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Correlation between the Dependent and Independent Parameters in the Extended Hodgkin and Huxley Neuron Model Using Partial Least Square Regression Technique

Devi kannan[1] and AkhilRanjanGarg[2],
Atria Institute of Technology,Bangalore[1]Jai Narayan Vyas University, Jodhpur[2]
devi.kannan@atria.edu[1], agarg@jnvu.edu.in[2]

Abstract-Parameter sensitivity analysis is the vital technique in finding the correlation between the independent and dependent parameters in the computational modelling. Partial least square (PLS) regression technique is used for parameter sensitivity analysis. This simple method gives a robust model, which shows the correlation between the 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 extended Hodgkin and Huxley (HH) model with synaptic currents.

Keywords - Ionic conductance; synaptic current; regression coefficient; residual; standard deviation.

I. INTRODUCTION

Biological neuron modelling is the vast area in which various neuron models were developed. Each modelhas its own goal, prerequisite, limitations, etc. Out of these several models Hodgkin and Huxley (HH) [5] model is one of the models which only satisfy the neuro-computational properties of the spiking neurons [6]. HH model is the nonlinear model which consists of several parameters. At the time of model development, in order to get the desired action potential,they derive the equation which consists of several free parameters also. From these nonlinear equations, finding the correlation of input variable with the output variable is a time consuming process.The input parameter is manually changed one by one and the variability in the output parameter is validated. The computational cost also increases in this process. Many types of sensitivity analysis has been done in order to find the correlation between the input and output parameters. One such approach is the Bayesian method of analysing the HH model [4]. In this paper, they analysed the free parameters in the HH model. Calderhead [3] addressed the local parameter sensitivity analysis based upon the Geometric Markov chain of Monte Carlo method. In addition to the local sensitivity analysis. Saltelli in his paper suggest a method to find the correlation in the model parameters based upon the Global sensitivity analysis [9]. The free parameter in the nonlinear model has some uncertainty in the model.Gutenkunst in his paper address this uncertainty issues by highlighting the sloppy spectrum of parameter sensitivity analysis[10]. The parameter estimation in the biological network models are addressed in [2]. They addressed this issue based upon the Bayesian statistical method. In this paper we applied partial least square regression method to identify the correlation between the input and output parameters. This method is applied in various excitability cell models. Sobie in his paper addressed the parameters sensitivity analysis in the cardiac cell models where more number of nonlinear equations isinvolved [12]. Also he addressed the detection and elimination of free parameters in the nonlinear cardiac cell model in [14]. This partial least square method is applied in other cardiac cell models also because of its simplicity [7]-[8] [11] [13].

II. EXTENDED HODGKIN AND HUXLEY NEURON MODEL

The HH model in the original paper is extended with a network of 1000 excitatory and 200 inhibitory synapse and the model equation is given as follows

$$C_m \frac{dV}{dt} = -\bar{g}_{Na} m^3 h(V - E_{Na}) - \bar{g}_K n^4 (V - E_K) - \bar{g}_L (V - E_L) + I_{syn} \quad (1)$$

where I_{syn} is the synaptic current. The synaptic current is the summation of excitatory and inhibitory currents which is given below

$$I_{exe} = -\bar{g}_{exe}(V - E_{Na}) \quad (2)$$

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$I_{in} = -\bar{g}_{in}(V - E_K)$ (3)
$I_{syn} = I_{exe} + I_{in}$ (4)
This (4) is substituted equation (1) to get the membrane potential and the new(1) becomes
$C_m \frac{dV}{dt} = -\bar{g}_{Na} m^3 h(V - E_{Na}) - \bar{g}_K n^4 (V - E_K) - \bar{g}_L (V - E_L) - \bar{g}_{exe}(V - E_{Na}) - \bar{g}_{in}(V - E_K)$ (5)

In the extended HH model, the only driving force to generate the action potential is the combination of excitatory (f_{ex}) and inhibitory (f_{in}) firing frequency. In this extended HH model the input parameters or independent parameters are the maximal conductance of $\bar{g}_{Na}$, $\bar{g}_K$, the firing frequencies f_{ex} and f_{in}. The standard value for $\bar{g}_{Na}$, $\bar{g}_K$, f_{ex} and $f_{in}$are 120 mS/cm^2, 36 mS/cm^2 , 15 and 10 respectively. These independent parameters are randomly stimulated with random scale factors which are chosen from a log-normal distribution with median value of 1. To produce simulated data, computations are performed for 10 sec time period.These random stimulations are done for several samples in order to get the output or dependent parameters. In our model we have the following dependent variables

- APD - the action potential duration (msec)
- V_{peak}-the peak voltage of the action potential(mV)
- V_{rest}-the restingvoltage of the action potential (mV).
- ISI -the coefficient of variation of interspike interval of the generated spike train.

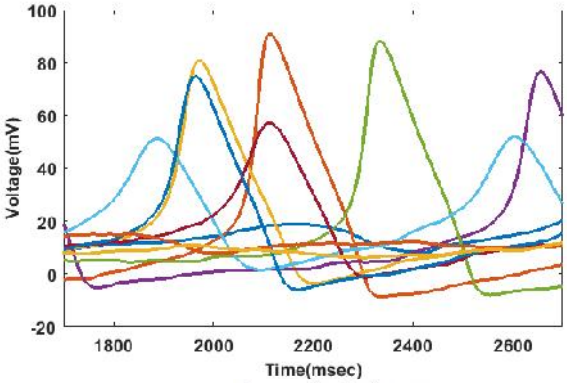

Fig.1 Action potential generated by randomly varying ionic conductance in the extended HH model.

- Peaks -the mean firing rate of the action potential per second.
- Ent-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.

- g_{ex}- the excitatory synaptic conductance.
- g_{in}-the inhibitory conductance.
- V -the mean membrane potential.
- Condratio -the mean synaptic conductance ratio ($\bar{g}_{in}/\bar{g}_{exe}$)
- Currratio- the mean synaptic current ratio(I_{exe}/I_{in}).

II. PLS Regression

PLS regression technique[1] is used for parameter sensitivity analysis.The nonlinear iterative partial least squares (NIPALS) algorithm is a simplified procedure that analyze the correlation between the input and output parameters. The inputs for NIPALS algorithm are Z-score matrix of independent, dependent variables and number of components of the computational model. Number of components should be less than or equal to minimum number of dependent or independent variables. In the NIPALS algorithm we are going to find the correlation between the independent and the dependent parameters. This is done based upon the followingsix steps. The normalized independent (E= Z_X) and the

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dependent (F=Z_Y) variables are the input to the NIPALS algorithm. Before starting iteration process, the vector u is initialized with column of Y which has the largest square of sum.

Step 1: Estimate the predictor score (P_s) iteratively until it converges.

Step 1.1: Estimate the predictor weights using (6) and then normalize it.

$$P_w = E' * R_u \quad (6)$$

Step 1.2: Estimate the predictor score latent variables using (7)

$$P_s = E * P_w \quad (7)$$

Step 1.3: The response loading weights are estimated using

$R_L = F' * P_s$ and normalize it.

Step 1.4: The response latent score variables are estimated using (8)

$$R_s = F * R_L \quad (8)$$

If 'P_s' is converged, then compute the value of R_b which is used to predict Y, otherwise go to step 1.

Step 2:Estimate the predictor loadings and the regression coefficient using (9) and (10)

$$P_L = E' * P_s \quad (11)$$

$$R_c = t' * R_s \quad (12)$$

Step 3:Now partial out the effect of 'P_s' from both E and F using (13) and (14).

$$E = E - P_s - P_L' \quad (13) \qquad F = F - R_c * P_s * R_L' \quad (14)$$

Step 4: The residual of X and Y are calculated using (15) and (16)

$$\text{Residual}(X) = (P_s' * P_s) * (P_L' * P_L)/SS_X \quad (15)$$

$$\text{Residual}(Y) = (P_s' * P_s)(R_c)^2 * (R_L' * R_L)/SS_Y \quad (16)$$

Step 5:If E is a null matrix, then whole set of latent vector has been found, otherwise the procedure is repeated from step 1.Scalar R_c is stored as a diagonal element of B.

Step 6:The dependent variables are predicted using the multivariable regression which is given by (17)

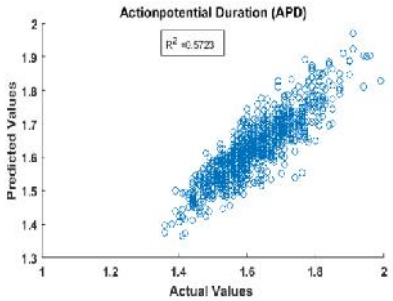
$\hat{Y} = X * B_{pls}$ (17)

The matrix of regression coefficientB_{PLS}, has important role in PLS regression, because, dependent variables are predicted using B_{PLS} matrix. Each column of B_{PLS} matrix shows impact on particular dependent variable by all independent variables. This matrix is calculated using (14).

$$B_{pls} = (P_L^{T+}) * B * R_L^T \quad (18)$$

Where (P_L^{T+}) is the Moore-Penrose pseudo-inverse of P_L

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. Simulations are performed with many sets of log normal distribution of mean of 0.1and 'a', where s is the number of sets of random parameters and 'a' is the number of independent parameters varied in themodel. Output matrix of dependent parameters 'B' had dimension of 'sYb', where b is number of dependent parameters in the model. The data that are generated usingthese random stimulations are of different units. So these values have to be normalized in order to bring the data in



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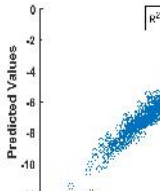

Fig.2. Scatter plot of the actual and predicted values of the dependent values. (A) APD (B) V_{rest} ratio (C) Mean firing rate using NIPALS algorithm.

one baseline, standard deviation of 0.15 to generate input
and output matrices.In our model, the stimulations are performed on 2000 samples out of which 833 samples are selected.The remaining 50 % of samples are rejected since the action potential that never repolarized. The Fig. 1 shows the generated action potentials of few samples. So the input matrix 'X' of independent parameters had dimension 'sX
The PLS regression performed on matrices A and B using the NIPALS algorithm [1] and it produces a regression coefficient matrix B_{PLS} of size a X b. The NIPALS algorithm predicted the dependent variables using the relation (18) This $Y_{predicted}$ is close to the original output matrix 'Y'. Also the sign of the parameter sensitivities in the regression matrix B_{PLS}shows the correlation between the independent and dependent variables. The sign of the coefficient matrix may be positive or negative.

B. Predictions of Dependent variable in PLS regression

The randomly stimulated independent and dependent values are regressed using the NIPALS algorithm. In our modelthe simulated data set consists of 833 samples. The Fig.2 (A)-(C) shows the predictions of the actual values and predicted values generated by PLS regression algorithm.The residual R^2 is the sum of squares of the difference between the actual and predicted responses and it indicates percentage of data which are correctly predicted.The minimum value of the residual is 57 % for action potential duration and 99 % of the data are predicted correctly for mean membrane potential. This indicated that this PLS regression technique is highly predictive in spite of having several nonlinear equations in the extended HH model.

C. Regression Coefficient of PLS regression

The correlation between the input and output parameter is identified by the regression coefficient matrix. The regression coefficient matrix indicates how much variation in the input parameter causes change in the output parameter. This examination shows the contribution of input parameter in the model to generate the output. The impact of the B_{pls} matrix is shown in the bar chart 3.The numbers in the following description represents the row in the bar chart 3.

(1) **APD**- increase in $\bar{g}_{Na}$ and decrease in $\bar{g}_K$ lengthening the APD. The f_{ex} and f_{in}has negligible effect of 12% and 5 %respectively on APD.

(2) **V_{peak}**- increase in $\bar{g}_a$ by 56% and decrease in $\bar{g}_K$and fexby 22 % and 56 % respectively, increases the peak voltage. The f_{in} has negligible effect.

(3) **V_{rest}**- the decrease of both $\bar{g}_a$ and $\bar{g}_K$ and 8% increase in f_{ex} increases the resting potential. The f_{in} has negligible effect on $V_{rest.}$

(4) **Mean firing rate**- The increase 0f 76% in $\bar{g}_{Na}$and decrease in $\bar{g}_K$, f_{ex} and f_{in} by 53%, 17% and 10% respectively increases mean firing rate.

(5) **ISI**- 46 % increase in potassium conductance $\bar{g}_K$and 34% increase in f_{ex} and 86 % decrease in $\bar{g}_a$.

(6) **Entropy**- The increase in $\bar{g}_K$ by 56% and decrease in $\bar{g}_a$ by 63% increases the entropy. The f_{ex} and f_{in} have has negligible effect of 6 %.

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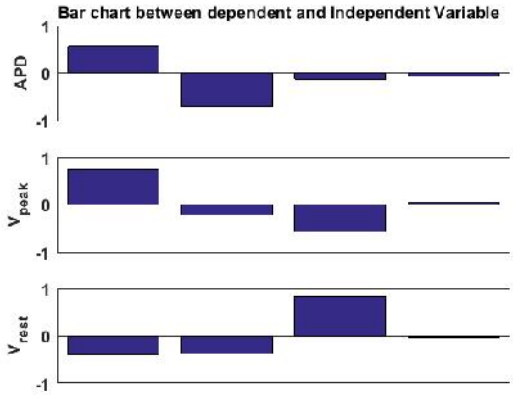
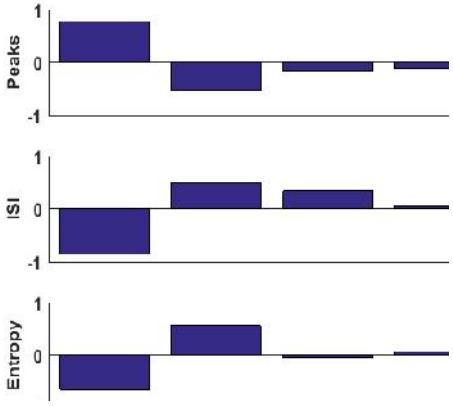
(7) **Synapticconductance(gex)**-The synaptic conductance (gex),it depends only on increase in $f_{ex.}$ T[illegible] $\overline{g_{Ca}}$, $\overline{g_K}$ and f_{in} has no effect on synaptic conductance (g_{ex}).
(8) **Synaptic conductance (g_{in})**-The synaptic conductance ([illegible]), it depends only on increase in f_{in}. The $\overline{g_{Ca}}$, $\overline{g_K}$ and f_{ex} has no effect on synaptic conductance (g_{in}).
(9) **Membrane potential (V)** - The increase of 42% in $\overline{g_{Ca}}$ and decrease in $\overline{g_K}$, f_{ex} and f_{in} by 79%, 44% and 11% respectively increases membrane potential.
(10) **Synaptic conductance Ratio** Increase in f_{ex} and decreases inf[illegible] increases the membrane potential.
(11) **Synaptic current ratio** crease in f_{in} by 88 % and increase in $\overline{g_{Ca}}$ $\overline{g_K}$, f_{ex} by 35%, 17% and 28 % increases the current ratio





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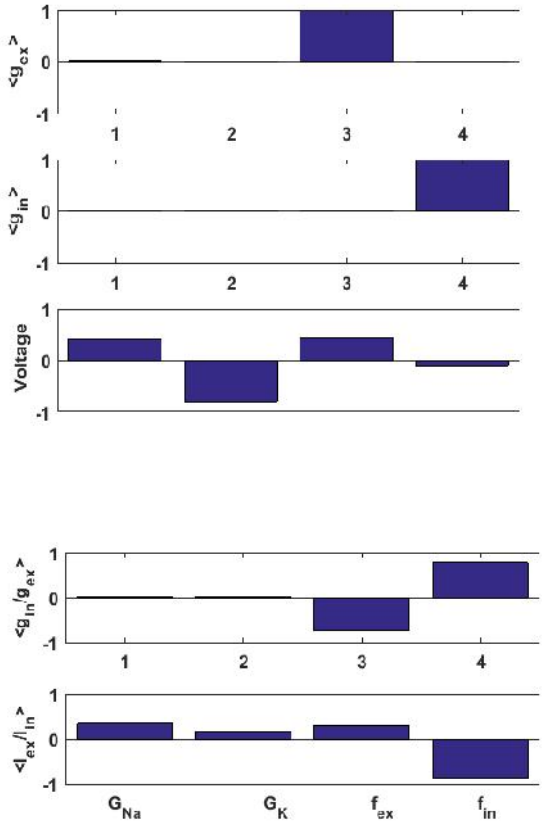

Fig.3. Barchart showing the relationship between the input andoutput paramters.

The bar chart representation of the regression coefficient is an efficient way to identify the correlation between the independent and dependent parameters in the model.

D. 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 samples. The random stimulations are done for 0.15 deviations and for 100 samples we got 46 data and the remaining samples are rejected since the action potential that never repolarized. Likewise for 400 samples, we got 186 data, for 1000 samples we got 522 samples and the resultant Bplsmatrix for these data is shown in the fig 4. The fig. 4 consists of

11 subplots each showing the parameters of the output parameters. Each subplot consists of four bars each

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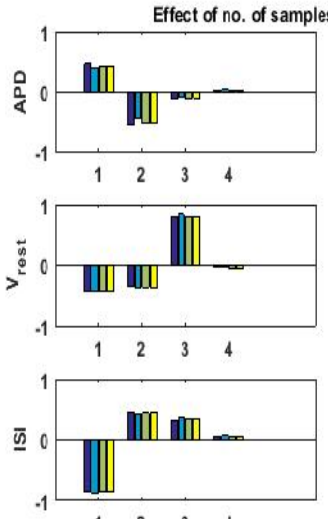
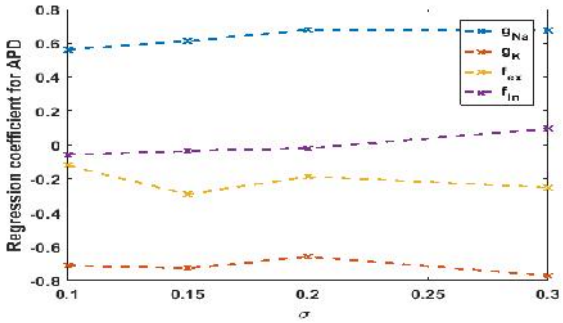


Fig.4. Effect of number of samples on regression coefficient

showing the effect regression confident of the input parameter.The fig. 4 is the replication of fig. 3 with each bar for different samples. The coefficient of variation of the regression coefficient for different samples is very less. This shows that the regression technique can be ableto find the correlation between the variables of computational model even when the numbers of samples are less.***E. Impact of standard deviation in PLS regression.***

In the simulations shown in fig.2-4, the variation in the input parameters is relatively narrow in range. In our stimulations the deviation is set at 0.15 such that maximum values are within the standard values as prescribed in the published models. In order to validate the model for higher range of values we have varied the deviation. The deviation is varied from 0.1to 0.3 and the table I shows the range of input matrix when the sigma is varied.



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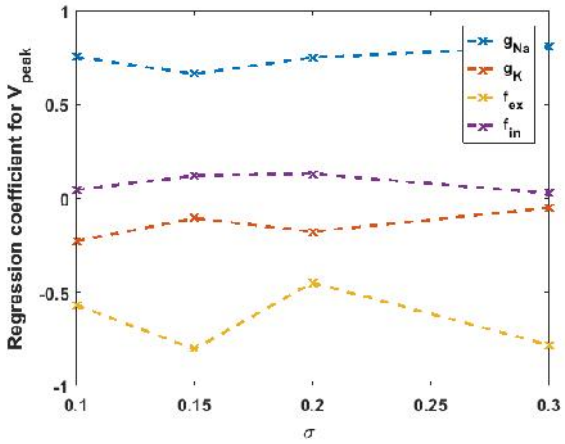

ig.5. Effect of values in the regression matrix B_{PLS} for various distribution of σ. Effect of $\bar{g}_a$,$\bar{g}_K$,I_{inj} in the B_{pls} matrix for various values of σ.(A) APD(B) V_{peak}

The stimulations are done for various values of deviation values and the resultant samples are regressed using NIPALS algorithm. The impact of sigma is validated from the resultant regression coefficient value and is shown in the fig. 5.

In the fig. 5 (A), the subplot for APD shows the change in the regression coefficient for APD when the deviation is increased. Increases in sigma shows negligible change in $\bar{g}_a$ and $\bar{g}_K$. However f_{ex} and f_{in} shows 34 % and 12 % variation in B_{pls} coefficient when the sigma value is increased. In fig.5.(C) shows the change in the regression coefficient for V_{rest} when the deviation is increased. The $\bar{g}_a$and$\bar{g}_K$ shows negligible change and f_{ex} and f_{in} shows 12% and % variation when the sigma is varied.

The fig.5.(D) shows variation in regression coefficient for mean firing rate when sigma is increased. $\bar{g}_a$shows negligible effe while the sigma i increased. However f_{ex} and f_{in} sh s variations. In fig.5 (E) t e regression coef ient of ISI shows that crease in the dev ation have negligible effect on $\bar{g}_a$ and f_{in} whereas f_{ex} and $\bar{g}_K$ shows variation in the regression coe cient when the va iation increased beyond 0.15.Th ig.5 (F) showsthat increa e in the sigma shows 12%change in the $\bar{g}_a$and 10% in the $\bar{g}_K$. However $f_{ex}$and f_{in} shows variation when the sigma is beyond 0.2.The fig.5(G) and (H) shows the gression coefficie for synaptic conductance g_{ex} and g_{in} respectively when the sigma is increased. All the four Values show negligible change when sigma is increased. The fig.5 (I) shows the regression coefficient for mean membrane potential when the sigma is increased. All the four values show negligible change when sigma is increased. The fig.5 (J) and (K) shows the regression coefficient for mean synaptic conductance and current ratio respectively when the sigma is increased. In fig.5 (J) f_{in} shows some changes and the remaining the remaining three values shows negligible change when sigma is increased. In fig.5 (K) all the four values show negligible change when sigma is increased.

From this subsection we can conclude, in our model the change in the deviation shows negligible change in the regression coefficient.

III CONCLUSION

In this paper, the HH model with synaptic inputs is analysed. The HH model with excitatory and inhibitory synaptic parameters of HH models is randomized and numerous simulations are performed with different combinations of parameters. Input parameters included both maximal conductance of ionic currents and synaptic currents in basic HH model. The outputs included important measures such as APD, Peak voltage, mean firing rate, entropy, etc. The PLS

regression procedure produced an empirical, linear model that shows the correlations between input and output parameters 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 70 % of the data. The dependencies of all the output parameters with input parameters in the extended HH model are predicted correctly. While changing the sigma value the overwider range, the regression coefficient of all
The variables show same results.The extended HH model with excitatory and inhibitory synapse shows better results as compared to the other two models. This is due to the balanced effect of the synaptic conductance. This effect can be extracted using the partial least square regression techniques.

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