Estimation of Parameter Distributions in a Model of Magnesium Dynamics in Cows to Predict the Risk of Tetany in Dairy Herds

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Keywords: *Hypomagnesaemia; Disease risk; Parameter distribution.*

EXTENDED ABSTRACT

The onset of tetany, when dairy cattle have insufficient magnesium, has a huge impact both economically and on animal welfare. We have previously adapted a model of magnesium dynamics in sheep (Robson *et al*. 1997) for use with dairy cattle as an aid to understanding aspects of magnesium metabolism which influence the risk of animals contracting tetany (Bell *et al*. 2005). To estimate this risk in a dairy herd, we carried out Monte-Carlo simulations in which model parameters for individual animals in the herd were varied randomly according to their statistical distributions (McKinnon *et al*. 2003). In this approach the choice of parameter distributions can significantly influence the risk estimates. In some cases the distributions are available from the literature, but in other cases they must be obtained using some sort of parameter refinement process to estimate the parameter distributions from measured data corresponding to a model output (Figure 1).

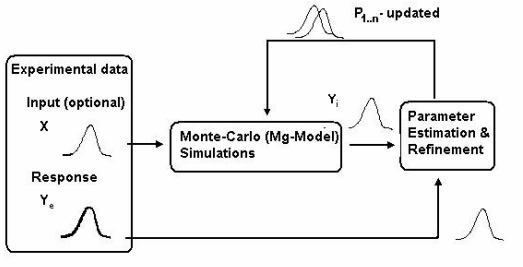

Figure 1. The parameter refinement process

In this paper we present an overview of a generalised algorithm which was developed to improve the accuracy of *a priori* parameter distribution estimates obtained from literature data using an iterative refinement process. At each iteration a response distribution for the current parameter distribution estimate is evaluated using the Monte-Carlo method and compared with a corresponding experimental sample response distribution. A parameter filter is constructed using the iterative parameter estimates and response distributions so that the filter entries form an approximate solution space of the desired refined state. This permits estimates of the parameter distributions to be calculated from the parameter filter.

The requirement for a parameter refinement algorithm is that in the magnesium model, *a priori* estimates of parameters for the flux equations which represent physiological processes of magnesium transport, may have a low accuracy. The reasons for this include; low numbers of experimental observations, the application of parameters derived from *in-vitro* studies which may not represent *in-vivo* conditions, and the use of parameters derived from experimental studies in other species. In biological models a particular concern is that the repeatable phenotypic variation in a subpopulation, such as a dairy herd, is expected to be less than the phenotypic variation across the full population and should be accommodated.

A single parameter example was used to develop the algorithm equations, which were then extended to permit simultaneous refinement of multiple parameter distributions. We use the algorithm to estimate parameter distributions of renal Mg handling which determine urinary magnesium excretion. The estimated parameter distributions were found to repeatably predict urinary Mg excretion in an experimental dataset. The refinement process was then applied in the full dairy cattle magnesium model to refine parameter distributions associated with magnesium absorption and secretion along the gastrointestinal tract. The parameterised model was used to simulate an experimental trial of induced hypomagnesaemia, and was found to accurately estimate plasma Mg concentrations on which the tetany risk estimates are based.

1. NOTATION AND UNITS

Standard notation and units have been defined for the magnesium models in the work of Robson (1991) and extended by Bell (2005). Key symbol definitions used in this paper are; U for flux equations with units $mol^{-1}d^{-1}$, C for concentrations with units mol/l. To simplify comparison with experimental data in this paper, we convert model data presented for the daily urinary excretion flux U_{HlUr} to units of g/d, and the plasma magnesium concentration C_{Pl}, and cerebrospinal fluid magnesium concentration C_{Cs}, to units of mmol/l.

a priori is used as an adjective applied to distributions with the meaning "previous best estimate, from any source".

2. INTRODUCTION

In our work a dairy cattle model of magnesium metabolism (Bell *et al*. 2005), has been developed from an existing magnesium metabolism model for sheep (Robson *et al.* 1997). Hypomagnesaemic tetany occurs when the cerebrospinal fluid (CSF) magnesium concentration falls below approximately 0.66 mmol/L (Meyer and Scholz 1972). CSF Mg concentrations are related to plasma magnesium concentration and are described by the model of Robson *et al.* (2004). These models are systems of non-linear differential equations, evaluated using numerical integration. We have represented biological variation between animals by implementing model parameters as distributions. The Monte-Carlo method is then used to generate distributions of model response variables by repeatedly evaluating the model (McKinnon *et* a*l*. 2003). A simplified schematic diagram of the dairy cow model showing the model configuration and Mg fluxes relevant to this paper is shown in Figure 2.

Parameter refinement is performed in two separate steps.

2.1. Urinary magnesium excretion.

Using the magnesium model notation, daily urinary magnesium excretion U_{HlUr} is described (Bell, 2005) in general terms by the function

$$U_{HlUr}(C_{Pl}, BW, k_{Ur\_a}, k_{Ur\_c}, k_{Ur\_d}), \quad (1)$$

derived from the inverted form of (2) developed by Robson and Vlieg (2000):

$$y = a(1 + d/x) + cx \quad (2)$$

The parameter distributions k_{Ur_a}, k_{Ur_c}, and k_{Ur_d} are refined in step 1, using (1) in the Monte-Carlo simulation. Results of this refinement are used to verify the refinement process. Examining (2) it is evident (1) and (2) are highly nonlinear. A large variation component in the relationship between U_{HlUr} and C_{Pl} is apparent in the data Thielen *et al.* (2001). These two factors present a substantial problem for the design of the refinement algorithm.

2.2. Gastrointestinal magnesium transport.

In this step we refine parameters determining gastrointestinal magnesium transport using the full dairy cattle model. Bell *et al.* (2005) have redefined the fluxes U_{PlHg} and U_{HgPl} recognising the importance of magnesium absorption and secretion processes operating in the small and large intestines. Experiments used to estimate parameters of $U_{PlHg,}$ and U_{HgPl} have been carried out largely using sheep as an experimental model. Consequently the *a priori* estimates of parameters controlling these fluxes have low accuracy.

The general functions;

$$U_{HlUr}(C_{Di}, S_{Hw}, S_{Hg}, S_{Si}, v_{LqPl}), \quad (3)$$

$$C_{Pl}(C_{Di}, S_{Hw}, S_{Hg}, S_{Si}, v_{LqPl}), \quad (4)$$

and $$C_{Cs}(C_{Di}, S_{Hw}, S_{Hg}, S_{Si}, v_{LqPl}) \quad (5)$$

describe the calculation of model outputs; daily urinary magnesium excretion (3), plasma magnesium concentration (4), and cerebrospinal fluid magnesium concentration (5).

We use (5) to estimate tetany risk. Parameter refinement may be performed using (3) and (4), however, since sample data of U_{HlUr} is more readily obtained in practical farm situations, we use (3) for parameter refinement in this paper as a test of the procedure.

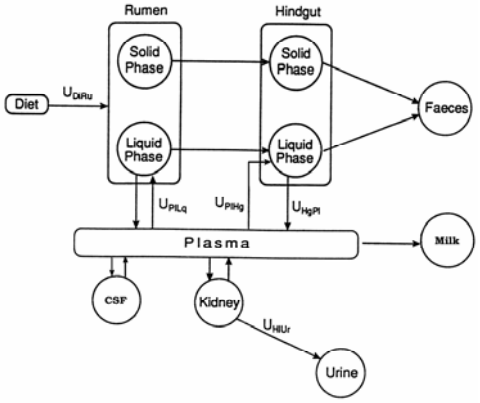

Figure 2. Schematic diagram of dairy cattle magnesium model, showing Mg transport fluxes to which parameter refinement was applied

The model parameter C_{Di} is used to generate the flux U_{DiRu}, v_{LqPl} is a parameter of the flux U_{PlLq}, and the parameters S_{Hg}, S_{Hw} and S_{Si} are dimensionless parameters used to represent both the variation, and relative differences between sheep and cattle, of the fluxes U_{HgPl} and U_{PlHg}.

S_{Hw} (hindgut water) alters the hindgut magnesium concentration, S_{Hg} (hindgut) alters flux U_{HgPl} independent of the magnesium concentration gradient, and S_{Si} alters flux U_{PlHg}.

2.3. Parameter variance.

In designing the algorithm, refinement of parameter variance was considered important since genetic variation of Mg absorption has been demonstrated in experiments using monozygotic twin cattle by Field (1961), and repeatable phenotypic variability of milk Mg concentration is demonstrated by Thielen *et al.* (2001) implying a genetic component. Since phenotypic variation within a subpopulation is expected to be less than in the full population, a means of refining the variance component of parameter distributions is necessary. In biological data the coefficient of variation is often large, with values up to 30% being common. The presence of substantial variance and the non-linearity of (1) and (2) require simultaneous refinement of the parameter distributions.

The parameter distribution variance and standard error of the mean (SEM), contribute to the SEM and variance of simulated responses. The effects are determined by the model equations, so the accumulated effect of multiple parameters may lead to large errors in simulated responses.

3. DEVELOPMENT OF THE ALGORITHM

The approach taken to the parameter refinement problem was to simultaneously refine the mean and variance components of several parameter distributions. It uses a gradient search method based on a linear approximation to the solution space of the distribution refinement objective constructed using a filter, in conjunction with a random search of the parameter distribution error space. The *a priori* error range of each parameter distribution mean and variance are used as constraints.

3.1. Single parameter case.

We use the notation of capital letters to represent distributions, with X an input distribution, Y a model response, and P a parameter distribution to be refined. The individual model evaluations may be represented using the equation

$$y = f(x,p)\,. \tag{6}$$

The Monte-Carlo based generation of the response distribution Y is

$$Y = F(X,P)\,, \tag{7}$$

where Y is a sample distribution of a model output variable, such as the plasma magnesium concentration C_{Pl} at the end of a simulated 10 day trial. Since X is constant for a given simulation scenario, (7) reduces to

$$Y = F(P)\,. \tag{8}$$

The parameter distribution P can be obtained using the inverse of (8):

$$P = U(Y) \tag{9}$$

The parameter distributions were separated into components of mean and variance. This approach has been carried through to the final algorithm for all response and parameter distributions. Using this concept (9) becomes

$$P = U(\mu_Y, \sigma_Y)\,. \tag{10}$$

For which we also consider the related function

$$\mu_P = U'(\mu_Y, \sigma_Y)\,. \tag{11}$$

Taking Y_e to be an independent experimentally derived sample distribution corresponding to Y, and Y_i the simulated distribution, the error of each response distribution component at iteration i is defined as:

- error of the response distribution mean

$$\Delta y_i = \mu_{Yi} - \mu_{Ye}\,, \tag{12}$$

- response distribution variance error

$$\left|1 - \alpha_i\right|\,, \tag{13}$$

where,

$$\alpha_i = \frac{\sigma_{Y_i}^2}{\sigma_{Ye}^2}\,. \tag{14}$$

Numerical approximations of (10) and (11) require several estimates of μ_P, μ_Y, and σ_Y, and therefore several iterations of the Monte-Carlo model evaluations of Y. A filtering method uses data collected from several iterations to generate the iterative parameter distribution estimates. At this point it is useful to develop the equations used to constrain the parameter distributions within their *a priori* error range before developing the parameter filter concept further.

3.2. Parameter constraints.

The error range of the parameter variance is specified as an estimate of the upper limit σ_{P_0}, and constant k to set the lower limit $k \cdot \sigma_{P_0}$. Adjustment of σ_P is restricted using the constraint

$$k \cdot \sigma_{P_0} \le \sigma_P \le \sigma_{P_0}. \quad (15)$$

The normalised error of the parameter distribution mean μ_{P_i} from the *a priori* mean μ_{P_0}, using the *a priori* standard error of the mean, SEM(μ_{P_0}) as the unit error is defined as:

$$\hat{\Delta}\mu_{p_i} = \frac{\mu_{p_i} - \mu_{p_0}}{SEM(\mu_{p_0})} \quad (16)$$

The constraint function $c(\mu_p)$, is defined to generate parameter constraint values based on the normalised error of the mean. An example is shown in Figure 3, for $\mu_{P_0} = 1, SEM(\mu_{P_0}) = 0.05$. Further details of the function which has a piecewise construction, may be obtained from Bell (2005).

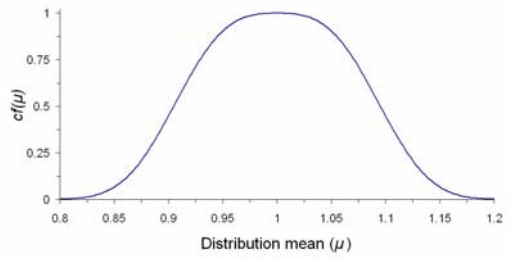

Figure 3. Parameter constraint function $c(\mu_p)$ for $\mu_{P_0} = 1, SEM(\mu_{P_0}) = 0.05$

For completeness the multi parameter constraint C_i is defined for parameter distributions $P_1 \ldots P_n$ by

$$C_i = c(\mu_{P_{1i}}) \cdot c(\mu_{P_{2i}}) \cdot \ldots \cdot c(\mu_{P_{ni}}). \quad (17)$$

3.3. Parameter filtering.

The term parameter filter refers to a stored data list where each entry contains the iterative parameter distribution estimate P_i, the response distribution Y_i, and the constraint value C_i.

As the refinement procedure progresses, the filter entries are selected to minimise the error terms Δy, $|1-\alpha|$, and the constraint C_i. Under these conditions the filter entries form an approximate solution space for the parameter refinement process. This property of the filter provides an alternative to (11) for estimating iterative updates of μ_P using

$$\mu_P = g(\Delta y, \alpha, C), \quad (18)$$

where the filter function (18) may be approximated by the general linear model (GLM)

$$\mu_P = a_0 + a_1 \Delta y + a_2 \alpha + a_3 C + \varepsilon \quad (19)$$

after evaluating $a_0,..,a_3$ using the least squares method of multiple linear regression.

In the single parameter case, the parameter variance component is adjusted independently using the equation

$$\sigma_{P_{i+1}} = \sigma_{P_i} \frac{\nu}{\alpha}, \quad (20)$$

where ν is a control parameter set to a small value (0.005) so that only limited variance adjustments are possible in any one iteration.

The parameter filter is constrained to a maximum size. As new entries are added a selection algorithm ranks multiple refinement objectives, and removes the lowest ranking entries. Ordinal ranking functions r() are defined, for each of the objective characteristics; Δy, $|1-\alpha|$, C, $sign(\Delta y)$, $sign(1-\alpha)$, and *shape*. The *shape* constraint is calculated when an experimental sample of the response distribution is available, using the methods of Siegel (1988). Matched pair data points are obtained by sorting the experimental and simulated distributions into ascending order, each point in the simulated distribution being paired with the equivalent ranked point in the experimental distribution. The shape constraint is defined as the sum of squares error term;

$$shape = \sum_{l=1..N_{Yi}} (y_{il} - y_{em})^2 \quad (21)$$

where subscripts l and m represent equivalent ranked position.

Including the sign characteristics permits selection of parameter distribution entries, which both over and underestimate the response mean μ_Y and α creating a desirable bisection property of the filter.

Filter entries are ranked for selection using

$$\begin{aligned} Rank = \; & w_1 \cdot r_1((\Delta y) + w_2 \cdot r_2(|1-\alpha|) \\ & + w_3 \cdot r_3(C) + w_4 \cdot r_4(sign(\Delta y)) \\ & + w_5 \cdot r_5(sign(1-\alpha)) + w_6 \cdot r_6(shape), \end{aligned} \quad (22)$$

where $w_{1..6}$ are constant weighting factors.

3.4. Multiple parameters.

The extension to multiple *(n)* parameters has two main parts. First, (10) is extended using

$$P_j = U_j(\mu_Y, \sigma_Y, P^{n-1}), \quad for\ j=1..n. \qquad (23)$$

Where P^n is the set of n parameters $P_1,..,P_n$, and P^{n-1} is the set P^n with P_j removed.

The filter function (18), may be replaced by n functions, described by the equation

$$\mu'_{P_{ji}} = g_{ji}(\Delta y, \alpha, C, \mu_P{}^{n-1}) \ . \qquad (24)$$

Defining ψ_{ji} as a sample from a Gaussian noise distribution with $\sigma_{\psi_{ji}} = 4 \cdot SEM(P_{ji})$, a random search is included by:

$$\mu_{P_{ji+1}} = (1-\nu_\mu)\mu'_{P_{ji}} + \nu_\mu(\mu'_{P_{ji}} + \psi_{ji}). \qquad (25)$$

Where ν_μ controls the random search around the parameter error space.

The second part defines a series of equations which replace (20) used to update the parameter variance component.

Defining the variance adjustment

$$\Delta\sigma_{Y_i} = \sigma_{Y_i} - \sigma_{Y_e}, \qquad (26)$$

the significance of $\Delta\sigma_{Y_i}$ is tested using the parameter α from (14), and the percentage points $\chi^2/d.f.$ distribution (Beyer, 1968). For significant values of $\Delta\sigma_{Y_i}$ the updated parameter variance is calculated using the equations

$$\sigma'_{P_{ji}} = \sigma_{P_{ji}} + \frac{k_{\sigma_1}}{(1+k_{\sigma_2}\gamma)n}\left(\Delta\sigma_{Y_i}\right)\frac{\sigma_{P_{ji}}}{\sigma_{Y_i}}, \qquad (27)$$

and $$\sigma_{P_{ji+1}} = \nu_\sigma\sigma'_{P_{ji}} + (1-\nu_\sigma)(\sigma_{P_{ji}} + \Psi_{ji}). \qquad (28)$$

Where Ψ_{ji} is a Gaussian noise distribution with

$$\sigma_{\Psi_{ji}} = 0.1(\textit{ s.d. of the filter } \sigma_{P_j} \textit{ entries}). \qquad (29)$$

Adaptive adjustment of ν_σ is used to improve the rate of convergence, and stability of the process. An overview of the adjustment is that ν_σ ranges between 0.5-0.99 depending on a measure of the quality of σ_Y entries in the filter. As quality improves $\nu_\sigma \to 0.99$, which reduces the magnitude of the noise term in (28). k_{σ_1} is set to 0.1, and used in conjunction with γ and $k_{\sigma_2} = 0.001$ to decrease the second term of (27) as the convergence rate slows. Since the SEM of Y_i is proportional to $\sqrt{N_{Y_i}}$, the refinement process computational requirement is proportional to $N^2_{Y_e}$. As a means of reducing the numerical intensity of the algorithm we initialise the algorithm with *N=10*, and progressively increase this to a final value determined by the desired tolerance for testing $Y_i = Y_e$. Due to the random methods employed by the algorithm, we use statistical testing to terminate the process when we reach

$$Y_i = Y_e \textit{ at 98\% confidence level}. \qquad (30)$$

Evaluation of equations (25) and (28) forms the method of iteratively updating the parameter distribution estimates. A full description of the adaptive processes is provided in Bell (2005).

4. PARAMETER REFINEMENT AND SIMULATIONS.

4.1. Urinary magnesium excretion.

The *a priori* parameter distribution estimates of (1) shown in Table 1, were derived by manual inspection of the scalar function (2) overlayed on plotted experimental data shown in Figure 4.

Table 1. *a priori* parameter distributions of the daily urinary magnesium excretion flux U_{HlUr}

Parameter	mean	s.d.	k	SEM
k_{Ur_a}	2.35	0.22	0.5	0.3
k_{Ur_c}	0.065	0.02	0	0.05
k_{Ur_d}	0.16	0.3	0.5	0.15

Figure 4. Relationship between plasma Mg concentration and; (○) Experimental, and (+) simulated urinary magnesium excretion flux (U_{HlUr}). Experimental data is from Phillips (2005)[1]

[1] Data points removed by random selection to improve clarity of figure

The procedure was run several times to produce refined parameter distributions shown in Table 2, which also demonstrates the procedure produces non-unique solutions.

Table 2. Refined parameter distributions of the daily urinary magnesium excretion flux U_{HlUr}

k_{Ur_a}		k_{Ur_c}		k_{Ur_d}	
μ	s.d.	μ	s.d.	μ	s.d.
2.246	**0.134**	**0.062**	**0.0067**	**0.079**	**0.177**
2.246	0.177	0.072	0.0078	0.077	0.241

The Monte-Carlo method was used to generate simulated U_{HlUr} distributions for the *a priori* and the refined parameter distributions in Table 2. The simulated U_{HlUr} distributions are shown in Table 3.

Table 3. U_{HlUr} response distributions of; (a) experimental sample (using data of Phillips, 2005), (b) simulation of *a priori* parameter set, and (c) repeated simulation using refined parameters. 95% confidence intervals in italics

N=188	(a)Sample	*(b)a priori*	(c)sim 1	(c)sim 2
mean	2.27	2.56	2.25	2.35
	(1.94-2.61)	*(2.2-2.91)*	*(1.93-2.58)*	*(2.67-2.67)*
s.d.	2.34	2.47	2.28	2.38
	(2.13-2.6)	*(2.24-2.74)*	*(2.07-2.53)*	*(2.16-2.65)*

Comparison of the refined parameter distributions (Table 2) with Table 1, confirms they fall within the *a priori* distribution range. Confirmation that the U_{HlUr} response distribution is accurately reproduced in subsequent simulation is by Table 3 and Figure 5, which was obtained by plotting the matched pair data points obtained from the sorting and ranking method used in the calculation of (21).

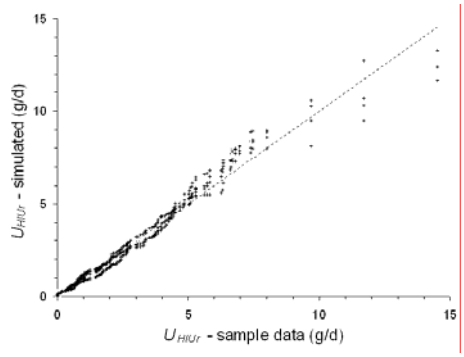

Figure 5. Matched pair comparison of simulated U_{HlUr} distributions with an experimental U_{HlUr} sample distribution (data from Phillips, 2005)

4.2. Gastrointestinal magnesium transport.

Distributions from row 1 of Table 2 were used to refine gastrointestinal Mg transport parameter distributions using (3).

A detailed description of the parameter distribution estimates and findings of this process is provided by Bell (2005). It is reported here that for each parameter, distributions were obtained consistent with; the *a priori* distribution range, and supporting our view that the differences in water content of the hindgut between sheep and cattle (Hecker and Grovum, 1975) may be an important factor for accurately modelling magnesium transport in this location.

4.3. Tetany risk evaluation.

Using the refined parameter distributions we ran a simulation of the experiment of McCoy *et al.* (2001), as an independent means of verifying the complete process. Distributions of plasma and cerebrospinal fluid magnesium concentrations were generated by Monte-Carlo simulation of (4) and (5). The results of this simulation are presented in Table 4.

Table 4. Plasma Mg and CSF Mg concentrations (mmol/l) of induced hypomagnesaemic tetany in cattle fed magnesium deficient diets over a 16 day period; a) experimental study of McCoy *et al.* (2001), b) simulation. (tetanic – developed tetany symptoms; non-tetanic – no symptoms)

		tetanic	non-tetanic	control
(a)	plasma	0.14(0.05)	0.20(0.02)	0.87(0.05)
		0-0.29	0.14-0.26	0.75-0.99
	CSF	0.41	0.57	0.72
		0.28-0.54	0.5-0.64	0.62-0.81
	N	4	6	6
	Risk	40%		
(b)	plasma	0.14(0.00)	0.29(0.01)	0.81(0.01)
	CSF	0.61(0.0)	0.76(0.01)	0.95(0.0)
	Risk	35.2%	(2.5)	

5. DISCUSSION

The parameter refinement algorithm must produce parameters which, when used in subsequent Monte-Carlo simulations with the model, can generate response distributions within the expected distribution range, and variance confidence interval limits. The numerical intensity of this task requires the efficient estimation of parameters if it is to be successful. The adaptive search strategy combining the gradient search methods of (24) and (27) with random searches (25) and (28) of the parameter error space, appears to be a useful method to achieve this. Computational intensity is also reduced by incremental adjustment of *N*. The use of the Monte-Carlo method provides an opportunity for parallel computation, allowing larger tasks to be tackled.

A high degree of replication of the shape of the response distribution is apparent in the simulated data (Figure 5), largely resulting from the transformation of the input and parameter distributions by the model equations, with (21) considered to be largely a non-essential constraint included to improve the rate of convergence.

The accuracy of the predicted plasma Mg concentrations and risk estimates in Table 4 is perhaps surprising given the number of parameters to which the refinement procedure has yet to be applied. However the CSF Mg concentrations are over estimated by the model and tetany risk estimates would be expected to be higher as modelling of the CSF Mg is improved. This suggests it will be necessary to revise our method of evaluating tetany risk, which currently uses a threshold value of $C_{Cs.}$ A possible approach to this would be to estimate risk using a joint probability of risk over a range of C_{Cs} threshold values.

6. CONCLUSIONS

The parameter refinement algorithm is able to estimate parameter distributions with reduced variance components consistent with stated *a priori* error ranges. Subsequent Monte-Carlo simulations using the refined parameters in the model are able to predict simulated response distributions of the required accuracy in the test case.

The method of modelling biological variance by implementing model parameters as distributions and using the Monte-Carlo simulation method is a valuable modelling technique, and good accuracy is achieved by refining a small number of the most sensitive parameters.

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