

A Local Sensitivity Analysis Method for Developing Biological Models with Identifiable Parameters: Application to L-type Calcium Channel Modelling

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Abstract—Computational cardiac models provide important insights into the underlying mechanisms of heart function. Parameter estimation in these models is an ongoing challenge with many existing models being overparameterised. Sensitivity analysis presents a key tool for exploring the parameter identifiability. While existing methods provide insight into the significance of the parameters, they are unable to identify redundant parameters in an efficient manner. We present a new singular value decomposition based algorithm for determining parameter identifiability in cardiac models. Using this local sensitivity approach, we investigate the Mahajan 2008 rabbit ventricular myocyte L-type calcium current model. We identify non-significant and redundant parameters and improve the Ical model by reducing it to a minimum one that is validated to have only identifiable parameters. The newly proposed approach provides a new method for model validation and evaluation of the predictive power of cardiac models.

I. INTRODUCTION

Cardiac mathematical modelling is widely used to describe and predict physiological functions of the heart, as well as to reduce significantly the cost of experimental studies [5], [6]. Calcium ions play a significant role in regulation of both electrical and mechanical activity of the heart [1]. One of the most important cardiac ionic currents is the L-type calcium current (I_{CaL}) as it enables the excitation-contraction coupling by allowing initial entry of Ca^{2+} inside the cell. Mutation or blockage of L-type calcium channels (LCCs) can lead to cardiovascular disorders (e.g. Timothy syndrome), causing cardiac arrhythmias and in some cases sudden cardiac death. Therefore, the use of mathematical I_{CaL} models as a tool to explore the underlying mechanisms and cellular effects of I_{CaL} can be extremely important, in particular when investigating calcium related arrhythmias.

One of the common drawbacks of complex nonlinear mathematical cardiac models is overparameterisation. In this paper we present a new local sensitivity analysis method which allows to reliably assess parameter identifiability in a given model for a given set of experiments. Using the newly developed method, we (i) analyse the I_{CaL} formulation in the Mahajan 2008 model [4], (ii) demonstrate the existing

overparameterisation, and (iii) develop a reduced model which can reproduce the key properties of I_{CaL} .

II. METHODOLOGY

Local sensitivity analysis is an important tool for examining parameter identifiability¹ in biological models [2], [3]. Issues encountered with parameter estimation include model overparameterisation, and, specifically, the following challenges are faced: (i) varying parameter values locally produces non-significant shifts on the model output, (ii) parameters may be linearly dependent, so that removing one redundant parameter and at the same time varying the other linearly dependent parameters accordingly yields the same model output.

A. Parameter Identifiability and Local Sensitivity Analysis

To investigate the significance and redundancy of model parameters, local sensitivity methods can be used. The local effect of a parameter P_j on the output variable y_i at time t can be described by sensitivity factor J_{ij}

$$J_{ij}(t) = \frac{\partial y_i(t)}{\partial P_j} \quad (1)$$

with sensitivity matrix J being constructed such that each column describes the sensitivity of all outputs with the respect to a particular parameter.

Existing approaches include, for example, Eigenvalue Decomposition (EVD) and QR based algorithm developed by Fink et al. 2009 [2], where (1) the EVD is performed on $J^T J$ (or on J if J is a square matrix) and eigenvalues normalised with respect to the maximum eigenvalue are recorded, and (2) the QR decomposition is performed on $J^T J$ (or on J if J is a square matrix) to obtain a permutation vector E , so that the final score is calculated by associating the normalised eigenvalues with the parameters according to E . Such existing methods may provide partial insight into the significance of the parameters. However, even though this approach helps in

¹Parameter is defined as identifiable if it is both significant and non-redundant.

categorising parameters according to whether or not these are identifiable or non-identifiable, it cannot determine the cause of non-identifiability. In particular, such approach is unable to identify redundant parameters in an efficient manner.

To identify redundant and non-significant parameters in an efficient manner, we propose a new Singular Value Decomposition (SVD) based approach.

Newly Developed SVD Based Parameter Identifiability Algorithm: While the above EVD approach focuses on identifying the most significant parameters, the newly proposed SVD approach focuses on identifying the redundant and least significant parameters. Specifically, information about the redundant parameters can be determined by investigating linear dependence of the columns of J . In particular, in the proposed method,

- (a) Singular value decomposition is performed on J such that

$$J = USV^*, \quad (2)$$

where U is an m by n unitary matrix, S is a diagonal matrix, V is an n by n unitary matrix and V^* denotes the conjugate transpose of V ;

- (b) Linearly dependent parameter subset(s) are identified by investigating vectors v_i which span the null space of J , so that

$$J * v_i = 0, \quad (3)$$

where v_i defines the subset of the singular vectors that correspond to vanishing values of J .

The final score for each parameter is calculated by summing the contributions of the parameter in each of the parameters' directions in the space spanned by the sensitivity matrix, represented by entries in V and associated with corresponding singular values.

B. Cardiac Modelling and Numerical Simulations

For parameter identifiability studies, the Mahajan 2008 I_{CaL} 7-state Markov Model of rabbit ventricular myocyte L-type Calcium Current [4] is used. We choose the Mahajan 2008 I_{CaL} model as it is one of the most advanced I_{CaL} models, being developed using both training and validation data sets. Specifically, it was derived based on experimental data when fitting the transition rates as well as other parameters related to voltage- and calcium-dependent inactivation of I_{CaL} . Table II summarises the training and validation protocols.

All models and methods are coded using MATLAB R2008a. The ordinary differential equations are solved using ode15s, with the maximum relative error tolerance of integration set to 10^{-6} .

To examine parameter identifiability (and, if required, to reduce the model to include only identifiable parameters), we need to identify model parameters of interest as well as experimental protocols (both training and validation sets) used to estimate these parameters (see Section below).

C. Experimental and Simulation Protocols and Choice of Model Parameters

In this work, we examined the influence of 30 model parameters on the I_{CaL} shape using local sensitivity analysis methods: EVD and SVD. Protocols and parameters investigated are summarised below in Tables I and II. The comparison between two different local sensitivity methods is performed to assess their respective strengths, and the results are summarised in Section III.

We assess the parameter estimation of voltage-dependent inactivation (VDI) and calcium-dependent inactivation (CDI) of I_{CaL} related parameters using training experimental protocols as described in [4]. We consider voltage clamp protocols, where standard rectangular pulse protocols are delivered as step pulses from 30 to +30 mV in 10 mV increments from a holding potential of -80 mV, holding for 300 ms at each step, under various conditions, namely (i) control, (ii) depleted sarcoplasmic reticulum (SR), (iii) 1.8 mM Ba, where Barium (Ba^{2+}) is introduced instead of extracellular calcium of 1.8 mM Ca_e . As in [4], we use separate protocols to estimate CDI and VDI transition rates. Specifically, to fit voltage-dependent inactivation I_{CaL} transition rates, we fit VDI related parameters to reproduce the I_{CaL} recorded under voltage clamp with SR-depleted and 1.8 mM Ba. To fit CDI related parameters, both control voltage clamp and SR-depleted (with 1.8 mM Ca^{2+}) protocols are used.

To mimic the estimation procedure in [4], we split parameters of interest into the following three subsets: (a) parameters involved only in the CDI pathway (pure CDI parameters), (b) parameters involved only in VDI pathway (pure VDI parameters), and (c) parameters involved in both pathways (shared CDI and VDI parameters). The list of parameters used for estimation² is summarised in Table I. I_{CaL} related parameters which can be uniquely determined by the independent fitting from the above set of experiments are excluded from the list of parameters of interest shown in Table I. In particular, P_{ca} (LCC open probability), g_{ca} (maximum conductance of LCC), as well as R(V) related parameters are not used for sensitivity studies in this work, and hence not shown in Table I, as these are estimated using independent set of experiments such as the density of LCCs, maximum conductance rate of LCC, and voltage clamp recovery protocol, respectively.

III. RESULTS AND DISCUSSION

In our sensitivity studies outlined below, we use protocols summarised in Table II to perform the following analysis. First, we perform sensitivity analysis using the training protocols to determine whether or not the CDI, VDI and shared parameters are identifiable, and compare results of applying EVD and

²Often parameters presented as model parameters in Tables inside the papers do not form the full list of parameters that the model contains and which were estimated based on the experimental data. For instance, as shown in Figure 2 in Equation for T_{Ca} , the value of 0.1 is not listed as a parameter in [4], yet it is one of the parameters which was fitted by [4] using the training data sets. Thus, one has to carefully define the list of model parameters for estimation.

TABLE I
 I_{CaL} RELATED PARAMETERS IN THE MAHAJAN 2008 MODEL

Category	I_{CaL} related parameters
only VDI related	k2t s1t k1t const-tauba
only CDI related	cpt cat k2 tca const-Tca2 const-S const-k1 power-Tca const-Tca1 power-fca const-fca
VDI and CDI shared	taupo r1 r2 s6 vx sx tau-3 vyr const-pr const-ps const-poinf syr vy sy const-k3

TABLE II
EXPERIMENTAL PROTOCOL AND CORRESPONDING SIMULATED PROTOCOL
USED FOR THE MAHAJAN 2008 I_{CaL} SENSITIVITY ANALYSIS

Experimental Protocols in [4]	Simulations Performed
Training protocols:	
Voltage step clamp under normal conditions	Original model parameters are used
Voltage step clamp under SR depleted conditions where SR uptake and release are blocked by drugs	Flux from SR is zeroed; Submembrane Ca^{2+} is clamped to its initial value
Voltage step clamp under i.e. Barium protocol: Barium influx instead of Calcium to remove CDI of I_{CaL}	CDI transition rates are turned to zero
Validation protocols:	
AP clamp	Original model parameters are used

SVD methods, highlighting the advantages and disadvantages of each. The sensitivity results are verified to check if the non-identifiable parameters can be removed and whether or not the reparameterised newly proposed reduced I_{CaL} model

reproduces the original model behaviour under application of training protocols. Finally, we validate the newly proposed reduced I_{CaL} model to confirm that it contains only identifiable parameters and is able to reproduce the results of the original model under application of validation protocols.

A. I_{CaL} Model and Parameter Identifiability

Table III shows the sensitivity results of EVD and SVD methods. The newly developed SVD method provides information both on non-significant parameters and linearly dependent parameter subset(s) (hence, redundant parameter(s)). Further detailed comparison of the sensitivity results obtained by the EVD and SVD methods is presented in Table IV, where the results are shown for four parameters (Tca , $constTca2$, $constTca1$, cpt) which were identified as non-significant or linearly dependent by the newly developed SVD method.

As discussed in Section II-A, while the EVD method can group parameters as identifiable and non-identifiable, it cannot distinguish the cause of the non-identifiability of parameters, i.e. whether or not the non-identifiable parameters are non-significant or linearly dependent. Moreover, as shown in Table III, the EVD method identified a larger number of non-identifiable parameters than the SVD method. However, these results are misleading, since the normalisation according to the largest eigenvalue (inherent feature of the EVD method, Section II-A) may lead to false results sometimes as the parameter score may not accurately correlate with the parameters' significance. For example, results in Figure 1 illustrate that some of the parameters found as non-identifiable by the EVD method are actually significant. Specifically, as demonstrated in Figure 1, parameters $power - Tca$ and $power - fca$, which were found to be non-identifiable by the EVD method, actually have a significant effect on the shape of I_{CaL} , hence the EVD method is misleading in suggesting that there parameters are non-identifiable.

B. Reduced I_{CaL} Model with Identifiable Parameters

The mathematical formulation of the I_{CaL} 7-state Markov model is shown in Figure 2, where the non-identifiable parameters obtained by the SVD method (Table IV) are highlighted by arrows and boxes. To improve the I_{CaL} model, we reduce the model to exclude the non-identifiable parameters. Specifically, the reduced I_{CaL} model is obtained by removing non-significant and redundant parameters, where, if any redundant parameters were found, the reduced model would be a reparameterised version of the original model³.

As demonstrated in the upper panel of Figure 3, removal of parameter $constTca2$, which was identified as non-significant by the SVD method, indeed yields no effect on the I_{CaL} current under voltage clamp experiment. Moreover, similarly no effect is seen on I_{CaL} shape when $constTca2$ is removed

³When removing redundant parameter(s) from the original model, the remaining linearly dependent parameter(s) are refitted accordingly in the newly obtained reduced model to accommodate for the removal of the redundant parameter(s).

TABLE III
PARAMETER IDENTIFIABILITY RESULTS FOR THE TRAINING SET
PROTOCOLS FROM TABLE II USING EXISTING EVD AND THE NEWLY
DEVELOPED SVD ALGORITHMS.

Parameter category	Non-Identifiable parameters found by each method:	
	Existing Eigenvalue Decomposition algorithm	Newly developed SVD algorithm
only CDI related	power-fca power-Tca k2 tca constTca1 const-k1 constTca2 const-s1	Linearly dependent: cpt tca constTca1 Non-significant: constTca2
only VDI related	None	None
VDI and CDI shared	r2 syr sy tau3 sx	None

TABLE IV
LOCAL SENSITIVITY RESULTS ON THE I_{CaL} MAHAJAN 2008 RABBIT
MODEL USING EVD AND SVD BASED ALGORITHMS

Parameter	Existing Eigenvalue Decomposition Algorithm	Newly developed SVD Algorithm
<i>constTca2</i>	Low score	Non-significant Non-redundant
<i>Tca</i>	Medium/High score	Highly significant Linearly dependent
<i>constTca1</i>	Low score	Medium significant Linearly dependent
<i>cpt</i>	High score	Medium/Low significant Linearly dependent

under application of voltage clamps under SR depleted conditions and(or) Barium protocols described in Table II (data not shown).

Figure 3 shows results of removal of the redundant parameter *cpt*, which is chosen to be the one to be removed as among the three linearly dependent parameters it is the least significant (see Table IV). Removal of *cpt* parameter (red curve, lower panel of Figure 3) without reparameterization of the model affects the I_{CaL} shape, which is consistent with the SVD method results, as the parameter was identified as linearly dependent but has not been found to be non-significant. As expected, however, after reparameterising the model upon the removal of the redundant *cpt* parameter, the resulting model produces I_{CaL} results identical to the control case (green curve, lower panel of Figure 3) upon application of voltage clamp protocols which were used to identify the parameter identifiability. Similar results are obtained when applying voltage clamps under SR depleted conditions and(or)

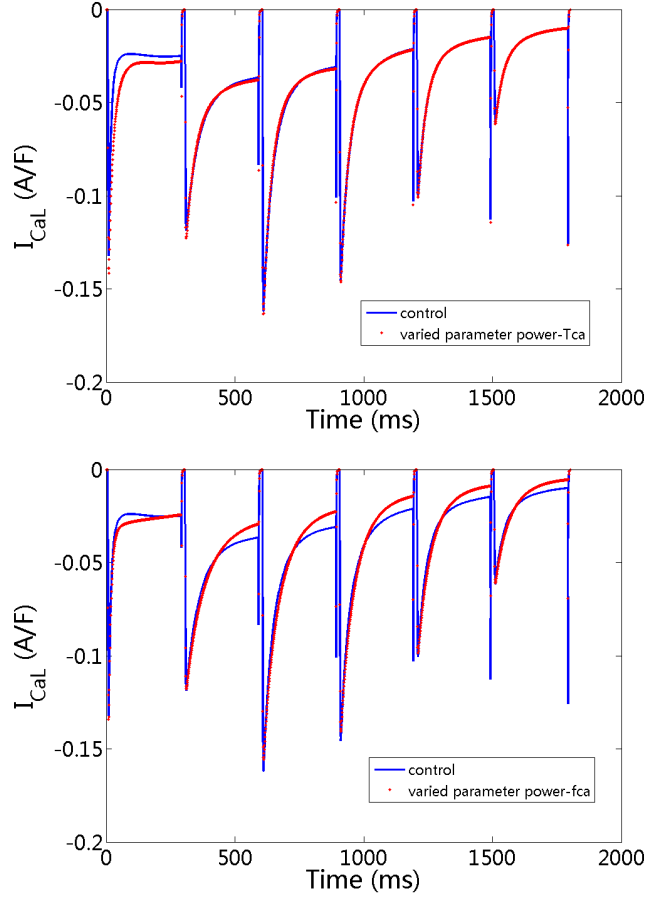


Fig. 1. I_{CaL} plot in normal cell voltage clamp before and after varying power-Tca (4 to 1) (top plot), and power-fca (3 to 1) (bottom plot)

Barium protocols described in Table II (data not shown).

Next, by applying SVD analysis to the reduced I_{CaL} model, we validated that the new model contained none non-identifiable parameters, which also indicates that the model of a given formulation contains a minimum set of parameters required to describe the I_{CaL} recordings under the given voltage clamp protocols, summarised in Table II.

C. Validation of the Reduced I_{CaL} Model

Previous sections focused on the training experimental protocols in order to identify whether or not the model is overparameterised, and to reduce the model to a minimum one that contains only identifiable parameters when tested against the training data. In this Section, we validate the new reduced I_{CaL} model using validation protocol sets to confirm that the newly proposed model is able to reproduce the key properties. Also, the success of testing the validation protocol sets would also be indicative of whether or not the choice of training protocols is reasonable.

As demonstrated in Figure 4, applying the AP clamp, which is the validation protocol used by the Mahajan 2008 [4] (see Table II), yields same results whether the original (blue

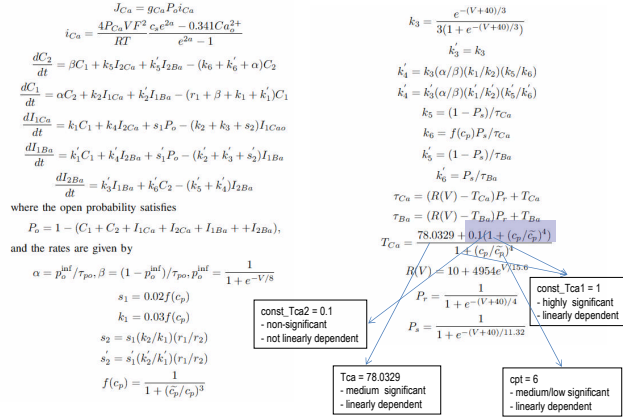


Fig. 2. The Mahajan 2008 I_{CaL} 7-state Markov model formulation with highlighted non-significant and linear dependent parameters that are identified by the newly developed SVD method.

curve) or the new reduced (red curve) I_{CaL} model is used. Further, the model is successfully validated for the AP clamp protocol applied under (i) SR depleted and (ii) Barium protocol conditions (data not shown). These validation studies show that the new reduced model can be used instead of the original I_{CaL} model.

IV. CONCLUSION

In this paper we present a new parameter identifiability method which is more powerful than the previously developed approaches. Applying the newly developed method to the Mahajan 2008 model allowed us to obtain a minimal model which we validated to contain only identifiable parameters.

The results presented are also important as they illustrate that even in the case of one of the most advanced parameter estimation approaches which uses training and validation protocols (as in the case of the Mahajan 2008 I_{CaL} model), there is still a possibility of having an overparameterised system. Thus, the method presented here is of importance when choosing the models to work with as well as when developing the models, as it allows to verify which parameters are non-significant and/or linearly dependent.

The limitation of the developed method is that at present the reparameterisation step is done manually. In future we will automate this procedure; specifically, the newly developed method will be extended to improve the refitting procedure, so that nonlinear minimization methods are used to identify a new set of parameter values in reparameterised models.

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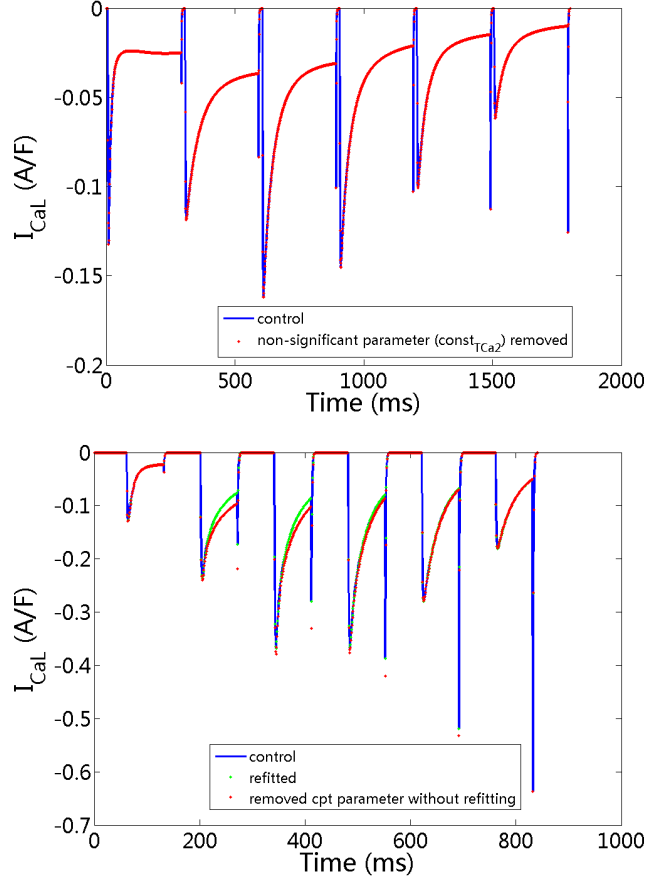


Fig. 3. **UPPER PANEL:** The Mahajan 2008 I_{CaL} current under control conditions and with non-significant parameter $const_{Tca2}$ removed. The protocol is I_{CaL} recorded under voltage clamp from -80 mV to -20, -10, 0, 10, 20, 30 mV and depleted SR conditions. **LOWER PANEL:** The Mahajan 2008 I_{CaL} current under control conditions and with redundant parameter cpt removed. The protocol is I_{CaL} recorded under voltage clamp from -80mV to -20, -10, 0, 10, 20, 30 mV and depleted SR conditions.

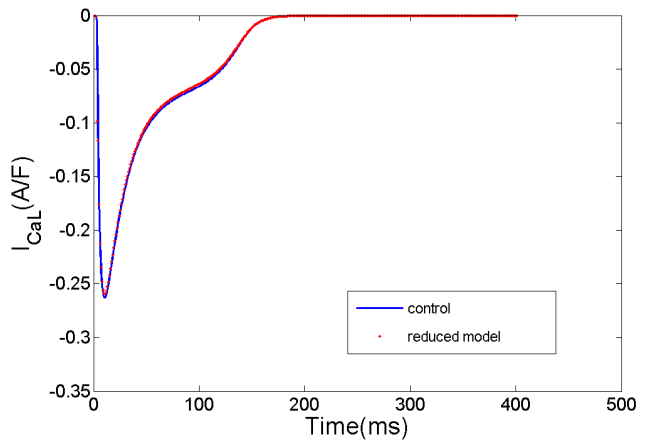


Fig. 4. AP clamp protocol applied to reduced Mahajan model with AP generated from the Mahajan original model. I_{CaL} from original Mahajan model (blue) and reduce model (red) are plotted here

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