Parameter Sensitivity Analysis of Hodgkin & Huxley Models using Partial Least Square Regression

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Abstract— PLS regression technique is used for parameter sensitivity analysis. This simple method gives a robust model, which shows the impact on dependent parameters when independent parameters are varied in certain range. The goal of the PLS regression is to generate a new simplified and empirical model which predicts the output resulting from a new set of input parameters. It also generates regression coefficient matrix which is reflection of parameter sensitivities of input parameters. In this paper we are going to do parameter sensitivity analysis of the Hodgkin and Huxley (HH) model.

Keywords: ionic conductance, injected current, regression coefficient, residual, standard deviation

I. INTRODUCTION

Mathematical models of neurons are extensively used as predictive and illuminator tools. Models generate novel predictions, suggest experiment and provide quantitative understanding of mechanisms, but have been developed for decades using a suboptimal process. The models are typically constructed by manual adjustment of independent (free) parameters to fit sample data and therefore often underperform when used to predict complex behavior. A major challenge in computational biology is constraining free parameters in mathematical models. Sometimes when we tune the parameter to make a given model more realistic has unexpected and undesirable effect on another parameters of the model. To understand the model in detail, we not only require the generated output using standard set of parameters, but we should have some knowledge of how change in parameters affects its behavior.

Sometimes a situation occurs when values of some parameters are unknown and direct measurements are frequently lacking. In such cases, experimental researchers narrow down the values of the unknown model parameters based on the model behavior. Then the set of parameters which generates unrealistic outputs are rejected and reasonable outputs are accepted until they fail in some important respect.

To understand how variability in parameter space leads to changes in model outputs, the independent parameters are varied (increased or decreased) one by one while keeping other parameters at their standard (baseline) value and the simulation results are recorded. When this procedure is performed for various independent parameters and the output is expressed in quantitative terms, that are change in output with respect to change in independent parameters, the result is sensitivity analysis. This strategy has provided insights into various models of excitable cells [2] [4] [5]

In recent years, the parameter sensitivity analysis is done by varying all parameter at once, to capture and understand the intrinsic variability of populations [6]. They applied multivariable regression to relate the parameters or independent variables to the outputs or dependent variables, thereby defining the mapping between the parameter space and the output space. In this paper, we will analyze how Partial Least Square regression (PLS) is useful for the researcher to understand and predict the causes of functional variability between different samples. Here PLS is used to constrain free parameters in the Hodgkin Huxley model [3] with injected current.

$$C_m \frac{dV}{dt} = -\bar{g}_{Na} m^3 h (V - E_{Na}) - \bar{g}_K n^4 (V - E_K) - \bar{g}_L (V - E_L) + I_{inj} \quad (1.1)$$

A. PLS regression - Prerequisite notions

PLS regression technique is used for parameter sensitivity analysis. In this method input parameters are randomized, repeated simulations are run, important output parameters are calculated and multivariable PLS regression is performed on the collected results. Initially, maximum values of ionic conductance in excitability models are varied randomly, so that there will be variation in the magnitude of corresponding ionic current. The maximal values of ionic conductance are varied by scaling the standard maximal conductance values listed in published HH model (Hodgkin AL, 1952). Random scale factors for conductance are chosen from a log-normal distribution with median value of 1. To produce simulated data, computations are performed for 10 sec time period. For each set of chosen conductance the resulting AP's are computed. Simulations are performed with many sets of log normal distribution of mean and standard deviation of 0.15 to generate input and output matrices. Input matrix 'X' of independent parameters had dimension 'n X p', where n is the number of sets of random parameters and p is the number of independent parameters varied in the model. Output matrix of dependent parameters 'Y' had dimension of 'n Y m', where m is number of dependent parameters in the model. Before performing regression, data is pre-processed to suitable form, so that it will be suitable for regression analysis. Normalization of data is done using Z-score method. Z-score is linearly transformed data values having a mean of zero and standard deviation of one.

The PLS regression performed on matrices X and Y using the NIPALS algorithm and it produces a regression coefficient matrix B_{PLS} of size p X m. When we apply new sets of inputs, the B_{PLS} matrix can be used to predict the resulting output$\hat{Y}$, which is given by

$$Y_{predicted} = \hat{Y} = X * B_{pls} \quad (1)$$

$Y_{predicted}$ is close to the original output matrix 'Y'. The magnitude of the parameter sensitivities in the regression matrix B_{PLS} indicates how variation in a given independent parameter affects a particular output. The sign of these values indicate whether an increase in the independent parameter causes an increase (positive sign) or decrease (negative sign) in the corresponding output.

II. PLS REGRESSION FOR HH MODEL WITH INJECTED CURRENT INPUT

The HH model with injected current input consists of some dependent parameters and some independent parameters. The maximal values of ionic conductance $\overline{g_{Na}}$, $\overline{g_K}$ and I_{inj} are independent parameters which are varied randomly by scaling the standard maximal conductance values listed in published model [3].The standard value for $\overline{g_{Na}}$, $\overline{g_K}$ and I_{inj} are 120 mS/cm^2, 36 mS/cm^2 and 6.5µA/cm^2 respectively. Input matrix X has (p=3) columns

$$[X]= [\overline{g_{Na}}, \overline{g_K}, I_{inj}]_{n*p}$$

and output matrix Y has (m=6) columns

$$[Y]=[APD, V_{rest}, V_{peak}, ISI, Peaks, Ent3]_{n*m}.$$

Where APD is the action potential duration, V_{rest} and V_{peak} are the resting and peak voltage of the action potential. ISI is the interspike interval of the generated spike. Peaks is the mean firing rate of the action potential per second. Ent3 is the entropy which is calculated by $-\sum_{i=1}^{n} p_i \log_2 p_i$ where p_i is the probability of occurrence of spike. The random changes could cause dependent variables to increase or decrease, depending on the combination of conductance and injected current in a particular trial.

The figure 1 shows action potentials produced by randomly varying the three maximum ionic conductances in the HH model with injected current for 4 samples along with the standard value and the dotted line shows the action potential generated for the standard values as mentioned in the original HH model. The simulation is performed for each sample till the shape of action potential is proper. For this HH model the simulation is done for 5000 samples out of which 2366 samples are selected. The remaining 52 % of samples are rejected due to the generation of unrealistic output, such as APs that never repolarized. The size of X matrix is 2366 x 3 and the size of Y matrix is 2366 x 6. The input and output matrix have to be log transformed if the randomly generated values does not obey the log normal distribution. Then the X and Y matrix have to be normalized in order to keep all the data units in one baseline.

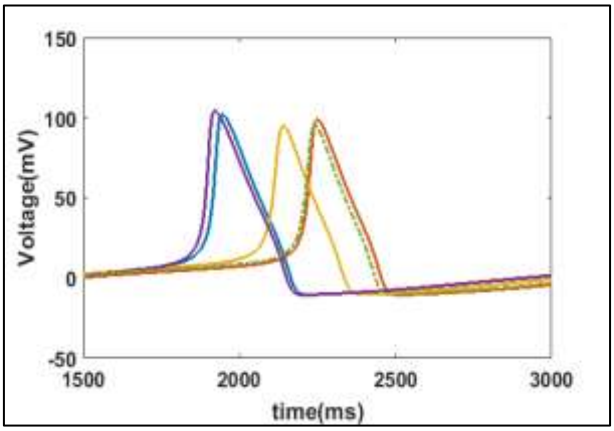
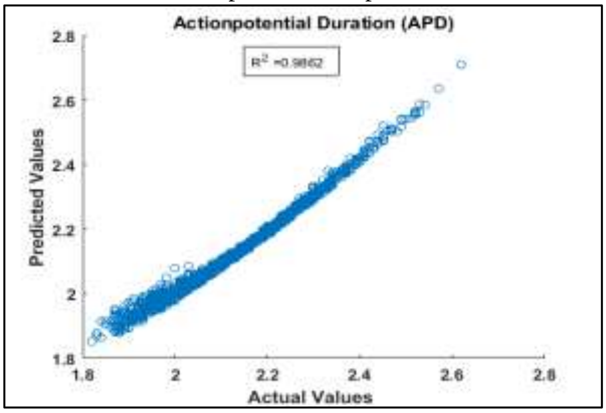


Fig 1: Action potential generated by randomly varying ionic conductance in the HH model.

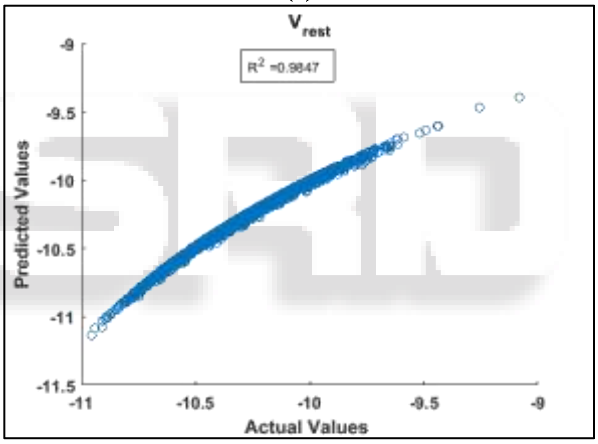
The normalized inputs (X and Y matrix) are regressed using the NIPALS algorithm [1].

A. *Predictions of Dependent variable in PLS regression*

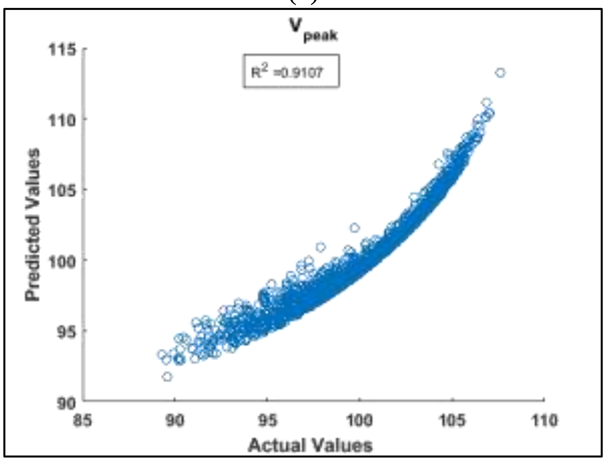
Regression is performed on a simulated data set containing 2366 samples. The Figure 2 shows the predictions of linear empirical model generated by PLS regression and predictors represent the independent variables. Scatterplots are displayed for six outputs. Each plot shows the value computed by numerical integration of HH model equations versus the estimate generated by the PLS regression model. The residual R^2 is the sum of squares of the difference between the actual and predicted responses.



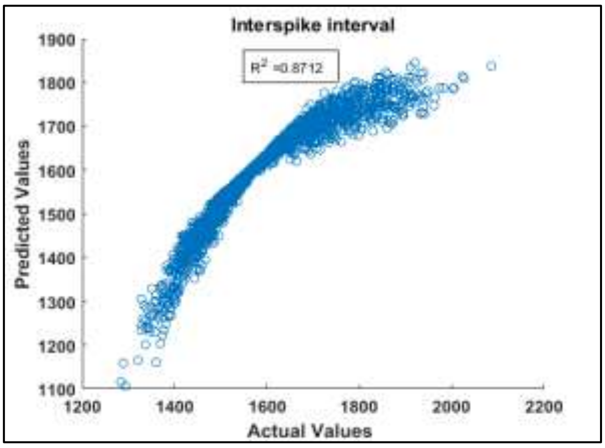
(a)



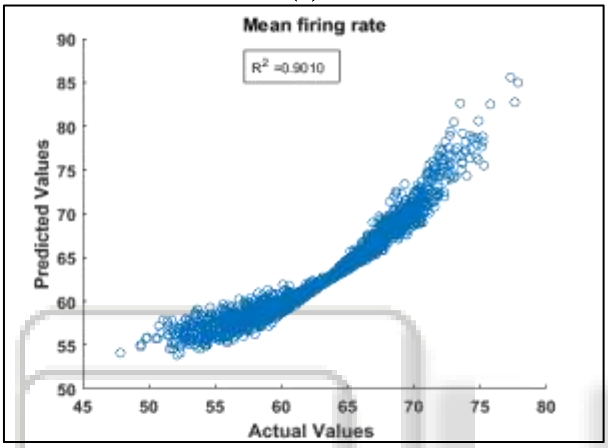
(b)



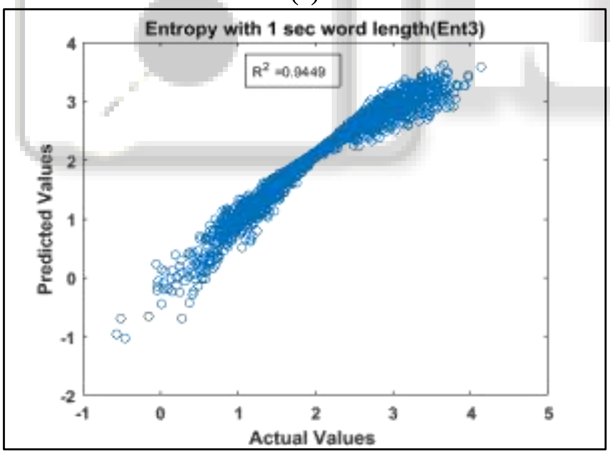
(c)



(d)



(e)



(f)

Fig. 2: Scatter plot shows the actual value of the (a) Action potential duration (APD) (b) V_{rest} (c) V_{peak} (d) ISI (e) peaks (f) Ent3 calculated from the HH model and the predicted value calculated from the NIPALS algorithm.

The residual (R^2) values are almost above 90 % that it shows almost 90 % of the data are predicted correctly. It also indicates that the simplified linear model is highly predictive, despite the nonlinear differential equations in the HH model.

B. Regression Coefficient of PLS regression.

The regression coefficients in the (matrix B_{PLS}) indicate how changes in parameters lead to changes in outputs, with each column reflecting the effects on a particular output. Examining these coefficients allows for an assessment of the relative contributions of the various input parameters on output parameters. Therefore, both the increase (and decrease) in input and the increase (or decrease) in output can be understood as percentage changes relative to the baseline level.

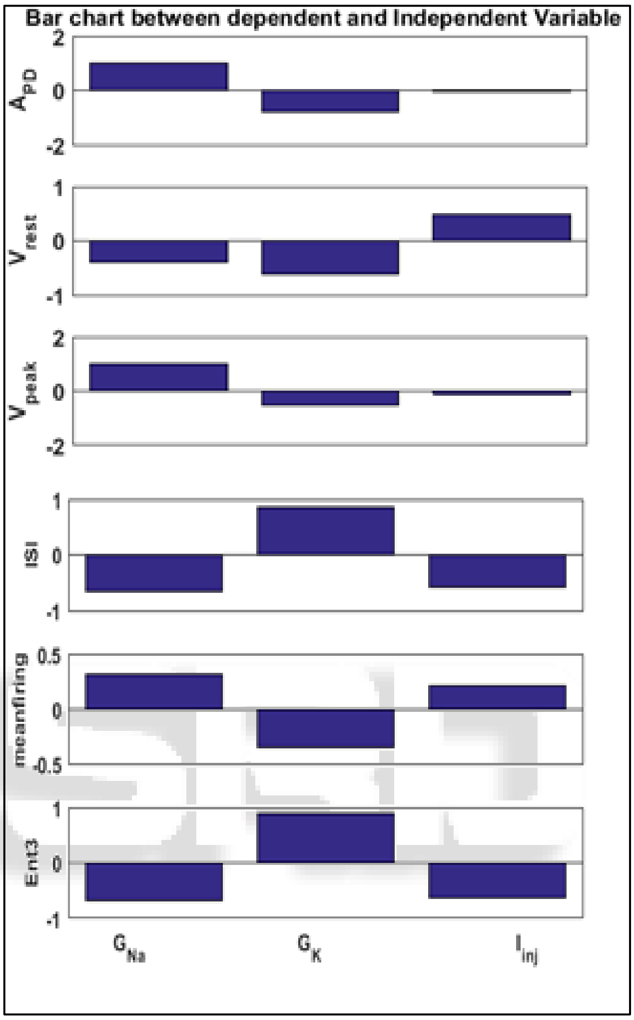


Fig. 3: Barchart showing the relationship between the input and output paramters.

The impact of the B_{pls} matrix is interpreted as in subplot of APD shows that increase in $\overline{g_{Na}}$ and decrease in $\overline{g_K}$ lengthening the APD. The input current has negligible effect on the APD. Likewise the dependency of the output parameter on input parameters are easily interpreted using this bar chart.

C. Impact of sample selection in PLS regression

In order to see the impact of regression coefficient whether it works on less number of samples also, we have executed the PLS regression for various sample. For the random stimulation with standard deviation of 0.15 for various samples are stimulated and the resultant B_{pls} matrix for these data is shown in the figure 4. The figure 4 consists of six subplots each showing the parameters of the output matrix and each subplot consists of five bars each showing the effect regression coefficient of the sample data.

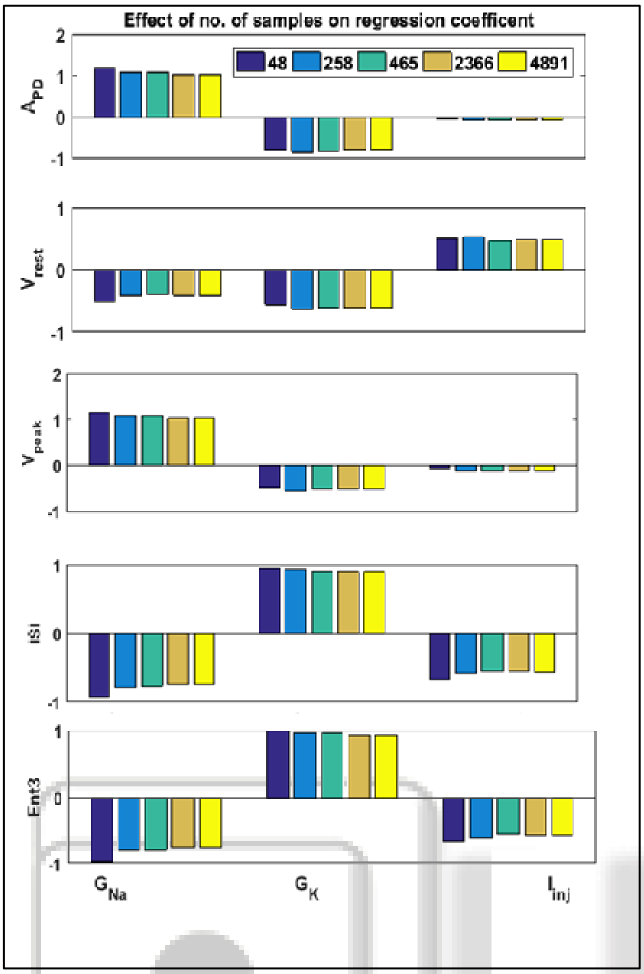


Fig. 4: Barchart showing the effect of number of samples on regression coefficient

The bar chart 4 shows that even if the number of samples are less (n=48), PLS still provides reasonable estimates of regression coefficients. The percentage of variation is very less. So we can conclude that computational model with less number of samples can also be effectively predicted by this PLS regression method.

D. Impact of standard deviation in PLS regression.

In the simulations shown in figure 1-4, input parameters are varied over a relatively narrow range. The parameter σ, which controls random variation of maximum input parameters, is set at 0.15. In order to examine that how increasing σ affected the regression model, we have generated the random generations for variable whose σ ranging from 0.1 to 0.3. The residual value calculated for the various values of σ is shown in the bar chart 5.

The bar chart 5 chows negligible change in the residual values when the deviation is increased. This demonstrates that when parameters are allowed to vary over a wider range, the parameter sensitivity analysis generated using this procedure is remarkably robust, despite a slight decrease in accuracy

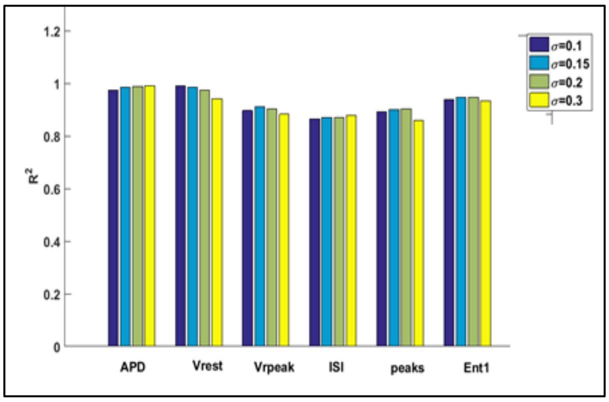


Fig. 5: Bar chart showing the impact of increase the range of standard deviation over the residual.

III. CONCLUSION

In this study, parameters of HH models are randomized, and numerous simulations are performed with different combinations of parameters. Computations are performed with the randomized parameters and the AP characteristics computed from the simulations, as input and output matrices respectively, are subjected to multivariable regression. Input parameters included both maximal conductance of ionic currents and injected currents in basic HH model. The outputs included important measures such as APD, Peak voltage, mean firing rate, entropy, etc. The randomization regression procedure produced an empirical, linear model that quantified correlations between parameters and outputs. In HH model despite of the many nonlinear equations, the predictive power of the regression models is quite strong. In the standard HH model, the PLS algorithm predicted almost 90 % of the data. The dependencies of all the output parameters with input parameters in the HH model are predicted correctly. While changing the sigma value the over wider range, the regression coefficient of all the variables shows same results.

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