Optimal parameter estimation of the Izhikevich single neuron model using experimental inter-spike interval (ISI) data

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Abstract—We propose to use the Izhikevich single neuron model to represent a motor cortex neuron for studying a control-theoretic perspective of a neuroprosthetic system. The problem of estimating model parameters is addressed when the only available data from intracortical recordings of a neuron are the Inter-Spike Intervals (ISIs). Non-linear constrained and unconstrained optimization problems are formulated to estimate model parameters as well as synaptic inputs using ISIs data. The primal-dual interior-point method is implemented to solve the constrained optimization problem. Reasonable model parameters are estimated by solving these optimization problems which may serve as a template for studying and developing a model of ensemble cortical neurons for neuroprosthesis applications.

I. INTRODUCTION

Brain Machine Interfaces (BMIs) provide an interface between the brain and a machine whereby electrophysiological measurement of neuronal firing activity in the brain is interpreted by the computer in real-time and translated to provide actuation commands for a variety of motor tasks such as hand grasping in artificial arms. This interface can be used to control a prosthetic device in severely paralyzed patients or amputees using raw cortical neural activity measurements available from the patient’s primary motor cortex area (M1) [1]. Current applications in neuroprosthesis use these raw cortical neural activities in “open-loop” controller forms to actuate the prosthetic device. Implicit or explicit feedback are not formally incorporated in designing the control action. To incorporate feedback information, there is a need to develop a closed-loop system [2] that is amenable to a control-theoretic study of the neuroprosthetic system.

A control-theoretic approach of a neuroprosthetic system requires an appropriate mathematical model for representing cortical neurons. It is a well known fact in neuroscience that the central nervous system carries information in the form of action potential trains [3] generated by neurons. The time gap between two action potentials, the Inter-Spike-Interval (ISI), carries most of the neural information [4]. This suggests a need for an appropriate single neuron model as a basic building block which can predict these action potential intervals or ISIs reasonably [5] and is computationally efficient for use in subsequent control-theoretic analysis of the closed-loop neuroprosthetic system. Several models [6] such as leaky integrate-and-fire [7], quadratic integrate-and-fire, Izhikevich single neuron model [8], Hodgkin-Huxley model [9], stochastic models [10], [11] etc., have been developed in this direction for modeling a single neuron. To choose any of these models for control-theoretic study of a neuroprosthetic system, it is necessary to validate the efficacy of these models using experimentally recorded single neuron data [12]. Also, estimation of several unknown parameters within these models using experimental data is necessary for making use of these models in a closed loop context.

Previous work has reported several results on model validation [13], [14] and model parameter estimation of stochastic models [15], [16], [17], [18], [19], [20], [21], [22], [23] using statistical analysis of experimental neuronal data obtained from rats, cats and pigs as well as stochastic methods. These methods use detailed neuronal recorded data such as subthreshold voltage traces, stimulus current traces which are not always available for validating a model. However, in most experimental studies, ISIs are the only available experimental data to validate a model as well to estimate model parameters. One of the major challenges in the estimation of model parameters and model validation using ISIs is the large variability obtained in the spike intervals as well as lack of information such as synaptic input currents. Very few results have been reported for estimating model parameters using ISI data only [24], [25] for leaky integrate-and-fire model. These results use model generated ISIs for validating the method for model parameters estimation, where ISIs are vary in a very small range. In experimentally recorded data, ISI variations are typically large, which is limiting the usefulness of these methods. To the best of our knowledge, no results are available in the literature for estimating single neuron model parameters using only experimentally recorded ISI data from the primary motor cortex area (M1 neurons).

In this work, we propose to use the Izhikevich single neuron model [26] for theoretical validation of single neuron dynamics using experimental data. For this purpose, we use ISIs data recorded from a single cortical neuron from a primate study [27]. To the best of our knowledge, this is the first time this model is validated and optimal model parameters are estimated using experimental ISIs data from a...
primate study. In order to estimate optimal model parameters, two different non-linear optimization problems (constrained and unconstrained) are formulated and shown in Section II. Algorithms for solving these problems are described in Section III. Numerical results are summarized in Section IV which is followed by conclusions in Section V.

II. MODEL PARAMETERS ESTIMATION PROBLEM

We will use the following model proposed by Izhikevich to model the dynamics of a single neuron:

\[
\begin{align*}
\dot{v}(t) &= 0.04v^2(t) + 5v(t) + 140 - u(t) + I(t); \\
\dot{u}(t) &= a(bv(t) - u(t));
\end{align*}
\]

(1a, 1b)

if \(v(t) \geq 30\text{mV}\), then \(v(t) \leftarrow c \) and \(u(t) \leftarrow u(t) + d;\)

(1c)

where \(v(t)\) is the membrane potential at time \(t\); \(u(t)\) is the membrane recovery variable; \(a, b, c, d\) are dimensionless model parameters; \(I(t)\) is the synaptic current input. \(v(t)\) is reset to \(c\) and \(u(t)\) is reset to \(d\) whenever \(v(t)\) exceeds \(30\text{mV}\).

The recovery variable \(u(t)\) accounts for the activation and inactivation of \(K^+\) and \(Na^+\) currents respectively and provides a negative feedback to the membrane potential \(v(t)\). The time scale of the recovery variable \(u(t)\) is described by the parameter \(a\) whereas the sensitivity of \(u(t)\) to the subthreshold fluctuations of the membrane potential \(v(t)\) is characterized by the parameter \(b\). After-spike reset value of the membrane potential caused by the fast high-threshold \(K^+\) conductances is described by the reset parameter \(c\). After-spike reset of the recovery variable \(u(t)\) caused by slow \(Na^+\) and \(K^+\) conductances is given by parameter \(d\) [26]. Detailed geometric characterization of these variables are given in [8]. The membrane potential reset value \(c\) is chosen to be the membrane resting potential or equilibrium potential \(v_{eq}\) and calculated as

\[
v_{eq} = \frac{(b - 5) - ((5 - b)^2 - 22.4)^{0.5}}{0.08}.
\]

(2)

The time at which this reset occurs is called the spike time and the interval between successive spikes is called the Inter-Spike Interval (ISI).

The parameter estimation problem is to determine optimal values of \(a, b, c, d\) and \(I(t)\) such that the ISIs calculated from the model match the experimentally obtained single neuron ISIs data from a primate study. Non-linear optimization problems are formulated to solve this parameter estimation problem as follows:

A. Unconstrained Optimization Problem

\[
\min_{a,b,d,I_j} J = N(T_j - T_{ej})^2;
\]

(3a)

such that

\[
\begin{align*}
\dot{v}(t) &= 0.04v^2(t) + 5v(t) + 140 - u(t) + I_j; \\
\dot{u}(t) &= a(bv(t) - u(t));
\end{align*}
\]

(3b, 3c)

if \(v(t) \geq 30\), then \(v(t) \leftarrow v_{eq}\) and \(u(t) \leftarrow u(t) + p;\)

(3d)

where \(j = 1, \cdots, m\) is the index of the experimental ISI data; for fixed \(j\), \(T_{ej}\) represents the \(j^{th}\) experimental ISI data; \(T_j\) represents the \(j^{th}\) ISI obtained from the model; \(a, b, d\) are unknown model parameters; \(I_j\) represents input current for the \(j^{th}\) inter-spike interval; \(N\) is the number of copies of the \(j^{th}\) ISI; \(\beta\) is the objective function.

B. Constrained Optimization Problem

We formulate a constrained optimization problem using equations (3a, 3b, 3c, 3d) along with following system constraints:

\[
\begin{align*}
22.4 - (5 - b)^2 < 0; \\
\Re(0.08v_{eq} + 5 - a + ((a - 0.08v_{eq} - 5)^2 - 4a(b - 0.08v_{eq} - 5))^{0.5}) < 0;
\end{align*}
\]

(4a, 4b)

where constraint (4a) has been defined such that the system possesses a feasible equilibrium state in the absence of any external input current \((I_1 = 0)\); the system stability at equilibrium has been defined using the constraint equation (4b) such that the real part of the eigenvalues are negative at equilibrium in absence of any external input current. These constraints have been defined such that a neuron possesses stable or saddle focus equilibrium at rest. \(\Re\) represent real part of a complex number.

III. ALGORITHM

The following strategies are applied in order to solve both constrained and unconstrained optimization problems defined above:

1) minimizing objective function \(J\) w.r.t. \(a, b, d, I_1\) to obtain optimal \(a, b, d\) and \(I_1\) by using the first experimental ISI data;

2) minimizing objective function \(J\) w.r.t. \(I_j\) for \(j = 2, \cdots, m\) using \(a, b, d\) estimated in the previous step and \(c\) from equation (2) to estimate synaptic current input \(I_j\) by using the rest of the ISI data.

A. Unconstrained System

The solution of the unconstrained optimization problem leads to the following conditions:

\[
\min_{a,b,d,I_1} J \Rightarrow \nabla J = 0 \quad \text{and} \quad \nabla^2 J > 0;
\]

(5)

where \(\nabla J\) represent the gradients of \(J\) w.r.t. \(a, b, d, I_1\); \(\nabla^2 J\) represent the second derivative of \(J\) w.r.t. \(a, b, d, I_1\). With initial guesses of \(a, b, d, I_1, \nabla J\) and \(\nabla^2 J\) are calculated numerically using finite difference schemes. Parameters are updated using the Newton method for convergence as follows:

\[
x^{new} = x^{old} - t(\nabla^2 J)^{-1}\nabla J;
\]

(6)

where \(x = [a \ b \ d \ I_1]^T\); Value of \(c\) is updated using equation (2); \(t\) is the step size calculated at each iteration using backtracking line search method. Stopping criterion is determined by the Newton decrement function, \(\beta(x) = (\nabla J(x)^T \nabla^2 J(x)^{-1} \nabla J(x))^{0.5}\) [28].
B. Constrained System

The Primal-dual interior-point method [28] is applied to solve the constrained optimization problem. The following modified Karush-Kuhn-Tucker (KKT) conditions are used for the implementation of the interior-point algorithm:

$$r_t(x, \lambda_1, \lambda_2) = \begin{bmatrix} \nabla J(x) + \lambda_1 \nabla g(x) + \lambda_2 \nabla h(x) \\ -\lambda_1 g(x) - \frac{1}{\eta} \\ -\lambda_2 h(x) - \frac{1}{\eta} \end{bmatrix} = 0; \quad (7)$$

where $g(x) = 22.4 - (5 - b)^2$; $h(x) = \Re(0.08v_{eq} + 5 - a + ((a - 0.08v_{eq} - 5)^2 - 4a(b - 0.08v_{eq} - 5))^{0.5})$; $v_{eq} = \frac{0.08}{(b-5)-(5-b)^2-22.4}^{0.5}$; $\lambda_1, \lambda_2$ are the Lagrange multipliers; $t = \frac{n}{\eta}$; $\hat{f} = -\lambda_1 g(x) - \lambda_2 h(x)$ is the duality gap.

IV. NUMERICAL RESULTS

In this section, numerical results for the optimization problems mentioned in section II are reported using experimentally obtained cortical neuron ISI data from a primate study. Experimental set-up and details are discussed in [27], [29]. In brief, a male rhesus monkey - K-, trained to perform visually-cued finger and wrist movements, placed his right hand in a pistol-grip manipulandum in order to extend or flex a digit by a few millimeters. For instructing the monkey to close the switch by extension or flexion, visual cues were presented to the monkey using LEDs.

Experimental data acquisition was accomplished using single unit recordings of neuronal activities in the primary motor cortex (M1) of the monkey. Self-made, glass-coated, Pt-Ir microelectrodes [29] were implanted through surgical procedure advanced through a surgically implanted chamber to record the time of single neuron action potential. All the experiments were carried out at the University of Rochester Medical Center in a protocol approved by the local IACUC. A schematic diagram of recording from a single neuron is shown in Figure 1.

![Experimental recordings of spike timings from a single neuron](image)

Fig. 1. Experimental recordings of spike timings from a single neuron; the neuron figure has been taken www.brainconnections.com

ISI data for two neurons, “K11404” and “K15906” recorded during an extension of the right hand index finger of a primate [30] have been used to show the validity of the algorithms mentioned in section III. The finger movement trials selected for the present analysis lasted in an approximate time duration of 700ms – 1300ms [27]. The 34 and 43 recorded ISI data occurred during this time period for neurons “K11404” and “K15906”, respectively, have been used to estimate model parameters. The unconstrained optimization problem is solved first for the neuron “K11404” to show the need for using the constrained formulation.

A. Unconstrained system

For the unconstrained optimization problem mentioned in section II-A, $N = 20$ was used in equation (3a). The first ISI data were used for estimating model parameters $a,b,d$ and synaptic current $I_1$. The optimization problem was solved numerically by following the unconstrained optimization algorithm in section III using MATLAB. Initial guesses for parameters $a,b,d$ were chosen as 0.02, 0.25,6 respectively as given by Izhikevich for phasic-tonic spiking of cortical neurons. $I_1 = 20$ was chosen as an initial guess for the current input. Stopping criteria for the convergence was set to $\frac{b^2}{T^2} < 10^{-4}$. Model parameters were estimated to be $a = 0.0805$, $b = 0.5889$, $d = 15.5703$. Following step 2 in section III, synaptic input currents $I_2$ were estimated using the calculated model parameters $a,b,d$ for the remaining 33 ISIs. Initial guess for these synaptic inputs was set to the minimum possible synaptic input for generating an action potential. Using estimated parameters, the model was solved numerically. Numerical results are shown in Figure 2.

In Figure 2, the top graph represents the experimentally obtained ISIs. The second graph shows the ISIs calculated from the model using estimated model parameters and synaptic current inputs. Almost exact matching of theoretical and experimental ISIs shows that the estimated model parameters are appropriate to characterize properties of the “K11404” neuron. The third graph represents the membrane potential in the absence of any synaptic input ($I = 0$). The variation in the synaptic current from one ISI to another is shown in the fourth figure. It is assumed that the synaptic current is constant during each ISI. A positive current represents an excitatory and a negative current represents an inhibitory input. Action potentials estimated by the model in the absence of synaptic current input (third figure) do not show single neuron behavior at the resting potential. Presence of spikes indicates that the model parameters contain enough synaptic information to fire an action potential which is not true in the case of a physical neuron which fire only in the presence of synaptic inputs. Thus these estimated parameters are not appropriate to characterize the neuron.

Mathematical analysis of the Izhikevich model (1a),(1b),(1c) with $I(t)=0$ shows that $(5-b)^2 - 22.4 \geq 0$ is necessary for obtaining real equilibrium points of the system which further state that the model parameter $b \in (-\infty, 0.2671] \cup [9.7329, \infty)$. Solution of the unconstrained problem clearly shows that $b = 0.5889$ is outside the domain.
of the feasible equilibrium space. This clearly shows that the above estimated model parameters are not appropriate to represent the neuron behavior.

The infeasible model parameter estimation for the neuron using unconstrained optimization problem suggests that there is a need to put constraints on parameters to satisfy feasible equilibrium criteria as well as stability of the system in the absence of any synaptic input and solve a constrained optimization problem as in section II-B. Although results for other recorded neurons are not shown in this paper, the feasible model parameters were estimated for many of the recorded cortical neurons by solving the unconstrained optimization problem and lead to similar conclusions.

B. Constrained system

For the constrained optimization problem defined in section II-B, we use $N = 5$ in equation (3a). The primal-dual interior-point method was implemented using MATLAB to solve this constrained problem using the first experimental ISI data for the neuron “K11404” and “K15906”. It should be noted that none of the MATLAB in-built optimization algorithms has been implemented to solve the problem. $\mu = 10$ and $\mu = 4$ were chosen to calculate $t$ for the neuron “K11404” and “K15906” respectively. Initial guesses for parameters $a, b, d$ were chosen as 0.02, 0.25, 6 respectively as given by Izhikevich for phasic-tonic spiking of cortical neurons for all neurons. $I_1 = 20$ and $I_1 = 25$ were chosen as initial guesses of the input current to the neuron “K11404” and “K15906”. Stopping criteria were chosen based on $||r(x, \lambda)||_2 \leq 0.3$. The model parameters $a, b, d$ and synaptic current input $I_1$ were calculated by solving the constrained optimization problem for both neurons. Synaptic current inputs for the remaining 33 ISIs were calculated by solving the unconstrained optimization problem using the estimated model parameters $a = 0.2273$, $b = 0.2401$ and $d = 27.1925$ for the neuron “K11404” and $a = 0.2062$, $b = 0.2455$ and $d = 16.7083$ for the neuron “K15906”. Using the estimated model parameters and synaptic inputs, the model was solved numerically. Numerical results are shown in Figure 3 for the neuron “K11404” and in Figure 4 for the neuron “K15906”.

In Figure 3, the top figure represents the experimentally recorded ISIs. The second figure represents ISIs calculated from the model for the neuron “K11404” in the presence of synaptic input. The third figure represents the membrane potential predicted by the model in the absence of synaptic input. The fourth figure shows the variation in the synaptic current from one ISI to another. Variations in synaptic current based on ISIs clearly support the physical behavior of a neuron that fast or slow firing of an action potential train (small or large ISIs correspondingly) is based on synaptic information. Availability of large synaptic information in the fixed time duration leads to faster spiking (small ISIs) and small synaptic information leads to slow spiking (large ISIs) rate. The fifth figure in Figure 3 shows the percentage error between experimental and model estimated spikes time. Error is calculated as $\frac{100(t_{ei} - tm_i)}{te_i}$, where $te_i$ and $tm_i$ are experimental and model estimated spike time for the $i^{th}$ spike.

The membrane potential of the neuron is at the resting potential in the absence of any synaptic input (third figure in Figure 3) which indicates that the estimated parameters are appropriate to characterize the neuron “K11404”. There is very small error (shown in the fifth sub-figure in Figure 3) between the theoretical and experimental ISIs. Similarly, numerical results shown in Figure 4 indicate that the estimated parameters are appropriate to characterize the neuron “K15906”.

In support of the reasonable estimated parameters, mathematical analysis of the Izhikevich model was carried for both neurons, “K11404” and “K15906”, using the estimated model parameters with $I(t) = 0$. Equilibrium points $(-53.1631, -12.7629)$ and $(-65.8352, -15.8051)$ for the neuron “K11404” and $(-53.7657, -13.1985)$ and $(-65.0973, -15.9802)$ for the neuron “K15906”, calculated using these estimated model parameters, clearly show that the system possesses real equilibrium states in the absence of any external synaptic information which was not true in the case of the unconstrained optimization problem. Each pair of equilibrium points represent $(v, u)$, membrane potential...
Fig. 3. Constrained parameter estimation for the neuron “K11404”: top figure represents experimentally recorded action potential spike times; second figure represents spike times predicted by the model in presence of synaptic input; third figure represents membrane potential in absence of synaptic input; fourth figure represents synaptic input current; last figure represents percentage deviation in experimental and theoretical spike times.

Fig. 4. Constrained parameter estimation for the neuron “K15906”: top figure represents experimentally recorded action potential spike times; second figure represents spike times predicted by the model in presence of synaptic input; third figure represents membrane potential in absence of synaptic input; fourth figure represents synaptic input current; last figure represents percentage deviation in experimental and theoretical spike times.
and membrane recovery variable respectively, at equilibrium.

\[ v = -65.8352mV \] and \[ v = -53.1631mV \] for the neuron “K11404” and \[ v = -65.0973mV \] and \[ v = -53.7657mV \] for the neuron “K15906” are the neuron resting potential and the neuron threshold respectively. Eigenvalues calculated at the neuron resting potential are \(-0.2470 \pm 0.2327i\) for the neuron “K11404” and \(-0.2070 \pm 0.2250i\) for the neuron “K15906” which shows that the resting potential is a stable focus in both neurons. The existence of this stable focus supports experimental evidence that a neuron stays at its resting potential in the absence of any external synaptic input. Eigenvalues calculated at the threshold potential are \(0.6873 \pm 0.1676\) for the neuron “K11404” and \(0.6388 \pm 0.1463\) for the neuron “K15906” which clearly indicate existence of a saddle at the threshold in both neurons. A positive eigenvalue at the threshold indicates the existence of an action potential in both neurons whenever the membrane potential crosses this threshold based on synaptic information. This is true in experimentally observed dynamical behavior of a realistic motor cortical neuron.

Mathematical analysis of the model using estimated parameters for neurons “K11404” and “K15906” supports the experimentally recorded behavior of neurons. Based on the parameter estimation results from other M1 neurons, we have found that this approach can be used to estimate model parameters for all neurons from the primary motor cortex (M1) using only inter-spike intervals (ISIs) data.

V. CONCLUSION

Optimal parameter values were estimated for the Izhikevich single neuron model using experimentally recorded single neuron inter-spike intervals (ISIs) data from a primate study. Non-linear constrained and unconstrained optimization problems were solved to characterize the neuron physical properties appropriately. Numerical results were shown for two different neurons (“K11404” and “K15906”). Results were compared for unconstrained and constrained problems. Need for the constrained optimization problem was emphasized and discussed using mathematical analysis. We believe that this approach can be used to efficiently estimate model parameters of the Izhikevich single neuron model based on using ISIs only.

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REFERENCES


