An eigen-analysis of the relationships between model structure, discrete data, measurement error and resulting parameter identification distributions

Erin J. Mansell*, Paul D. Docherty*, J. Geoffery Chase*
Balázs Benyó**

**Department of Mechanical Engineering, University of Canterbury, Christchurch, Private Bag 4800, New Zealand (Tel: +64 3 3642987; e-mail: erin.mansell@pg.canterbury.ac.nz).*
***Department of Control Engineering and Information Technology, Budapest University of Technology and Economics, Hungary*

Abstract: Practical rather than structural identifiability is often the determining factor whether effective parameter identification is possible in a physiological model. This paper presents analysis into relationships between the population outcomes, and the original model and data properties as part of ongoing research into a deterministic approach to evaluate *a-priori* identifiability.

Data size, output noise variance and true parameter values were varied for a simple 2-parameter model with a linear regression equation $\mathbf{Ax} = \mathbf{b}$ for discrete data points. Principal Component Analysis of a Monte Carlo simulation was compared to these varied properties and the eigendecomposition of $\mathbf{A}^T\mathbf{A}$.

Principal component vectors were found to be parallel with $\mathbf{A}^T\mathbf{A}$ eigenvectors and the eigenvalues were inversely related. Principal component eigenvalues decreased in inverse proportion to data size, were scaled by the sum of squared parameter values and noise variance. $\mathbf{A}^T\mathbf{A}$ eigenvalues on the other hand were unchanged by output noise and parameter value, but increased in linear, rather than inverse proportion, to data size. The ratio of principal component eigenvalues to each other was affected by data size and some parameter values, while the $\mathbf{A}^T\mathbf{A}$ eigenvalue ratio was affected by data size only.

Deterministic relationships have been found between population parameter identification outcomes, model properties and data. If all of the factors determining principle components can be calculated then population variance can be estimated from a single set of data, facilitating confidence of individual outcomes and evaluation of practical identifiability.

Keywords: parameter identification, practical identifiability, Monte Carlo simulation, Principal Component Analysis, eigenvectors, eigenvalues, linear systems, deterministic behaviour

1. INTRODUCTION

Physiological modelling is becoming a standard approach to investigating complex biological systems to recover parameter values that cannot be directly measured (Saccomani, 2013). Nonetheless, outcomes of such parameter identification should not necessarily be accepted without evaluation of the credibility of the results and models. Structural identifiability is a discernible model property that states that under ideal data conditions the unknown parameters can be uniquely and exactly recovered from input-output relationships, without which well-posed parameter estimation cannot occur (Bellu *et al.*, 2007). However, affirmation of structural identifiability is not in itself sufficient to ensure precision in identifying true parameter values.

In recent years, analysis methods have emerged to detect and evaluate practical rather than structural non-identifiability. These methods determine when the data quantity and quality is insufficient for the size of a model, resulting in mutual interference of two or more parameters (Docherty *et al.*, 2011, Raue *et al.*, 2009, Saccomani, 2013). The result of such interference is increased parameter variability and bias with no clear cause. Thus, practical identifiability analyses are greatly beneficial when designing and utilising models identified from noisy data, since they can diagnose problems that structural identifiability analyses cannot (Docherty *et al.*, 2011).

This paper presents preliminary research into a new method of practical identifiability analysis that aims to link properties of a model, data size and measurement error to variance in results expected from a population of data. Information about population variance can be captured by a Principal Component Analysis (PCA), which is a multivariate analysis that reduces data variability to a new set of variables calculated from an eigendecomposition problem (Jolliffe, 1986). Thus, Monte Carlo (MC) simulations were carried out *in-silico* to find the

connections from *a-priori* model and data information to PCA outcomes.

2. METHODS

All analysis used MATLAB R2014a.

2.1 The model

To prevent complex effects from obscuring underlying behaviours, a simple model was used as a precursor to larger physiological models. The output, $b(t)$, for discrete time steps, $t = (1, t_n)$, was produced from the superposition of step and ramp functions (pictured Figure 1):

$$b(t) = \alpha \cdot H\left(t - t_{\frac{n}{2}}\right) + \frac{\beta}{n} \cdot t \qquad (1)$$

where n is the number of discrete time steps, H indicates a binary step, $t_{n/2}$ is rounded up to the nearest integer, and α and β are constant parameters equal to 1 unless stated otherwise.

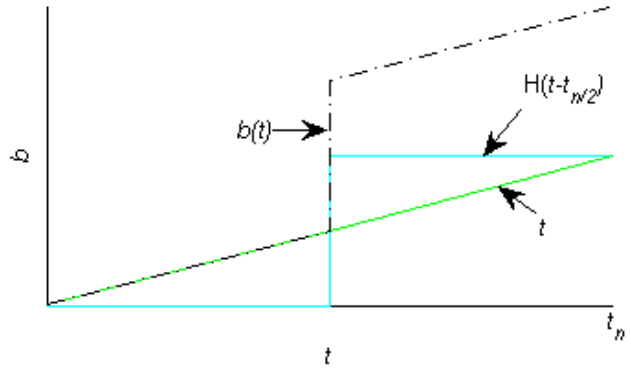

Figure 1. A graphical representation of the model

2.2 Parameter identification

Linear regression of the model for discrete output data gives:

$$\begin{bmatrix} 0 & 1/n \\ 0 & 2/n \\ \vdots & \vdots \\ 0 & t_{\frac{n}{2}-1}/n \\ 1 & t_{\frac{n}{2}}/n \\ 1 & t_{\frac{n}{2}+1}/n \\ \vdots & \vdots \\ 1 & t_n/n) \end{bmatrix} \begin{bmatrix} \alpha \\ \beta \end{bmatrix} = \begin{bmatrix} b_1 \\ b_2 \\ \vdots \\ b_{n/2-1} \\ b_{n/2} \\ b_{n/2+1} \\ \vdots \\ b_{n-1} \end{bmatrix} \qquad (2)$$

$$\mathbf{Ax} = \mathbf{b}$$

Random multiplicative white noise was introduced to **b** to create an imperfect data set ($\hat{\mathbf{b}}$):

$$\hat{\mathbf{b}} = \mathbf{b} \odot (1 + \mathbf{e}) \text{ for } \mathbf{e} \subset \mathbb{N}(0, \sigma^2) \qquad (3)$$

where the $\odot$ symbol indicates element-wise vector multiplication.

The least-squares solution ($\hat{\mathbf{x}}$) of the variables for α and β to the noisy data set was calculated as:

$$\hat{\mathbf{x}} = (\mathbf{A}^{\mathrm{T}}\mathbf{A})^{-1}\mathbf{A}^{T}\hat{\mathbf{b}} \qquad (4)$$

2.3 Monte Carlo simulation and variables

Parameter outcomes from multiple data sets 1 through *r*, each with random multiplicative white noise of variance σ^2, were stored in a matrix:

$$\mathbf{X} = [\hat{\mathbf{x}}_1\ \hat{\mathbf{x}}_2 \cdots \hat{\mathbf{x}}_r]^T \qquad (5)$$

This process was carried out using 10^6 repeats for each combination of noise variance (σ^2), true parameter values (**x**), and data length (*n*). Several testing schemes, described in Table 1, were investigated. Schemes 1a-c used single combinations of these properties while schemes 2-4 used variable inputs over a range in order to capture trends.

Table 1. Variable definitions for Monte Carlo simulation schemes, where *n* = data size, x is the true solution to the parameters, and σ = output error standard deviation

Scheme	Constants	Variables
1a	$n = 10$, $\mathbf{x} = [1,1]^{\mathrm{T}}$, $\sigma = 0.1$	none
1b	$n = 10$, $\mathbf{x} = [1,1]^{\mathrm{T}}$, $\sigma = 0.2$	none
1c	$n = 50$, $\mathbf{x} = [1,1]^{\mathrm{T}}$, $\sigma = 0.2$	none
2	$n = 10$, $\mathbf{x} = [1,1]^{\mathrm{T}}$	$\sigma = 0,0.1,0.2,\ldots,1$
3a	$n = 10$, $\sigma = 0.1$	$\mathbf{x} = [1,\gamma]^{\mathrm{T}}$, $\gamma = 4,8,\ldots,100$
3b	$n = 10$, $\sigma = 0.1$	$\mathbf{x} = [\gamma,\gamma]^{\mathrm{T}}$, $\gamma = 4,8,\ldots,100$
3c	$n = 10$, $\sigma = 0.1$	$\mathbf{x} = [\gamma,\gamma^{1.5}]^{\mathrm{T}}$, $\gamma = 4,8,\ldots,100$
4	$\sigma = 0.1$, $\mathbf{x} = [1,1]^{\mathrm{T}}$	$n = 4,8,\ldots,100$

2.4 Analysis

For schemes 1a-c, two dimensional objective surfaces were created over a range of α and β of -0.5 to 2.5 by taking the norm of residual error between the output created by these combinations of **x** and that of true output (**b**):

$$\psi = \|\mathbf{Ax} - \mathbf{b}\|_2 \qquad (6)$$

Correlation between the matrix equation and resulting MC scatter was sought by carrying out eigendecomposition on the 2×2 $\mathbf{A}^{\mathrm{T}}\mathbf{A}$ matrix, and comparing it to outcomes of the PCA on the **X** matrix. PCA first involves calculation of a mean-centred matrix (**B**) that contains both columns of **X** in Equation 5 with their mean value subtracted. This is followed by an eigendecomposition of the covariance matrix (**C**), defined:

$$\mathbf{C} = \frac{1}{r-1}\mathbf{B}^{\mathrm{T}}\mathbf{B} \qquad (7)$$

Both PCA and $\mathbf{A}^T\mathbf{A}$ eigenvectors were compared and eigenvalue trends correlated to other independent variables.

3. RESULTS

Eigen-decomposition analysis showed that the $\mathbf{A}^T\mathbf{A}$ eigenvectors were parallel with the principal components of the parameter distribution from the MC analysis of scheme 1a, Figure 2. PCA produced the greatest eigenvalue in the direction of greatest spread, while the smallest eigenvalue of $\mathbf{A}^T\mathbf{A}$ was in this direction.

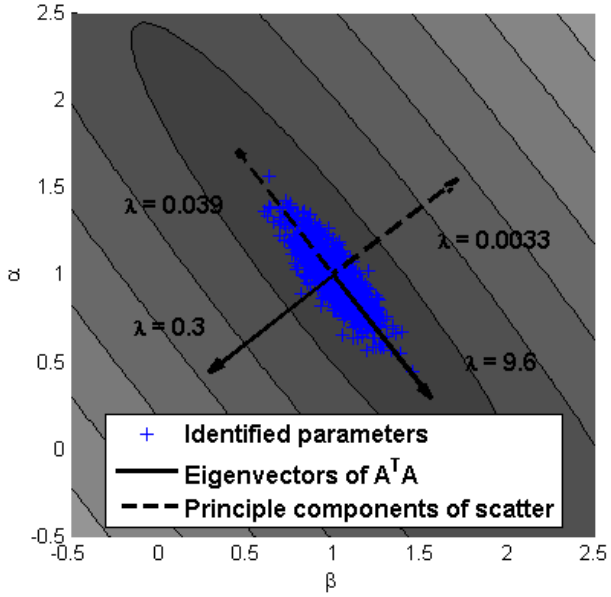

Figure 2. A comparison of $\mathbf{A}^T\mathbf{A}$ eigenvectors and principal components of parameter identification scatter, pictured on an error objective surface. $\sigma = 0.1$, $n = 10$.

Doubling the standard deviation of noise in the output data (scheme 1b) did not affect the eigenvector direction but created a larger distribution of parameters, as seen in Figure 3. The change in output noise did not affect the $\mathbf{A}^T\mathbf{A}$ eigenvalues but PCA eigenvalues were both quadrupled in value.

Increasing the data quantity by 5 times (scheme 1c) reduced the parameter spread to a comparable width of scheme 1a although the output noise was still that of scheme 1b. In this case, increased steepness in the objective surface was accompanied by greater $\mathbf{A}^T\mathbf{A}$ eigenvalues, 533% and 435% of their scheme 1a-b values, and decreased PCA eigenvalues, at 13% and 23% of their scheme 1b values. There was also a reduced eccentricity of the elliptical contours in the objective surface and an alteration in both the eigenvalue ratios (λ_1/λ_2), increasing for $\mathbf{A}^T\mathbf{A}$ and decreasing for PCA, which in both cases corresponded to a reduced difference between λ_1 and λ_2.

Scheme 2 was effectively a further extrapolation of scheme 1a to 1b, investigating more fully the effect of output noise on the PCA eigenvalues, though the $\mathbf{A}^T\mathbf{A}$ eigenvalues were unaffected. The results gave a strong linear correlation between PCA eigenvalues and noise variance ($R^2 = 1.0000$ for $\lambda_{1\text{-}2}$), with the full relationships listed in Table 3. The eigenvalues had zero-value for zero noise and the ratio between eigenvalues, λ_1/λ_2, was consistent at approximately 11.8 through all noise values.

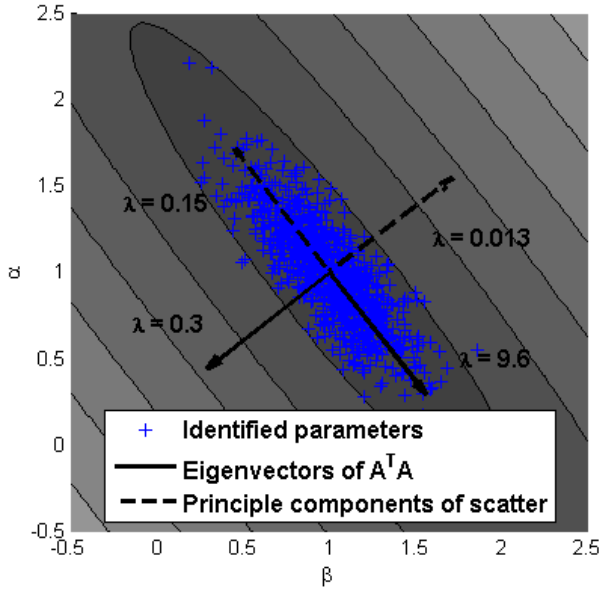

Figure 3. A comparison of $\mathbf{A}^T\mathbf{A}$ and PCA eigenvectors with double the noise from Figure 2. $\sigma = 0.2$, $n = 10$.

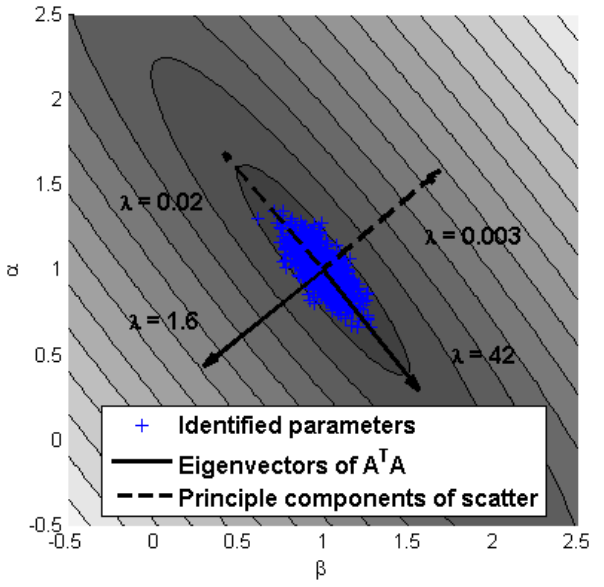

Figure 4. A comparison of $\mathbf{A}^T\mathbf{A}$ and PCA eigenvectors now with times the data compared to Figure 3. $\sigma = 0.2$, $n = 50$.

Like the effect of noise, changes to the parameter values in $\mathbf{x}$ influenced PCA and also had no effect on the properties of $\mathbf{A}^T\mathbf{A}$. Scheme 3a and 3b both resulted in strong linear correlation between the eigenvalues of the PCA and the square of the variable γ (relationships listed in Table 3, $R^2 = 1.0000$). However, eigenvalues $\lambda_{1\text{-}2}$ for scheme 3b were approximately 4-5 times greater than those of 3a. In scheme 3c, where one parameter was equal to $\gamma^{1.5}$, the PCA eigenvalues were now proportional to γ^3 (Table 3, $R^2 = 1.000$). The ratio PCA eigenvalues fitted well with a two-term power model: $\lambda_1/\lambda_2 = a\gamma^b + c$ for both schemes 3a and 3c while 3b

showed no changes in the ratio, seen in Figure 5. Table 2 gives the value of these power model parameters and the R^2 values.

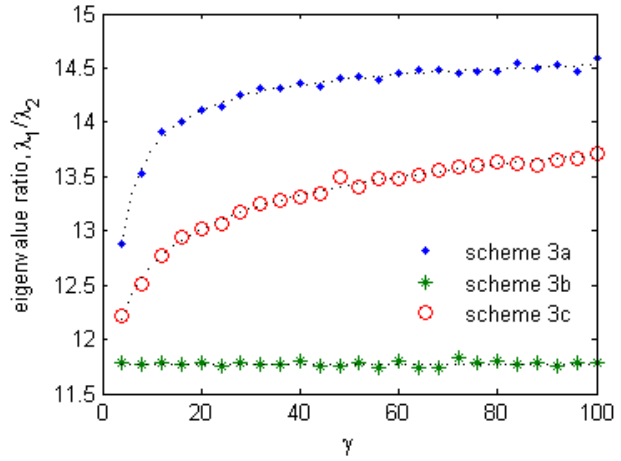

Figure 5. Results for PCA eigenvalue ratio compared with changes in γ, which influences **x**. Schemes 3a and 3c are fitted to two-term power models while 3b is fitted to a horizontal function.

The results of scheme 4 showed that the $\mathbf{A^TA}$ eigenvalues were linearly proportional to data size while the PCA eigenvalues were inversely so (Table 3, $R^2 = 1.000$). Ratios of λ_1/λ_2 were affected by data size in both cases. A two-term power model was fitted to this trend, Figures 6-7 (PCA $R^2 = 1.0000$, $\mathbf{A^TA}$ $R^2 = 0.997$). However, the residual error (not shown), particularly for $\mathbf{A^TA}$ data, reveals behaviour uncaptured by these models.

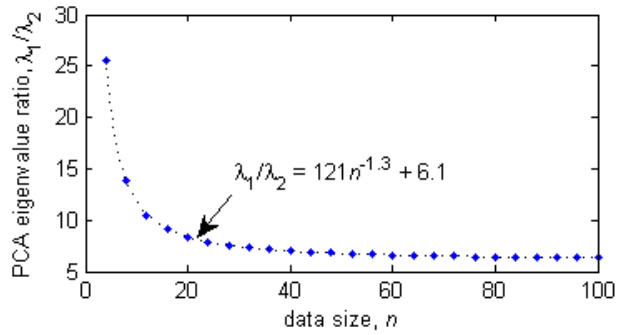

Figure 6. Results for PCA eigenvalue ratio against n.

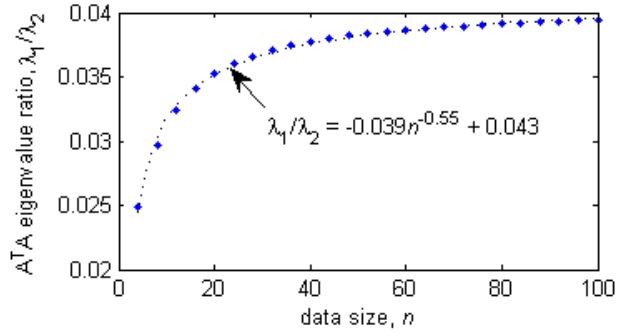

Figure 7. Results for $\mathbf{A^TA}$ eigenvalue ratio against n.

Table 2. Model fits for eigenvalue ratio compared to the variable γ for two schemes where x = f(γ).

Model	Sch.	a	b	c	R^2
$\lambda_1/\lambda_2 = a\gamma^b + c$	3a	-4.74	-0.674	14.7	0.993
	3b	0	-	11.8	-
	3c	-5.46	-0.124	16.8	0.994

Table 3. Relationships found between model and data variables against the eigenvalues of PCA and $\mathbf{A^TA}$ eigenvalues against variables for schemes 2-4.

Sch.	PCA relations	$\mathbf{A^TA}$ relations
2	$\lambda_1 = 3.88\sigma^2$	$\lambda_1 = 0.30$
	$\lambda_2 = 0.33\sigma^2$	$\lambda_2 = 9.6$
3a	$\lambda_1 = 0.0090\gamma^2 + 0.35$	$\lambda_1 = 0.30$
	$\lambda_2 = 0.00062\gamma^2 + 0.035$	$\lambda_2 = 9.6$
3b	$\lambda_1 = 0.039\gamma^2 - 0.041$	$\lambda_1 = 0.30$
	$\lambda_2 = 0.0033\gamma^2 + 0.0017$	$\lambda_2 = 9.6$
3c	$\lambda_1 = 0.011\gamma^3 + 65$	$\lambda_1 = 0.30$
	$\lambda_2 = 0.00079\gamma^3 + 6.0$	$\lambda_2 = 9.6$
4	$\lambda_1 = (4.4n - 19)^{-1}$	$\lambda_1 = 0.032n - 0.027$
	$\lambda_2 = (26n - 41)^{-1}$	$\lambda_2 = 0.80n + 1.5$

4. DISCUSSION

The relationships between eigenvectors of the model equation matrix ($\mathbf{A^TA}$) and Monte Carlo parameter spread shown in Figures 1-3, show deterministic behaviour that could contribute to advances in *a-priori* model identifiability analysis. Should all the factors determining PCA eigenvalues be ascertained in a useable and broadly applicable manner, then there is potential to estimate wider outcomes of a population of data when only a single set is processed, as in some cases with real data. Several linearised relationships have been discerned for a simple model ($R^2 = 1$).

Principal component information could be further processed into useful statistical measures such as variance or confidence limits on identified parameters *a-priori*. For physiological models and analysis, these, in turn, could be used to evaluate the certainty of outcomes for diagnosis or control, or the degree of practical identifiability of model parameters with assumed data. Infinite confidence intervals indicate practical non-identifiability (Raue *et al.*, 2009) and since identifiability is a continuous artefact (Docherty *et al.*, 2011), smaller finite intervals could be useful in evaluating whether the degree of identifiability is acceptable, subject to the needs of the research or application. Where multiple models of a system are available, the practical identifiability of each could be compared to determine the best model for the data.

It is a useful outcome that the effect of noise in the output data on the resulting data spread was linearly correlated with noise variance by the relationship: $\lambda_{PCA} \propto \sigma^2$ with no changes to the ratio between eigenvalues. This result makes intuitive sense since noise drives the spread of identified parameters. With no noise, the true parameters would be identified and the spread would be zero in all directions, even for a practically non-identifiable, but structurally identifiable model. This relationship is likely applicable over a range of models where noise is confined to output data and is zero-mean.

The results clearly indicate a relationship between the PCA eigenvalues and the value of **x**. This outcome was expected since the identified parameter set, $\hat{\mathbf{x}}$, is dependent on the noisy $\hat{\mathbf{b}}$ vector, defined Equation 3, which can also be defined as a function of the original parameter set:

$$\hat{\mathbf{b}} = \mathbf{Eb} = \mathbf{EAx} \tag{8}$$

where **E** is a diagonal matrix of (1+**e**). Thus substitution into Equation 4 yields an identified parameter definition of:

$$\hat{\mathbf{x}} = (\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\mathbf{EAx} \tag{9}$$

The parameters **x** are further propagated into the data storage matrix, **X**, and into the covariance matrix, **C**, before eigendecomposition where the eigenvalues for a 2x2 matrix can be calculated with:

$$\lambda = \frac{T_r}{2} \pm \sqrt{\frac{T_r^2}{4} - D} \tag{10}$$

where T_r and D are the trace and determinant of the matrix respectively. The calculation of these eigenvalues therefore appears to be deterministic, especially since it has already been shown that the effect of the noise can be described purely by the variance. Given the convolution involved in the substitution of full definitions of $\hat{\mathbf{x}}$ into the PCA eigenvalue equation, results drawn instead from MC simulations were highly valuable.

The evidence in Table 3 suggests that the eigenvalues are scaled by the dot product of **x** with itself, which is the sum of squared parameters:

$$\lambda_{PCA} \propto \mathbf{x} \cdot \mathbf{x} = \sum x_i^2 \tag{11}$$

Both eigenvalues in each case are affected in the same manner proportionally and the order of that proportionality is the square of the highest order by which an **x** parameter changes. When one or both parameters was equal to γ then λ_{PCA} were strongly proportional to γ^2, though with greater magnitude for scheme 3b than 3a which shows an accumulative effect of changes in the two parameters. Further, when one parameter was equal to $\gamma^{1.5}$ then λ_{PCA} were strongly proportionality to γ^3. In addition to this relationship, changing **x**-parameters altered eigenvalue ratios but only when parameters were affected to different orders than each other, otherwise the ratio was constant, as with scheme 3b when $\mathbf{x} = [\gamma,\gamma]^T$. For cases 3a and 3c, the eigenvalue ratio changes fitted well with two-term power models where the exponent term on γ was between -1 and 0 in both cases. This outcome indicates that the eigenvalue ratio is related to the relative difference in appearance or in this case magnitude of the two species in the model: the step and ramp.

The relationships of $\mathbf{A}^T\mathbf{A}$ and PCA eigenvalues to n and n^{-1} respectively for the step-ramp model (Table 3) highlights the inverse nature of the two. The PCA eigenvalues describe the level of spread in the direction of the principal components while the $\mathbf{A}^T\mathbf{A}$ eigenvalues could be described as evaluating the steepness of the objective surface in the principal directions of the surface geometry. As the quantity of data increases, the steepness of the objective surface increases, confining the MC spread to a smaller area. There was also an n-dependence for both $\mathbf{A}^T\mathbf{A}$ and PCA eigenvalue ratios, λ_1/λ_2, the latter of which fitted well to a two-term power model (Figure 6) where the exponent of n was -1.32. Similar to the case with the changing parameter values, the ratio change may be related to the relative changes in magnitude of the step and ramp as they appear in the matrix. For this model, as n increases, the norm of each column in **A** increases but at different rates due to the different forms of the species.

There are several limitations to this first analysis based on our findings. The foremost limitation is its restriction to systems with separable parameters where a matrix equation $\mathbf{Ax} = \mathbf{b}$ can be defined. There may also be issues with parameter models that yield non-elliptical objective surfaces, as they are poorly described by PCA. This issue could, in some cases, be remedied by identifying related parameters and inferring the desired parameter, for example identifying and evaluating $1/x_i$ instead of x_i. Another small limitation is that true noise variance will not be a known quantity in real data, though an educated estimate would likely be sufficient in most cases. Since PCA eigenvalues are dependent on **x**, systems with low levels of practical identifiability and subsequent reduced accuracy in $\hat{\mathbf{x}}$ will likely influence how the identifiability of the system is perceived by the analysis. Model systems with $\mathbf{A} = f(\mathbf{x})$ have been shown in unpublished results to introduce much larger error than could be accounted for by the analysis, and further research needs to be done to overcome this.

Using a simple model was extremely useful for discerning some of the relationships between $\mathbf{A}^T\mathbf{A}$ and PCA, all of which could contribute in some way to fundamental relations for more complex biological models. Ultimately, PCA eigenvalues could be robustly calculated with $\mathbf{A}^T\mathbf{A}$, circumventing the need for population-wide data. There is still a missing link between changes in the properties of the **A** matrix and the resultant scaling of the eigenvalues and the altered eigenvalue ratio. All relationships must be found for the simple case prior to a deterministic approach for all models can be developed. Furthermore, direct links between PCA and parameter confidence estimates require research, though there appears to be deterministic relationships between the two.

Models can be used to measure, diagnose and predict the behaviour of many phenomenon. However, even well justified model formulations can cause failure of model-based analyses. Structural non-identifiability occurs when multiple model parameters trade off to describe the same behaviour. While

some methods for determining model structural identifiability have been in existence for many decades (Pohjanpalo, 1978, Bellman and Åström, 1970, Ritt, 1950), there remains a consistent stream of research in this field (Audoly *et al.*, 2001, Bellu *et al.*, 2007, Audoly *et al.*, 1998). This research is driven, in part, by the group that proposed the leading model of glycaemic dynamics (Bergman *et al.*, 1979) trying to determine why their model fails to perform adequately for individuals with established diabetes – the key demographic (Cobelli *et al.*, 1998, Pillonetto *et al.*, 2003, Pillonetto *et al.*, 2002). More recently it has been discovered that the cause of this failure was practical rather than structural identifiability (Docherty *et al.*, 2011). The approach to practical identifiability analysis in this paper is presently descriptive rather than predictive but the relationships found and deterministic nature of the MC analyses implies that the concept could become a predictive a-priori practical non-identifiability analysis. This is a highly novel area of research with only one other group in the field (Raue *et al.*, 2009, Raue *et al.*, 2014, Saccomani, 2013).

5. CONCLUSIONS

There are deterministic links between properties of the step-ramp model equation, data size and measurement noise to the resulting principal component analysis of a Monte Carlo simulation. Eigenvectors for $\mathbf{A}^T\mathbf{A}$ and PCA line up directly and the eigenvalues are inversely related. $\mathbf{A}^T\mathbf{A}$ eigenvalues describe magnitude of steepness in the objective error surface, increasing linearly with data size for the model, and PCA eigenvalues describe the magnitude of spread from a population of data, with an inverse relationship to data size. Noise in output data increased PCA eigenvalues in proportion to noise variance. Principal component eigenvalues also appear to be scaled dot product of the parameter set, $\mathbf{x} \cdot \mathbf{x}$, and differing orders of change between parameters alters eigenvalue ratio, likely due to different comparative magnitudes of the step and ramp in the model. Data size also produced eigenvalue ratio changes, but in both PCA and $\mathbf{A}^T\mathbf{A}$, likely also related to comparative step-ramp magnitude.

Most but not all factors for direct PCA eigenvalue calculation have been ascertained for the simple step-ramp model. Future research will include aims to find the missing links as well as research more complex biological models, and interval estimation on the basis of PCA. Confidence intervals estimated for a single parameter identification outcome, as opposed to a whole population, would be useful where little information is available. The level of confidence in parameters for diagnosis and control would be useful, along with the ability to evaluate the practical identifiability of a model and, where applicable, choose the best model for a set of data.

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