Calibration of dynamic responses in a physiological model

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EXTENDED ABSTRACT

Dynamic physiological models are often constructed to gain insight into the operation of a complex biological function. In applications such as the study of disease risk, different individuals may vary in susceptibility to disease or response to treatment. An example of this type of application is the dairy cow magnesium model (Bell *et al*. 2008) used to asses the proportion of animals in a herd at risk of developing hypomagnesaemic tetany. The onset of tetany occurs when the concentration of Mg in cerebrospinal fluid (CSF) falls below a critical level of ~0.54 mmol.l^{-1} (Allsop & Pauli, 1985). The CSF magnesium concentration is determined by the exchange of Mg between plasma and CSF (Robson *et al.* 2004). Bell (2006) used the experiment of McCoy *et al.* (2001) to demonstrate simulation of dynamic changes of plasma and cerebrospinal fluid (CSF) magnesium concentration in dairy cattle that occur in response to feeding a magnesium deficient diet over a period of 15 days.

Biological variation between animals was modelled by implementing selected parameters of the dynamic model as distributions, and then a Monte-Carlo method was used to generate a distribution of a selected model response variable (response distribution). A problem with this approach is that the accuracy of the response distribution depends on the accuracy of the parameter distributions used in the model simulations. The refinement algorithm described by Bell *et al*. (2006) provides a method to obtain parameter distributions that minimise the error between a simulated response distribution and a corresponding experimentally observed response distribution (such as Mg excreted in urine). The adjustments to parameter distributions are constrained within their feasible biological range (*a priori* range), and are made by combining information for each parameter about both the sensitivity of the response to change in the parameter, and the constraint to the *a priori* range. The refinement procedure is currently limited to using a single response distribution when calculating updated parameter distributions.

An important issue is the calibration of model parameters specific to the dairy herd in which the risk of tetany is estimated. In the model Mg intake is determined by feed intake and pasture characteristics, which may change from day to day due to changes in feed management practice on the farm. Measuring feed and Mg intake directly is not practical for a commercial dairy herd. A possible method of calibrating the model to a specific herd is to take measurements of Mg in samples of urine on successive days, then estimate parameters for feed and Mg intake that minimise the error between the simulated and measured urinary Mg excretion.

This paper describes an extension of the refinement procedure to include time-series dynamic response data into the selection of updated parameter distributions, which allows improved calibration of dynamic responses in the model.

1. INTRODUCTION

Magnesium is an important macro element in many physiological processes. Magnesium deficiency has a detrimental effect on animal health and causes sizeable economic losses to farming industries resulting from animal deaths. Hypomagnesaemic tetany is a nervous disorder that occurs when the concentration of magnesium in cerebrospinal fluid (CSF) falls below a critical level of ~0.54 mmol.l^{-1} (Allsop & Pauli, 1985). The CSF magnesium concentration is determined by the exchange of Mg between plasma and CSF (Robson *et al.* 2004).

Bell *et al.* (2008) have developed a model of magnesium dynamics in dairy cattle as part of a programme to develop a tool to assess the risk of hypomagnesaemic tetany in a dairy herd. Biological variation was modelled by implementing selected parameters of the model as distributions, and then using a Monte-Carlo method to generate the distribution of selected model response variables, such as the distribution of CSF and plasma Mg concentration in the simulated herd. The model is able to simulate the dynamic changes in plasma Mg concentration that occur over several days when animals are fed a low Mg diet, as in the experiment of McCoy *et al.* (2001) shown in Figure 1.

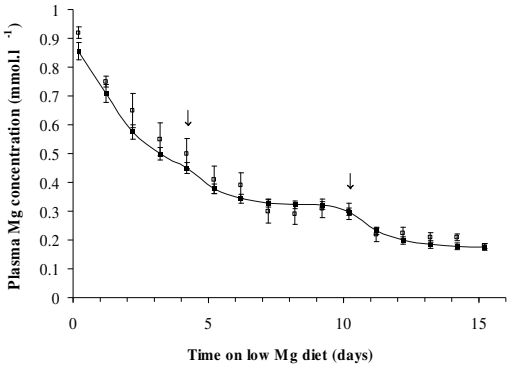

Figure 1. Simulated (mean) plasma Mg concentrations (■), compared with experimental measurements of plasma Mg concentration (□) from a simulation of the experiment of McCoy *et al.* (2001) in 10 dairy cows. The error range shown is SE. (refer to section 4 for simulation details)

The distribution of CSF Mg concentration in the simulated herd at day 15 was used to estimate the tetany risk. The accuracy of the risk estimate depends on the accuracy of the simulated CSF distribution, which in turn, depends on the accuracy of model parameters and their statistical distributions.

The refinement method (Bell, 2006; Bell *et al.* 2006) is designed to improve the accuracy of the initial (*a priori*) parameter distributions. It may be used to estimate parameter distributions that, when used in subsequent simulations, generate a simulated response distribution (such as the distribution of plasma Mg concentration on day 15) not significantly different from a corresponding measured response distribution. During the refinement process parameter distributions are constrained within their specified biological ranges (*a priori* error ranges).

A limitation of the refinement algorithm is that it does not use all the available information when estimating parameter distributions. For example, when estimating parameter distributions using a measured distribution of plasma Mg concentration at day 15 as the response distribution, the measurements of plasma Mg concentration from days 0 through 14 are not used. Therefore, although subsequent simulations with the model using the refined parameter distributions will satisfactorily reproduce the distribution of plasma Mg concentration at day 15, the accuracy of the distribution of Mg in plasma at earlier times, on which CSF Mg is highly dependent, is not assured.

Another problem is that some model parameters (and inputs) may change from one day to the next. For example, on a real dairy farm, cows are moved from one block of pasture to another on a regular (daily) basis. This may affect Mg intake, which depends on several pasture characteristics. Errors in model parameters (such as Mg intake) may cause the simulated plasma Mg concentration to deviate from correct values. When the error is consistently biased, the deviation will increase as the simulation progresses forward in time. To address these problems it is necessary to use some method of estimating model parameters that may change from day to day (such as Mg intake).

A modification of the refinement method is proposed to use information from time-series measurements of model responses (such as the plasma Mg concentration from day 0 through 14 shown in Figure 1) when estimating parameter distributions.

2. THE MAGNESIUM MODEL

The model of Mg dynamics in dairy cattle developed by Bell *et al.* (2008) shown in Figure 2 comprises a system of non-linear fluxes (Table 1) that describe the biological processes for magnesium movement between the model

compartments, Rumen (*Ru*), Hindgut (*Hg*), Plasma (*Pl*), Cerebrospinal Fluid (*Cs*), and Undegraded-diet-in-rumen (*Um*). The quantity of magnesium in each compartment is represented by the symbols Q_{Ru}, Q_{Hg}, Q_{Pl}, Q_{Cs}, and Q_{Um}. The hindgut compartment in the model represents both the small and large intestines.

Magnesium dynamics of the dairy cow model are described by the five differential equations (1-5) used to calculate changes in the quantity of magnesium in each compartment. Flux equations represented by symbols U_{xy} describe the movement of magnesium from compartment x to compartment y.

$$\frac{dQ_{Pl}}{dt} = U_{LqPl} + U_{HlPl} + U_{HgPl} - U_{PlHl} - U_{PlHg} - U_{PlLq} - U_{PlSa} - U_{PlLa} + (U_{CsPl} - U_{PlCs}) \quad (1)$$

$$\frac{dQ_{Cs}}{dt} = U_{PlCs} - U_{CsPl} \quad (2)$$

$$\frac{dQ_{Ru}}{dt} = U_{DiRu} + U_{PlLq} + U_{PlSa} - U_{SpHg} - U_{LqHg} - U_{LqPl} \quad (3)$$

$$\frac{dQ_{Hg}}{dt} = U_{SpHg} + U_{LqHg} + U_{PlHg} - U_{HgPl} - (U_{LqFa} + U_{SpFa} + U_{UmFa}) \quad (4)$$

$$\frac{dQ_{Um}}{dt} = U_{Ds} - U_{UmLq} - U_{UmFa} \quad (5)$$

Absorption of Mg from the diet is necessary to replace the quantity of Mg excreted each day in milk (U_{PlLa}), urine (U_{HlUr}) and endogenous losses into the gastrointestinal tract. When insufficient Mg is absorbed from the diet, the concentration of Mg in plasma (C_{Pl}) decreases over time, which in turn causes CSF Mg concentration to fall (Allsop & Pauli, 1985).

The value of dietary Mg intake (U_{Di}) in the model is estimated from farm production data and measurements of the Mg (C_{Di}), dry matter (*DM*), and metabolisable energy content of pasture samples. Milk production (V_{La}) and Mg content in milk determine the flux U_{PlLa}, which has a significant effect on the rate that Mg concentration in plasma decreases in response to reduced Mg intake. Bell *et al.* (2008) represented post-ruminal Mg absorption (U_{HgPl}) by a passive process using:

$$U_{HgPl} = k_{HgPl}(C_{Hg} - C_{Pl} - k_{CgHg})BW, \quad (6))$$

where C_{Hg} is the concentration of Mg in the hindgut compartment (liquid phase) and *BW* is bodyweight. The constant k_{CgHg} represents the Mg concentration gradient (between intestines and plasma) when the driving forces for Mg uptake due to chemical and electrical gradients are in equilibrium. The value of k_{CgHg} is dependent on electrical gradients in the small and large intestines, which are dependent on the diet.

Table 1. Flux symbols used in the dairy cow magnesium model.

Flux	Function in model
U_{Di}	Dietary Mg intake
U_{DiRu}	$=U_{Df}+U_{UmLq}$, Mg entering rumen liquid phase.
U_{Df}	Fast degrading dietary Mg entering liquid phase pool from diet
U_{Ds}	Slow degrading Mg entering Q_{Um} pool from diet
U_{UmLq}	Slow degrading Mg flux from Q_{Um} to rumen liquid phase pool
U_{UmFa}	Undegraded Mg leaving rumen
U_{LqHg}	Liquid phase Mg flux from Rumen to hindgut
U_{SpHg}	Solid phase Mg flux from Rumen to hindgut
U_{LqPl}	Mg absorption from the rumen
U_{PlLq}	Mg secretion into the rumen
U_{PlSa}	Mg flow from plasma to rumen via saliva
U_{LqFa}	Liquid phase Mg flux from hindgut to faeces.
U_{SpFa}	Solid phase Mg flux from hindgut to faeces
U_{PlLa}	Mg excreted in milk
U_{HlUr}	Mg outflow from kidney into urine
U_{PlCs}	Mg flow from Plasma to CSF
U_{CsPl}	CSF clearance (bulk flow from CSF to plasma)
U_{HlPl}	Mg reabsorption in kidney loop of Henley
U_{PlHl}	Mg flux into kidney
U_{PlHg}	Hindgut secretion-flux (into small-intestine)
U_{HgPl}	Hindgut absorption-flux (distal to small-intestine)

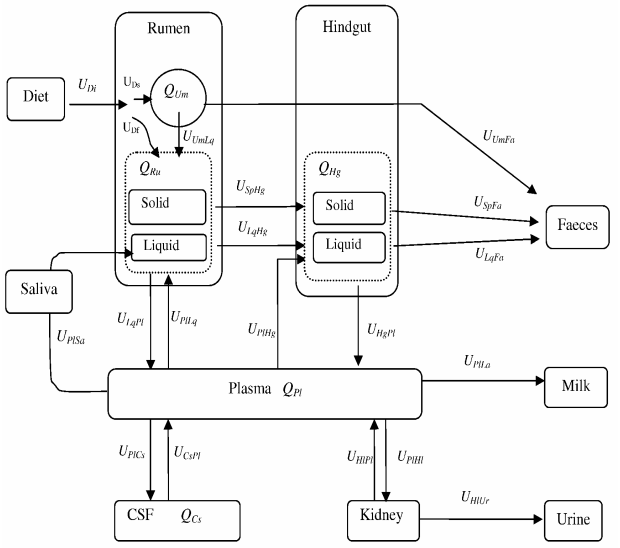

Figure 2. Schematic diagram of the dairy cow magnesium model.

C_{Di} and k_{CgHg} are examples of parameters whose distributions may not be known accurately *a priori* and which therefore need to be calibrated when the model is being used to simulate a particular experimental situation.

3. THE REFINEMENT PROCEDURE

Using *M()* to represent the Monte-Carlo simulation process, the simulated response distribution *S* corresponding to parameter distributions $P_1,..,P_n$ (for *n* parameters) is given by:

$$S = M(P_1,..,P_n) \tag{7}$$

Using a measured response distribution *Y* corresponding to *S,* the refinement procedure described by Bell (2006) provides a method to obtain parameter distributions that generate *S* with no significant difference from *Y* by an iterative procedure, which is summarised as follows:

At each iteration, the parameter distributions are updated (Eqns 8 & 9 below), then the simulated response distribution *S* is determined using (7) and details of the simulation are stored as an entry in a fixed length table for later use. As new entries are added to the table at successive iterations, a rank for each entry is calculated using (10), then the lowest ranking table entry is removed to maintain the fixed table length.

The mean (μ_{P_j}) and standard deviation (σ_{P_j}) of the parameter distribution *j* are updated at iteration *i* using:

$$\mu_{P_{ji+1}} = \mu'_{P_{ji}} + \nu_\mu \psi_{ji} \tag{8}$$

$$\sigma_{P_{ji+1}} = \sigma'_{P_{ji}} + \nu_\sigma \Psi_{ji} \tag{9}$$

Terms $\mu'_{P_{ji}}$ and $\sigma'_{P_{ji}}$ are calculated using information stored in the table. Terms ψ_{ji} and Ψ_{ji} are random perturbations. ν_μ and ν_σ are control terms and have values from 0-1.0.

Characteristics, $|\Delta y|$, $|1-\alpha|$, *C*, $sign(\Delta y)$, $sign(1-\alpha)$, *shape*, and N_S, are stored for each entry in the table. Functions $r_1,..,r_7$ return an ordinal rank for each characteristic respectively, and the overall rank for each table entry is calculated by:

$$\begin{aligned} Rank = {} & r_1(|\Delta y|) + r_2(|1-\alpha|) \\ & + r_3(C) \\ & + r_4(sign(\Delta y)) \\ & + r_5(sign(1-\alpha)) \\ & + r_6(shape) + r_7(N_S) \end{aligned} \tag{10}$$

Where Δy is the error of the response distribution mean given by:

$$\Delta y = \mu_S - \mu_Y, \tag{11}$$

and the error or the response distribution variance is:

$$1-\alpha, \text{ where } \alpha = \frac{\sigma_S}{\sigma_Y}. \tag{12}$$

The significance of α is tested using the percentage points χ^2/d.f distribution (Beyer 1968). In (10) *C* is a term to constrain parameters $P_1,..,P_n$ to their stated 95% confidence interval, *shape* is an optional parameter used to minimise the error between the cumulative frequency distributions of *S* and *Y* (not used in this paper), and N_S is the number of samples in distribution *S*.

Using the procedure just described, parameter distributions $P_1,\ldots P_n$ are improved to minimise the error terms (11) and (12).

3.1. Modifications to the refinement procedure.

In order to accommodate the requirement that the refinement procedure uses all the time series data available, it has been modified as follows:

Measurements of response distribution *Y* at times $t_1,..,t_n$ are represented by:

$$Y_{t_1}, Y_{t_2}, ..., Y_{t_n}, \tag{13}$$

and the corresponding simulated response distributions as:

$$S_{t_1}, S_{t_2}, \ldots, S_{t_n}. \tag{14}$$

Defining ε_t to be the 95% confidence interval for μ_{Y_t}, the normalised error between the simulated and measured response distribution mean at time *t* is given by:

$$\frac{\mu_{Y_t} - \mu_{S_t}}{\varepsilon_t} \tag{15}$$

Normalisation is necessary since over time μ_{Y_t} (and ε_t) may vary over a large dynamic range. The sum of squared normalised error for the dynamic response data (*DSS*) is given by:

$$DSS = \sum_{t=t_1..t_n} \left(\frac{\mu_{Y_t} - \mu_{S_t}}{\varepsilon_t} \right)^2 \tag{16}$$

The *DSS* was added to each table entry and (10) was modified to include *DSS* by:

$$\begin{aligned} Rank = {} & r_1(|\Delta y|) + r_2(|1-\alpha|) \\ & + r_3(C) \\ & + r_4(sign(\Delta y)) \\ & + r_5(sign(1-\alpha)) \\ & + r_6(shape) + r_7(N_S) \\ & + r_8(DSS) \end{aligned} \tag{17}$$

4. TEST OF THE MODIFIED REFINEMENT PROCEDURE

In this section we use the modified refinement procedure to calibrate the model using the experiment of McCoy *et al.* (2001), in which animals were fed a magnesium deficient diet.

4.1. The experiment.

In the experiment of McCoy *et al.* (2001), animals in the treatment group were introduced to a control diet with a Mg content of 1.7 g.kgDM^{-1} over a period of 10 days. On day 11 the Mg content in the diet was reduced to 0.8 g.kgDM^{-1} and further unspecified reductions in the Mg content of the diet were made between day 11 and day 26 with a final Mg content of 0.6 g.kgDM^{-1}. Bell *et al.* (2008) used assumed values for the diet adjustments between days 11 and 26. Errors in the assumed dietary Mg content may have an influence on the estimate of tetany risk. A similar situation arises when applying the model to practical on-farm use, where factors such as Mg intake may change from day to day as animals are moved from one block of pasture to another.

Estimation of the unknown diet adjustments in the McCoy *et al.* (2001) experiment provides a suitable test case for the modified refinement procedure. Simulations of this experiment performed previously using parameters obtained by manual methods are in good agreement with the experimental data (Bell, 2006; Bell *et al.* 2008). Consequently, it is known that solutions exist and should be attainable by the refinement procedure.

Many model parameters contribute to the rate at which plasma Mg decreases in response to a reduction of dietary Mg intake. This paper performs the simultaneous estimation of parameters k_{CgHg}, V_{La}, and C_{Di} (on days 0-15), which are all known to have a significant effect on simulated plasma Mg concentration for animals on a low Mg diet (Bell, 2006).

4.2. Manual calibration of the model.

The magnesium model was configured to represent the experiment of McCoy *et al.* (2001) using parameters and methods described by Bell *et al.* (2008).

An initial combination of parameters to run the model was obtained manually in the following way. The diet was reduced on days 4 and 10 of the low Mg treatment period by an equal amount of 0.1 g.kgDM^{-1}. Milk production was set to the average value (13.45 litres per d) from McCoy *et al.* (2001). The values of k_{CgHg}=1.0 mmol.l^{-1}, and $\sigma_{V_{La}}$ =1.5, were obtained by a trial and error process (Bell, 2006). Figure 1 shows simulated plasma Mg concentrations using these parameters (Table 3a).

4.3. Calibration using the modified refinement procedure.

The time-series distribution of plasma Mg concentration from day 2 to day 15 on the Mg deficient diet from McCoy *et al.* (2001) is used as the time-series response data represented by (13). Corresponding data from simulations using the model (represented by Eqn 7), were substituted into (14). Days 0 and 1 are excluded as plasma Mg concentration on these days is dependent on the initial conditions, and largely independent of the parameters being estimated.

It was assumed that a more detailed set of diet adjustments could be applied to the model on days 4, 6, and 10 of the Mg deficient diet. These days correspond to days where there is a change in the apparent rate of reduction of plasma Mg concentration in the experimental data (refer Figure 3). *A priori* parameter choices for this assumption are given in Table 2. The refinement procedure has been developed to operate on parameter distributions that remain constant over time. However, in this example the dietary Mg content (C_{Di}) has been refined for 3 discrete time periods. The technique was applied to improve the *a priori* parameter estimates in Table 2 using the modified refinement procedure, which while obtaining parameters that yield $S_{t_{15}}$ not significantly different from $Y_{t_{15}}$, also selects combinations of parameters that reduce the error term (16). The refined parameters are given in Table 3b, and when used in subsequent simulations with the model, provide good agreement between simulated and measured plasma Mg concentration from days 0-15 on the low Mg diet (Figure 3).

Table 2. *a priori* parameter distributions supplied to the refinement procedure.

	Parameter	*apriori*	Range	Units
	k_{CgHg}	1.2	± 1.0	mmol
	$\mu_{V_{La}}$	13.45	± 0.5	litres
	$\sigma_{V_{La}}$	1.5	1.0-1.7	" "
C_{Di} on:	day 4	0.73	± 0.07	g.kgDM^{-1}
	day 6	0.66	± 0.10	" "
	day 10	0.59	± 0.12	" "

The increase in the range of C_{Di} occurs because changes in C_{Di} were specified as a series of fixed adjustments (-0.07 ± 0.07) on days 4,6 & 10.

Table 3. Parameters used to simulate plasma Mg concentration obtained by manual methods (a), and modified refinement procedure (b).

Parameter		Parameter values (a)	(b)	Units
	k_{CgHg}	1.16	1.032	mmol
	$\mu_{V_{La}}$	13.45	13.44	litres
	$\sigma_{V_{La}}$	1.5	1.22	" "
$C_{Di,}$	Initial	1.7	1.70	g.kgDM^{-1}
	Day 0-3	0.8	0.80	" "
	Day 4-5	0.7	0.73	" "
	Day 6-9	" "	0.66	" "
	Day 10-15	0.6	0.59	" "

5. DISCUSSION

In Table 3 the parameter distributions obtained using the modified refinement procedure are similar to the parameter distributions obtained by the manual calibration method and confirms the operation of the modified refinement method, which offers a convenient alternative to manual calibration, in a test case with a known solution. In future, the modified refinement method may be applied to similar types of problems with unknown solutions, such as the estimation of Mg intake in a real dairy herd.

When estimating Mg intake in a real dairy herd, it would not be practical to use measurements of plasma Mg concentration as the response variable. However, measurements of the Mg concentration in urine are easily obtained and may be used to determine the U_{HlUr} flux, which is related to plasma Mg concentration by a non-linear function (Robson and Vleig, 2000). Bell (2006) has calibrated the parameter distributions of the U_{HlUr} flux and demonstrated good repeatability between simulated and experimental data for plasma Mg concentrations less than ~0.7 mmol.l^{-1}. When animals are fed Mg deficient diets sufficient to induce hypomagnesaemia and tetany, the plasma Mg concentration is likely to be less than 0.7 mmol.l^{-1}. Consequently, the model may be calibrated using the methods described in this paper, using measurements of the U_{HlUr} flux rather than plasma Mg concentration. The accuracy of model calibrations will depend on how well the U_{HlUr} flux equation models the relationship between plasma Mg concentration and magnesium excreted in urine, and has yet to be determined using real farm data.

In the experimental data from McCoy *et al.* (2001) it can be seen (in Figure 3) that there is only a small overlap in the error range of the

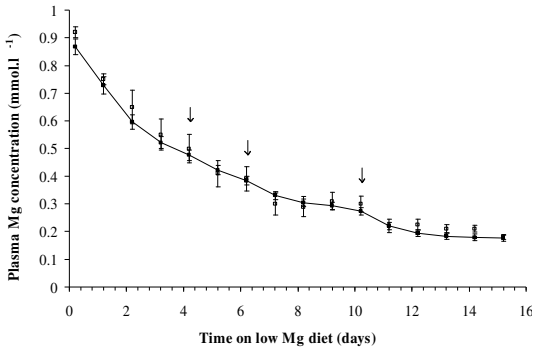

Figure 3. Plasma Mg concentrations simulated using refined parameters from Table 3b (■), compared with experimental measurements of plasma Mg concentration (□) from McCoy *et al.* (2001). The error range shown is SE. Arrows indicate times when the Mg content of the diet was reduced.

plasma Mg concentrations from days 12-14 and day 15 (Figure 3). In this situation it is possible that introducing the DSS term into (17) could adversely affect the performance of the algorithm due to conflict between minimising $|\Delta y|$ and $|1-\alpha|$, and selection of low values of DSS. Although, this did not appear to occur in this example, this type of situation should be considered (and avoided) when setting constraints in other problems.

The number of iterations required to find improved parameters using the refinement procedure is variable (Bell, 2006), due to factors such as the random perturbations in Eqns (8) and (9). Approximately 50-100 iterations were required to obtain refined values of the parameters in Table 2. The computation time at each iteration is dominated by the Monte-Carlo simulation with the model, which is independent of the number of parameters being refined. The number of iterations required to reach a solution is determined by a number of factors such as the number of table rows, *a priori* distribution values and properties of the model. An investigation of the algorithm performance and convergence properties in different situations is planned as a future study.

As the number of parameter distributions to be calibrated increases, the modified refinement procedure offers advantages over manual methods of calibration, by reducing the time required to perform calibrations. In future, tests of repeatability, sensitivity and measures of optimality for each parameter distribution may be incorporated into the software to improve the utility of the refinement method.

In Eqn (16) only the mean of the plasma Mg concentration distribution for each day in the time-series data is used. No attempt has been made to include the time-series standard deviation information. At the current stage of model development calibrating the standard deviation of plasma Mg concentration on a single day by using the distribution of plasma Mg concentration at day 15 as the response distribution has been sufficient. However, normalisation of (12) using the percentage points χ^2/d.f. distribution (Beyer 1968) could provide the basis for development of an error term for time-series variance data should this become necessary in future.

In this paper three diet adjustments have been estimated in a single refinement step. Consequently each diet adjustment in Table 2 has a low accuracy. In practice, the procedure would be applied on each day measurements are made, so only the last diet adjustment in the series would have a low accuracy. This should be an easier task for the algorithm to handle and would require fewer iterations to reach a solution.

6. SUMMARY

The refinement procedure has been modified to include time-series dynamic response data into the selection of updated parameter distributions. The modified refinement procedure was then applied to estimate changes in dietary Mg content in a simulation of the McCoy *et al.* (2001) experiment. This demonstrates the feasibility of using the modified refinement procedure to estimate a time varying model input, such as Mg intake, using time-series measurements corresponding to a model output, and has direct application to the calibration of the magnesium model in practical situations.

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