\[
y^* = y - f(\hat{\beta}, \hat{b}) + \hat{X}\hat{\beta} + \hat{Z}\hat{b} = \hat{X}\beta + \hat{Z}b + e_5.
\]  

(9)

It then follows that, approximately, the marginal distribution of the pseudo-data vector is:

\[
y^* \sim N(\hat{X}\beta, \hat{V})
\]  

(10)

where \( \hat{V} = \hat{Z}(I \otimes \Sigma)\hat{Z}' + I \sigma^2 \) (Wolfinger and Lin, 1997). Then the restricted or residual log-likelihood (based on \( y^* \)) is approximately:

\[
\ell(\Sigma, \sigma^2|y^*) = \text{constant} - \frac{1}{2} \log|\hat{X}'\hat{V}^{-1}\hat{X}| - \frac{1}{2} \log|\hat{V}|
\]

\[
- \frac{1}{2}(y^* - \hat{X}\beta)'\hat{V}^{-1}(y^* - \hat{X}\beta).
\]  

(11)

This has the same form as the log-restricted likelihood for a linear mixed effects model, so any standard REML algorithm can be applied to obtain new values of \( \Sigma \) and \( \sigma^2 \). The process iterates between the maximum penalized likelihood step (7) and the REML search (11). Whenever (1) is linear in the parameters, (7) leads to BLUP and (11) is exactly the restricted log-likelihood. The standard errors of the estimates of the variance components can be computed from the inverse of the estimated information matrix. To assess whether a random effect should be removed from the model a likelihood-ratio test was used. Computations were carried out with SAS 6.11 (SAS Institute Inc., 1996).

2.4. Models describing SCS trajectory

The nonlinear functions represented by (1) used to describe SCS lactation patterns were:

1. Wood’s (1967) equation (W):

\[
y_{ij} = a(t_{ij})^b \exp(-dt_{ij}) + e_{ij}
\]  

(12)

where \( y_{ij} \) and \( t_{ij} \) are the SCS and test-day, respectively, of observation \( j \) taken on cow \( i \). The parameters are: \( a \), associated to SCS level at the beginning of lactation; \( b \), a declining slope parameter, and \( d \) an increasing slope parameter.

2. An inverse quadratic (IQ) model studied by Nelder (1966) and Ratkowsky (1990). Its form is:
\[ y_{ij} = [t_{ij}(a + bt_{ij} + dt_{ij}^2)] + e_{ij}. \] (13)

Parameter \( a \) describes the rate of decrease after calving, \( d \) is the increase on SCS level at the end of lactation and \( b \) is a scale parameter.

3. Mitscherlich’s model with an exponential term (Rook et al., 1993), or ME, can be expressed as:
\[ y_{ij} = [1 - a \exp(bt_{ij})] \exp(-dt_{ij}) + e_{ij}. \] (14)

Parameter \( a \) describes the curve’s scale, \( b \) gives the rate of decrease at early stages of lactation and \( d \) is associated to the rate of increase in SCS observed after a minimum has been reached.

4. Morant and Gnanasakthy (1989), or MG, is the four-parameter model:
\[ y_{ij} = a \exp[b(t_{ij}) + d(t_{ij})^2 + f(t_{ij})] + e_{ij} \] (15)

where \( t_{ij} = (t_{ij} - 150)/100 \). Parameter \( a \) characterizes the expected SCS at day 150 of lactation and \( b \) represents the relative rate at which SCS changes at 150 days of lactation (% per day). Parameter \( d \) measures the extent to which the rate of increase in SCS changes during lactation and \( f \) is related to the rate of decrease in SCS early in lactation.

5. Ali and Schaeffer (1987) proposed the five-parameter model (AS):
\[ y_{ij} = b_0 + b_1(t_{ij}/300) + b_2(t_{ij}/300)^2 \\
+ b_3 \log(300/t_{ij}) + b_4 \log[\log(300/t_{ij})]^2 + e_{ij}. \] (16)

The \( b \) parameters do not have a mechanistic interpretation although the second and third terms are related to the rate of increase of SCS at mid and late lactation, and the fourth and fifth parameters describe the fall at the beginning of the lactation.

6. Wilmink’s (1987) model (WI) was included in the study. The three-parameter model was:
\[ y_{ij} = a_0 + a_1 t_{ij} + a_2 \exp(-0.05 t_{ij}) + e_{ij}. \] (17)

Actually, this is a four-parameter model, the fourth one being set equal to \(-0.05\) to improve numerical behavior. Parameter \( a_0 \) is associated with a baseline level of SCS, \( a_1 \) with the increase in SCS after a minimum is achieved in the course of lactation and \( a_2 \) with the decrease after calving.

The constant \(-0.05\) is related to the time at minimum SCS, expected to occur at about 50 days post-partum. Linear mixed effects model methodology was used to analyze AS and WI models, because these are linear in the parameters. In all the models considered (linear and nonlinear), the parameters at the second stage have a varying degree of collinearity.

2.5. Models for describing parameter variation

Parameters for each of the six models were described as a linear combination of fixed effects and of random effects peculiar to each cow. The full model had the form:
\[ \theta_{ijklm} = \mu + \text{IMI}_i + P_j + S_k + L_l + \beta_{ijklm} A_{ijklm} + b_m \] (18)

where \( \theta_{ijklm} \) is a parameter (of any of the models); \( \mu \) is a constant; \( \text{IMI}_i \) is a fixed effect of infection status \( i \) \((i = 0, 1)\) during lactation; \( P_j \) is a fixed effect of period of calving \( j \) \((j = 1, 2, 3)\); \( S_k \) is a fixed effect of season of calving \( k \) \((k = 1, 2, 3, 4)\); \( L_l \) is a fixed effect of lactation number \( l \) \((l = 1, 2, 3)\); \( \beta_{ijklm} \) is a regression of the parameter on age at calving for the current lactation and cow; \( A_{ijklm} \) is the age at calving of cow \( m \) with infection status \( i \), calving in period \( j \) and season \( k \) and with lactation number \( l \); \( b_m \) is a random effect peculiar to the appropriate parameter of cow \( m \). Two-factor interactions were not significant. For each model, effects not different from zero \((P<0.01)\), based on likelihood ratios and \(t\)-tests were removed from the model. A strategy based on the eigenvalues of \( \Sigma \) suggested by Pinheiro and Bates (1997) for identifying random effects to be included in the model was used. Results were corroborated using significance tests for dispersion components (Self and Liang, 1987). In theory, the assumption of unrelatedness between cows and of independence between lactations of the same cow leads to underestimation of the asymptotic standard errors of the maximum likelihood estimates. Hence, final models may have more parameters than actually needed. However, the relationship matrix was very sparse (88% of the off-diagonal elements of the relationship matrix were zeroes), so it is unlikely that this is a
serious problem. Comparisons between non-nested models relied on Akaike’s Information Criteria (AIC; Akaike, 1974) and Schwarz’s Bayesian Criterion (BIC; Schwarz, 1978), both of which adjust likelihood ratio tests by the number of parameters in the model. Also, the residual variance was used to compare models.

3. Results

Mean 305-day, mature equivalent milk yield was about 7600 kg. Average SCC and standard deviation was 671,000 and 897,000 cells/ml, respectively. A few cows, with clinical mastitis symptoms, have very high levels of SCS, causing the average to be higher than the values usually associated to minor pathogens. As shown in Table 1, SCS decreased to a nadir at about 60 DIM and then increased, although not in a monotonic fashion, without regaining the initial level. The standard deviation followed an inverse pattern. All parameter estimates subsequently are from the reduced models, as mentioned earlier. In all models, lactation number was not a significant source of variation for any of the parameters.

Estimates from Wood’s model (Table 2) indicate that intramammary infection status affects the two shape parameters (b and d). The a scale parameter was higher in infected animals, but the difference was not significant. This is sensible because the IMI variable pertains to status during and not at the onset of lactation. Animals that had positive pathogen isolations during lactation had a less sharp fall in SCS at the beginning of lactation (positive parameter b estimate when IMI = 1) than cows free of infection throughout lactation. However, infected cows had steeper rates of increase after nadir (positive parameter d estimate when IMI = 1) than non-infected cows. The period of calving affected the shape parameters significantly: cows calving in period 3 (last 3 years of the trial) tended to have larger b and d values than those calving at periods 1 or 2. The between-cow variation was significant for parameters b and d. The variance components cannot be expressed in terms of

![Table 1]

**Table 1**

Average somatic cell score and standard deviation (S.D.) by test-day

<table>
<thead>
<tr>
<th>Days in milk</th>
<th>Mean</th>
<th>S.D.</th>
</tr>
</thead>
<tbody>
<tr>
<td>14</td>
<td>5.425</td>
<td>1.418</td>
</tr>
<tr>
<td>30</td>
<td>4.910</td>
<td>1.519</td>
</tr>
<tr>
<td>60</td>
<td>4.875</td>
<td>1.616</td>
</tr>
<tr>
<td>90</td>
<td>5.096</td>
<td>1.463</td>
</tr>
<tr>
<td>120</td>
<td>5.105</td>
<td>1.295</td>
</tr>
<tr>
<td>150</td>
<td>5.132</td>
<td>1.386</td>
</tr>
<tr>
<td>180</td>
<td>5.264</td>
<td>1.331</td>
</tr>
<tr>
<td>210</td>
<td>5.017</td>
<td>1.274</td>
</tr>
<tr>
<td>240</td>
<td>5.171</td>
<td>1.296</td>
</tr>
<tr>
<td>270</td>
<td>5.163</td>
<td>1.357</td>
</tr>
<tr>
<td>300</td>
<td>5.038</td>
<td>1.374</td>
</tr>
</tbody>
</table>

![Table 2]

**Table 2**

Parameter estimates, asymptotic standard errors (S.E.) and 95% confidence limits (lower, upper), from Wood’s model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>S.E.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_i$</td>
<td>5.668</td>
<td>0.238</td>
<td>5.201</td>
<td>6.314</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>-0.055</td>
<td>0.017</td>
<td>-0.088</td>
<td>-0.023</td>
</tr>
<tr>
<td>$\mu_r$</td>
<td>-3.9×10^{-4}</td>
<td>2.8×10^{-4}</td>
<td>-9.1×10^{-4}</td>
<td>2.2×10^{-4}</td>
</tr>
<tr>
<td>IMI</td>
<td>0.055</td>
<td>0.010</td>
<td>0.035</td>
<td>0.075</td>
</tr>
<tr>
<td>IMI</td>
<td>8.4×10^{-4}</td>
<td>2.3×10^{-5}</td>
<td>4.2×10^{-5}</td>
<td>0.001</td>
</tr>
<tr>
<td>$P_{i1}$</td>
<td>-0.055</td>
<td>0.012</td>
<td>-0.078</td>
<td>-0.032</td>
</tr>
<tr>
<td>$P_{i2}$</td>
<td>-0.035</td>
<td>0.011</td>
<td>-0.065</td>
<td>-0.014</td>
</tr>
<tr>
<td>$P_{i3}$</td>
<td>-0.001</td>
<td>2.7×10^{-4}</td>
<td>-0.002</td>
<td>-9.2×10^{-4}</td>
</tr>
<tr>
<td>$P_{i4}$</td>
<td>-9.4×10^{-4}</td>
<td>2.5×10^{-4}</td>
<td>-0.001</td>
<td>-5.1×10^{-4}</td>
</tr>
<tr>
<td>Var($b$)</td>
<td>0.003</td>
<td>4.0×10^{-3}</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Var($d$)</td>
<td>1.2×10^{-6}</td>
<td>3.8×10^{-6}</td>
<td>7.7×10^{-7}</td>
<td>3.1×10^{-6}</td>
</tr>
<tr>
<td>Cov($b$, $d$)</td>
<td>4.7×10^{-4}</td>
<td>8.6×10^{-6}</td>
<td>2.9×10^{-4}</td>
<td>7.7×10^{-5}</td>
</tr>
<tr>
<td>Var($e$)</td>
<td>1.181</td>
<td>0.038</td>
<td>1.110</td>
<td>1.258</td>
</tr>
</tbody>
</table>

* $\mu_i$, intercept for parameter $i$; IMI, effect of presence of intramammary infection; $P_{ik}$, effect of the k period of calving as a deviation from the third one; Var($i$), between-cow variance for parameter $i$; Cov($i$, $j$), covariance between parameters $i$ and $j$; Var($e$), residual variance.
fractional contribution to the total variance because of the nonlinearity. The residual variance is in the SCS scale (Eq. (1)), whereas the components are expressed at the level of the parameters (Eq. (2)).

The correlation between random effects affecting parameters $b$ and $d$ was about 0.78, suggesting that cows with rapid decline of SCS early in lactation tend to regain levels slowly after nadir.

The presence of intramammary infection affected all three parameters of the IQ model (Table 3). The infected cows had a slower rate of decrease of SCS in early lactation (larger parameter $a$), and a somewhat higher rate of increase in late lactation (positive estimates of parameter $d$) than healthy cows. The SCS curve tended to be `flatter' in the presence of infection (positive estimates of parameter $d$ and negative estimates of parameter $b$ describing the fall and follow up increase in SCS levels, respectively), in agreement with results from Wood’s model. Period affected variation in $b$ and $d$ parameters significantly. Season of calving affected only the scale parameter $b$. Cows calving in seasons 2 and 3 (April–September) had larger $b$ parameter estimates than those calving at other times; this implies that such cows had higher levels of somatic cells when a minimum had been reached. All components of dispersion were significant and the random effects had a strong intercorrelation that could have consequences in selection for specific features of the SCS pattern.

With the ME model (Table 4), only IMI status and cow were significant sources of variation. Infected cows had lower values of parameter $a$, which means a higher baseline SCS level. The four parameters were strongly intercorrelated, especially $b$ and $d$, which had an almost perfect correlation. This suggests potential computational problems (at least with the present data structure), thus estimates should be interpreted with caution.

The estimates obtained from the MG model are in Table 5. Presence of intramammary infection increased the level of somatic cell score (parameter $a$), decreased the rate of increase of SCS at 150 days after calving (parameter $b$) and reduced the rate of fall of somatic cell levels immediately after calving (parameter $f$). Parameter $b$ was higher in cows that calved in the first period and lower for cows calving in the third period. Components of dispersion and

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>S.E.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\mu_i$</td>
<td>-0.816</td>
<td>0.168</td>
<td>-1.145</td>
<td>-0.487</td>
</tr>
<tr>
<td>$\mu_a$</td>
<td>0.245</td>
<td>0.011</td>
<td>0.223</td>
<td>0.268</td>
</tr>
<tr>
<td>$\mu_d$</td>
<td>-1.1×10^{-4}</td>
<td>4.3×10^{-5}</td>
<td>-2.1×10^{-4}</td>
<td>-1.3×10^{-4}</td>
</tr>
<tr>
<td>IMI$^a$</td>
<td>0.582</td>
<td>0.190</td>
<td>0.209</td>
<td>0.955</td>
</tr>
<tr>
<td>IMI$^b$</td>
<td>-0.059</td>
<td>0.011</td>
<td>-0.081</td>
<td>-0.037</td>
</tr>
<tr>
<td>IMI$^c$</td>
<td>1.6×10^{-4}</td>
<td>4.2×10^{-5}</td>
<td>1.4×10^{-4}</td>
<td>2.1×10^{-4}</td>
</tr>
<tr>
<td>P$^a$</td>
<td>0.037</td>
<td>0.008</td>
<td>0.022</td>
<td>0.052</td>
</tr>
<tr>
<td>P$^b$</td>
<td>0.021</td>
<td>0.007</td>
<td>0.007</td>
<td>0.034</td>
</tr>
<tr>
<td>P$^c$</td>
<td>-1.8×10^{-4}</td>
<td>3.5×10^{-5}</td>
<td>-2.3×10^{-4}</td>
<td>-1.1×10^{-4}</td>
</tr>
<tr>
<td>P$^d$</td>
<td>-1.1×10^{-4}</td>
<td>3.2×10^{-5}</td>
<td>-2.1×10^{-4}</td>
<td>-1.0×10^{-4}</td>
</tr>
<tr>
<td>S$^a$</td>
<td>-0.002</td>
<td>0.005</td>
<td>-0.012</td>
<td>0.008</td>
</tr>
<tr>
<td>S$^b$</td>
<td>1.8×10^{-4}</td>
<td>0.006</td>
<td>-0.011</td>
<td>0.012</td>
</tr>
<tr>
<td>S$^c$</td>
<td>0.028</td>
<td>0.006</td>
<td>0.017</td>
<td>0.039</td>
</tr>
<tr>
<td>Var($a$)</td>
<td>0.563</td>
<td>0.129</td>
<td>0.376</td>
<td>0.933</td>
</tr>
<tr>
<td>Var($b$)</td>
<td>0.003</td>
<td>4.7×10^{-4}</td>
<td>0.002</td>
<td>0.004</td>
</tr>
<tr>
<td>Var($d$)</td>
<td>3.1×10^{-4}</td>
<td>1.1×10^{-5}</td>
<td>1.9×10^{-4}</td>
<td>5.6×10^{-4}</td>
</tr>
<tr>
<td>Cov($a, b$)</td>
<td>-0.031</td>
<td>0.007</td>
<td>-0.044</td>
<td>-0.017</td>
</tr>
<tr>
<td>Cov($a, d$)</td>
<td>7.6×10^{-5}</td>
<td>2.5×10^{-5}</td>
<td>3.6×10^{-5}</td>
<td>1.2×10^{-4}</td>
</tr>
<tr>
<td>Cov($b, d$)</td>
<td>-7.4×10^{-5}</td>
<td>3.5×10^{-5}</td>
<td>-5.1×10^{-5}</td>
<td>-1.1×10^{-5}</td>
</tr>
<tr>
<td>Var($e$)</td>
<td>1.102</td>
<td>0.037</td>
<td>1.031</td>
<td>1.178</td>
</tr>
</tbody>
</table>

$^a$ $\mu_i$, intercept for parameter $i$; IMI$^a$, effect of presence of intramammary infection; P$^a$, effect of the $k$ period of calving as a deviation from the third one; S$^a$, effect of the $k$ season of calving as a deviation from the fourth one; Var($i$), variance for parameter $i$; Cov($i, j$), covariance between parameters $i$ and $j$; Var($e$), residual variance.
variation in any of the linear regression parameters suggesting that cows with a lower baseline SCS information criterion.

Table 4
Parameter estimates, asymptotic standard errors (S.E.) and 95% confidence limits (lower, upper), from the Mitscherlich-exponential model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>S.E.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_a )</td>
<td>-3.581</td>
<td>0.129</td>
<td>-3.834</td>
<td>3.328</td>
</tr>
<tr>
<td>( \mu_b )</td>
<td>0.004</td>
<td>0.002</td>
<td>1.0 × 10^{-4}</td>
<td>0.008</td>
</tr>
<tr>
<td>( \mu_c )</td>
<td>0.004</td>
<td>0.002</td>
<td>-4.1 × 10^{-4}</td>
<td>0.088</td>
</tr>
<tr>
<td>( \text{IMI}_1 )</td>
<td>-0.529</td>
<td>0.104</td>
<td>-0.733</td>
<td>-0.325</td>
</tr>
<tr>
<td>( \text{Var}(a) )</td>
<td>1.314</td>
<td>0.219</td>
<td>0.972</td>
<td>1.877</td>
</tr>
<tr>
<td>( \text{Var}(b) )</td>
<td>5.1 × 10^{-4}</td>
<td>1.0 × 10^{-4}</td>
<td>4.1 × 10^{-4}</td>
<td>8.3 × 10^{-4}</td>
</tr>
<tr>
<td>( \text{Var}(d) )</td>
<td>4.7 × 10^{-4}</td>
<td>9.2 × 10^{-5}</td>
<td>3.0 × 10^{-4}</td>
<td>7.2 × 10^{-4}</td>
</tr>
<tr>
<td>( \text{Cov}(a, b) )</td>
<td>-0.016</td>
<td>0.004</td>
<td>-0.024</td>
<td>-0.008</td>
</tr>
<tr>
<td>( \text{Cov}(a, d) )</td>
<td>-0.016</td>
<td>0.004</td>
<td>-0.024</td>
<td>-0.008</td>
</tr>
<tr>
<td>( \text{Cov}(b, d) )</td>
<td>4.9 × 10^{-4}</td>
<td>9.7 × 10^{-5}</td>
<td>3.3 × 10^{-4}</td>
<td>7.1 × 10^{-4}</td>
</tr>
<tr>
<td>( \text{Var}(e) )</td>
<td>1.095</td>
<td>0.037</td>
<td>1.025</td>
<td>1.172</td>
</tr>
</tbody>
</table>

* \( \mu_i \), intercept for parameter i; \( \text{IMI}_i \), effect of presence of intramammary infection; \( \text{Var}(i) \), variance for parameter i; \( \text{Cov}(i, j) \), covariance between parameters i and j; \( \text{Var}(e) \), residual variance.

Table 5
Parameter estimates, asymptotic standard errors (S.E.) and 95% confidence limits (lower, upper), from the Morant and Gnanasakthy’s model

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>S.E.</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \mu_a )</td>
<td>4.292</td>
<td>0.120</td>
<td>4.057</td>
<td>4.526</td>
</tr>
<tr>
<td>( \mu_b )</td>
<td>0.060</td>
<td>0.022</td>
<td>0.016</td>
<td>0.104</td>
</tr>
<tr>
<td>( \mu_c )</td>
<td>-0.020</td>
<td>0.011</td>
<td>-0.040</td>
<td>9.1 × 10^{-4}</td>
</tr>
<tr>
<td>( \text{IMI}_1 )</td>
<td>4.737</td>
<td>0.814</td>
<td>3.139</td>
<td>6.334</td>
</tr>
<tr>
<td>( \text{IMI}_2 )</td>
<td>0.853</td>
<td>0.137</td>
<td>0.584</td>
<td>1.121</td>
</tr>
<tr>
<td>( \text{IMI}_3 )</td>
<td>-0.074</td>
<td>0.021</td>
<td>-0.115</td>
<td>-0.034</td>
</tr>
<tr>
<td>( \text{IMI}_4 )</td>
<td>-2.791</td>
<td>0.860</td>
<td>-4.478</td>
<td>-1.105</td>
</tr>
<tr>
<td>( P_{10} )</td>
<td>0.096</td>
<td>0.019</td>
<td>0.060</td>
<td>0.132</td>
</tr>
<tr>
<td>( P_{20} )</td>
<td>0.062</td>
<td>0.017</td>
<td>0.029</td>
<td>0.096</td>
</tr>
<tr>
<td>( \text{Var}(a) )</td>
<td>0.742</td>
<td>0.093</td>
<td>0.589</td>
<td>0.964</td>
</tr>
<tr>
<td>( \text{Var}(b) )</td>
<td>0.006</td>
<td>0.001</td>
<td>0.004</td>
<td>0.009</td>
</tr>
<tr>
<td>( \text{Var}(d) )</td>
<td>0.008</td>
<td>0.001</td>
<td>0.005</td>
<td>0.011</td>
</tr>
<tr>
<td>( \text{Cov}(a, b) )</td>
<td>0.008</td>
<td>0.007</td>
<td>-0.005</td>
<td>0.022</td>
</tr>
<tr>
<td>( \text{Cov}(a, d) )</td>
<td>-0.049</td>
<td>0.010</td>
<td>-0.069</td>
<td>-0.030</td>
</tr>
<tr>
<td>( \text{Cov}(b, d) )</td>
<td>-0.001</td>
<td>8.6 × 10^{-4}</td>
<td>-0.003</td>
<td>5.2 × 10^{-4}</td>
</tr>
<tr>
<td>( \text{Var}(e) )</td>
<td>1.043</td>
<td>0.035</td>
<td>0.977</td>
<td>1.116</td>
</tr>
</tbody>
</table>

* \( \mu_i \), intercept for parameter i; \( \text{IMI}_i \), effect of presence of intramammary infection; \( P_{ij} \), effect of the k period of calving as a deviation from the third one; \( \text{Var}(i) \), variance for parameter i; \( \text{Cov}(i, j) \), covariance between parameters i and j; \( \text{Var}(e) \), residual variance.

Fixed factors were not a significant source of variation in any of the linear regression parameters of Ali and Schaeffer’s model, but there was significant variation and covariation between cows. In Wilmink’s model, presence of intramammary infection was associated with higher levels of SCS during lactation, in agreement with W, IQ and MG models. Cows calving on the first and second periods had lower a values than those calving in the third period, and higher increases in SCS levels in mid and late lactation. There was significant variation between cows for parameters of this model.

Numerical values of end-points used for comparing models are in Table 6. The Ali and Schaeffer’s (parameter a) would be expected to have a more variable rate of increase of SCS in the middle of lactation.

Table 6
Comparison between models

<table>
<thead>
<tr>
<th>Model</th>
<th>MSE</th>
<th>LIK</th>
<th>AIC</th>
<th>BIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>W</td>
<td>1.181</td>
<td>-7784.017</td>
<td>-3896.01</td>
<td>-3907.56</td>
</tr>
<tr>
<td>IQ</td>
<td>1.102</td>
<td>-7803.159</td>
<td>-3908.58</td>
<td>-3928.78</td>
</tr>
<tr>
<td>MG</td>
<td>1.043</td>
<td>-7640.905</td>
<td>-3827.45</td>
<td>-3847.66</td>
</tr>
<tr>
<td>ME</td>
<td>1.095</td>
<td>-7720.616</td>
<td>-3867.31</td>
<td>-3887.52</td>
</tr>
<tr>
<td>AS</td>
<td>0.950</td>
<td>-7644.072</td>
<td>-3838.04</td>
<td>-3884.24</td>
</tr>
<tr>
<td>W1</td>
<td>1.098</td>
<td>-7707.943</td>
<td>-3860.97</td>
<td>-3881.18</td>
</tr>
</tbody>
</table>

* W, Wood’s; IQ, inverse quadratic; MG, Morant and Gnanasakthy’s; ME, Mitscherlich-exponential; AS, Ali and Schaeffer’s; W1, Wilmink’s model.

* MSE, residual variance; LIK, 2×maximized restricted log-likelihood; AIC, Akaike’s information criterion; BIC, Schwarz’s information criterion.
(AS) model had the lowest residual variance, but the largest number of parameters; the ME model was second and the one with the poorest fit (in the MSE sense), was Wood’s. The MG model had the largest maximized restricted likelihood, followed by AS. Based on Akaike’s and Schwarz’s criteria, the MG model was better, followed by AS or WI, depending on the criterion considered. The residuals plots did not exhibit any patterns, suggesting that the model assumptions were suitable.

4. Discussion

The overall trend of SCS during lactation is consistent with reports by Emanuelson and Philips-son (1984) and Wiggans and Shook (1987). The nonlinear (in time) SCS pattern observed could be explained by effects of stress at the onset of lactation and of dilution thereafter (Wiggans and Shook, 1987). Some of the models studied here have been used, with variable success, to describe milk yield. However, it is a challenge to find an appropriate model for SCC or SCS. Immunological responses may fluctuate more than yields. There is an inconsistent increase in SCS levels in mid lactation, and a slow down in the rate of increase of SCS near its end seems to make the inverse quadratic and Wood’s equations inadequate to describe SCS patterns. The MG model allows for a variable relative rate of increase in SCS in mid and late lactation, and this may be a reason for its better fit. Further, its parameters provide a simple description of the main features of a SCS curve. Variation in standard deviation was small, suggesting that the assumption of homoscedasticity was reasonable from an operational point of view.

Based on Wood’s, IQ and MG models, intramammary infection increases the overall SCS level but, also, attenuates fluctuations during lactation. This is in agreement with Hogan et al. (1987), who found that Staphylococcus spp. and Corynebacterium spp. infections, the most common pathogen isolations in this data set, were associated with a significant increase in SCS, relative to non-infected quarters. In the present study and in the Hogan et al. (1989) study the bacterial group most frequently found was Staphylococcus spp. Corynebacterium bovis was not the second most common quarter isolation in the Hogan et al. (1989) study, but the number of infected quarters ranged between 1% (calving) and 8.8% (drying off), the latter being close to the incidence found in this data set. An improvement in the management-health conditions during the study may be reflected by the lower rate of increase of SCS found in the third period of calving (MG model) and by the lower predicted values for this period (W model). The relatively warm and humid conditions during peak lactation experienced by cows calving between July and September may have facilitated contamination and prevalence of pathogens. This would explain the higher values of parameter b for cows calving in season 3 (Table 3, IQ model). Smith et al. (1985) found that in this herd, the rate of infection and the coliform levels in bedding materials were highest between June and August.

Components of dispersion and co-dispersion were significant in all models, highlighting the importance of genetic and permanent environment factors as a source of differences between cows in the shape and scale of SCS lactation curves. This suggests the possibility of modifying SCS curves by selection, but taking into account the correlations between parameters. For example, the correlation between a and d, and b and d in MG’s model were negative, whereas the correlation between a and b was positive. The lack of significance of dispersion components in some models may be either due to a real lack of variance between cows, or to low information provided by the data to estimate some specific parameter. For example, with few SCS measurements at the beginning of lactation, it may be difficult to estimate precisely cow variability in that declining phase of lactation.

The likelihood-based criteria used (e.g. Akaike’s and Schwarz’s), suggested that the MG model was better, followed by AS or WI, depending on the criterion considered. Other models can be considered to describe lactation patterns, such as orthogonal polynomial models, multiple-trait models and covariance functions of various orders. Rodriguez-Zas and Southey (1999) compared nonlinear and linear models. These included covariance function models of order 1 to 11; random regression models and multiple-trait models for describing the pattern of SCS in a subset of the data set considered here (first
lactation Holstein cows). Likelihood and Markov chain Monte Carlo Bayesian approaches were implemented by these authors. The likelihood criteria and Bayes factors indicated that a five-degree orthogonal polynomial (Legendre polynomial) had a slightly better fit than Ali and Schaeffer’s random regression model, but still worse than Morant and Gnanasakthy’s model. The superiority of Morant and Gnanasakthy’s model over the other models from a likelihood and Bayesian point of view is consistent with the results found in this study.

The likelihood-based approach employed relies on approximations (e.g. linearization, approximate integration and asymptotic theory) for inferences and hypothesis testing. These may not be always appropriate, particularly in data sets having a low informational content. Shun and McCullagh (1995), Vonesh (1996), Demidenko (1997) and Wolfinger and Lin (1997) show that there may be large biases in estimates when there are few observations per cow, irrespective of the number of individuals. Also, the (co)variance component estimators may be unstable when the true parameters are small relative to the residual variance.

This study used a simplistic approach to account for incidence of intramammary infection. The cows that had a single positive isolation were grouped with those that had more positive isolates. In addition, this coding did not provide an adequate description of the dynamics of the infections. The approach considered in this study permitted to include the effect of intramammary infection within the second stage of the model, so inferences on the effect of this variable on the shape and scale of the SCS curve could be made. On the other hand, time-dependent infection status could be included in the first stage of these models. For example, in the simplest possible model, an IMI status at each of the test days can be included in a linear fashion at the first stage. These effects would switch the curve up or down for a cow at the appropriate test-day. Another possibility is to use a lag-1 or lag-2 status. For example, test at time 3 as a function of IMI status at test 2, or whatever is appropriate.

The assumption of unrelated cows made it impossible to partition the variation between cows into additive genetic and other components. However, there were few genetic links between cows in this data set; thus, the assumption of unrelatedness provided an adequate approximation. Also, records from the same cow in different lactations were treated as uncorrelated, leading to an underestimation of standard errors.

5. Conclusion

Somatic cell score lactation patterns in dairy cows were described with nonlinear mixed effects models. Parameter estimates may be useful for selection schemes or management. In this study, four nonlinear and two linear mixed effects model were used. Within these, Morant and Gnanasakthy’s model provided the best fit. There was a significant association between intramammary infection and SCS trajectory. Cows calving between 1983 and 1985 had higher SCS levels and flatter curves, based on the estimates of the parameters describing the fall and increase in this trait. The lactations that started between October and March had higher overall SCS levels, and more even curves. Lactation number was not a significant source of variation of parameters.

Further studies are needed to investigate alternative ways to incorporate the test-day intramammary infection status in the model. A time-dependent test-day infection status can be included in a linear fashion, at the first stage of the model. The covariate may represent the status at the same test-day as the observation or the status in previous test-days (e.g. lag 1 or lag 2). Furthermore, to adequately describe the effect of different patterns of infection on the SCS curves, interactions between the test-day intramammary infection status covariate should be considered. This could permit to identify non-additive effects (e.g. the effect of infection at day 90 depends on the infection status at day 60). For this model, a large data set would be required for precise estimation of the effect of all the potential infection status sequences.

The main focus of this study was to explore nonlinear mixed effects models to describe SCS lactation curves. Other approaches to analyze repeated measurement data while accounting for the variation between and within subjects are: covariance functions, spline and multiple trait models. An advantage of the nonlinear models over other models...
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parameters in nonlinear mixed effects models has
limitations. Asymptotic theory and Taylor series
approximation may not perform well on small data
sets, or particular data structures. In addition, the
likelihood approach does not use information other
than the data, a criticism that is often advanced in
Bayesian analysis (Bernardo and Smith, 1994).

is the biological or geometrical interpretation that
some of the parameters have. In addition, nonlinear
models can provide an adequate and less parame-
terized description of a trend than multivariate
models or random regression/covariance function of
high order. This study showed that some nonlinear
models can provide a parsimonious description of the
data and that likelihood approaches are available for
estimation and inference purposes.

Using maximum likelihood to infer the values of
parameters in nonlinear mixed effects models has
limitations. Asymptotic theory and Taylor series
approximation may not perform well on small data
sets, or particular data structures. In addition, the
likelihood approach does not use information other
than the data, a criticism that is often advanced in
Bayesian analysis (Bernardo and Smith, 1994).

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