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Spike Response Fitting and Prediction of a Single Neuron Model

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Abstract

Conductance based detail biological models of neurons are able to predict various forms of spiking patterns with great accuracy, but the computational resources required to simulate large network of such neurons are still incomprehensible. As an alternative various simplified spiking models of neurons have been proposed. These models achieve computational efficiency through dynamical system techniques such as linearization, bifurcation analysis etc. Although, these simplifications have enabled researchers with large scale network simulations, but they require multiple parameters to be fitted and optimized for specific simulation requirements such as spiking behavior, site of action potential initiation etc.

It is known that cortical pyramidal neurons are independently capable of generating action potential from various segments of the cell structure such as the soma, apical and basal dendrites, axon hillock, axon initial segment etc. These action potentials interact with each other due to antidromic and orthodromic propagation and may affect the overall cortical dynamics. Furthermore, the Axon Initial Segment was shown as the preferred site of action potential initiation.

The result presented in this study focuses on the analysis, fitting and prediction of spikes generated during Action Potential Initiation at Axon Initial Segment (AIS). The Adaptive Exponential Integrate and Fire (AdEx) model was implemented for the purpose in the NEURON simulator and fitted to a biologically accurate neuron model. The study also verifies the shape of individual fitted action potential generated at the AIS and modifies the generic model for more efficient simulation.

Keywords: Neuron, Action Potential, Axon Initial Segment, Spiking Patterns, Spiking Neuron Model.

1. Introduction

Brette (2005) described the Adaptive exponential integrate-and-fire model as an effective description of neuronal activity. In their study, they introduced a two-dimensional integrate-and-fire model by combining exponential spike initiation with sub-threshold and spike triggered adaptation. Further, they investigated methods of model parameter estimation by applying simple electrophysiological protocols to detailed conductance based models.

It is known that (Colbert, 1996; Mainen et al, 1995;Milojkovic et al, 2005; Stuart et al, 1997a, b) cortical pyramidal neurons are independently capable of generating action potential from various sections of the cell structure such as the soma, apical and basal dendrites, axon hillock, axon initial segment etc. Which of these sections generate the Action Potential first and how they interact with each other due to antidromic and orthodromic propagation may affect the overall cortical dynamics.Later, it was shown that the preferred site of Action Potential initiationis the Axon Initial Segment (Shu et al, 2007).

In this study we implemented the Adaptive Exponential Integrate and Fire model in the NEURON Simulator, estimated its parameters to describe a reference neuron and in the process optimized the implementation for more efficient simulation. Further, we also verified the spike initiation dynamics of the implemented model for action potential initiation at the Axon Initial Segment.

2. Model Methods

2.1 Reference Data Generation

The reference model was run using NEURON 7.3 (Hines, 1997) and was based on the multi-compartmental model of the full dendritic and somatic structure of a layer 5 cortical pyramidal cell (Mainen, 1996). All simulations were carried out onan Intel I5 based laptop running at 2.5GHz with 4 GB DDR3 SDRAM.

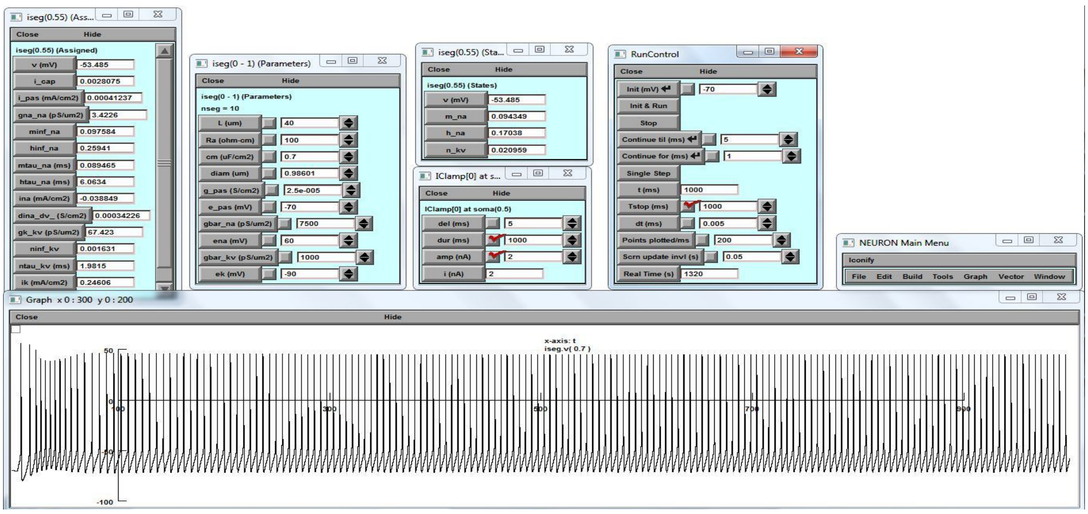


Fig. 1: Reference data generation at Axon Initial Segment.

To generate the reference data a 2nA Heaviside Current Clamp protocol was applied to the seventh segment (0.7) of the AIS. The data was recorded for 1000ms with temporal resolution of 0.005ms(

Fig. **1**). As can be seen, a regular spiking pattern was generated from the current clamp experiment. Other spiking patterns were also observed by varying the stimulus. During the initial part of the simulation from 0 to 50ms, variations in the generated data were observed, but this eventually settled down from 50ms onwards. The inter-spike interval (ISI) was measure and observed to decrease gradually, indicating spike adaptation.

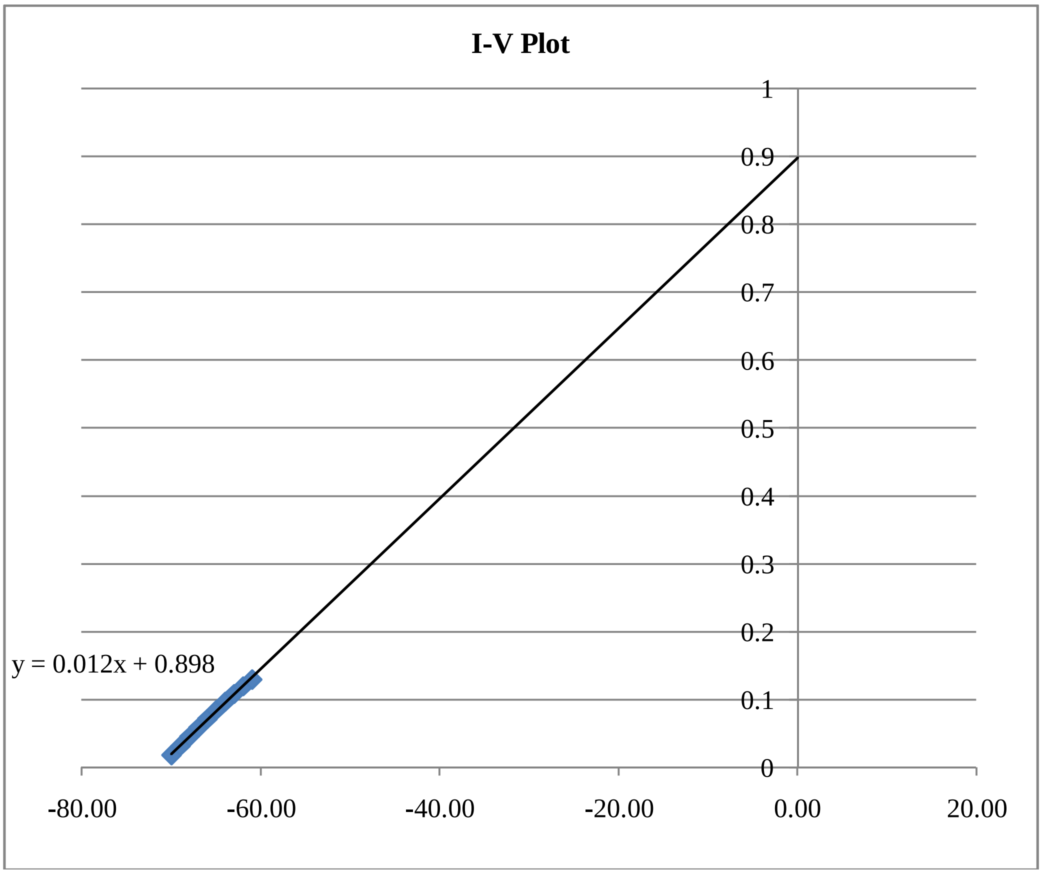
2.2 Implementing AdEx in NEURON

The model is described by two differential equations (Brette, 2005):

$$\frac{Cdv}{dt} = -g_l(V - E_l) + g_l \,.\, \Delta_T . e^{\left(\frac{V - V_T}{\Delta_T}\right)} - w + I$$

$$\frac{\tau_w dw}{dt} = a(V - E_l) - w$$

A POINT_PROCESS wasopted as the primary interface to take advantage of NEURON's NetCon sub-systemand the NET_RECEIVE block was used to implements its core state machine (Fig. 2).



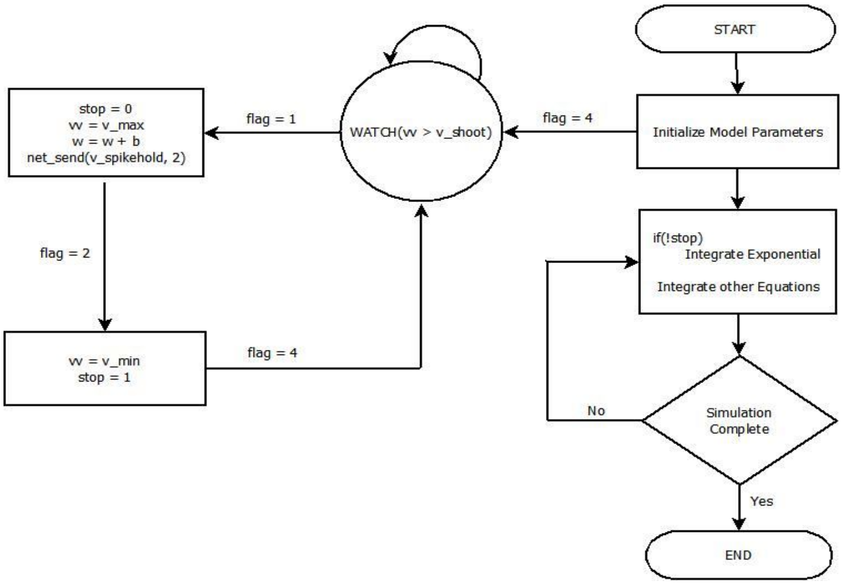


Fig. 2: V-I characteristics at AIS (left) and AdEx model implemented in NEURON (right).

At the start of the simulation, the AdEx model equations are integrated. The WATCH statement iterates until the membrane voltage exceeds the spike voltage (v_shoot). At that point, a self-event is generated with flag = 1, this marks the beginning of the spike. Next, the integration of the model equations is stopped and the membrane voltage is set directly to v_max. This continues until v_spikehold time, after which a reset is applied. The process continues until simulation time expires.

2.3 Assumptions for Fitting

Spikes generated by the AdEx model within ± 2ms of the reference model, were considered fitted. Furthermore, effects of the axial currents and extracellular fluidin the reference neuron were ignored.The estimated parameters and the actual parameters fitted were allowed to vary up to $\pm 10\%$ of each other.

2.4 Model Parameter Fitting

The parameters of the AdEx model were determined as per the techniques described by Brette (2005). The membrane surface area was determined directly from the neuron simulator. The length of the AIS was found to be 40 μm with a diameter of 0.098601μm. This gave surface area of the membrane to be 1.239E+02 μm^2.The passive membrane properties were also directly determined from the NEURON simulator. The membrane capacitance (cm) was found to be 0.7$\mu F/cm^2$. This gave a total capacity of 8.673E-01 ρF. The leak conductance was found to be 2.50E-05 S/cm^2 giving a total conductance of 3.0976E-05μS .E_L directly observed at AIS was found to be -70mV. But at this value of E_L, the steady state current was nonzero. To measure the actual leak potential, voltage clamp experiment were performed to minimize the steady state current. The leak potential measured by this method was -71.34mV.

To determine the value of ‘a’, the I-V characteristics of AIS was determined using a Voltage Clamp Protocol (Fig. 2). The range of voltage chosen was between -70 and -61 mV–an inflection was observed beyond this range of measurement. The value of parameter ‘a’ determined from the slope of the best linear fit to the I-V curve after subtracting the slope G_L was found to be 1.2469E-02 μS. For verification, ‘a’ determined through the equation below was found as 1.3216E-02μS.

$$I = (G_L + a)(V - E_L)$$

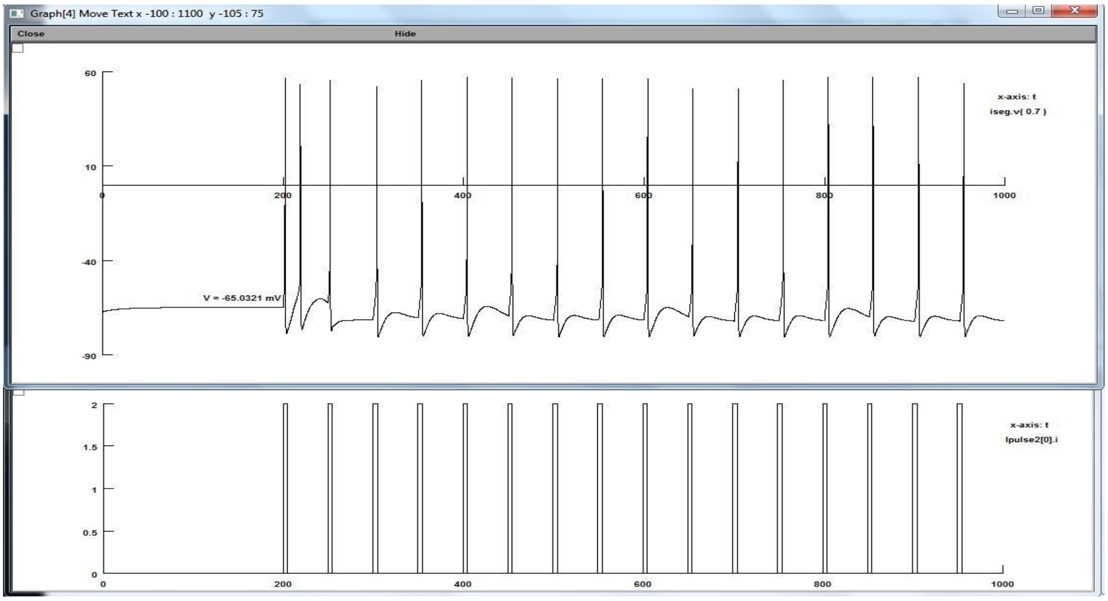


Fig. 3: Voltage response of the reference model to a series of regularly space current pulses.

To determine the value of spike-triggered adaptation ‘b’ and the adaptation time constant τ_w, the membrane potential was depolarized to approximately -65mV (using constant current injection) and then a periodic series of short current pulses were injected (2nA for 5ms at frequency of 20Hz, 10Hz, 33.33Hz and 14.28Hz) to initiate spikes (Fig. 3). The value of the adaptation current was then estimated from the equation:

$$w = -C\frac{dV}{dt} - G_L(V - E_L) + I$$

The value of $\frac{dV}{dt}$ was estimated from the slope of the membrane depolarization when far away from the threshold. The difference between this estimation of ‘w’ and sub-threshold adaptation gave the value for the spike-triggered adaptation. The approximate value of ‘b’ was found to be -0.0872nA. As expected, this estimation was robust.To find the value of τ_w, different exponential fits were attempted, but in all cases, τ_w varied unpredictably. Hence, a trial and error approach was opted to fit this value.

For Saddle-Node bifurcation, the rheobase is well defined (Izhikevich, 2007); hence the value of V_{th} was determined by stimulating the reference neuron with the minimum current which could generate a spike (rheobase). A very slow current ramp was used to estimate this current. V_{th} estimated by this method was found to be less than -61mV at 0.22nA.

Fitting the individual action potential with v_spikehold helps to delay enabling the exponential integration. This also aids achieving a better fit of the spike train from the predicted parameters of the reference model.v_max is fitted when the reference Action Potential reaches maximum amplitude whereas v_min is fitted when the Action Potential reaches the hyperpolarized values. The values seem to vary during the initial 50ms, henceforth it settles approximately at 46mV and -74mV respectively.

When the membrane voltage reaches v_shoot the exponential integration is stopped and the membrane voltage set to v_max. It may seem that v_shoot be fit at the lowest possible value to stop the integration earliest, but it should be noted that this sudden reset is unnatural and distorts the action potential dynamics. Hence, fitting v_shoot is a balancing act, where setting it lowest help save computational resources and setting it highest preserves natural action potential dynamics, but not too high as that would make the integration unstable.

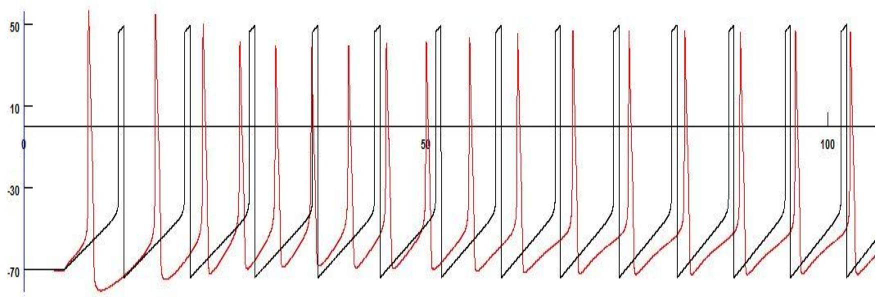
The value of Δ_T was fixed at 2mV, this was kept constant across the experiment (Brette, 2005).

2.5 Performance Measures

Spikes generated within ± 2ms of the reference model were considered a match. With this assumption, the spikes generated by the AdEx model were compared with the ones generated by the reference model for 2nA, Heaviside Step injection. The coincidence factor (Jolivet, 2004) was calculated as:

$$\Gamma = 1 - \frac{E+M}{2}$$

Where, M is the percentage of missed spikes (w.r.t ref model) and E is the percentage of extra spikes (w.r.t AdEx model)., five spikes are considered missed and two spikes are extra. The approximate number of spikes generated by the reference model was 168 and that of AdEx model was 164. This gave a Coincidence factor of 0.979.



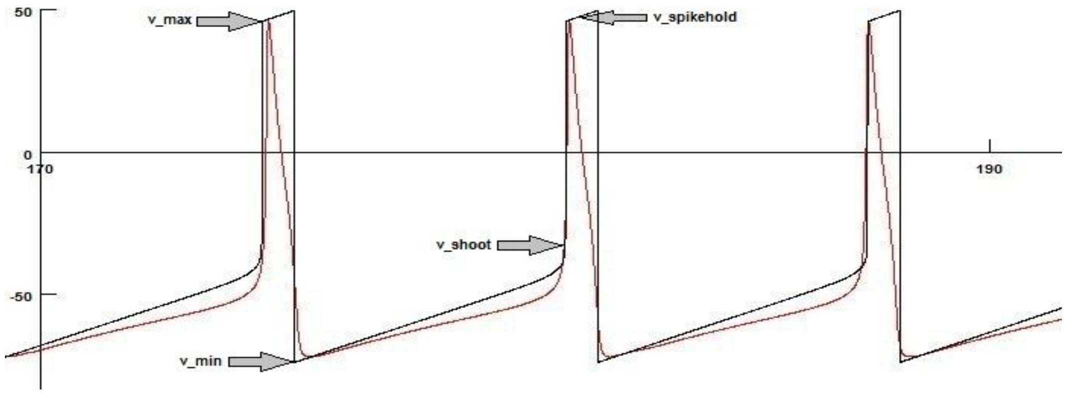


Fig. 4: Initial 100ms of simulation showing missed and extra spikes (left) and fitted individual AP (right)

3. Conclusions

3.1 Discussion

Fig. shows the actual model fitting exercise. The Praxis multi-run fitter available in NEURON simulator was attempted to be used for optimizing the predicted parameters, but did not yield favorable results.

The parameters used for the fit is shown in the parameter window (Fig. 5). Initially, V_{th} was observed to have more than 20% variation from the predicted values. Possible reasons could be due to the axial current or extracellular mechanisms of the multi-compartment reference neuron. To circumvent the issue, a series capacity was added to the membrane capacitance. Henceforth, all parameters were within 6-10% of the predicted values.

Within 1000ms of simulation, approximately 3% spikes were missed and 2% spikes were extra, which yields a coincidence factor (Jolivet, 2004)of $\Gamma = 0.979$ (Fig. 4).The voltage traces are also almost indistinguishable for individual Action Potential shape in the sub-threshold region. Some variations are observed in the super-threshold region.

The time evolution of the adaptation current is also shown in the

Fig. . The growth of the adaptation current was not pure exponential. An exponential was attempted to be fit into this, but the adaptation time constant $\tau_w$yielded large variations (~20-500ms) shows the shape of the spike generated from the AdEx model. Some of the fitted parameters are mentioned. When v_shoot is reached, the exponential integration is stopped and voltage set to v_max. After v_max is reached, the spike still keeps growing at a much slower pace. This is due to the passive properties of the model. But, the computational resources used to integrate these linear parameters are much less when compared to the stiff exponential integration. The voltage traces are also almost indistinguishable for individual Action Potential shape in the sub-threshold region. Some variations are observed in the super-threshold region.

3.2 Findings

The AdEx Exponential is too stiff for NEURON running on conventional PC. Unpredictable overshoot of spikes and numerical instabilities were observed. v_spikehold and stop variable were introduced to circumvent the issue.

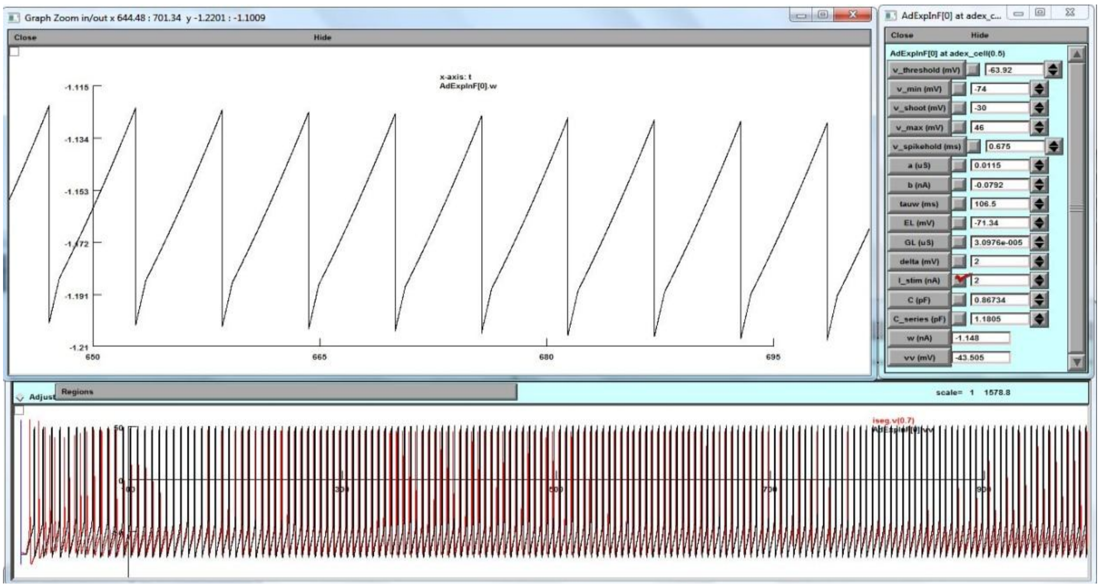


Fig. 5: Fitted AdEx model.

The predicted parameters did not achieve a very good fit at the AIS, but adding a capacity in series to the membrane capacity, gave a coincidence factor of more than 0.97 within 10% of the predicted parameters.Good fit for individual action potential shape was achieved with the data generated at the AIS, even without the series capacity.

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