

Characterisation of the iterative integral parameter identification method

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Abstract Parameter identification methods are used to find optimal parameter values to fit models to measured data. The single integral method was defined as a simple and robust parameter identification method. However, the method did not necessarily converge to optimum parameter values. Thus, the iterative integral method (IIM) was developed. IIM will be compared to a proprietary nonlinear-least-squares-based Levenberg–Marquardt parameter identification algorithm using a range of reasonable starting values. Performance is assessed by the rate and accuracy of convergence for an exemplar two parameters insulin pharmacokinetic model, where true values are known a priori. IIM successfully converged to within 1% of the true values in all cases with a median time of 1.23 s (IQR 0.82–1.55 s; range 0.61–3.91 s). The nonlinear-least-squares method failed to converge in 22% of the cases and had a median (successful) convergence time of 3.29 s (IQR 2.04–4.89 s; range 0.42–44.9 s). IIM is a stable and relatively quick parameter identification method that can be applied in a broad variety of model configurations. In contrast to most established methods, IIM is not susceptible to local minima and is thus, starting point and operator independent.

Keywords Parameter identification · Physiological modelling · Pharmacokinetics · Pharmacodynamics

1 Introduction

Physiological models are used to mathematically describe, replicate or predict the dynamics or mechanics of biological

phenomenon. Suitable models accurately describe or re-create observed behaviour of an appropriate range of subjects by varying the value of key model parameters. The values of these model parameters can then be used to characterise the observed behaviour with respect to the model configuration. Most frequently, the optimal model parameter values are considered those that minimise the difference between the observed data and a response simulated by the model. Numerous algorithms have been postulated for the purpose of identifying the optimal model parameter values as a function of the model formulation and observed data [3].

However, parameter identification is intrinsically complex. An insufficient ability to effectively apply parameter identification methods or diagnose and remedy their failure can become an insurmountable research obstacle. Thus, there is some significant demand for a parameter identification method that is robust, convex and relatively intuitive and straightforward to apply.

Most algorithms attempt to identify the optimal parameter values by characterising the error change as a function of variances in the model parameters. For example, the Levenberg–Marquardt algorithm is a very commonly used form of nonlinear-least-squares that optimise model parameters in the direction of descending simulation error [11, 15]. The algorithm steps towards convergence by measuring the derivative of an error-surface with respect to changes in model parameters and defines a parameter change that is a function of the derivative and a manually defined proportional driver. Thus, the method can be used for numerous model configurations, and has been accepted as a preferred method in a number of fields. However, the method is susceptible to instability when there is an insufficient error gradient at the initial conditions, or the proportional driver value is over-estimated. Under-estimation

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of the driver will slow the rate of convergence. Furthermore, the method is non-convex and can converge to false local minima giving incorrect parameter values. Thus, the method requires some operator experience and care for best results, which cannot necessarily be provided by some research groups.

The single integral parameter identification method has been proposed as a simple-to-use, convex algorithm that is robust to sample error [8]. It has been used in a number of applications [4, 10, 13, 14, 16, 18]. However, the single integral method does not necessarily converge to a minimal least-square error. The iterative integral method (IIM) is an extension of the single integral method and has previously been presented in application [5, 7], but without formal validation or comparison. This article presents IIM methodology, and compares it to the frequently used Levenberg–Marquardt nonlinear-least-squares method [11, 15].

2 Methods

2.1 Steps of the iterative integral method

A general coupled first order differential equation will be used to define the overall IIM algorithm. We may write this in a general form such that for a vector of measured species variables \mathbf{x} with $\mathbf{x} \in \mathbb{R}^n$ then the k th differential equation can be written as:

$$\dot{x}_k = \sum_{j=1}^M \zeta_{jk} f_j(\mathbf{x}, t, \theta) \tag{1}$$

where x_n is a co-dependent species of the subset of \mathbf{x} , $\mathbf{x} \in \mathbb{R}^{n-1}$, f_j are functions of \mathbf{x} and a priori known parameters and/or known external time-variant inputs (θ), while ζ_{jk} are the matrix of unknown parameters to be identified. To illustrate the method, we simplify the system of o.d.e.s to a pair of coupled equations given by:

$$\dot{x} = \sum_{j=1}^M \zeta_{1j} f_j(\mathbf{x}, t, \theta) \tag{2}$$

$$\dot{y} = f_{M+1}$$

with the constraints

$$f_i \neq f_j \text{ for } i \neq j$$

$$\zeta_M = 1$$

These constraints enable a priori model identifiability and unique identification of all the ζ_j 's [7, 17].

If none of f_i are functions of \mathbf{x} , the first iteration of IIM will produce the optimal parameter values and further iterations would not improve the outcome. In this case, the

single integral method is sufficient. However, if any of the f_i are functions of \mathbf{x} , then IIM is needed to converge to the solution. The IIM algorithm is defined in Steps 1–7:

1. The governing equation is integrated over time

$$x(t) - x(0) = \sum_{j=1}^M \left[\zeta_j \int_0^t f_j(\mathbf{x}, t, \theta) d\tau \right] \tag{3}$$

2. The equation is re-arranged with unknown coefficients (ζ_{jk}) on the RHS and the remaining terms on the LHS with $x(t) = x_t$ and $x(0) = x_0$, we have that

$$x(t) - x(0) - \int_0^t f_M(\mathbf{x}, t, \theta) d\tau = \sum_{j=1}^{M-1} \left[\zeta_j \int_0^t f_j(\mathbf{x}, t, \theta) d\tau \right] \tag{4}$$

3. The LHS and the coefficients of the model parameters are evaluated over a series of periods between t_0 and the sample times t_1, t_2, \dots, t_n where x_t and x_0 are the measured data. In contrast, functions f_i are evaluated by simulations of x_n . The initial f_i simulations can be evaluated using simple linear interpolations of the measured data or a vector of zeros.
4. The values evaluated in Step 3 are arranged in the matrix formulation over all evaluated periods:

$$\begin{aligned} \mathbf{A}\zeta &= \psi \\ \mathbf{A} &= \{A_{ij}\}; \quad A_{ij} = \int_0^{t_i} f_j(\mathbf{x}, \tau, \theta) d\tau \\ \psi &= \{\psi_i\}; \quad \psi_i = x_t - x_0 - \int_0^{t_i} f_M(\mathbf{x}, \tau, \theta) d\tau \end{aligned} \tag{5}$$

Since the matrix is non-square, the system is over-determined and \mathbf{A}^{-1} does not exist and careful analysis is needed to find the modelling parameter vector (ζ). To solve the matrix system, the Moore–Penrose pseudo inverse is used. However, this approach does not automatically produce a unique solution and there is no indication that the matrix is necessarily of full rank. A solution may be obtained in the least squares sense by minimising the error (E):

$$E = \|\mathbf{A}\zeta - \psi\|_2 \tag{6}$$

where we assume that the M columns of \mathbf{A} are linearly independent.

5. \mathbf{x} is re-simulated using the identified vector ζ and the governing Eqs. 1 and 2.
6. Equation 5 can be re-defined using the updated f_i to re-evaluate ζ
7. Steps 5 and 6 are iterated until convergence is declared.

It should be noted that this process is mechanistic. Neither does it require initial starting values to be estimated nor does it require the calibration of the proportional driver functions to stabilise or accelerate convergence. Hence, the method is operator independent.

2.2 Insulin pharmacokinetic example

The iterative method will be used to identify insulin pharmacokinetic parameters from the dynamic insulin sensitivity and secretion test (DISST) model [14] defined in Eqs. 7 and 8. This coupled model is indicative of a number of physiological models. The DISST model fits to the insulin data by finding the optimal values of the first pass (x_L) and proportional (n_T) insulin clearance rates [14].

$$\dot{I} = -n_T \frac{I}{1 + \alpha_I I} + \frac{n_T}{V_P} (Q - I) + \frac{x_L U_N + U_X}{V_P} \tag{7}$$

$$\dot{Q} = \frac{n_I}{V_Q} I - \left(n_C + \frac{n_I}{V_Q} \right) Q \tag{8}$$

where I and Q are the plasma and interstitial insulin concentrations [x_n in Eq. 1]; V_P and V_Q are the distribution volumes of plasma and interstitium [θ]; U_N and U_X are the endogenous and exogenous insulin inputs [θ]; n_I is the a priori known rate of transfer between plasma and interstitium [θ]; n_C is the a priori known clearance rate in the interstitium [θ]; α_I is the saturation of insulin clearance [θ]; n_T is the proportional plasma clearance rate [ζ_1]; and x_L is the proportion of endogenous insulin that is not extracted on the first hepatic pass [ζ_2].

$$\text{if : } \zeta_1 = n_T \therefore f_1 = \frac{-I}{1 + \alpha_I I}$$

$$\text{if : } \zeta_2 = x_L \therefore f_2 = \frac{U_N}{V_P}$$

$$\zeta_3 = 1 \therefore f_3 = \frac{n_I}{V_P} (Q - I) + \frac{U_X}{V_P}$$

$$f_4 = \frac{n_I}{V_Q} (I - Q) - n_C Q$$

2.3 Analysis

Clinical data obtained from one insulin resistant (IR) and one healthy, normo-glucose tolerant (NGT) participant of the DISST pilot investigation [14] are used to characterise the range of test responses that may be expected from a

general cohort. Participant characteristics are summarised in Table 1. Parameter values from these participants are used to simulate 60-min insulin response to the DISST test stimulus in silico. The DISST stimulus includes 10 g intravenous (IV) glucose bolus at $t = 10$ and 1 U IV insulin bolus at $t = 20$ min. The endogenous insulin production response (U_N) will be modelled as a three-stage block step infusion with three rates: the basal rate (U_B) from $t = 0$ –10, the first phase (U_1) response to glucose stimulus from $t = 10$ to 15 and the second phase response (U_2) $t = 15$ –60 min. Data in terms of I will be ‘sampled’ from the synthetic profiles at 5-min interval.

In order to provide context and comparison, IIM and the frequently used nonlinear least-squares method are used to identify the true values of n_T and x_L from the ‘sampled’ data using 16 starting points. The 16 initial conditions are within the values that may be reasonably assumed [14] and are shown in Fig. 1. Convergence is declared when both model parameters are within 1% of the true values, while non-convergence is declared if at least 1 parameter is outside 1% after 100 iterations.

Nonlinear least-squares will be applied with the proprietary Matlab™ (version 7.10.0, R2010a) function lsqnonlin.m. The IIM method is also applied in Matlab™ (version 7.10.0, R2010a).

Step 3 of IIM states that the method does not necessarily require accurate simulations for the initial estimate. Thus, six initial condition cases are tested:

1. I_t = interpolation of measured data. This is the typical approach used in application,
2. I_t = interpolation of measured data $I_t \times 0.5$,
3. I_t = interpolation of measured data $I_t \times 2$,
4. I_t = interpolation of measured data $I_t \times 5$,
5. $I_t = 0$,
6. $I_t = I(0)$.

Finally, if the nonlinear least-squares method converges to local minima, the local minima values will be used to simulate I_t and Q_t profiles that will be used as initial conditions of IIM.

3 Results

Figure 2 presents the error distribution as a function of model parameter variances across the axis shown in Fig. 1.

Table 1 Summary characteristics of participant physiology

	BMI [kg m ⁻²]	U_N [mU min ⁻¹]			n_T [min ⁻¹]	x_L	SI [10 ⁻⁴ L mU ⁻¹ min ⁻¹]
		U_B	U_1	U_2			
IR	33.9	115	233	151	0.123	0.178	2.23
NGT	21.4	26.6	487	9.69	0.278	0.203	20.9

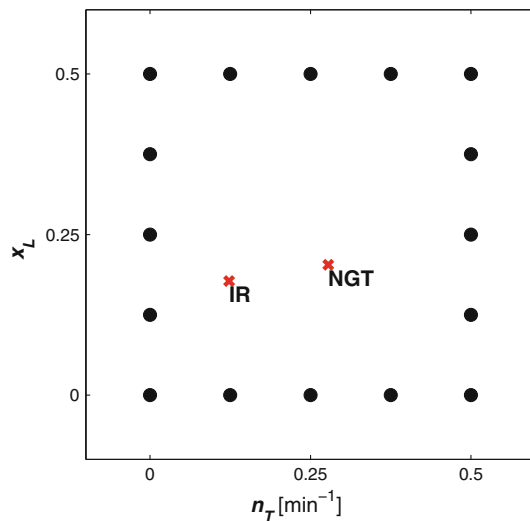


Fig. 1 Starting conditions and true values of n_T and x_L for the IR and NGT participants

Note that the *in silico* data used in this analysis does not include simulated noise to represent assay error. Hence, there are ‘zero error’ conditions at the true values which would not occur in real clinical data.

Iterative integral method successfully iterated to the true values from every starting condition. The nonlinear least-squares method failed to converge on 7 of the 32 cases tested (22% failure). Table 2 indicates the initial conditions that caused failure of nonlinear least-squares and provides an indication of the nature of the failure.

Table 3 shows that while IIM typically requires more iterations than nonlinear least-squares, those iterations are less computationally expensive, and convergence is

achieved faster. Figure 3 shows the convergence patterns of the two methods as a function of time.

The convergence paths from the 16 starting positions for both participants and both identification methods are shown in Fig. 4. Note that IIM followed distinct convergence patterns for each participant, and while some initial iterations actually produced parameter values that diverged from the true values, the convergence path always reduced in I_t simulation error. In contrast, nonlinear least-squares converged in the direction of descending error gradient.

The starting point analysis was undertaken to directly compare the performance of IIM and nonlinear-least-squares. However, typical application of the IIM uses interpolation of the measured data as an initial condition rather than initial parameter estimates. Figure 5 shows the convergence of the parameters when the different initial I_t and Q_t profiles are tested. Note that for most cases, the initial parameter estimation using the simple initial simulation is within the range of expected values, and converges quickly to the true values. However, for the NGT $I_t = I(0)$ case, the parameter values identified in the initial iteration were very erroneous, and while it eventually converged to the simulation values, the rate of convergence was slow. Hence, placing bounds that limit parameters to realistic values significantly increased the rate of convergence. The effect of such bounding shown in Fig. 5, where n_T is bound below 1 min^{-1} .

Figure 5 also shows successful convergence when the local minima identified by nonlinear least-squares (listed as failures numbered 2–4 in Table 2) are used to simulate I_t and Q_t profiles which are then used as initial conditions for the IIM.

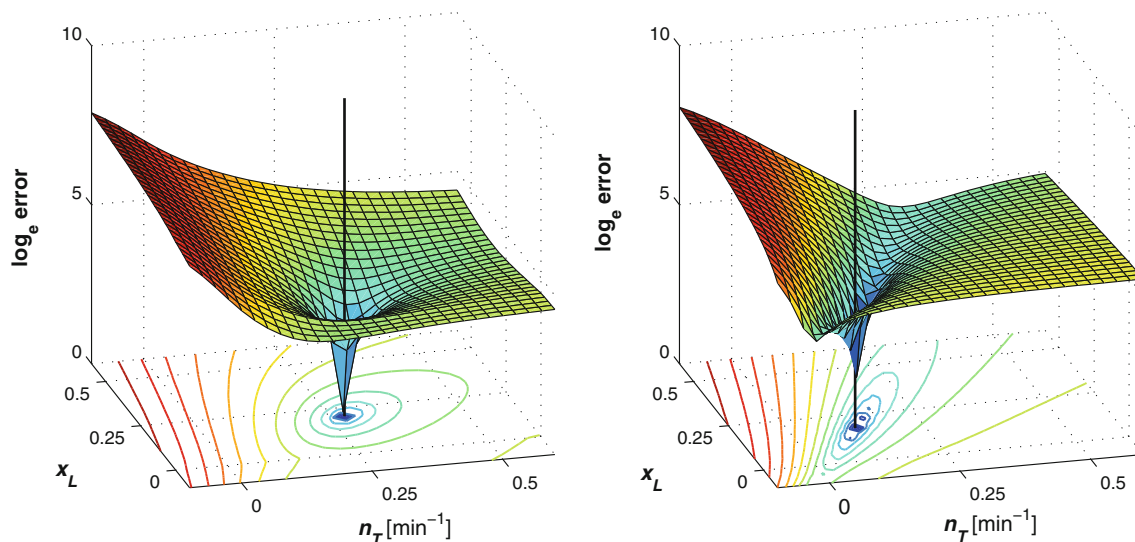


Fig. 2 Error distribution across the identified model parameters. (NGT left, IR right)

Table 2 Cases of nonlinear least-square failure

Failure no.	Participant	Starting conditions		Reason
		n_T	x_L	
1	NGT	0.5	0.5	Insufficient initial gradient
2	IR	0.125	0.5	Converged to local minima (0.129, 0.190)
3	IR	0.375	0.5	Converged to local minima (0.135, 0.201)
4	IR	0.5	0.375	Converged to local minima (0.167, 0.266)
5	IR	0.5	0.125	Insufficient initial gradient
6	IR	0.5	0	Insufficient initial gradient
7	IR	0.25	0	Insufficient initial gradient

Table 3 Convergence of methods and indicative identification times from the respective methods

Method	Convergence from starting points	Iterations to convergence ^a Min, Q1, Q2 , Q3, Max	Time to converge (seconds) ^a Min, Q1, Q2 , Q3, Max
Iterative integral	32/32 (100%)	15, 21, 31 , 38, 78	0.61, 0.82, 1.23 , 1.55, 3.91
Nonlinear-least-squares	25/32 (78%)	3, 8, 11 , 15, 74	0.42, 2.04, 3.29 , 4.89, 44.9

Median in bold

^a Cases that did not converge are not included

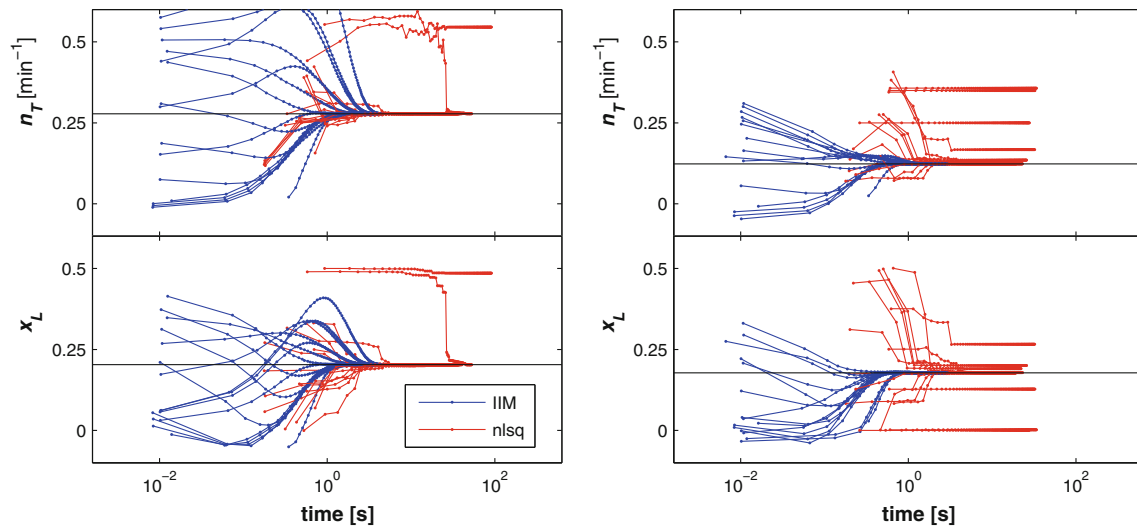


Fig. 3 Convergence of parameters as a function of time. (NGT left, IR right)

4 Discussion

Iterative integral method is a robust and relatively fast method of parameter identification. For each of the initial and local minima conditions tested, the method successfully converged to the true values. The convergence path of IIM consistently reduced the I_t simulation error. Although model parameter values from the initial iterations of the method actually diverged from the true values in some cases, convergence ultimately occurred and the true parameter values were always identified. IIM is comparatively simple to apply, starting point independent (Fig. 3), and requires no special operator input or care. In particular, the method can use arbitrary initial simulations

of the observed analytes (Fig. 5), which are significantly advantageous over non-convex starting-point-dependent methods.

For the cases presented, IIM is more robust than nonlinear least-squares. Seven of the 32 cases failed to converge to the true parameter values when the nonlinear least-squares method was used (Tables 2, 3). A very low gradient of the error-surface at four of the starting conditions meant that nonlinear least-squares failed to initialise iteration towards the true values. Three of the failed cases resulted in iteration towards local, rather than global, minima. While the cases which failed to initialise may be quickly recognised by the researcher and could be potentially remedied via alternative initial conditions, the cases

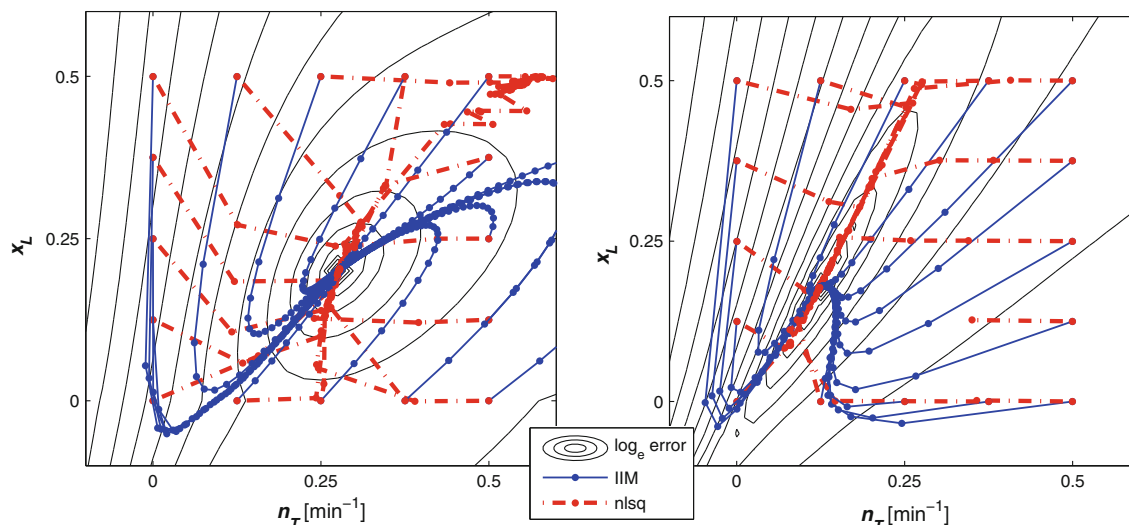


Fig. 4 Convergence paths for IIM and nonlinear least-squares for both participants and all 16 starting conditions tested. (NGT *left*, IR *right*)

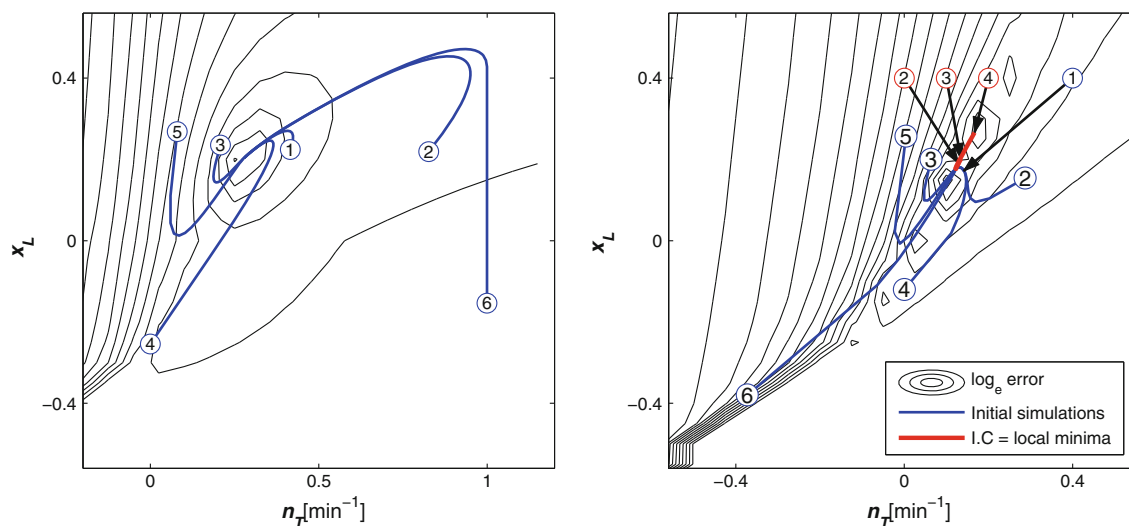


Fig. 5 Convergence of IIM from the simple initial simulations of the analytes and the local minima identified by nonlinear least-squares. Paths are numbered according to the initial simulation conditions listed in Sect. 2.3, and the local minima listed in Table 3. (NGT *left*, IR *right*)

of convergence to local minima would not be as easily observed, and thus, non-optimal parameter values would generally be reported.

The median convergence time for IIM was faster than for nonlinear least-squares. Table 2 and Fig. 4 show that the median required iterations for convergence of the nonlinear least-squares method was less than the iterative integral method. However, the overall computational requirement of IIM was significantly less than nonlinear least-squares. This result is due to the different number of forward simulations required by the two methods. While IIM requires only one simulation per iteration, the nonlinear least-squares method requires numerous simulations at each iteration to compute a Jacobian. As the model of Eqs. 7 and 8 had a saturation term, analytical solutions

were not possible. Thus, comparatively computationally expensive Picard iterations [9, 19] were used to simulate I_t and Q_t . Importantly, such non-linearity features in many physiological models and identification problems. Hence, much of the computational cost of each method is attributable to the number of forward simulation processes.

Nonlinear least-squares seem to be slightly more complex than IIM and thus could be more difficult to write into computational code form. However, there are numerous proprietary nonlinear least-squares computational packages that require the user to define the model error given certain parameter values. These packages then perform the more complex iterative steps. However, when the proprietary nonlinear least-squares packages fail to converge, an in-experienced user may not be able to correctly diagnose

and overcome the cause. Hence, the lack of robustness or transparency can result in subpar results.

Iterative integral method has a major limitation in comparison to the nonlinear least-squares method. Specifically, it cannot be used to identify non-separable parameters. While this issue is not problematic for a wide variety of models and research applications, it is impossible to use in some situations. For example, the proportional and saturation terms in Michalis–Menton formulations cannot be concurrently identified with IIM [6].

Furthermore, IIM requires the identified model parameters to be functions of the observed species (i.e. \mathbf{x} in Eq. 1). Most often, model parameters are direct functions of the measured species. However, when the identified model parameters are functions of unobserved species, re-arrangement of the model equations generally enables an expression of the model variables in terms of the observable species. Indeed, if the model parameters were not dependent on the observed species, then the model would not be a priori identifiable [1, 7, 17].

For example, the widely used Minimal Model (Equations 9 and 10) of insulin/glucose pharmacodynamics utilises three model parameters, two of which are not a direct function of glucose, the typically observed species (p_2 and p_3) [1, 2].

$$\dot{G} = p_1(G_B - G) - XG \tag{9}$$

$$\dot{X} = p_3(I - I_B) - p_2X \tag{10}$$

where G is the measured glucose (G_B denotes basal glucose); I is the interpolation of measured plasma insulin data (I_B denotes basal plasma insulin); X is a lumped insulin action and concentration parameter [$X(0) = 0$ assumed]; and p_{1-3} are identified model parameters with p_1 representing glucose-related inhibition of endogenous glucose production, and insulin sensitivity defined as p_3/p_2 .

In order to identify p_{1-3} as model parameters, Eq. 10 must be incorporated into Eq. 9 to make p_2 and p_3 functions of G . Equations 11–13 show how the Minimal Model can be defined as a single equation in terms of G with separated coefficients of the model parameters, thus enabling the IIM approach.

$$X = p_3 \int I - I_B dt - p_2 \int X dt \tag{11}$$

$$\dot{G} = p_1(G_B - G) - G \left(p_3 \int I - I_B dt - p_2 \int X dt \right) \tag{12}$$

$$G - G_B = p_1 \int G_B - G dt + p_2 \int G \int X d\tau dt - p_3 \int G \int I - I_B d\tau dt \tag{13}$$

Hence, when the Minimal Model parameters are identified with IIM, both G and X must be simulated

between iterations, these equations demonstrate the flexibility of the presented method.

This article presented the IIM approach in general and evaluated it in comparison to the nonlinear-least-squares method for a validated insulin pharmacokinetic model [12] and two indicative individuals. A two-variable case was used in this analysis to allow the convergence paths to be easily visualised. However, IIM is capable of identifying models with a greater number of parameters. This analysis enabled two distinct error-surfaces to be defined. These distinct error-surfaces showed the different iterative paths of IIM (Fig. 3). They also showed how the nonlinear least-squares methods can fail when the initial parameter estimations are located in areas of limited error gradient (Fig. 3). Furthermore, the analysis showed how the nonlinear-least-squares method located local minima in the IR participant’s error-surface (Fig. 3). Convergence to these local minima was due to the sharp valley in the error-surface limiting the efficacy of the Jacobian to identify the dominant error gradient. In effect, nonlinear-least-squares had reached convergence criteria. Equally, Fig. 5 (right) shows that the IIM overcame these issues in the cases tested.

Most importantly, IIM is robust to starting conditions, and is not susceptible to locating local minima. IIM could potentially be implemented in a wide range of physiological models as the method is quicker, more stable and more operator independent than the frequently used Levenberg–Marquardt gradient decent method.

References

1. Audoly S, Bellu G, D’Angio L, Saccomani MP, Cobelli C (2001) Global identifiability of nonlinear models of biological systems. *IEEE Trans Biomed Eng* 48(1):55–65
2. Bergman RN, Ider YZ, Bowden CR, Cobelli C (1979) Quantitative estimation of insulin sensitivity. *Am J Physiol* 236(6):E667–E677
3. Carson ER, Cobelli C (2001) *Modelling methodology for physiology and medicine*. Academic Press, San Diego
4. Chase JG, Hann CE, Jackson M, Lin J, Lotz T, Wong XW, Shaw GM (2006) Integral-based filtering of continuous glucose sensor measurements for glycaemic control in critical care. *Comput Methods Programs Biomed* 82(3):238–247
5. Docherty PD, Chase JG, Lotz T, Hann CE, Shaw GM, Berkeley JE, Mann JI, McAuley KA (2009) DISTq: an iterative analysis of glucose data for low-cost real-time and accurate estimation of insulin sensitivity. *Open Med Inform J* 3:65–76
6. Docherty PD, Chase JG, Hann CE, Lotz TF, Lin J, McAuley KA, Shaw GM (2010) The identification of insulin saturation effects during the dynamic insulin sensitivity test. *Open Med Inform J* 4:141–148
7. Docherty P, Chase JG, Lotz T, Desai T (2011) A graphical method for practical and informative identifiability analyses of physiological models: a case study of insulin kinetics and sensitivity. *Biomedical Eng Online* 10(1):39

8. Hann CE, Chase JG, Lin J, Lotz T, Doran CV, Shaw GM (2005) Integral-based parameter identification for long-term dynamic verification of a glucose-insulin system model. *Comput Methods Programs Biomed* 77(3):259–270
9. Kim C, Kim SB (2007) Modelling contaminant transport in a three-phase groundwater system with the Freundlich-type retardation factor. *Environ Technol* 28(2):205–216
10. Le Compte A, Chase JG, Russell G, Lynn A, Hann C, Shaw G, Wong X-W, Blakemore A, Lin J (2011) Modeling the glucose regulatory system in extreme preterm infants. *Comput Methods Programs Biomed* 102(3):253–266
11. Levenberg K (1944) A method for the solution of certain nonlinear problems in least squares. *Q Appl Math* 2:164–168
12. Lotz T, Chase J, McAuley K, Lee D, Lin J, Hann C, Mann JI (2006) Transient and steady state euglycemic clamp validation of a model for glycemic control and insulin sensitivity testing. *Diabetes Technol Ther* 8(3):338–346
13. Lotz T, Chase JG, McAuley KA, Shaw GM, Wong J, Lin J, Le Compte AJ, Hann CE, Mann JI (2008) Monte Carlo analysis of a new model-based method for insulin sensitivity testing. *Comput Methods Programs Biomed* 89(3):215–255
14. Lotz TF, Chase JG, McAuley KA, Shaw GM, Docherty PD, Berkeley JE, Williams SM, Hann CE, Mann JI (2010) Design and clinical pilot testing of the model based Dynamic Insulin Sensitivity and Secretion Test (DISST). *J Diabetes Sci Technol* 4(6):1195–1201
15. Marquardt DW (1963) An algorithm for least-squares estimation of nonlinear parameters. *SIAM J Appl Math* 11(2):431–441
16. McAuley KA, Berkeley JE, Docherty PD, Lotz TF, Te Morenga LA, Shaw GM, Williams SM, Chase JG, Mann JI (2011) The dynamic insulin sensitivity and secretion test—a novel measure of insulin sensitivity. *Metab Clin Exp* 60(12):1748–1756
17. Ritt JF (1950) *Differential algebra*. Am Math Soc
18. Wong X, Chase JG, Shaw GM, Hann C, Lotz T, Lin J, Singh-Levett I, Hollingsworth L, Wong O, Andreassen S (2006) Model predictive glycaemic regulation in critical illness using insulin and nutrition input: a pilot study. *Med Eng Phys* 28(7):665–681
19. Youssef IK, El-Arabawy HA (2007) Picard iteration algorithm combined with Gauss–Seidel technique for initial value problems. *Appl Math Comp* 190(1):345–355